Pilot Plants & Scale-up of Chemical Processes II

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Preface

Challenges for those responsible for translating bench chemistry up to 10 - 100 litre pilot plants, and those responsible for operating such pilot plants continue to increase. The challenge to improve productivity, to carry out ever more demanding chemistry and to operate with greater safety are but three. The papers presented here set out to address these challenges.

Productivity, particularly in relation to batch processing and meeting the threat from overseas manufacturing in low cost areas, is covered in the first paper. In this an analysis of the situation in the United Kingdom is followed by an account of the 'Britest Project', a collaboration between industry and academia under the UK Government's Innovative Manufacturing Initiative.

A consideration of the chemical aspects of scale-up can often be used to identify and thereby avoid potential problems in scale-up, in itself a contribution to productivity. The second paper discusses the impact of factors such as reaction time, heat transfer, mixing effects and two phase systems on chemistry during scale up, using selected examples.

The use of phase-transfer catalysis and the control of crystallisation are two fields where advances are being made and which are specially targeted at improving productivity. Each of these is covered in separate papers.

Organometallic chemistry is being used increasingly in fine chemicals synthesis, and two papers discuss the techniques used in the scale-up of organo-lithium and Grignard reactions.

The final paper illustrates some of the basic concepts of fire, explosion and chemical reaction hazards and their influence on scale-up of chemical processing.

The papers in this book present overviews or examples of best current practices in selected areas, including both chemists' and chemical engineers' perspectives. I am very grateful to all the contributors for giving so generously of their valuable time to make it possible to produce this book.

Bill Hoyle

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Speciality Chemical Manufacturing in the UK, Has it a Future?

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1 BACKGROUND

It is well recognised that manufacturing in the UK is in decline and has been so for the last 30 years or so. The decline has not been steady and periods of rapid decline have followed major changes in the economic climate. Manufacturing has now fallen to a level where it only contributes 20 % of GNP and is therefore seen as a minor contributor to the economy. Eddie George, The Governor of the Bank of England, has said as much, so it must be true.

Manufacturing only employs 16% of the workforce. The number has halved since the 1970's, with a reduction of 30% in the 80's, compared with Germany where there was no change.[1] In public debates there are few defenders of manufacturing and there are many who see it as a minor part of the economy. The only counter to this is when a factory closes and jobs are lost and regret is expressed at the increase in unemployment. The Government puts large sums, from our taxes, into attracting new investment from overseas, in recent years this means Far Eastern companies into depressed areas, yet the support for existing industry is lukewarm at best. These new investments generate jobs but profits are expatriated and wealth creation for the UK is reduced.

On the whole, manufacturing is seen as an activity in which few want to work, it has a poor image - low pay, it is dirty and often dangerous with health risks. Young people are directed to service industries as a growth area, clean office jobs and the city if you really want to earn some money.

The chemical industry is in an even worse position. It is dangerous and polluting, causing serious and unknown damage to the environment whilst causing nuisance to its neighbours. Worst of all it is making products that in many cases are not welcomed, if not greeted with outright antagonism. Chemicals are generally seen as dangerous and their value to the modern life style is hardly appreciated, e.g. pesticides are condemned by an increasing number of people and society's goal seems to be to eliminate them. Whilst I recognise that these generalisations do not reflect the good relations which many have with their neighbours and the regulatory authorities, they are statements with which much of the general population would agree.

1.1 Financial Climate

The UK financial climate doesn't favour manufacturing. It is well recognised as having short term interest and seeks higher rewards than our competitive countries. This is a long standing issue. In 1911 Lord Revelstoke of Barings said "I confess that I personally have a horror of all industrial companies and that I would not think of placing my hard-earned gains in such a venture."[2]

Investment can only be secured against high returns and high risk demands a higher reward, and is not expected to fail! The cost of money in the UK is considerably higher than other countries (20% compared with 15% for other developed countries). In the 1980's profits rose by 6% and emphasis was given to increasing dividends by 12%, whilst investment rose by only 2%.[3] Over the 1980's out of the USA, France, Japan, Germany and the UK, the UK was the only country in which dividends were increased as a proportion of profit and that was from 20% to over 50%.[4]

In Germany and Japan investment in industry is by banks which have a long term interest in the company and when times are hard they take an interest in helping recovery. They are not shareholders who sell to minimise losses and seek other more profitable ventures. It is interesting to note that after the extreme problems of the Eurotunnel refinancing that, in its notices of the AGM, they make the statement " The syndicate banks have become Unitholders in Eurotunnel and now have a vested interest in the future success of the Group." How much better would manufacturing industry be if its financiers had a vested interest in its success?

