Chimia 54 (2000) 724–730

ISSN 0009–4293

Plant 2000 – An Exercise in the Benchmarking of Multipurpose Chemical Manufacturing Plants in the Pharmaceutical Sector

Marco Born, Paul Foley, Robert Fretz, Richard Miess*, and Tim Oxley

Abstract: A study was performed to compare the investment costs and functionality of a number of different multipurpose chemical manufacturing plants, all used for the manufacture of active pharmaceutical ingredients and their intermediates. In parallel the functionality required to process a large number of steps was assessed and the results of the two studies were combined. A description of the methodology and of the key findings is given.

Keywords: API · Benchmark · Manufacture · Multipurpose plants · Pharmaceuticals

1. Introduction

Early in 1998, as one part of a many faceted efficiency improvement programme, Roche initiated the 'Plant 2000' project. This project was based on the hypothesis that the plants built by Roche were more complicated and expensive than they needed to be. To test this hypothesis a two-pronged approach was taken. Firstly it was decided to compare the investment costs for Roche facilities with others and to derive a relationship between cost and complexity (or cost and flexibility). The second angle was to determine how flexible a plant actually needed to be to be able to perform a useful number of the typical manufacturing steps in the Roche manufacturing portfolio.

M. Born

R. Fretz

R. Miess

T. Oxley

Correspondence: Dr. R. Miess
F. Hoffmann-La Roche Ltd.
Pharmaceutical Division
B74/2.OG-O
CH–4070 Basel
Tel.: +41 61 688 16 24
Fax: +41 61 688 16 65
E-Mail: richard.miess@roche.com

An international and multi-disciplinary team was formed with the objective of determining the future direction for investment in chemical manufacturing facilities. The use of such a team meant that the working environment was not always harmonious. The original hypothesis had several knee-jerk explanations and for each of these a different element of blame could be attached to the various functions represented on the team. Despite, or perhaps because of, the initial sensitivity and friction, the team gelled very well and the wider acceptance of the results was helped because people from different disciplines and backgrounds had arrived at the same opinion.

2. The Plant Benchmark

The first pillar of the project was the exercise to benchmark the plants built by Roche with the plants built by other companies. There were three categories of companies in the benchmark; Roche-owned subsidiaries, companies competing with Roche who agreed to participate in return for access to the benchmark data at the end, and companies which had been competing with Roche but that had since been acquired.

The traditional source of benchmark data has been third party consultants. The quality of data that was available was felt to be more interesting than useful, for instance the comparisons would be based on reactor volume or production building floor area. Among many shortcomings of this kind of data for testing the original hypothesis, the foremost is the complete absence of any measurement of plant flexibility. As a result Roche decided to prepare and carry out a more specific benchmarking exercise.

The criteria used to select plants for inclusion in the benchmark study were as follows.

- The plant should be a multipurpose (or at least multi-product) chemical manufacturing facility.
- The size range of the reactors installed should be 4–12 m^3.
- The projects should be green-field or brown-field. Brown field implies that the building and/or site infrastructure may be existing. Refurbishment projects were excluded.
- The projects should have been carried out between 1992 and 1998.
- The project should have run relatively smoothly. In other words it should

