CHIMIA 2000, 54, No.12

Chimia 54 (2000) 708–713
© Neue Schweizerische Chemische Gesellschaft
ISSN 0009–4293

Custom Manufacturing of Fine Chemicals in a cGMP Multipurpose Plant.
An Opportunity for a Niche Player

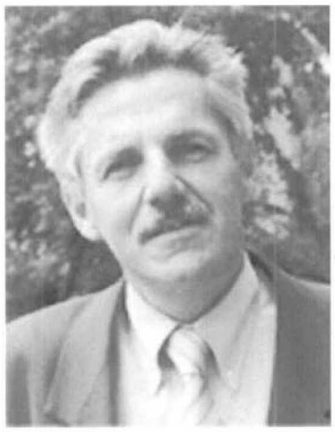
Erich Habegger*

Abstract: A brief background of the (pharmaceutical) fine chemicals market is given. Based on the requirements of the market, the critical design parameters of a cGMP multipurpose plant are discussed. A model is presented which describes the relative influence of various key-cost factors on the overall performance of the plant. The reference facility used in this study is the cGMP multipurpose plant which is currently being constructed at the Rohner site in Pratteln, Switzerland. The impact of selected technical parameters (reactor volume, campaign size, change-over time, *etc.*) on the performance of the plant is discussed. In view of a high labor cost situation (*e.g.* Switzerland), the relevance of the capital investment costs *versus* labor costs is investigated. A benchmark comparison is made with five different cGMP multipurpose plants which compares the capital investment costs with the capacity.

Keywords: Capital investment costs · cGMP multipurpose plant · Critical design parameters · Custom synthesis · Fine chemicals

The Market for Pharmaceutical Fine Chemicals [1]

The structure of the pharmaceutical industry is currently undergoing a pronounced change, which is characterized by:



*Correspondence: Dr. E. Habegger
Rohner AG
CH-4133 Pratteln
Tel.: +41 61 825 11 11
E-Mail: ehabegger@rohnerag.ch
http://www.dynamic-synthesis.com

- Mergers
- Concentration on core business and
- Outsourcing

The well-established leading pharmaceutical companies and the new, virtual life science companies tend to concentrate more and more on the big three DDD's (Discovery, Development and Distribution) and are increasingly outsourcing their chemical manufacturing activities, in addition to other services.

In daily business there are, however, still significant differences in the intensity and the pace as to how the outsourcing strategies by the different companies are handled. There are companies who have their entire chemical production in-house, on the other hand there are companies who have all their products made by third parties. The majority of companies do both, *i.e.* part of the products is manufactured in-house and part by a third party. The selection as to which compounds are kept for in-house manufacturing is part of the outsourcing strategy. There is a clear tendency first to outsource the 'less complex' compounds and to keep the strategically sensitive 'more complex' molecules in-house. If however the manufacturing requires highly specialized technologies (*e.g.* handling of extremely toxic or explosive materials, reactions under very high pressures or extremely low temperatures, chemicals to be handled in exotic materials of construction *etc.*) then even the outsourcing of strategically sensitive production steps becomes increasingly business-as-usual [2].

Due to the complex nature of the business the cooperation between customer and fine chemicals supplier must be very close to be successful. In order to avoid any undesired overdependence on one fine chemicals supplier, the customer usually builds up at least two suppliers for the same product, despite the extra effort it requires.

Of course, customers will try to utilize their existing capacity. Once, however, the plants are either running at full capacity or the constantly evolving cGMP-requirements cannot be met by the aging facilities, a fundamental decision needs to be taken. Is there available capital and other resources to invest in additional chemical manufacturing capacity or should the capital (and the extra

headcount and the extra management attention and...) be focused on the core business? The answer to this question is usually clearly in favor of the second option. Therefore, in the long run, the trend towards outsourcing will undoubtedly prevail. This is not only valid for the pharmaceutical industry but also for other 'high-tech' companies, which require the services of the fine chemicals industry [3].

The Niche Player

The market for pharmaceutical fine chemicals amounted in 1999 to over $22 billion and is expected to grow at an annual rate of 7% to 8% in the coming years [4].

The volume as well as the significant growth rate of this market is of course widely known and therefore the competition is accordingly tough. It is estimated that worldwide there are over 1000 companies active in the pharmaceutical fine chemicals business. It is a fact that the supply of fine chemicals to pharmaceutical industry is extremely fragmented.