Will Hutton[5] quotes Dr Herbert Levinstein, son of the founder of one of the most successful Victorian dye-stuffs firms and a prominent chemist, who wrote: "The application of knowledge requires finance and the capacity on the part of those who control finance to judge the value of a scientific discovery. The main cost of industrial research is not in the laboratory but in the application to the large scale...". Who in England is going to find the money for this? In Germany the banks would and did find it.

The firm which his father founded became part of ICI and the works closed many years ago. The business continued but was recently sold back to the Germans by Zeneca.

1.2 Manufacturing

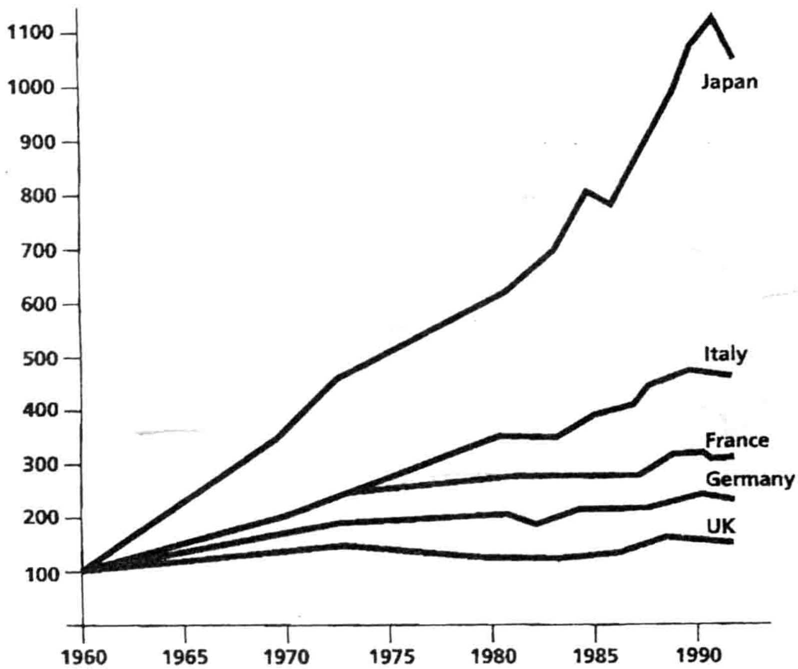
Over the 30 years from 1960 manufacturing output stayed constant, compared with Italy, where it quadrupled and Japan which increased output by an order of magnitude (Figure 1). In the same period the UK share of the exports of manufacturing countries has fallen from 15% to 8% and has also lost share in the domestic market.

Labour productivity in the UK has been consistently below that of our major competitors, by the early 1990's the UK had reached the productivity levels of the USA in the late 1960's with a manufacturing output of $15000 per head (Figure 2).[6]

1.3 Chemical Industry

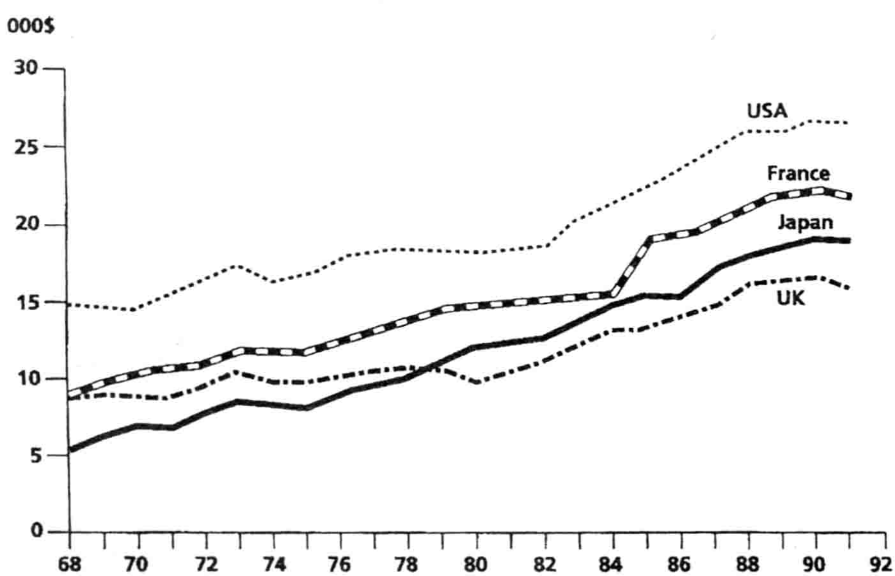
Against the bleak picture of manufacturing as a whole the chemical industry has performed reasonably well. It accounts for some 2% of GDP and has had twice the growth of the manufacturing sector over the 1980's. Taking the CIA's groupings, specialities, dyestuffs, paints pigments and pharmaceuticals amount to 80% of the chemical industry's total value added. For the purpose of this paper Specialities includes those groupings. It is a strong sector with a large trade surplus accounting for 4% of world sales. However the erosion of manufacturing industry is of concern as it accounts for 77% of the UK chemicals demand.[7]