CHIMIA 2000, 54, No. 12

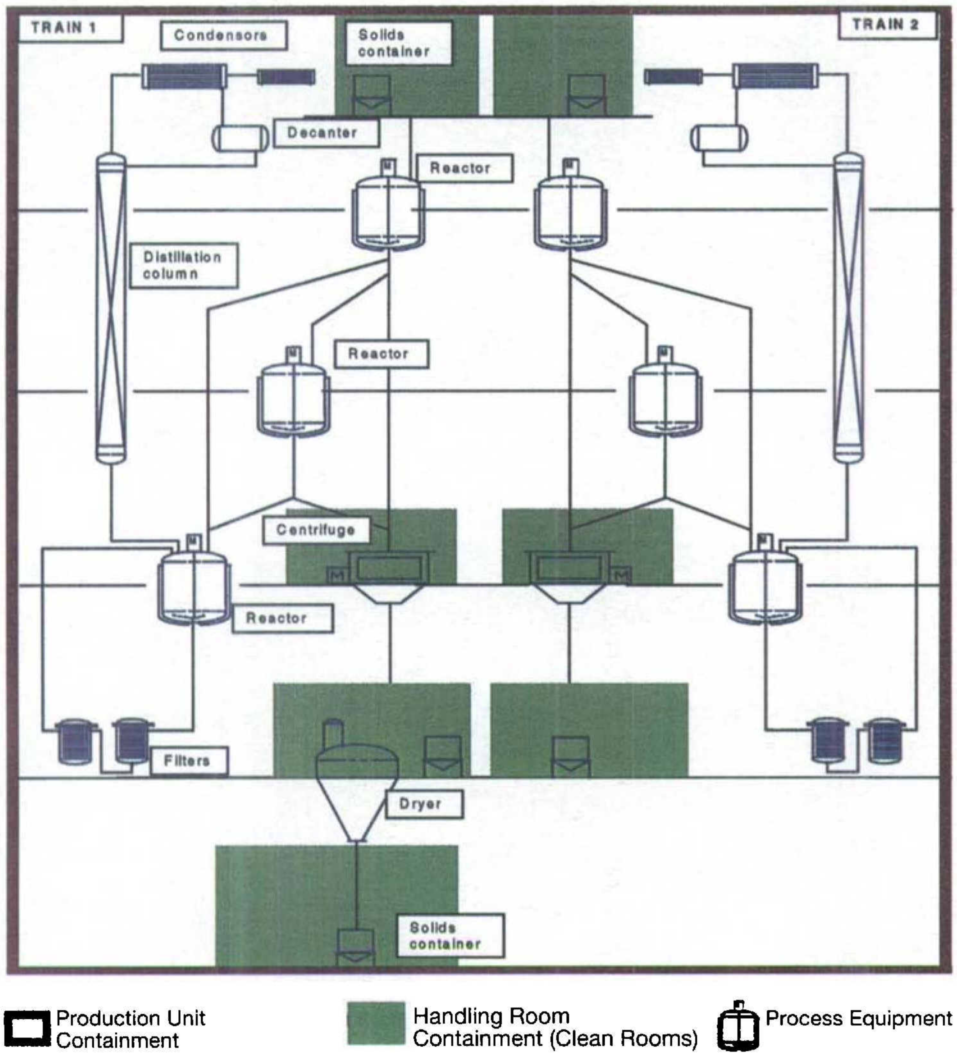

Fig. 1. Multipurpose production unit (MPU)

have been free of management go/no-go decisions, planning permission problems, labour disputes, major mid-project scope changes and so on. This could not be excluded from all of the plants and as a result, some of the plants have an adjusted cost to attempt to remove these effects.

- The process technology used should be normal for the pharma industry and based on batch chemical manufacture. For example there are no plants with process scale HPLC.
- No restriction was placed on the design concept, in fact the wider the range of concepts available for evaluation the more useful the benchmark should be.
- The project team had to be able to visit the facility in order to validate the data.
- The full cost breakdown of the project had to be available.

Ten plants were studied, in six different countries. The geographical range within Europe and the USA was quite good. There were no plants from developing countries available for inclusion in the study.

Within the limits of the selection criteria above there was still significant room for variation between the ten plants. There were obvious differences in terms of timing and location and more subtle differences concerning the number of reactors and separators installed and the ratio between them. It was clear that some basis was required to 'normalise' the data to allow like for like comparisons to be made.

Roche had already developed a standard model for the building of multipurpose plants (Fig. 1). This concept was well understood by the Plant 2000 project team. These plants consisted of a number of Multipurpose Units (MPU) and each MPU contained two trains of three vessels and a centrifuge. The functions of the vessels were relatively fixed. There was a reactor feeder into which solids could be charged, a reactor distiller that was fitted with a rectification column and a reactor crystalliser which also fed the centrifuge. Configuration of the transfers within the train and within the MPU was relatively easy but connection to vessels in other MPUs was difficult. Each reactor was fitted with three solvent feed lines. The heating and cooling was provided by a mono-fluid system. The plant was automated with a recipe driven sequence control system. The various features of the plant were designed and installed in a modular fashion and this approach was applied to both equipment and software.

This model was used as the basis for the benchmark study. Working with project teams from the benchmarked plants, the original data was manipulated so that it reflected the cost of building an MPU. For every plant in the study a revised scope was costed which included the reactors, separators, in-process distillation, process tanks, solvent and utilities distribution within the production area and the process transfer piping. Also included were the costs of any enclosures around charging and discharging points as that is a part of the operating concept of the plant. Explicitly excluded were other project costs associated with the building, the heating and ventilation systems, laboratory equipment, and furniture. Also excluded were site infrastructure costs such as solvent recovery, waste water treatment, air emissions treatment, utilities generation, central tank farm, electrical distribution and other buildings such as warehouse, administration or laboratories.

A questionnaire was designed and sent to the participating sites. This was then followed up with a visit from some members of the team to ensure that the interpretation of the questions was uniform. The parts of the questionnaire dealing with cost, project execution, installation data and so on were used to generate the cost comparisons.

This methodology gave one of the necessary dimensions to test the first part of the hypothesis, a means of comparing the cost. To complete the second part a measure of the flexibility was required. The initial thinking of the project team was that flexibility would be a function of functionality and 'changeability'. However as the benchmarking exercise progressed it became apparent that the changeability was highly subjective and that where hard data on changeovers did exist it was very dependent on local definition. Hence the flexibility measure that was used was not able reflect the ease of or time required for changeovers.

The benchmarking questionnaire had two, less subjective sections, which were used to define a flexibility index. The first of these was the plant concepts anal-

CHIMIA 2000, 54, No.12

ysis, the second was the operating mode analysis.

The plant concept analysis was intended to cover the key elements of a conceptual design description. 70 plant concepts were divided into six categories (general design, solid flow, liquid flow, safety and environment, utilities and automation). All of these were pre-defined in the questionnaire.

Some examples: 23 general design concepts were identified. These included operating temperature range, operating pressure range, and number of planned production campaigns per year. Among the automation concepts were the type of control system, the automation level, the data recording, the I/O system and the control room interfaces.

Each sub-concept was weighted, based on its contribution to the multipurpose capability of the plant. For example in the general design concept the sub-concept corrosion resistance had three predefined categories; 1) low resistance, carbon and/or stainless steel vessels, 2) medium resistance, a mixture of stainless steel and glass-lined vessels and 3) high resistance, highly corrosion resistant alloys and/or glass-lined vessels. A clear ranking can be made in terms of usefulness in a multipurpose environment. This was done for every sub-concept allowing a calculation of the plant concept score (a percentage of the maximum possible).

The operating mode analysis was carried out using a similar method. Operating modes are the different ways in which the plant is capable of performing a particular function. There are many ways in which the process temperature can be controlled (see Table 1) and each of these is a mode. In addition each of these can be achieved automatically, semi-automatically or manually. Finally these modes can be available on some or all of the vessels in the plant.

