The DEMING approach to quality

Enhancing productivity in pharmaceutical research by a focus on process and quality

To enhance productivity in pharmaceutical research, we have tended to look to innovations in science and technology, such as genomics, high-throughput screening and combinatorial chemistry. In this article, we take our inspiration elsewhere, by studying the research process itself, with a focus on quality. We explore the relevance to pharmaceutical research of the ideas of W. Edwards Deming, the statistician whose ideas on quality transformed the manufacturing sector of post-war Japan. Many of Deming's Fourteen Principles of Quality will instantly resonate with anyone in Pharma R&D: improve constantly; break down the barriers between departments. Others are more controversial, such as "eliminate management by numbers, substitute leadership". Many in Pharma Research organisations have witnessed bending of the rules to ensure that annual targets for drug candidates are met, hitting the quota at the expense of the quality of the drug candidates. We assert that a focus on compound quality may reduce attrition in the clinic, with corresponding improvements in productivity.

By John H. Van Drie

The pharmaceutical industry has produced stunning medical advances in the past 50 years. But our very success has created a dilemma. As Steven Nissen, the Cleveland Clinic cardiologist, has observed regarding cardiovascular drugs: "For every pharmaceutical company developing a new drug, the reality is that current therapy is pretty good… It is going to be very tough to find new therapies with incremental benefit."[1].

Our industry is structured in a way that demands constant innovation. All of us in Pharma are deeply concerned that investments in R&D continue to rise, while the number of approvals for new medical entities declines[2]. We are all motivated to look for new ways to approach pharmaceutical R&D. As scientists, our natural tendency is to look for solutions to this R&D productivity dilemma in novel science and technology. In the past 15 years, tremendous investments were made in high-throughput screening, combinatorial chemistry, and, most notably, genomics.

The time is ripe for us to begin to look elsewhere for inspiration on new ways to approach this dilemma. The purpose of this article is to direct our

attention to the processes we follow in pharmaceutical research, and explore the implications of a focus on quality. The aim is to stimulate thinking about how a such a focus could present opportunities to improve the productivity of pharmaceutical research, to ultimately change how we approach drug discovery.

There are many thought leaders on quality, and the one we have chosen to follow in this article is W. Edwards Deming. We will follow Deming's 1982 book *Out of the Crisis*[3], the most concise exposition of his thinking. Deming's fame as a consultant in quality stems from his role in the revival of Japanese industry in the 1950s, which began with his seminal lecture to Japanese industry leaders in 1950[4]. Deming's legacy may be seen in the rise to prominence of the Japanese auto industry (eg, Toyota is expected to overtake General Motors this year as the world's largest auto company), and the Deming Prize, awarded annually in Japan to the organisation making the greatest strides in quality (**Figure 4**). Deming was educated as a theoretical physicist, and worked primarily as a statistician prior to his involvement with Japan in the 1950s.

Deming is only one of many quality gurus, and one might do well to study any of them in context of the issues we face in Pharma. However, Deming's 'Fourteen Principles' which concisely summarise his approach will likely resonate to anyone active in pharmaceutical research in the past 10 to 20 years.

The proposal to focus attention on the research process is steadily gaining ground in the broader community. Ed Petrillo, in an earlier issue of this journal[5], has already made this point, in the context of applying 'lean-thinking' to the R&D process. "The right process will produce the right results" is a maxim central to the quality community.

What does it mean to talk about quality in pharmaceutical research? We assert that it is primarily an issue of compound quality – the quality of drug candidates we discover in research that are passed to development. From this perspective, the probability of attrition in the clinic provides a metric for quality; these statistics were recently compiled across all Pharma by Kola and Landis[6], and are shown in **Figure 3**. Our future success depends on us advancing higher quality molecules into the clinic.

