Pharm Res (2011) 28:1779–1781
DOI 10.1007/s11095-011-0479-5

COMMENTARY

The Evolution of the Manufacturing Science and the Pharmaceutical Industry

Stavros N. Politis • Dimitrios M. Rekkas

Received: 17 February 2011 / Accepted: 10 May 2011 / Published online: 17 May 2011

KEY WORDS manufacturing science · pharmaceutical industry · post mass production paradigm

Manufacturing methodology has significantly evolved during the last decades, aiming at quality improvement, innovation, waste reduction and flexibility to meet new challenges. This commentary will review the evolution of the manufacturing science from mass production to lean manufacturing and the most recent agile approach, while the reaction of the pharmaceutical industry to these changes will be also addressed.

The paradigm of accustomed mass production has reached a limit. The results of efficient and scientifically sound manufacturing methodologies, such as the lean approach, gave rise to new important approaches including, bionic, holonic, fractal and agile manufacturing (1). The latter refers to fast and flexible infrastructures emphasizing virtual partnerships, valuing human knowledge and skills, which are therefore capable of delivering quality to the customer while addressing market uncertainty and complexity through rapid change.

The above-mentioned post-mass-production paradigms are compliant with the IMS/GNOSIS (2) initiative on knowledge systemization for design and manufacturing, as well as the EU vision for assuring the future of manufacturing towards 2020 (3). According to these studies, the transition towards the factories of the future should be based on the following pillars for sustaining their competitive advantage:

- Achievement of reusability, reconfigurability and flexibility, taking into account the growing scarcity of natural resources, environmental concerns, rising energy costs, individualized customers needs, globalization, information technology, knowledge management, and web-based services.
- Shift from linearity to complexity, mono-disciplinarity to trans-disciplinarity, individual to system competition, and, finally, from resource-based towards adaptive, digital, networked and knowledge-based manufacturing.

Along the same line, the US National Science Foundation (NSF) in their Next Generation Manufacturing (NGM) report (4) suggested that the future manufacturers will be networked infrastructures forming flexible alliances with multiple business partners, rather than sovereign profit-making companies and concluded that only the agile will survive. This infrastructure facilitates quick response to customer needs by rapidly producing customized, inexpensive, and high quality products by empowered and knowledgeable employees. Sharing the same vision, the Integrated Manufacturing Technology Roadmap (5), a follow-up of the NGM report, was an attempt to define the future manufacturing technology requirements, addressing the following key-points: total connectedness, integrated enterprise management, fully integrated product realization, plug-and-play interoperability, seamless and flexible distributed operations, intelligent and efficient processes, and science-based manufacturing. This report also recognized modeling and simulation as the basis for lean, agile, and responsive manufacturing in the 21st century.

In the same concept, the recent initiative *monozukuri* reflects Japan's national strategy to re-affirm its strengths in

S. N. Politis · D. M. Rekkas (✉)
School of Pharmacy, Division of Pharmaceutical Technology
University of Athens
Panepistimiopolis Zografou
Athens 15771, Greece
e-mail: rekkas@pharm.uoa.gr

manufacturing and preventing de-industrialization. It describes technologies and processes integrating development, production, and procurement in a way which assures the duplication of design data into the product (6), while retaining intangible qualities, such as craftsmanship and dedication to *kaizen*, the Japanese word for continuous improvement. The fundamental scope of *monozukuri* is to emphasize the significance of efficient process transfer between design and production.

More or less, the above insights can be also traced either within the FDA PAT guidance, a broad and ambitious initiative for innovative pharmaceutical development, manufacturing, and quality assurance, or the more conservative ICH Q8 guideline on Pharmaceutical Development, focusing on the Quality-by-Design concept. They both form the regulatory framework to catalyze the shift of the pharmaceutical factory towards the post-mass-production paradigms already well explored in the literature and established in other industrial sectors.