In the benchmarking questionnaire all the modes that the team could think of were defined. The final list had 77 modes, grouped into 18 modules (liquid

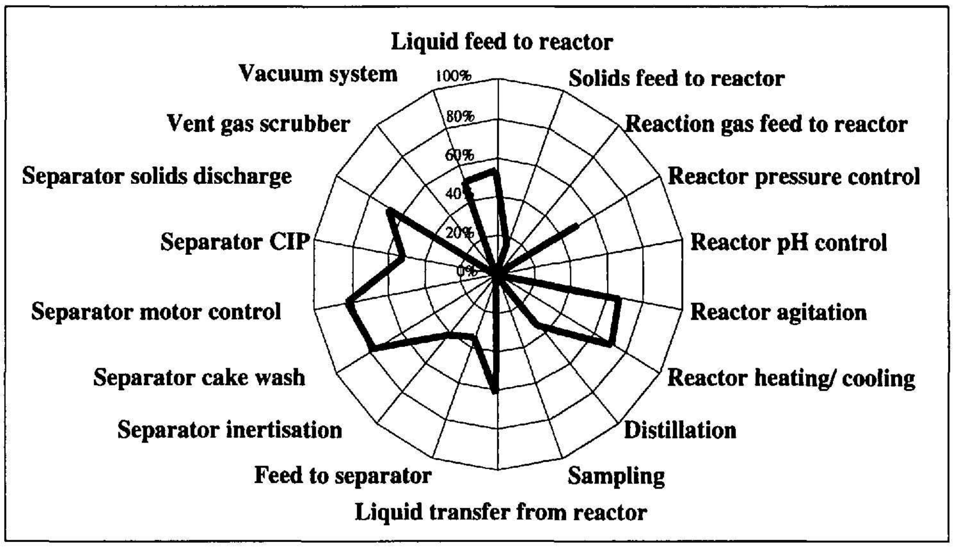

Fig. 2

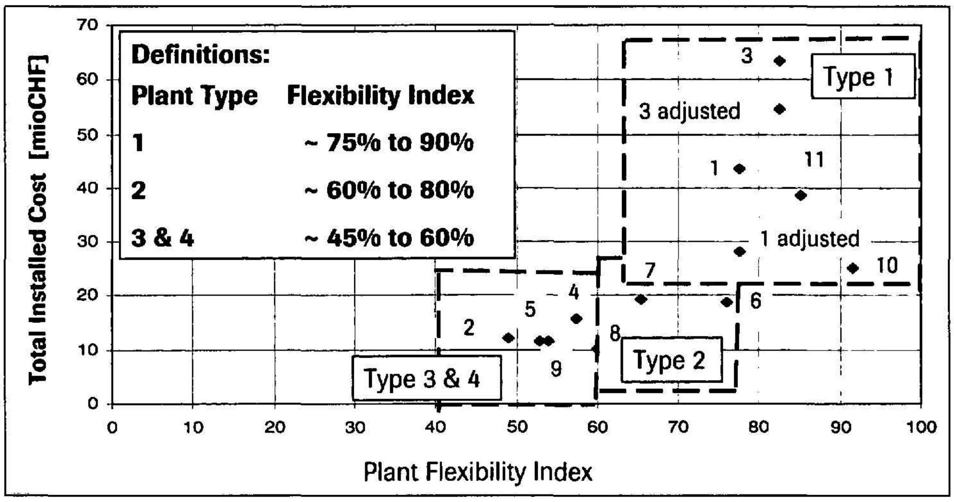

Fig. 3.

feed, pH control, addition of gaseous reagents *etc.*). The modes available on each process unit were recorded and then the average for the MPU was calculated. Then the percentage of the modes that are automated out of the maximum possible was calculated. Despite this percentage being based on all the modes we could think of, some plants scored greater than 100% as they had implemented all of these modes and some more.

This data is a key measure of the plant functionality. It defines what the plant can do and therefore what the plant can make. When presented graphically it can act as a 'functionality fingerprint' for the plant (see Fig. 2).

The numerical average of the calculated operating modes evaluation and plant concepts evaluation was called the plant flexibility index. This was used as the other axis on the cost *vs.* flexibility plot. All of the plants benchmarked can be seen in Fig. 3. As a test of reasonableness the numerical data was found to be in close correlation with the subjective impressions of the team members after the plants had been visited. This is the categorisation shown in Fig. 3. At first sight the data suggests that there is a relationship between cost and flexibility and that the more you want the more you must pay. Some comparisons can be made that would make one question this. Why does Plant 10 offer greater flexibility at a lower cost than Plants 1, 3 and 11, all of which are broadly similar? How does Plant 6 offer the same flexibility as Plant 1 at a lower cost?