The Technology Foresight report on Chemicals states "Research and innovation to



Source: US Bureau of Labor, Monthly Labor Review (Jan.1994), Table 49

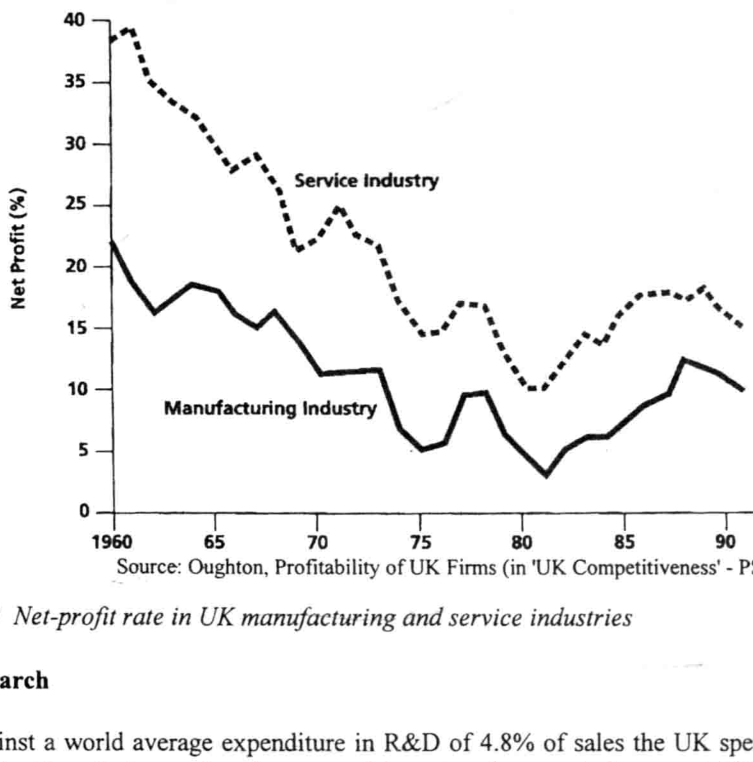
Figure 1 *Manufacturing output 1960-92(1960 = 100)*



Source:OECD, LBS

Figure 2 *Labour productivity in manufacturing - output per head: (US $'000 : 1985 PPP)* develop more efficient processes and to shift to higher added-value products will be key to future success."[8]

It is interesting to note that many companies are targeting the higher added-value sector of the market. This is probably most graphic in the massive change ICI is currently undergoing. There is a danger here in that, with increased focus on this area, competitive pressures will force prices down and the level of added-value will fall. It is worth noting that the definition of value added is " the *perception* by customers of the product or service resulting from the utilisation of the technology. This perception and the value associated with it governs both the price level that can be applied and the size of the potential market."[9] How much of the industry's success is based on that perception and how quickly can perceptions change (Figures 3-6)?



Source: Oughton, Profitability of UK Firms (in 'UK Competitiveness' - PSI)

