Manufacturing in the 21st century

A review of the principles underlying the design of modern, cost-efficient production facilities.

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Since the invention of the wheel about 5,000 years ago, until now with the development of the most powerful microchips, the history of humanity has been an uninterrupted succession of discoveries, improvements and therefore changes. It would seem that the world is divided into two groups of people: those who find the best reasons (shall we say excuses) for not changing, and those who have vision and dare to introduce changes - albeit cautiously - thereby making progress and attracting success. The person who is ahead of the rest of the crowd - sometimes even just a little ahead - is usually accompanied by success. This is true in many areas - sports, fashion, cookery - not just industry.

Just making changes, however, is not enough - one must make them intelligently if one is to succeed. Therefore, a clear vision is necessary, accompanied by modesty, cautiousness and a strong will and commitment to overcome all difficulties.

Progress in the pharmaceutical industry

This article will try to summarise the main innovations which have taken place recently within the field of pharmaceutical manufacturing, and indicate the lines along which the pharmaceutical industry can be expected to progress and develop in coming years - in the areas of manufacturing, plant design and pharmaceutical technology.

The pharmaceutical industry is considered by investors as a leading industry, applying methods and systems at the cutting edge of technology: gene isolation, genetic engineering, automation, powerful computer systems and so on. This view may be correct at a first glance; however, when one knows the pharmaceutical industry from the inside, one has to conclude that it still remains very conservative and that there is room for enormous progress.

It is true to say that more and more pressure is, being and will continue to be - applied to operations and production directors to become more and more creative, and to find ways of producing to a higher standard but at a lower cost. Manufacturing has often been considered as a necessary evil, and for many years all the glory was centred on research and marketing. This time is now over and savings on manufacturing costs are starting to be seen as a main contributor to company profits - but how can this contribution be improved upon?

Improvements in production

Based on our experience of more than 30 recent projects, it is not exceptional to reduce direct manufacturing costs by 50 per cent through rationalisation. But what is behind this magic word “rationalisation”?

Rationalisation, in this case, means a combination of efforts in multiple directions: simplification of manufacturing systems, a reduction of the production cycle-time, a decrease in the number of different raw materials and also the number of commercial presentations, rationalisation of packaging formats, optimisation of production batch sizes, a drastic simplification of the paperwork, elimination of staging, automation of material handling, and clever and reasonable use of computers. But rationalisation is not limited to technological groups. Marketing will need to be involved for the elimination of products which do not contribute to the profit of a company, and for accepting change and
standardisation in product presentations. This implies a thorough knowledge of the market and of production costs - which is easier to say than to do. This is a task which should be scheduled over two to five years, depending on the company.

With the continuing trend in “globalisation” and the merging of pharmaceutical companies, this pressure to reduce manufacturing costs will continue - and in fact probably increase. This means that the companies which survive will be those which have already understood the issues involved and have decided to follow the rationalisation route.

Selection of a good plant concept The construction of a new facility is often the ideal opportunity to undertake a rationalisation programme. The selection of an appropriate plant concept has a direct impact, not only on the cost of construction but also on the cost of manufacturing - which is a more serious issue because it lasts forever.

There is no doubt now that the old mono-level plant, the model of the 1950s and 60s, is no longer valid for the 21st century. Multi-level factories are the plants of the future (2). It is estimated that since the introduction of these concepts by Lhoest and Froment in 1980 (3), more than 200 facilities in the world have now put them into practice - either in part or in total.

Greater segregation Pharmaceutical factories built some 15 to 20 years ago were typically built in the pattern of a central circulation corridor with production rooms on both sides. This circulation corridor is used for cleaning operators, raw materials and all transfers of in-process goods and finished bulk products. In the case of a breakdown, it is used by maintenance; in addition, it is employed by visitors and after-hours by caretakers who will use it for the disposal of refuse. If some repairs or minor changes in room lay-out are needed, it is always this central corridor which is used by bricklayers and other trades.

In a nutshell, the central corridor is an incredible source of contamination and cross-contamination. Such a concept is no longer viable and tomorrow’s plants will require increasingly strict measures to segregate the circulation of people and products. For products, completely closed systems are and will remain the preferred solution. For oral solid forms, closed systems combined with vertical, gravity flow across at least three floors is the system of choice. As far as plant design is concerned, the division of the total plant volume into at least three completely independent sub-volumes will be seen more and more as essential. These three totally independent sections are as follows:

• Clean areas, built as small as possible, used exclusively for clean operators,
• Visitors’ corridors, reserved exclusively for visitors and persons who are not directly involved in the production process, and
• Technical areas, used by maintenance, as well as for all HVAC groups and conduits, services, sewers and energy distribution, and also for full sections of machines not directly needed in the clean room areas.