Table 1. Operating mode analysis

Heating / Cooling	Reactor 1			Reactor 2			Reactor 3			Average		
	M	SM	A	M	SM	A	M	SM	A	M	SM	A
Control Process T	1			1		1	1		1	1	0	0.67
Control Untility Supply	1		1							0.33	0	0.33
Control Boil-up				1						0.33	0	0
Control process flow T					1				1	0	0.33	0.33
Control T with ΔT	1		1	1		1				0.67	0	0.67
Control T with ramp			1						1	0	0	0.67
Total Modes	3	0	3	3	1	2	1	0	3	2.33	0.33	2.67

CHIMIA 2000, 54, No. 12

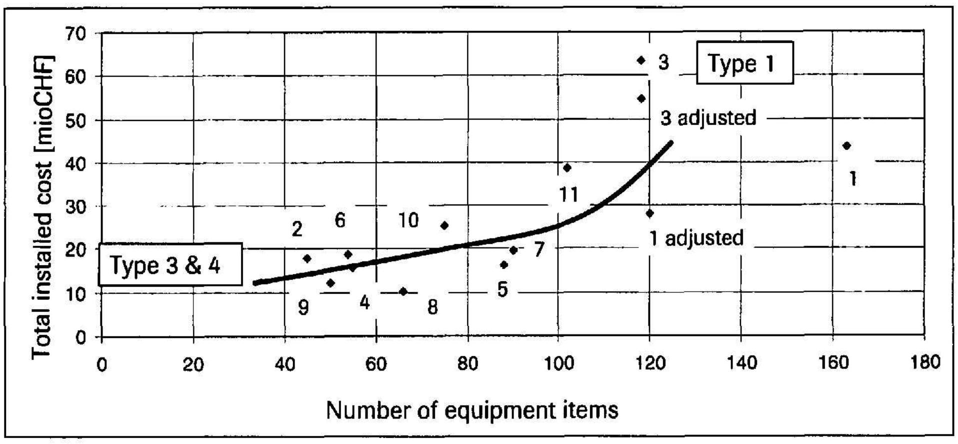

Fig. 4.

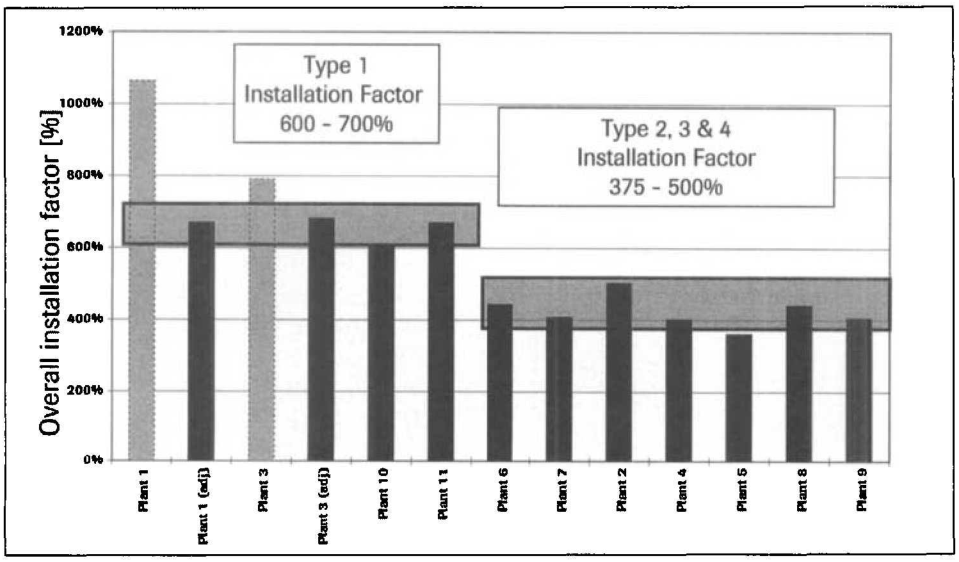

Fig. 5

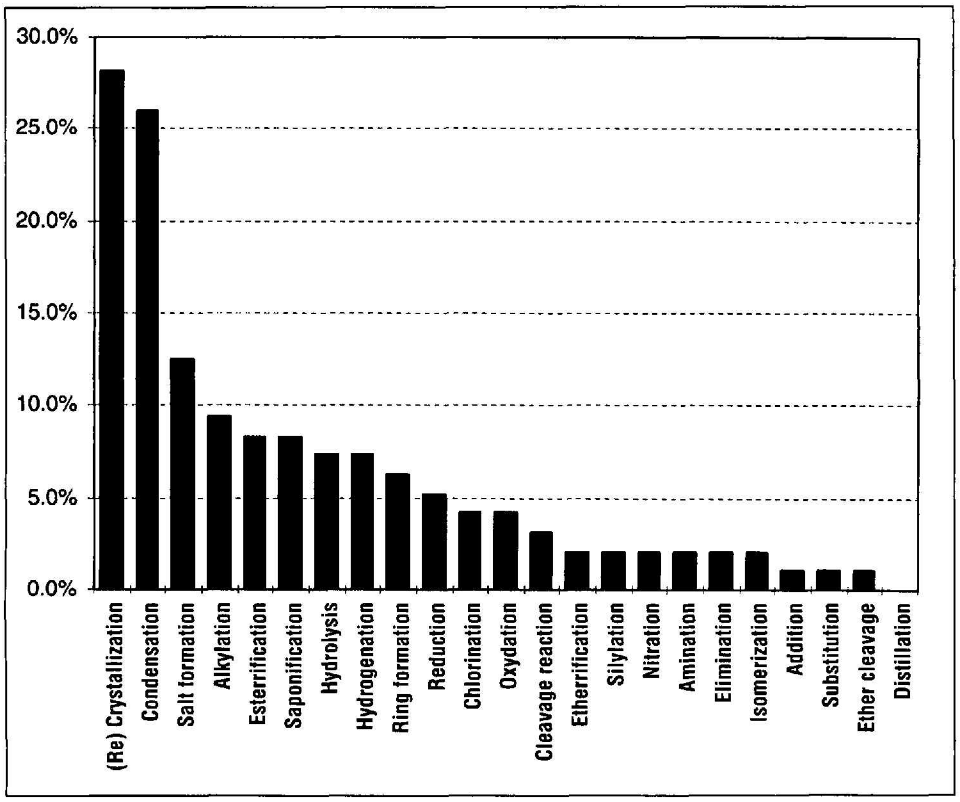

Fig. 6

To compare the effect of complexity rather than flexibility a simpler relationship is evident in Fig. 4.