Figure 3 *Net-profit rate in UK manufacturing and service industries*

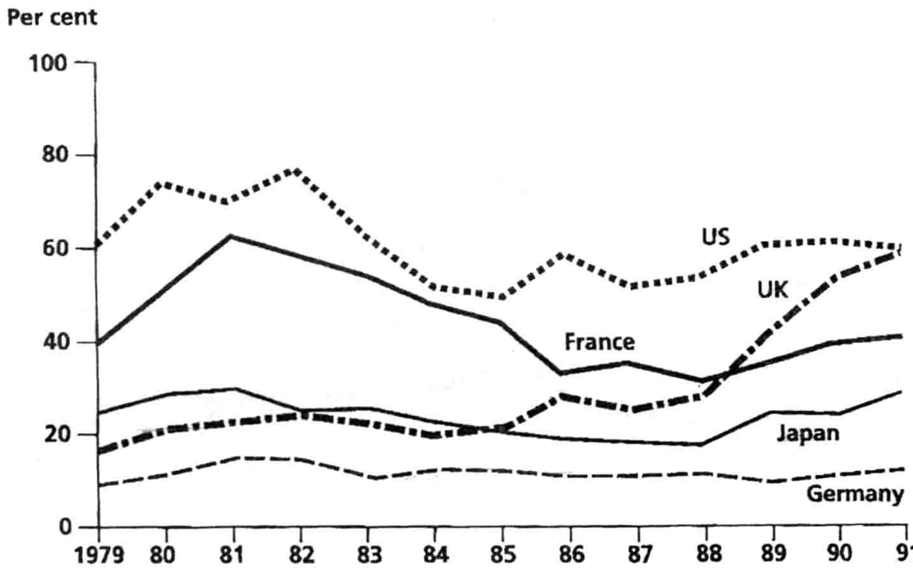
1.4 Research

Against a world average expenditure in R&D of 4.8% of sales the UK spends 2.4%. This is significantly lower than the competitive countries noted above, at 1.25% of GDP for the UK compared with over 2% in Japan. In 1993 this was £9.1 billion and over 90% of that expenditure was in 100 companies. The chemical industry accounts for a quarter of all industrial R&D expenditure at around 7% of sales.[10]

Expressing this when compared to dividends, the world's top companies' R&D spending is three times dividends whereas in the UK it is two thirds dividends.

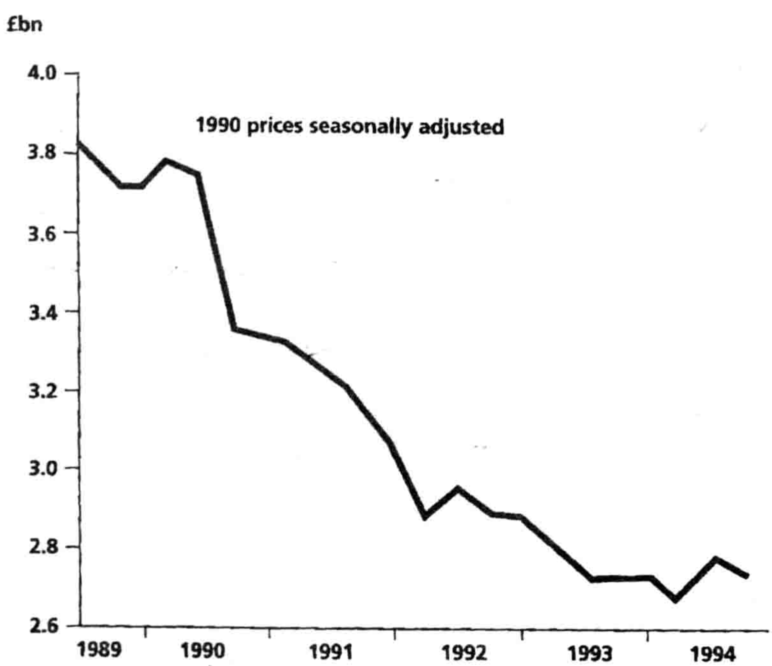
Much of this expenditure is in the pharmaceutical sector and is focused on research into new products. There is no denying the importance of new product research but how much is spent on process research? If the Technology Foresight report is to be believed the future success of the industry depends on "research and innovation to develop more efficient processes and to shift to higher added-value products.." - process innovation and the customers perception.

How strong a base is that for the future of the industry?



Source:CSO, OECD (in 'Competitiveness - Cm 2563')

Figure 4 *Dividends as a proportion of profit after tax, interest & depreciation*



Source:CSO/Bank of England, Datastream
FINANCIAL TIMES WEEKEND NOVEMBER 19/NOVEMBER 20 1994