Deming's 'fourteen points'

Deming acknowledged that his 'fourteen points', outlined in Chapter 2 of *Out of the Crisis*, formed a new "theory of management". In what follows, I have re-ordered his 14 points, based on my view their relevance to drug discovery. Only the first six will be examined closely; those remaining will merely be quoted.

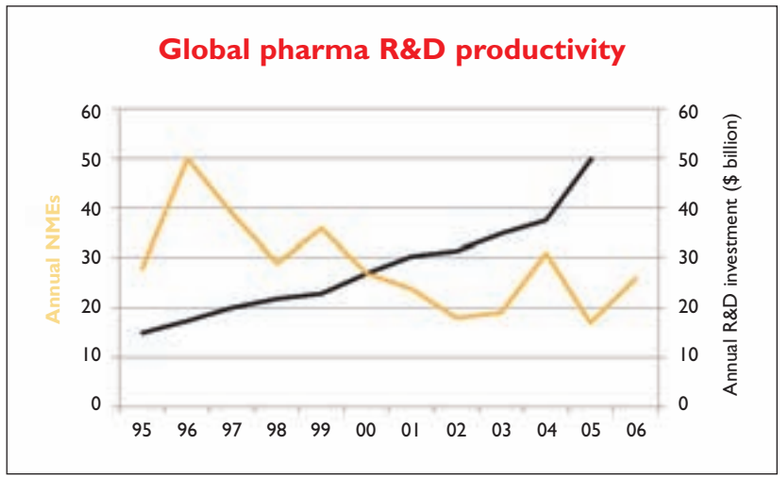

Figure 1
Looking across the entire pharmaceutical industry globally, R&D investments are rising, while the number of new molecular entities approved is declining

1. Create constancy of purpose for the improvement of products and services, with the aim to become competitive, stay in business and provide jobs.

This is the first of Deming's points, and the first to be considered here. Constancy of purpose he regards as an essential attribute to allow innovation to occur. Lack of constancy of purpose he traces back to short-term thinking in general, and a race to look good on the next quarterly earnings report. Related to that, Deming states "fear of unfriendly takeover may be the single most important obstacle to constancy of purpose" (words written in 1982)[7].

Very few researchers in drug discovery in the

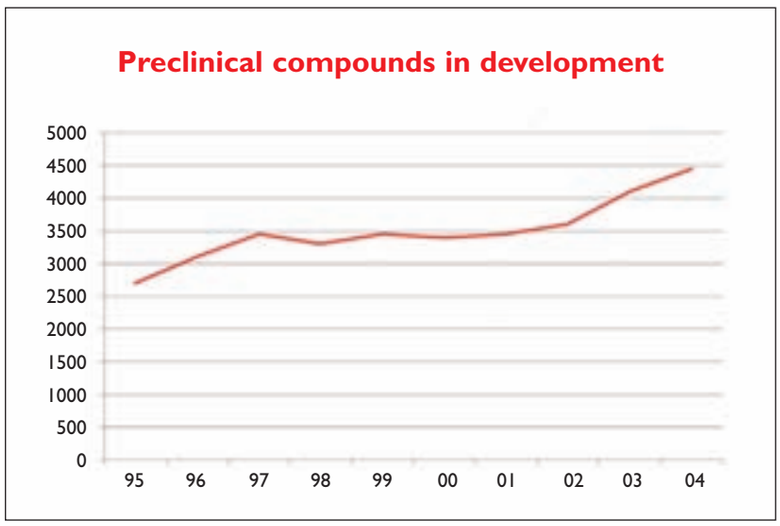

Figure 2
The number of candidates put into the clinic continues to rise, roughly in proportion to overall R&D spending