The fundamental law in this business is constant change: Developing new chemical entities in the life science industry is becoming considerably more difficult. Out of 1000 molecules identified in research, less than five are expected to reach the market. Fewer than 10% of all products entering preclinical testing eventually become commercial drugs. Therefore an increasing portion of fine chemicals needed for developmental drugs is manufactured only once.

The ability to react and to adjust in order to deliver constantly different compounds has a lot to do with the size and the quality of a company.

A successful fine chemicals company can be compared with a first class restaurant: in order to be able to serve its customers seven days a week, 24 h a day a high quality meal in an appropriately decorated environment, the restaurant has to have the right size; it should neither be too large nor too small.

The highly fragmented market for fine chemicals combined with well-established in-house technologies is in general a market for niche players.

The successful niche player not only sells products but also renders an integral top quality service to its customer:

- Design and development of the synthesis (including process validation, if required)
- Scale-ups, optimization of the manufacturing process
- Seamless development: faster time to market and finally:
- The manufacture of the product itself.

'The Best Fit'

The fine chemical manufacturer in Switzerland can depend on a well-trained, reliable and highly productive workforce. The training programs in place on the university level and on the vocational level are efficient and well proven. Unfortunately it is also a fact that the labor costs are relatively high. Taking all these factors into consideration, the profile of the product with 'the best fit', as well for the customer as for the fine chemicals manufacturer, can be characterized as follows:

- High quality standards
- Multistep, not optimized synthesis
- One product – one customer
- Typically, the amount of required product is between 1–10 to and is seldom higher than 100 to
- Very often products will be manufactured only once (this is especially true for GMP products which are still in the clinical development or even in an earlier development phase)

The cGMP Multipurpose Plant – Designed to Fit the Products that 'Fit Best'

Requirements of the cGMP Multipurpose Plant

The following outline relates specifically to the considerations made to design the cGMP multipurpose plant B40 at the Rohner site in Pratteln, Switzerland, which is currently under construction and will start commercial production mid 2002.

Rather than specific products, a cGMP multipurpose plant has to be designed for the most probable processes.

Based on the described market situation, the cGMP multipurpose plant must meet the following requirements:

- The plant must operate according to the required quality standards.
- The plant must be based on a broad and sound cGMP multipurpose technology basis (exotic equipment only to be installed for specific products).
- The plant must be really flexible (free space for new equipment / technologies must be made available, if needed).
- The plant must be easily cleanable.
- The plant must be easily adaptable to new products.
- The plant must be constructed to handle short campaigns.
- The plant must be operated safely and must be in full compliance with the relevant laws.

And last but not least:

- The plant must be run on an overall economically competitive basis.

The first seven points are firm and generally 'non-negotiable'. The last criteria will make, in light of the fierce competition, the difference: The successful fine chemicals supplier *must* deliver the product on an overall competitive basis.

Critical Design Parameters of the cGMP Multipurpose Plant

General Structure

The plant consists of a headblock, a production area and a tankfarm. The headblock, including the basement and the roof, houses the necessary infrastructure installations. The production area will host at full capacity up to twelve trains.

Based on the nature of the targeted products to be manufactured, the plant will be operated on a batch process basis.

The manufacturing flow is organized vertically (Fig. 1):

Level 5: Charging vessels/chemical reactions
Level 4: Chemical reactions
Level 3: Chemical reactions, crystallization
Level 2: Filtration
Level 1: Drying

The facility is organized into so-called trains. The train is considered to be the logical unit of the plant. Typically, a train consists of:

- 2–4 multipurpose reactors, fully equipped
- one filtration unit
- one drying unit.

In general a multipurpose reactor will be equipped as follows: heating-cooling system (temperature range: –20 °C to +150 °C); condenser and after condenser system, various head tanks and receivers, vacuum system *etc.*

The materials of construction mix has a dramatic impact on the chemical versatility of the plant. The following mix is considered to be optimal for today's requirements of a multipurpose plant:

- Glass lined, hastelloy: approximately $^2/_3$
- Stainless steel: approximately $^1/_3$