Figure 5 *Capital expenditure by UK manufacturing industry (£bn)*

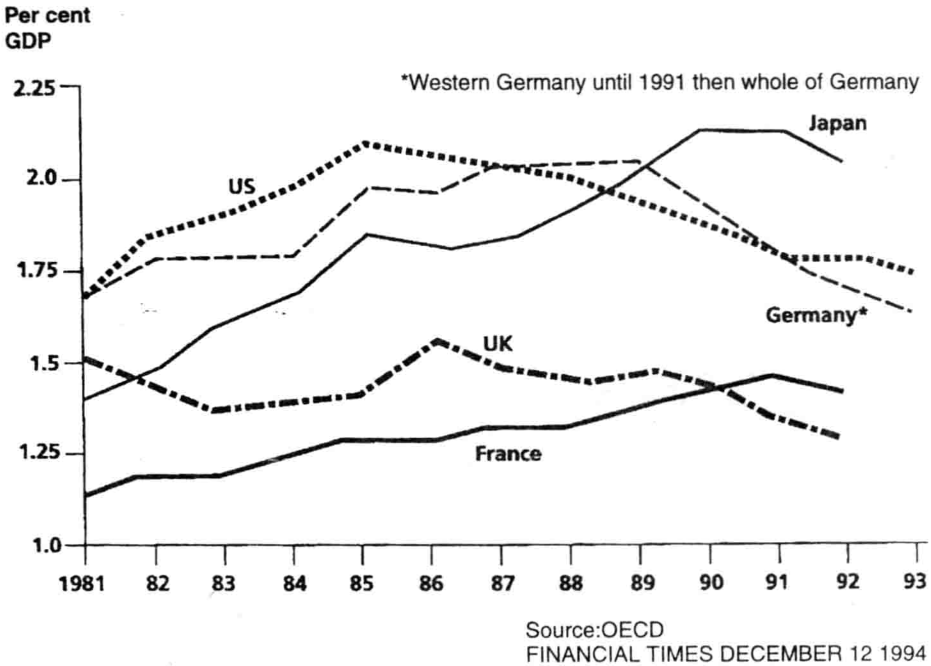


Figure 6 *Business enterprise R & D as a percentage of GDP*

2 RESPONSE

Companies have responded to the challenge: cost cutting has been a continual feature for over 30 years to my certain knowledge. This has taken a number of forms and there has been considerable creativity in thinking of new ways to continue cost and 'numbers' reduction. Strategic reviews, cost cutting exercises, repositioning, core competencies, Business Process Re-Engineering, Supply Chain Management, customer focus...... the list goes on. It is to the credit of the consultancy business that it continues to think of new names and different approaches to improving efficiency and reducing costs. There is no doubt that without these measures many more companies would have failed but are these measures enough to secure the future? Companies have been carrying out these activities over the last 30 years and yet the UK has still lost ground on the world stage as indicated above. Many companies are moving manufacturing to low cost areas. What proportion of manufactured goods are now made in China? You only have to look where many goods are made to see; note that it is not good enough to look at the maker's name, many well known brands have their products made in China.

Chemicals are not different. Everyone must be aware of the increasing import of chemicals from China and the extent to which companies are seeking to invest there. Imports from China in the 3 years to 1997 increased by over 33%, admittedly from a small base as yet (£85m). The Chinese presence at Eurochem98 was significant with a dozen companies offering to manufacture a wide range of complex chemicals. The trend is clear. Is it in our best long term interests to exploit low cost economies and lose capability in this country?

It is unrealistic to expect to change the financial system, particularly at a time when increasingly pension funds will be seeking rewards for the growing number of pensioners and the increasing investment in private pension plans. The industry and its representatives could do more to improve its image but that is not the subject of this paper.

However the motor industry has shown that, through major changes in manufacturing technology and practices, manufacturing in the UK can be viable. Management action can influence the future of the industry and it is not too late if action is taken now.

3· PROCESS DEVELOPMENT

Process development in the speciality batch manufacturing industry is primarily to achieve a cost effective manufacturing route, where that effectiveness is determined by the value of the end product, and secondly to develop a process which can be operated in existing plant. This is particularly important in the pharmaceutical industry for new compounds and the contracting industry, although the continued re-use of plants as products change is a feature of many in batch manufacture.

The ability to fit processes into existing plants is an important feature of the training of new development chemists. They must be aware of plant limitations and therefore do not waste time in developing a process which cannot be readily accommodated in either existing plant or standard plant. Standard plant is that which is most like the laboratory, i.e. glass lined mild steel vessel - equivalent to the laboratory glass flask. In many organisations chemical engineers work with development chemists and this provides further safeguards to ensure that the process will be most readily accommodated in standard plant.