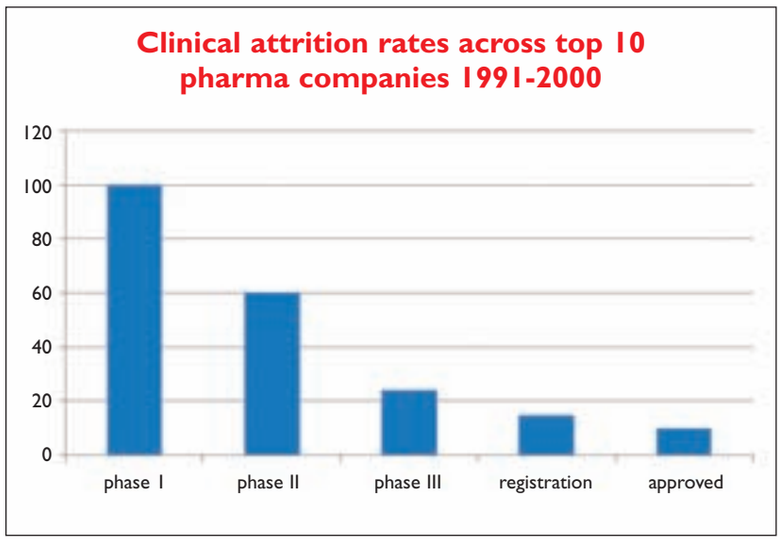

Figure 3
Shown here is the attrition of clinical candidates by each phase, plotted as the likelihood that a compound which has had a first-in-man advances to the indicated phase

past 20 years have remained unaffected by the wave of mergers, takeovers friendly and hostile, reorganisations, restructurings, etc. The setback to research productivity in the wake of a merger or takeover is well-acknowledged to anyone who has been through them, as researchers wait to learn which projects will be culled, which leaders will remain and which will go, etc. Gary Pisano at the Harvard Business School has studied the matter quantitatively, and concludes that "the track record for mergers and acquisitions (M&A) in terms of creating long-term shareholder value in pharmaceuticals appears to be exceedingly poor. The logic behind M&A is highly suspect"[8].

There is an understandable tendency to point to the investment community as the origin of this short-term thinking. While there is likely some truth to this sentiment, as a counter-balance one could look at the "Pharma Futures: Prescription for Long-Term Value" report[2], a study sponsored by a group of institutional investors heavily invested in Pharma. Their perspective, while offering no specific solutions, shows that some major investors are genuinely concerned about the long-term perspective in the Pharma industry. They make the point that "the industry will need to find the appropriate balance between incremental and step-change innovation, against a backdrop in which the decision to continue to invest strongly in incremental innovation is already being questioned".

Figure 4
The medal for the Deming Prize, awarded annually for strides in quality

Fixing short-termism and enhancing a constancy of purpose might seem to be an insurmountable challenge, especially for one department in a larger organisation. Clearly, one response from research executives could be to make it clearer to those running the business that a constancy of purpose goes hand-in-hand with innovation. In addition, as noted in the Pharma Futures report: "Increased transparency could yield greater investor patience and help to resist the trend to short-termism that currently characterises the market."

2. Eliminate numerical goals, numerical quotas, and management by objectives. Substitute leadership.

This item, originally number 11 on Deming's list, is of special importance to pharma research. In the 1990s, a combination of business pressures and the introduction of high-throughput screening has led to an increasing focus on measuring productivity by numbers: the number of high-throughput screens run, the number of compounds screened, the number of compounds synthesised, etc. The automobile industry was once in the throes of such numbers-driven management, and the result was a lot of lemons landing on the showroom floors. Those auto companies who have embraced a commitment to quality have now come to totally dominate the market, epitomised by Toyota.

The phrase 'substitute leadership' requires explanation. This cuts to the heart of the Deming approach. By leadership, he refers to management's job of identifying the source of quality issues, and resolving them (not blaming the people doing the work, to paraphrase Deming). The centrepiece of his approach is now called a Deming cycle (**Figure 5**), an iterative cycle of Planning (identifying an opportunity, developing a concept), Doing (designing and executing on the concept), Observing (observing the outcome), and Studying the result (identifying what one has learned), leading to a new cycle of Planning, etc.