There were an insufficient number of data points in the study to make any statement about the costs that can be expected for a six-reactor multipurpose plant more accurate than 25 to 45 million SFr. However a deeper analysis shows that the installation factor is type-dependent (see Fig. 5). In other words to complete a highly flexible multipurpose plant will cost six to seven times more than the equipment costs. For plants with slightly simpler concepts this multiplication factor drops into the range 3.75 to 5.

Clearly to build more costs more. But do you actually get more?

3. Benchmarking of Product Requirements and Installed Functionality

Companies outside the Roche family were happy to share information about historical prices and scopes for projects. But not surprisingly they were less willing to share information about the manufacturing processes which were run in them. This restriction did not apply in-house and a comprehensive evaluation of the process requirements of many Roche products was completed.

The products were selected so that there would be a mixture of established products, new products and development products, there was a mix of manufacturing volumes and only products that generated annual sales in excess of 50 million SFr. were considered. In the study there were 25 products with 96 production steps. As Fig. 6 shows, a broad range of chemical steps were included.

Another questionnaire was prepared, this one targeted at the people operating the plants. The first part of the questionnaire called for general information about the reaction, the process conditions, the capacity, the equipment used and seeking the opinion of the plant manager regarding which aspects of the process could be done in a more optimal way. The second part asked for the required plant functionality to perform the step. This intentionally mirrored the module analysis and the operating mode analysis from the plant benchmark.

These data allowed the project team to assess not only how many vessels were used for a step but also how many were needed.