CHIMIA 2000, 54, No.12

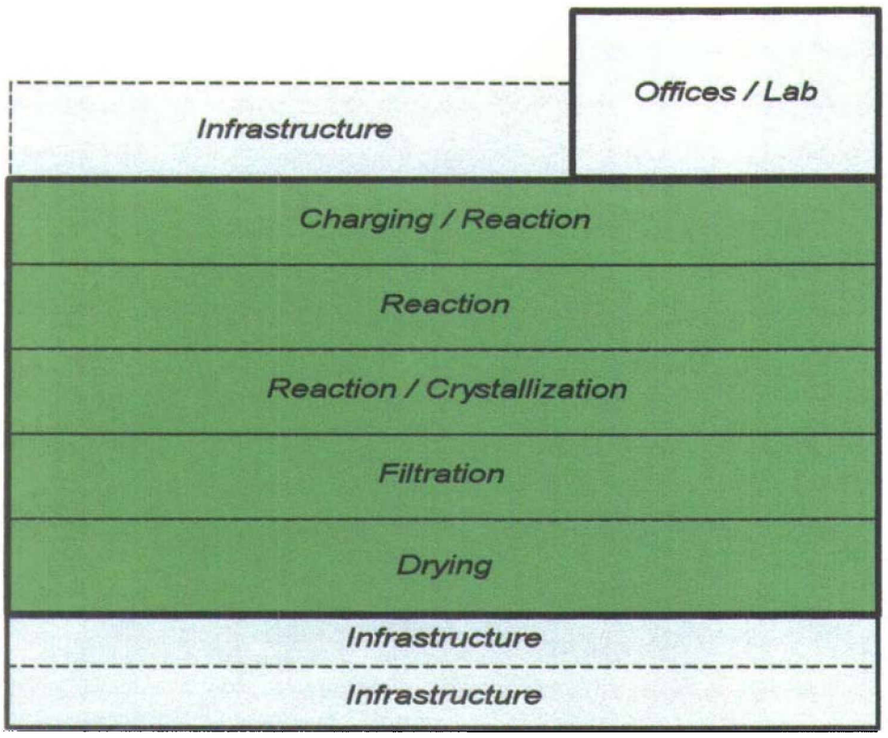


Fig. 1. cGMP multipurpose plant B40: sectional view

Special emphasis was placed on the fact that a cGMP multipurpose plant needs to have different types of filtration technologies available in order to cover the necessary range: centrifugation and stirred pressure filter capacities have to be available.

Drying operations are often run in separate facilities, independent from the chemical processing. In this case the drying operations are directly integrated into the chemical manufacturing process. The main advantage of this measure is to minimize the handling of solid materials (high quality requirement, labor hygiene).

Segregation

The plant is divided into two areas, each with a different quality of segregation (Fig. 2):

- Area I: Relative open structure, which will allow a maximum of flexibility.
- Area II: Strict containment structure, which will allow a maximum of segregation (*e.g.* for the manufacturing of active pharmaceutical ingredients).

This flexible arrangement allows different levels of segregation to be achieved in an economic manner.

The heating/cooling systems of the reactors will be partly segregated from the reactor itself in order to minimize the cleaning efforts in the manufacturing area.

The necessary local segregation will be provided for the charging operations of solid materials to the reactors. The transfer of solid materials from the filtration units to the drying units and the unloading area of the dryers will be completely enclosed. It has to be emphasized that segregation should be provided only when absolutely needed, unnecessary segregation substantially increases investment costs.

Size of Equipment

In light of the market situation the ideally desired range of available reactor sizes should be very broad. However, practical considerations dictate a much narrower range. After a detailed survey, the decision was made to install in the first project phase two trains equipped with 2.5 m^3 reactors and two trains equipped with 6.3 m^3 reactors. This configuration will permit campaign sizes ranging from 2 tons to over 220 tons.

Piping

The piping will have a decisive impact on the overall capital investment costs. Despite the multipurpose character of the plant it was decided to install an absolute minimum of piping. The trains will be configured to meet the requirements of specific products. This measure minimizes the capital investment costs and the change-over time for the equipment.

Automation

The level of automation has a tremendous impact on the overall investment costs and therefore also on the operating costs. The question is not whether automation is necessary, but is to what degree is automation necessary? Experience shows, that especially in the case of multipurpose plants, there is a tendency to miss the optimal balance between automation and manual operations: Excessive automation can impair flexibility and substantially increase capital investment costs.