In terms of pharma research, the great misperception is that this should be applied to minutiae, eg, minimising the number of steps in the transfer of a sample from one lab to another. By contrast, as pointed out in the introductory paragraphs, if we view clinical attrition as a quality problem, the key thing this identifies is the need for a feedback loop from compounds falling out in the clinic to

those people designing molecules in the research labs, ie learning why compounds are failing in the clinic and passing that learning back to those in research. In the distant past, this was accomplished haphazardly by 'institutional memory', scientists with long tenure who had been part of these clinical failures, and who had absorbed 'lessons learned'. There is a need to systematise this feedback loop in pharma R&D, especially since many of these long-tenured scientists are no longer around.

Clinical attrition is not the only place one should look for opportunities to improve feedback loops on lessons learned. For example, for projects with screening hits going into hit-to-lead efforts, one hears estimates that 40-60% of these projects are unsuccessful in advancing to lead optimisation. The team members involved usually retreat ignominiously at their failure, and move on to other efforts, usually with little attention paid as to why that particular hit-to-lead effort did not advance.

Of course, the greatest negative impact of a numbers-orientation is a phenomenon common to most pharma research organisation: a tendency to lower the standards near the end of the year to advance compounds into the clinic, in order to meet the annual quota. The data have never been compiled to my knowledge, but it would be fascinating to chart the number of clinical candidates approved as a function of quarter in the fiscal year, and to compare the attrition rates of each group of candidates, quarter-by-quarter. Anecdotally, one anticipates that the attrition rate would be much higher among Q4 candidates, compared to Q1 or Q2 candidates, and that the curve of approvals per quarter would rise sharply towards Q4.

Related to this is Deming's assertion that one of the deadly diseases of management is running a company on visible figures alone. Despite his orientation as a statistician, he often stated that the most important aspects of running an organisation are the unknowns and the unknowables.

3. Cease dependence on mass inspection to achieve quality. Instead, improve the process and build quality into the product in the first place.

It is obvious how this principle applies to manufacturing cars; it is less clear how this applies to pharma R&D. In a manufacturing process, one can well imagine a quality inspector assiduously inspecting the output at one station, shelving defective parts. If no effort is made to track down the origin of these quality problems, one is left only with an ever-growing pile of defective parts. Deming's maxim applied here says to put more effort into tracking down the origin of quality problems, to lessen dependence on quality inspection (where nothing really can be done to alter the work process). Enhanced productivity follows naturally from a reduction in waste, ie production of defective parts.