Some of the early findings are shown in Fig. 7–10. For example Fig. 8 can be

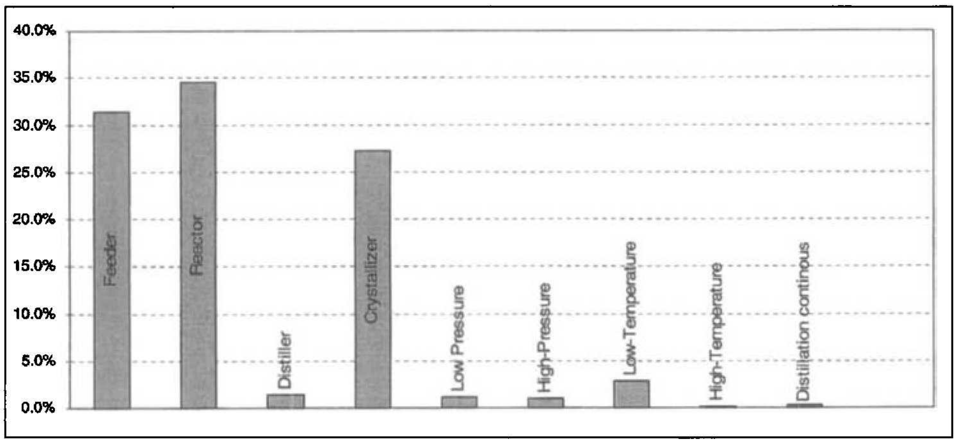

Fig. 7. Percentage of steps requiring particular equipment type

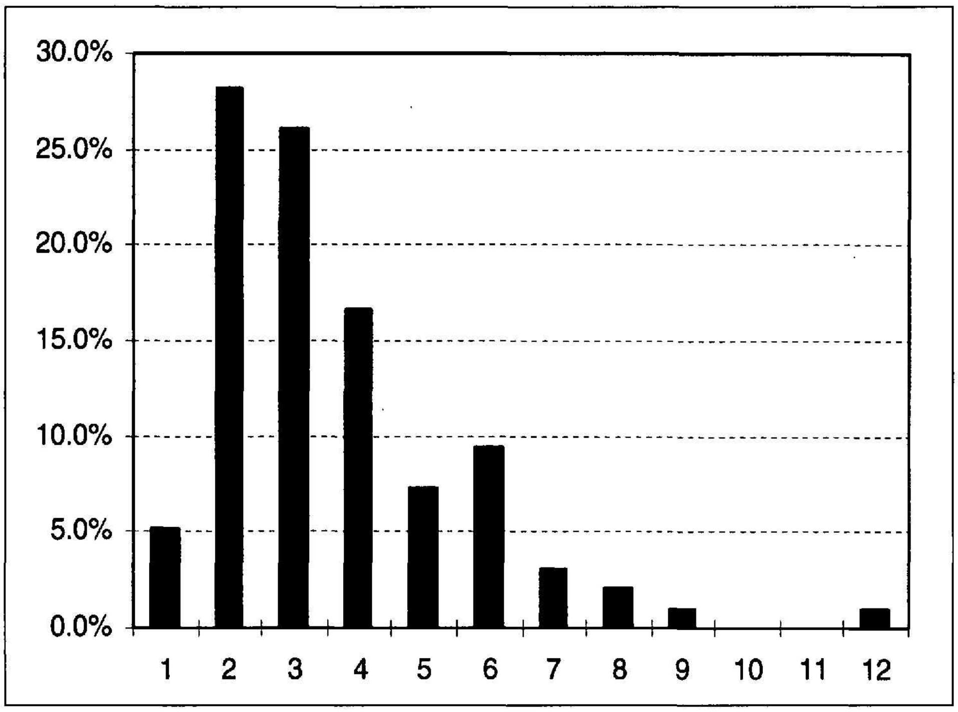

Fig. 8. Number of Reactors per Process Steps

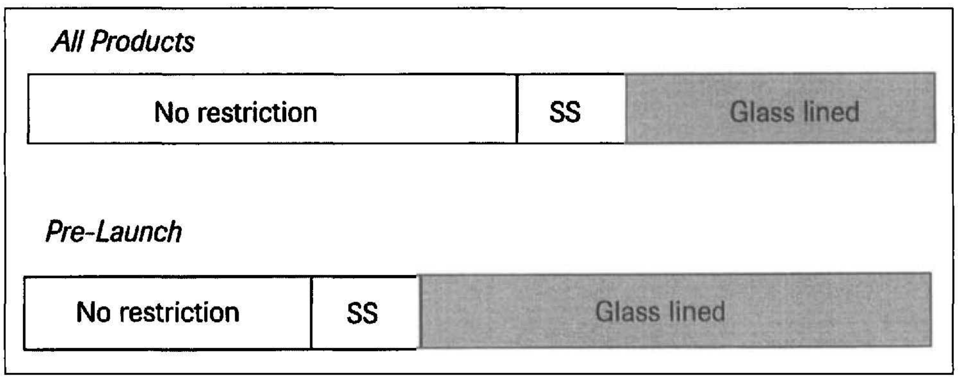

Fig. 9. Number of vessels which require a particular type of material

Table 2. Process requirements for the modules

Always Used	Often Used	Rarely Used
Liquid Feed	Solids Feed	Reaction Gas Feed
Pressure Control & Inerting	Distillation	Dosing pH control
Liquid Transfer Out	Sampling	Solids Conveying
Agitation	Vacuum Systems	Vent Gas Scrubber
Heating / Cooling		CIP System

used to show that the Roche MPU concept is very inefficient as only 37% of steps require a multiple of three reactors and as a result we have idle equipment which cannot be used for more than 60% of our steps. (This would be true if all the steps were produced on plants built according to the MPU model but as a result of the age profile of the plants and because of acquisitions this is not the case).

The most interesting results come from the analysis of the modes the processes require (see Fig. 10). By overlaying this on the modes installed in the plant it became possible to see which plants are capable of which steps. As expected the highly flexible Type 1 plants offered all the required functionality to perform the steps in the study (see Fig. 11). The surprising finding was that the Type 2 plants were nearly as capable (see Fig. 12).

The question 'how do the Type 2 plants not only score well on the Flexibility Index but also provide the same functionality for less cost ?' is now more obvious than ever. The analysis of the modules required by the processes provided some clues to the answer.

In the Type 1 plants a standard suite of modules was installed on each reactor. In the Type 2 plants a reduced set of modules is installed and in this case the determination of what to install is based on the known requirements of the processes that will be run in the equipment. The logic with the Type 1 plants was that as they would have to cope with a large number of steps, which could not all be known during the design of the plant, then they should be able to cope with almost anything.

When the process requirements for the modules was studied it was found that there were basically three groupings (Table 2). It is hardly astonishing that modules such as inertisation, pressure control and liquid addition should be widely needed but the study did allow differentiation between those modules that are often used and those that are rarely used. It is also worth noting that the rarely used modules tend to be the ones that are more expensive to implement.

4. Preliminary Conclusions

These results suggested that many of the modules installed were not required. This result was confirmed by a study of the history of the usage of the automation modules compiled for the Roche multipurpose plant in Basel. The plant benchmark data strongly suggested that the Ro-

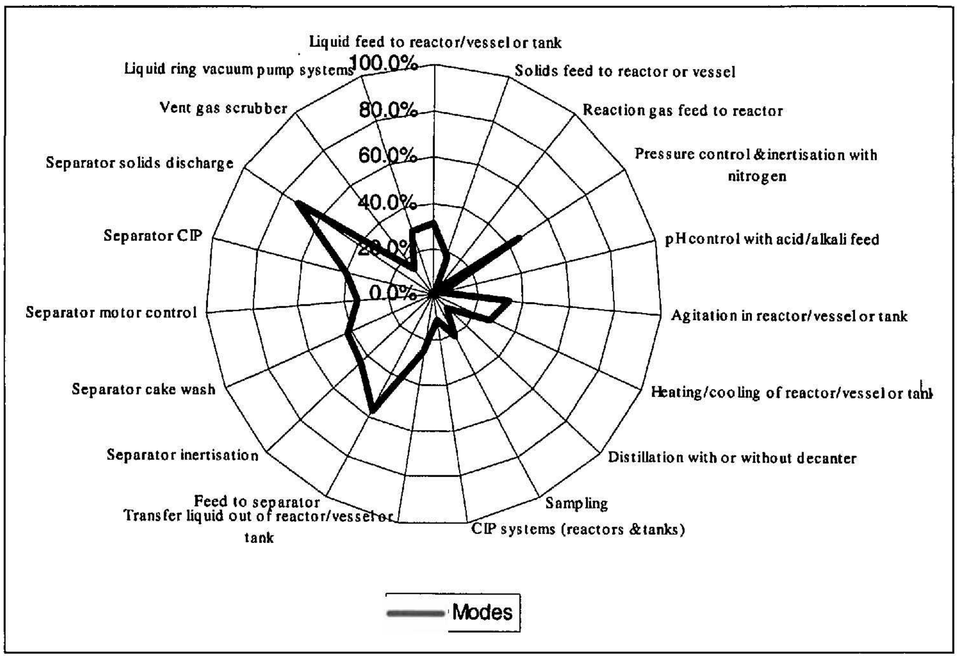

Fig. 10. Modes-requirements of 25 products.