In pharmaceuticals it is essential that all processes fit in standard plant because that gives most flexibility on available capacity, hence quicker response to demand changes and most importantly regulatory requirements. It is necessary to manufacture in plant which corresponds to development plant and once fixed the process cannot be changed.

Chemists have been very innovative, bringing to large scale manufacture many processes which have only been text book or laboratory possibilities. It is a tribute to their creativity that they have achieved good yields with all these constraints and have achieved complex syntheses with great ingenuity. It is only when standard plant will not operate under the only feasible conditions that different plant is necessitated, e.g. pressure or high/low temperature. The importance of fitting processes to plant is well recognised by Pisano in 'The Development Factory'.[11] It is important for development chemists to know what changes in performance there will be in the process on scaling up from the lab to the plant. Indeed that is a significant part of their experience and a measure of their success. Knowing what will and will not work, allowing for the reduction in yield on scale up, ensuring that the process is robust enough to be operated on the large scale with all its variances are all important aspects of a development chemists know-how.

Pisano quotes a process researcher[12] "I learned a lot from doing a plant startup. I learned that,.., only designated people can open a reaction kettle. These people are not always immediately available, so parts of the process may have to wait. This taught me that the chemistry has to be very robust. You cannot have a process where a few minutes make a big difference."

That is an indictment of the batch processing industry and a statement that it doesn't really care about having efficient processes.

The question is whether continuing this approach is good enough to secure the future against lower cost manufacturers increasing their range of manufactures and continuing to replace UK manufactures (Figures 7 - 10)?

Business Drivers

- Product OTIF and quality
- Lower risk
- Shorter product introduction times
- More responsive to changes
  - product changes
  - varying demand
- Lower capital
- Lower product costs

Figure 7 *Business drivers*

Problems in batch manufacturing

- Unreliable processes
- Sub-optimised processes
- High materials usages
- Difficult to modify plant
- Very low velocity ratio
- High capital cost / risk