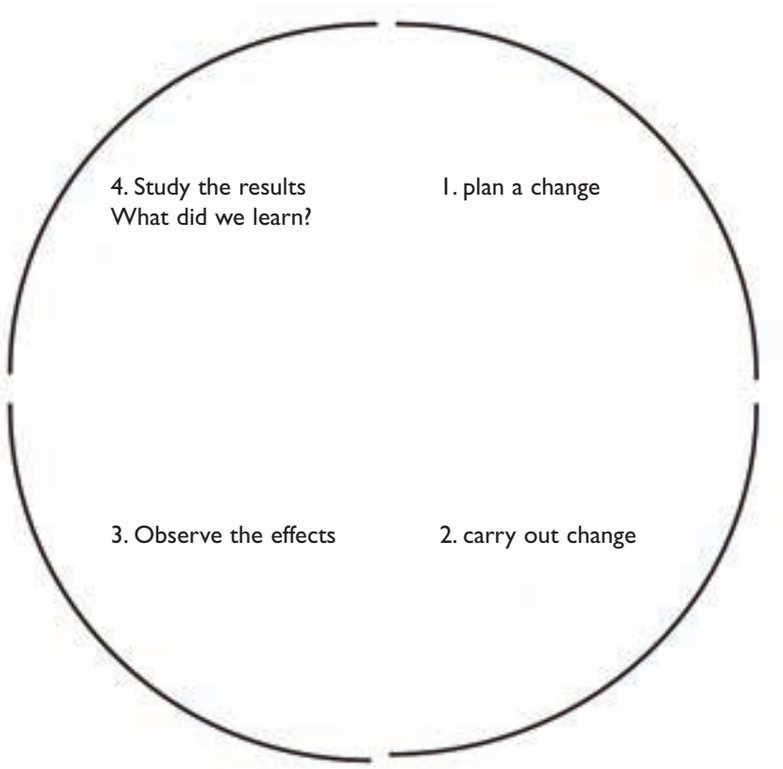

Figure 5
The 'Deming cycle' for continuous improvement

I will assert that our typical pre-clinical safety processes and human clinical trials are, in effect, quality inspections. When a molecule fails this 'inspection', it is added to a growing pile of failed molecules. If we miss the opportunity to learn from this failure, and to infer the attributes of that molecule that led to it, we will repeat this again and again, with the corresponding hit in productivity. Every molecule which dies in pre-clinical or clinical studies is a hit to productivity, and hence every improvement we can make in that will yield productivity improvements. The scientific foundation for performing such analyses exists (see, for example, Biller et al[9]); what appears to be lacking is the conviction that this is important and necessary. Furthermore, as noted by Phil Burton and colleagues, this learning must be applied with great care: "While the experimental models have been effective in reducing specific causes of clinical failure, by possibly being too restrictive, or inappropriately applied, they may have contributed to the elimination of viable clinical candidate; effectively throwing the baby out with the bath water."[10]

4. Break down barriers between departments. Abolish competition and build a win-win system of co-operation within the organisation. People in research, design, sales, and production must work as a team to foresee problems of production and use that might be encountered with the product or service.

The pharma R&D counterpart to this principle of Deming has already been articulated by E. H. Cordes[11]: if the members of a drug discovery team are only looking out for the interests of their own department, they will tend to optimise the performance of their piece of the overall effort at the expense of sub-optimising their contribution to the final output of the team. For example, if an assay can be reconfigured to produce the same number of datapoints with fewer FTEs, but at a cost of lower quality of the numbers, the team viewpoint might well be to pick the trade-off that produces higher quality data, while the assay department's view might be to minimise the FTEs committed to this project. A team, facing the choice between a series whose potency is easy to optimise but which contains a fatal flaw which will only appear in later pre-clinical safety assessment, and another series free of obvious flaws but involving difficult chemistry for potency optimisation, might call that trade-off differently than the chemists who need to deliver those results to the team. The goal is to discover a drug, and the most productive teams are those whose members have a horizon beyond their own department, and which maintain an 'end-to-end' view of the entire drug discovery process.

5. Adopt a new philosophy of co-operation (win-win) in which everybody wins and put it into practice by teaching it to employees, customers and suppliers.

6. Remove barriers that rob people of joy in their work. This will mean abolishing the annual rating or merit system that ranks people and creates competition and conflict.

No one will argue against the view that co-operation, win-win and teamwork are essential attributes of a productive R&D enterprise. And, yet, no one has yet found a way to properly evaluate performance, to grant recognition and rewards, that

emphasises teamwork over individual achievement. Deming, controversially, advocates that annual rating systems be abolished. None of Deming's principles are more difficult to imagine being implemented than this. Yet he catalogues example after example of the deleterious impact of rewarding individuals over group achievement.

7. Improve constantly, and forever, the system of production, service and planning of any activity. This will improve quality and productivity and thus constantly decrease costs.
Continual improvement is a cornerstone of the Deming approach, constant iteration around the Plan/Do/Observe/Study cycle, constantly unwilling to be complacent with the status quo. There are many examples in the literature on manufacturing quality showing that this approach can yield improvements in quality that could not be imagined at the outset. A perceived impediment to this in pharma R&D in the past 10 years has been the tremendous pressure to produce results – "we're trying to overhaul the airplane engine while in flight", in the words of one pharma research leader. Yet, the situation we face in Pharma cannot be more challenging than that faced by the Japanese manufacturing leaders who embraced Deming in 1950, in the immediate aftermath of World War 2.