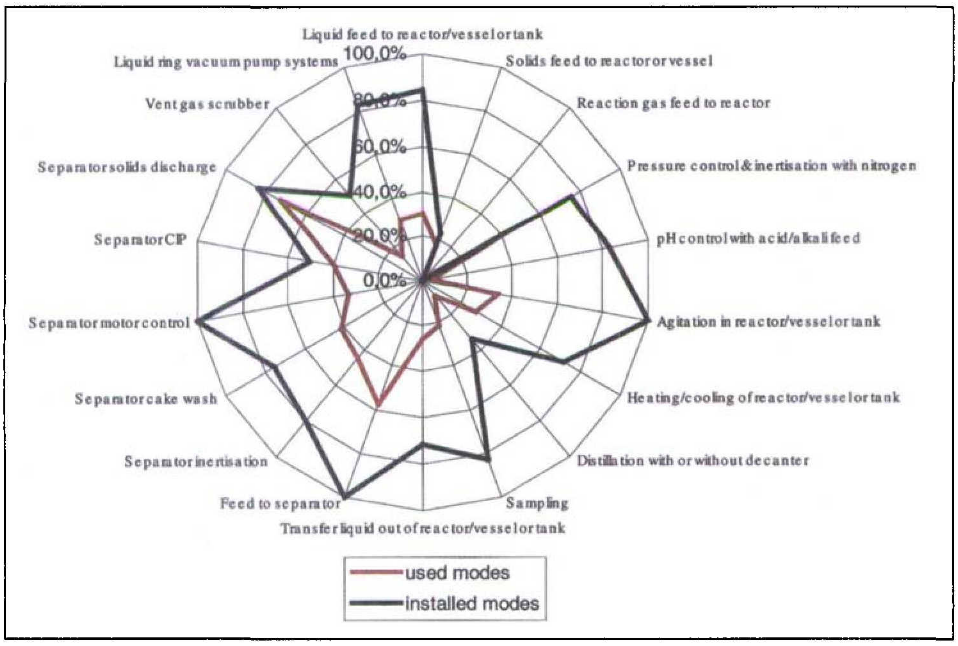

Fig. 11. Modes-requirements of 25 products compared with installed modes at 1A.

che plants were too complicated and had too many equipment items installed. The benchmark data also suggested that this was a key cost driver. The study of the process requirements along with the assessment of the benchmarked design concepts suggested that the train concept was limiting and inefficient.

The conclusions that were drawn from this was that.

- Future plants should be made up of freely configurable process units.
- The ancillary equipment should be shared between the main equipment.
- Reactors should be installed with a minimum set of modules that reflected those most often used.
- Other modules should be installed only if the process(es) are known to require them. However to maintain the flexibility for a plant expected to adopt new processes quickly the design of a further set of modules should be done and the physical space should be set aside in the plant to them to be installed quickly.

It was apparent at this point in the project that there were significant impacts for the automation system. In addition the move to freely configurable process units was adding considerable complexity to the plant and made planning of campaigns a crucial part of optimal plant utilisation. But as yet the benefits of this added operational difficulty were vague and non-quantified. As a result two further studies were undertaken and these are outlined in the sections that follow.

5. Impact for Automation

During the benchmarking exercise the team decided to restrict the study to systems actually controlling the plant rather than business information systems. Therefore the highest level of automation considered was recipe control. In the classical automation hierarchy this sits on top of a level of sequence control which in turn is on top of a functional control (individual valves, control loops, motors and so on) and measurement level.

In the plants with the highest degree of automation 100% of the installed process functionality was controllable by both the recipe and sequence levels. At the functional control level this was even greater than the 100% envisaged in the questionnaire. Only 70% of all the functional control level installed was actually used. In other words although many possible modes of operation were installed only a subset were ever used.

The relative costs of the different automation levels are shown in Table 3. These data were a little surprising as they suggest that higher levels of automation are relatively cheap. This was contrary to the expectation (or prejudices) of many of the team.

Another assumption of the team was that the automation of transfer was expensive in multipurpose plants. However the data revealed that this contributed only 4% to the total.

The analysis of the usage of the modules showed that of all the modes ever configured about 70% had been used at least once in the lifetime of the plant. During a typical period in which six different steps were manufactured 52% of the installed modes were used. The average number of modes used in any one step was 34%.

The implications of the proposed direction were minimal for automation. The changes proposed were in line with technical developments in the areas of field instrumentation and automation system architecture. The 'plug and play' approach to ancillary equipment is also consistent with these developments and with the modular approach. The findings from the automation studies were in-line with those from the rest of the study – that we should install everything that we

CHIMIA 2000, 54, No.12

need but no more – and this will give lower plant costs and lower automation costs without sacrificing plant flexibility.

6. Computer Modelling of Multipurpose Plant

The final part of the jigsaw was to assess the effect of the move away from process units organised in trains. This was done with a computer simulation of an existing multipurpose plant. The plant in question consisted of six trains (each with a reactor, crystalliser and centrifuge), three distillation vessels, three dryers and two columns for solvent recovery. The plant manufactures 350 tons per year of material across a range of 23 isolated substances.