Figure 8 *Problems in batch manufacturing*

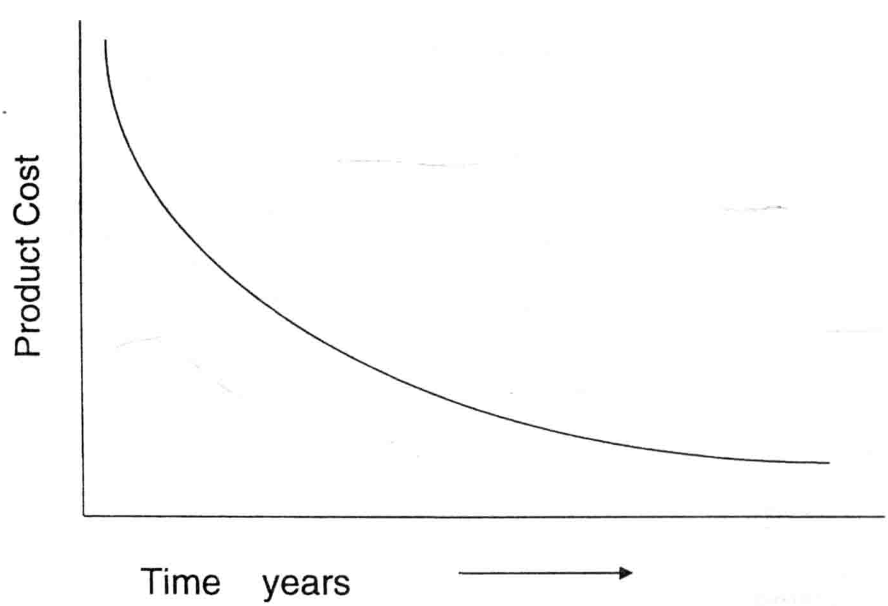


Figure 9 *Product cost with time*

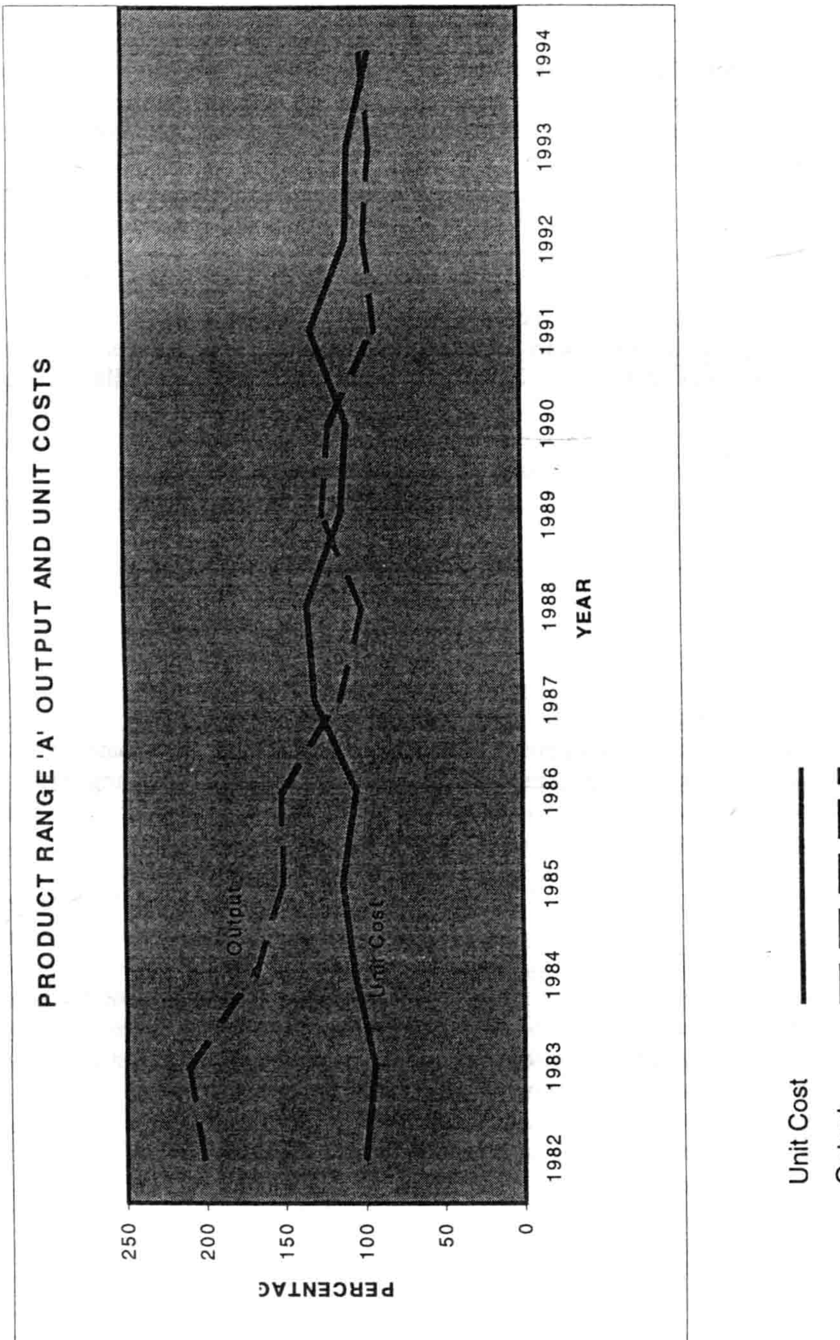


Figure 10 *Product range 'A' output and unit costs*

4 POTENTIAL

Changes in other manufactures, notably cars, have seen orders of magnitude improvement in output rates, defect levels, inventory levels etc.. I am not aware of similar studies in the batch processing industry but limited research shows that current performance leaves considerable scope for improvement.

Cost reduction has taken place through increasing scale, automation/computer control, mechanical handling, increased reliability, work restructuring and reduction in overheads from better organisation and general computerisation. There has been no fundamental improvement in manufacturing technology.

Equipment designs are better, scheduling is better, (though some would challenge that), engineering standards are better, especially containment. Most reactions are carried out in the very versatile scaled up flask, the glass vessel, unless a cheaper mild steel one is acceptable.

Significant cost reduction is achieved through process development. Initially this is to achieve a reasonable manufacturing cost when compared with the early process. Further development results in cost savings, though often this is improving plant performance towards the best laboratory results.

Batch manufacturing requires the use of large quantities of solvents and reagents such that the amount produced is many times less than the total material handled. Clearly that ratio depends on number of stages and which particular reactions are being followed, but it is good if the product is 10% of the materials handled in its manufacture (Figure 11). For a multistage manufacture the overall yield may be only 20% and then the product may be less than 1% of materials handled. That material costs money, to buy, to handle, to process, to store, to separate, to dispose of or recover. Reduction in these materials would result in savings throughout, capital productivity, working capital and operating costs.