Similar projections have also been published for the future of the pharmaceutical plant floor in particular. Industry experts have estimated that during the next years, it is expected to change substantially, as the monolithic blockbuster business model is disintegrating (7,8), and new strategies will eventually emerge to address the new challenges. These include customized therapeutic approaches, increasing pressure for cutting health costs, public awareness, and variable demand, which will require the optimization of the supply chain (9). In order to meet these new requirements, the manufacturing facilities should be redesigned to support modular configurations, wireless networking, and an agile environment. This will improve Pharma's major performance indicators, such as productivity, overall equipment effectiveness, lead times, inventory turns, and right-first-time indices, which as of now lag behind when benchmarked against other industries.

The pharmaceutical industry is innovative in developing new drugs and addressing unmet therapeutic needs. It is, however, also well established and extensively criticized either in the related scientific literature or even more widely in the mass media (10) for suffering from a series of symptoms falling into two major categories: the technical, which rooted to its current manufacturing practices are realized through the corresponding poor performance indicators (11), and the ethical, experienced through public or scientific debates focusing mainly on the issues of drug safety, pricing, importation/re-importation, clinical study design, and marketing practices (10). In February 2011, the Financial Times published an article entitled "Drugs Companies Have Lost Far More Than Their Health," presenting several relevant cases around the belief that the existing industry model is broken (12).

The most widely discussed symptoms reflecting Pharma's current functions:

- Production processes, some of which are out dated, operate far behind the level met by the semiconductor industry, not to mention other consumer products manufacturing practices (11). Manufacturing defects were found to be responsible for almost 75% of all drug product recalls in the US between 2000 and 2004 (13).
- The cost of manufacturing is almost twice the cost of R&D, while the financial risk due to non-compliance for the top 30 Pharma industries has been estimated at US$40–60 billion (13). Moreover, poor manufacturing performance costs the industry US$90 billion per year (14), which is considered equivalent with the current development cost for 80–90 new drugs (7). In addition, non-robust manufacturing processes can delay the period from launch of new products to their peak sales for as much as two years, reflecting a loss of US$600 million over the lifetime of a drug with peak annual sales of US$1 billion (13).
- In terms of the performance indicators, the pharmaceutical industry's manufacturing practices operate at 2.5–3.0 sigma, cycle times are approximately 700 h with an overall equipment use of 20–30%, while its capability to produce when it is required is 60–80%. Moreover, right-first-time is between 85% and 95%, and capability indices such as C_{pk} range between 1 and 2 (13). All of the above contribute to non-value-added activities and waste, which are estimated at 80% and 50%, respectively (14).
- While the processes operate close to 2.5 sigma, the ability of the Pharma's Quality Systems in place to prevent the internal failures from becoming external and thus reach the end user is approximately 5.0 sigma (13). It is estimated that if the process performance reaches 4.5 sigma levels, the defect rates will decrease by a 1000-fold compared to increasing the Quality Control System alone from 5.0 to 5.5 sigma. (13).

The latter is in accordance with the generally accepted fact that the practice of multi-quality inspections across the supply chain increases the manufacturing costs and does not assure product quality (15). Interestingly, it took several decades before realizing the importance of Deming's point, made half a century before, that the industry should cease dependence on mass inspection, as it is too late, costly, and ineffective.

All of the above facts reveal that the manufacturing efficiency of the pharmaceutical industry is far behind

several others, considered as the gold standard in manufacturing excellence, as for example the petro-chemicals and semi-conductor sectors operating near 6 sigma levels. All these symptoms could be attributed to a number of possible causes and may also explain why the plant floor operations were not included in Pharma's strategic business plans and visions:

- High profit margins often obscure the increased manufacturing costs (7).
- The past regulatory framework made the industry reluctant in performing, justifying, and communicating changes for improving its production methodologies. This should be considered in conjunction with the low level of knowledge regarding the scientific and engineering aspects of the established processes. Generally, the pharmaceutical industry suffers from the Data Rich Information Poor (DRIP) syndrome, which underlines its failure to transform data into knowledge (11).
- Heavy reliance of the current pharmaceutical industry's practices on inspection activities (7), reflecting its persistence on the Quality-by-Testing approach.