8. Drive out fear and build trust so that everyone can work more effectively.
9. Institute a vigorous programme of education and self-improvement.
10. Adopt and institute leadership for the management of people, recognising their different abilities, capabilities and aspirations. The aim of leadership should be to help people, machines and gadgets do a better job. Leadership of management is in need of overhaul, as well as leadership of production workers.
11. Institute training for skills.
12. Eliminate slogans, exhortations and targets asking for zero defects or new levels of productivity. Such exhortations only create adversarial relationships, as the bulk of the causes of low quality and low productivity belong to the system and thus lie beyond the power of the work force.
13. Put everybody in the company to work to accomplish the transformation.
14. End the practice of awarding business on the basis of price alone. Instead, minimise total cost in the long run. Move toward a single supplier for any one item, based on a long-term relationship of loyalty and trust.

Without going into detail on these remaining points of Deming, each has a relevance to pharmaceutical research, and many will likely resonate with those experienced in this endeavour.

Conclusion

A focus on quality could help resolve the dilemma we face in pharmaceutical R&D productivity. In particular, Deming's Fourteen Points appear to be quite relevant to Pharma R&D; we may have much to learn from his ideas. Actually implementing the complete Deming approach would require a top-to-bottom cultural change in an organisation, involving many factors outside the control of R&D management, but one can imagine that even small steps towards Deming's vision would yield improvements in productivity. In particular, each time a molecule fails to progress to a new phase is an opportunity for one to investigate the underlying causes, and to provide feedback to those designing molecules to lower the probability of recurrence of those issues. A feedback loop from clinical attrition would clearly have the greatest potential for productivity improvements, but productivity improvements could come from even simpler feedback loops, eg investigating why a lead discovery effort did not succeed. Distilling these lessons learned into guidance for those designing molecules, assays, etc must be done with great care, cognisant of the statistical uncertainties involved.

We are in an era with enormous challenges facing the pharmaceutical industry. Expectations are rising on what constitutes medical innovation, while at the same time the stakeholders are scrutinising us to unprecedented degrees. Once again, Deming's words are prescient[12]: "Darwin's law of survival of the fittest… holds in free enterprise as well as in natural selection… the only survivors will be companies with constancy of purpose for quality [and] productivity."

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References

1 Winslow, R. Wall Street Journal, Nov 18, 2005.
2 Tickell, S et al. "Pharma Futures II: Prescription for long-term value", available at www.pharmafutures.org/sustainability.
3 Deming, WE. Out of the Crisis. Cambridge: MIT Press, 2000, reprinted from 1982 edition.
4 Deming's 1950 lecture to Japanese management, informal translations are posted on the web, eg http://deming.eng.clemson.edu/pub/den/deming_1950.htm.
5 Petrillo, E. Drug Discovery World, Spring 2007.
6 Kola, I and Landis, J. Nat Rev Drug Discovery, 2004, 3: 711.
7 Out of the Crisis, p100.
8 Pisano, GP. Science Business, Cambridge: HBS Press, p 175.
9 Biller, SA et al. "The Challenge of Quality in Candidate Optimization". In: Borchardt RT, eds. Pharmaceutical Profiling in Drug Discovery for Lead Selection. Arlington, VA: AAPS Press. 2004; 413-429.
10 Burton, PS, Vidmar, TJ, Goodwin, JT. ADMETRx white paper "The challenge of improving the drug discovery process-An early ADME perspective". This is a manuscript in preparation for Chemical Biology and Drug Design; an early draft may be found on the web at http://www.healthtech.com/whitepapers.asp.
11 Cordes, EH. Personal communication, stemming from a private lecture delivered to employees of Vertex Pharmaceuticals.
12 Out of the Crisis, p.155.