Modern manufacturing looks at activities which add value to the product. Much effort goes into removing wasteful operations carried out by people, unnecessary paperwork for example. How much time does material spend on the works without undergoing an added value activity (Figure 12)? Activities such as storing, moving around e.g. from vessel to vessel, when material is being worked on slowly when it could be worked on quickly. How many operations are introduced because the one that would be best cannot be achieved? How often are reagents introduced to modify reactions because the desired conditions cannot be achieved? How often is process performance reduced on the plant because of scale-up issues? How often are processes modified from the best performance so as to improve robustness? A conservative estimate is that the manufacturing velocity, the time during which material is being worked on to effect, could be increased by an order of magnitude: so bringing about improved process effectiveness and major savings in plant required (Table 1).

Can speciality batch manufacturing survive in the UK without some of these issues being tackled?

The Technology Foresight report discusses the vision of the Chemical Industry over the next twenty years.[13] Emphasising the importance of the industry and its need to be at the leading edge of technology, the report refers to the continued move to speciality/performance chemicals and the need for process technology improvements. Pisano[14] stresses the importance of process development in generating advantage for pharmaceutical companies. Figure 13.

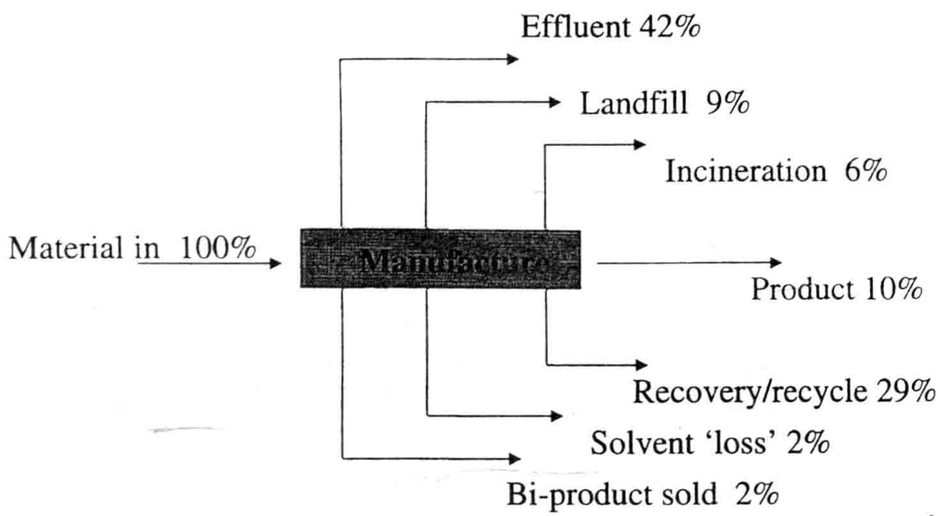


Figure 11 *Percentage product of material handled*

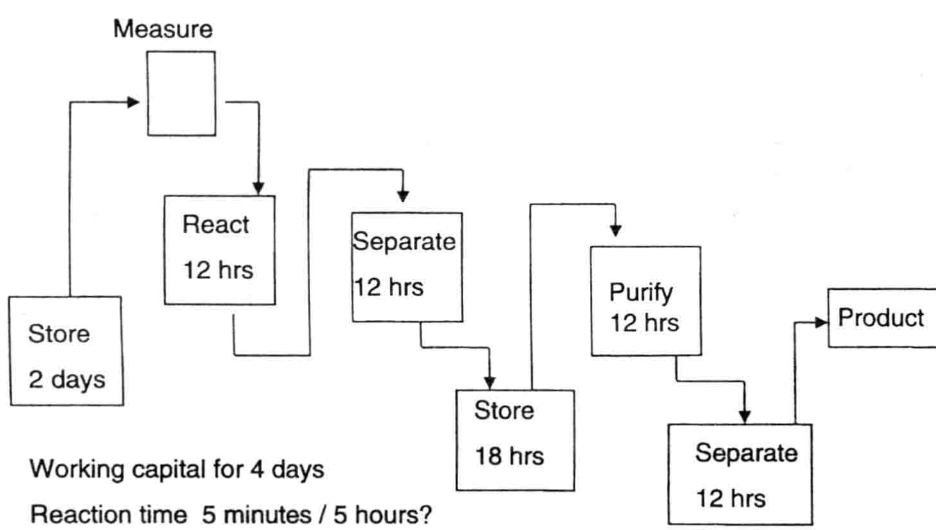


Figure 12 *Activities requiring working capital*