In an attempt to explore a most probably strong causal relationship between the symptoms and their reasoning, it is becoming quite obvious that the major root cause might be found lying deep within the management culture of the pharmaceutical industry, the values of which reflect much more the world of business rather than the rational world of statistical thinking and knowledge management (11,16).

The good news is that the few pharmaceutical plants which, after departing from the mass production harborage, adopted the lean and six sigma approaches, have reported significant results on minimizing costs and improving efficiency and quality, through process variability reduction (11). These islets of excellence, the new regulatory framework, and the reports from highly industrialized regions indicating the roadmap for a well-defined shift in manufacturing practices, are expected to inspire the pharmaceutical industry to reshape its business strategies. Meeting the requirements of the new post-mass-production paradigms will facilitate the pharmaceutical industry in addressing effectively the more demanding societal needs.

REFERENCES

1. Kuehnle H. Post mass production paradigm (PMPP) trajectories. J Manuf Tech Manag. 2007;18(8):1022–37.
2. GNOSIS Intelligent manufacturing systems (IMS): knowledge systematization: configuration systems for design and manufacturing, 1994. Available from: http://ksi.cpsc.ucalgary.ca/IMS/GNOSIS/TC7F1.html#RTFToC3 (accessed 02/11/2011).
3. European Commission. MANUFUTURE—a vision for 2020. Assuring the future of manufacturing in Europe. Luxembourg: Office for Official Publications of the European Communities; 2004. http://www.manufuture.org/documents/manufuture_vision_en%5B1%5D.pdf (accessed 02/11/2011).
4. NSF. Next generation manufacturing, Available from: http://www.nsf.gov/about/historynsf0050/pdf/manufacturing.pdf (accessed 02/11/2011).
5. IMTI, Integrated manufacturing technology initiative—Integrated manufacturing technology roadmapping project—an overview of the IMTR Roadmaps. London: IMTI; 2000. http://simula.cesga.es/document/docs/Integrated%20Manufacturing%20Technology.pdf (accessed 02/11/2011).
6. Pringle P. Monozukuri (making things). Japan Close Up Magazine. Available from: http://www.export-japan.com/jcu/sample/index.php?page=monozukuri-making-things (accessed 02/11/2011).
7. The Economist. Quality manufacturing: a blockbuster opportunity for pharmaceuticals. The Economist Intelligence Unit: London; 2005. http://graphics.eiu.com/files/ad_pdfs/eiu_ORACLE_PHARMA_WP.pdf (accessed 02/11/2011).
8. Gilbert J, Henske P, Singh A. Rebuilding the Big Pharma's business model. *In vivo*, the business &medicine report. 2003; 21(10).
9. Mendrics L, Vanroeyen J, Wang HY. The future of pharmaceutical engineering. J Pharm Sci. 2004;93:235–8.
10. Silupp GP, Porth SJ. Ethical issues in the pharmaceutical industry: an analysis of US newspapers. Int J Pharmaceut Healthc Market. 2008;2(3):163–80.
11. Korakianiti E, Rekkas DM. Statistical thinking and knowledge management for quality-driven design and manufacturing in pharmaceuticals, Pharm. Res. Online First™, 15 December 2010, doi:10.1007/s11095-010-0315-3.
12. Kay J. Drugs companies have lost far more than their rude health. 2011, The Financial Times Limited. 2011;37,537:9.
13. IBM. The metamorphosis of manufacturing: from art to science. New York: IBM Corporation; 2005. http://www-935.ibm.com/services/us/imc/pdf/ge510-4034-metamorphosis-of-manufacturing.pdf (accessed 02/11/2011).
14. Daneze J, Constantinou D. Lean practices in a life sciences organization. Contract Pharma. 2007; October.
15. Jiao RJ, Pokharel S, Kumar A, Zhang L. Development of an online quality information system for e-manufacturing. J Manuf Tech Manag. 2007;18(1):36–53.
16. Nunnally BK. Six sigma in the pharmaceutical industry. New York: Taylor & Francis; 2007.