This concept will be applied more and more and, in future, as even more segregation is needed, it will be possible to organise sub-classes within the so-called clean area, separated by additional changing rooms and appropriate HVAC protection.

More active substances Pharmaceutical research is leading to more and more active products; these are becoming increasingly specific and better targeted. One might speculate that, in future, only a few molecules of a given compound might be needed to produce a given therapeutic effect. Pharmaceutical compounds already require full protection of production personnel since the quantity inhaled during a shift may become greater than the effective dose. Another example is the risk involved in working with potentially carcinogenic compounds.

Automation Full automation of a pharmaceutical production plant is now technically feasible, but generally not financially justifiable. What is perfectly feasible and financially justifiable is the automation of material handling. It has been calculated that, in some cases, up to 60 per cent of the people working in a plant simply do nothing else but move loads around. Since salaries will continue to increase, while real working hours will continue to decrease, it is obvious that automation of material handling is the way to go - it enables a service to be provided 24 hours a day, seven days a week. Automation of material handling is a developing field which would require an article on its own. At present, some of the most interesting developments in this sector are the so-called French “Magnetic System”, and the recent introduction of the “Elvecar” - an automated material-handling system, especially suited for the handling of bins and presenting numerous advantages over its competitor, the AGV (automated guided vehicle).

Proper use of computers Computer systems used in automated pharmaceutical production plants can be classified at three levels:

• Level 1 includes all computers directly linked to production machines on the shop floor and to materials handling equipment.

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They are usually supplied by the machine manufacturers themselves. To this group should be added the functions of managing on-line, and constantly updating the inventory, as well as providing computer assistance to the weighing/dispensing function. In these fields, computers do indeed perform better than humans and this level of computerisation is justified.

- Level 2 allows the sequence of all manufacturing and quality control steps for every product to be memorised. It therefore provides good assistance to production operators; it also speeds up their training and may prevent errors. It can thus be regarded as a very useful tool, but not absolutely necessary. In some cases, for instance, if a manufacturing process is not perfectly structured - if formulations are not very robust or if process variations still need to be introduced - then the investment might take a long time to be repaid. In-house specialists must be on hand to continually update and improve the system.

- Level 3 is the upper management level, the ERP, which includes modules such as planning, purchasing, preventive maintenance, human resources, marketing, finance and so on. The direct linking of ERP with levels 1 and 2 is a great risk; it is also very expensive and difficult to implement, while its usefulness in production remains to be proven. A recent paper, based on the conclusions of the Oliver Wight Organisation (4), claims that in the pharmaceutical industry 80 per cent of the companies which have installed MRPII systems have not been able to see any significant difference in their efficiency and performance. In contrast to other industries, where such systems have been successful, the pharmaceutical industry still has much progress to make in the fields of rationalisation, before level 3 systems can really be of any benefit. Furthermore, the efforts required for rationalisation are less demanding and provide a greater pay-off.
Outsourcing  A new player is appearing in the field which appears to have an interesting future - namely, outsourcing. More and more companies seem to be attracted to the idea of outsourcing at least part of their development work. It is estimated that US companies now invest about 30 per cent of their R&D expenditure in outsourcing - a percentage which is increasing. Their main reasons are:

- To gain access to techniques and expertise which are not available in-house,
- To increase their flexibility and speed up the launch of products on the market,
- To lower their capital risks, and
- For foreign companies, to enter a market more easily.

It is expected that more than 40 per cent of US companies will move to contracting out processing within the next three years (5).

Subcontracting production of part of the product line appears an attractive alternative. Companies use this in foreign countries in order to gain access to lower cost labour; it allows them to keep on the market products which are no longer able to support any investment. Last but not least, generic products are often produced by this type of company - an area which is, of course, expected to expand.

Conclusion

Innovation will remain the most powerful tool for progress and, fortunately, innovation is linked to neither the size of a company nor the amount of money invested in research. It is worthwhile remembering that some years ago (1994) more than half of the ten top-selling medicines worldwide were invented by the research efforts of just three men - Sir James Black, Sir David Jack and the Belgian, Paul Janssen (6). The most important discoveries have often resulted from the efforts of a very small group - leaving everything to rest on the hopes of the individual - and it would seem fine for things to carry on in this way.

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References