A simulation tool called 'The Optimiser' was used to build a model and simulate the various scenarios. By removing the distinction between the vessel types and allowing vessels to be combined from any of the trains, as well as splitting the large campaigns into smaller ones, it was possible to achieve an almost 33% reduction in the plant time required to manufacture the materials. Fig. 13 shows typical output from the simulation software.

A fringe benefit of this software tool was the ability to analyse the percentage utilisation of each equipment type. From this we have been able to propose a ratio for future plants of:

Reactors	3
Centrifuges	1
Dryers	1
Dist. Vessels	0.75
Dist. Columns	0.5

7. Summary

The conclusions:

- From the benchmark – Roche's plants are more expensive and complex but more flexible than the industry average
- From the process analysis – The functionality installed is greater than the processes require
- From the simulation and costing exercises – Higher manufacturing output can be achieved with plants that cost less to build.
- From the automation studies – Highly automated plants need not be highly expensive, and an automated, freely configurable multipurpose plant is technically realistic.

Received: October 17, 2000

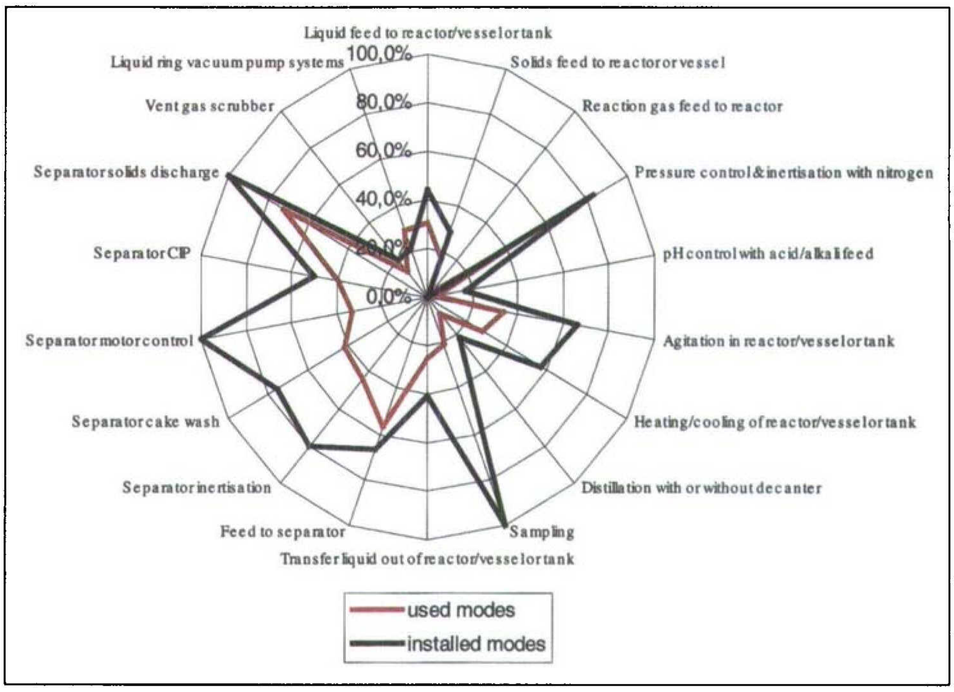

Fig. 12. Modes-requirements of 25 products compared with installed modes at 7A.

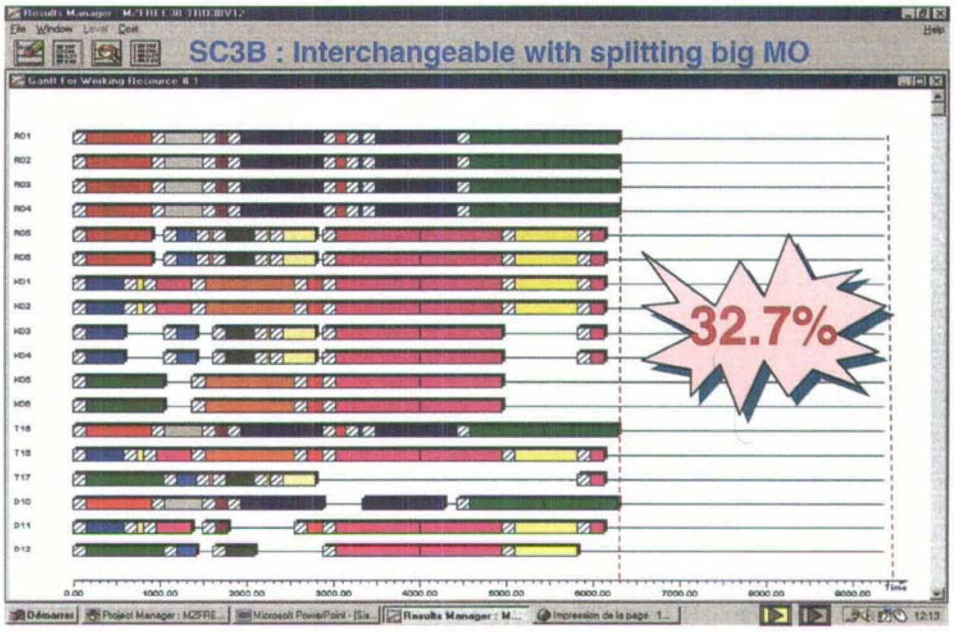

Fig. 13.

Table 3. Relative costs of the different automation levels

	Percentage of the total Automation Cost	
	Hardware and Software	Software only
Recipe Control	0.7%	3.2%
Sequence Control	1.3%	4.8%
Functional Control	98.0%	92%