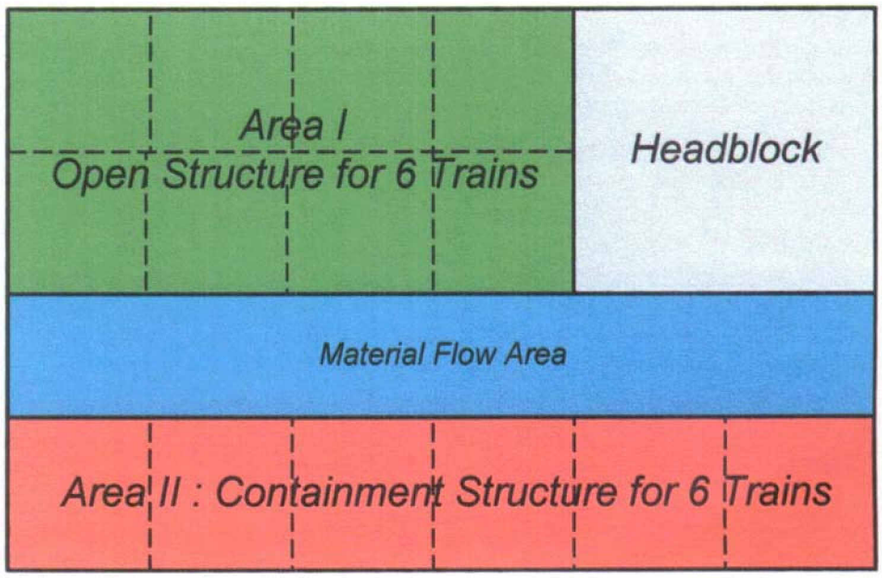


Fig. 2. cGMP multipurpose plant B40: schematic layout

Materials Handling Principles

Solid materials: Starting materials will be dispensed in a separate warehouse and will be moved to the charging vessel shortly before charging. The solvents will be supplied from the tankfarm. The finished product will be moved out of the manufacturing building immediately after drumming and sampling.

Special Equipment

A multipurpose plant has to be able to cover a certain minimum range of 'multipurpose technologies' in order to be attractive to customers and to operate efficiently. High pressure reaction capacity for hydrogenation processes and similar applications (preferable with an acid resistant material of construction and pressures up to 50–60 bar) as well as a low temperature unit (–100 °C) are considered to be essential attributes in a modern cGMP multipurpose plant.

Special equipment with a very limited multipurpose character: Proactive investments for highly specialized equipment is extremely risky and should therefore be avoided. Free space however is reserved, so that specialized equipment can be installed if needed to meet specific customer requests.

Ecology

Economical access to
- wastewater treatment capacities
- incineration facilities

is a must. 'Economical access' does not mean that all this services have to be on site, but it means, that these capabilities have to be readily available under commercially competitive conditions (by outsourcing selected services, considerable efficiency gains can be achieved also in this field).

Construction Sequence

The plant will be built in at least two phases. In the first phase the headblock, four trains and a tankfarm will be installed. This represents the 'critical mass' which is needed to operate the plant on an economical basis. Subsequent phases will allow expansion up to twelve trains. The fact that the completion of the plant will take place in a later point in time will allow reaction to any future developments in the market.

Economical Considerations

With a simple mathematical model the cost structure of a cGMP multipurpose batch plant is established. The total conversion costs at location L (TCC_L) are reflected by two cost elements: the capital related costs (CRC_L), which depend on the capital investment costs (CI_L), and labor related costs (LRC_L) which depend on the direct labor costs (DLC_L). In addition, both terms depend on the technical variables TV_i:

$$TCC_L = TCC_L (CRC_L, LRC_L) \quad (I)$$

$$CRC_L = CRC_L (CI_L, TV_1, TV_2, \ldots TV_i) \quad (II)$$

$$LRC_L = LRC_L (DLC_L, TV_1, TV_2, \ldots TV_i) \quad (III)$$

It has to be noted, that for the purpose of this discussion, the material costs are not relevant and are therefore not included in the total conversion costs (TCC_L).

The dependence of the capital related costs on the capital investment costs is determined by a linear correlation with the capital related cost elements $CRCE_i$ (Eqn. IV). The following capital related cost elements are considered:
- Energy costs
- Ecology costs
- Repair and maintenance, parts only
- Depreciation
- Return on investment

$$CRC_L = CRC_L (CI_L * \sum CRCE_i , TV_1, TV_2, \ldots TV_i) \quad (IV)$$

The capital-related costs depend mainly on the quality of the design and the efficiency of the realization and not necessarily on the geographical location of the plant. Different taxation laws are not considered. (Because of increasing competition regarding tax incentive programs it can be expected that the significant tax advantages which still are granted in certain countries, will gradually disappear.)

The dependence of the labor related costs on the local direct labor costs is determined by a linear correlation with the labor-related cost elements $LRCE_i$ (Eqn. V). The following labor-related cost elements are considered:
- Direct process labor
- Quality control, quality assurance
- Process development
- Repair and maintenance, labor only
- Overhead production
- Overhead company

$$LRC_L = LRC_L (DLC_L * \sum LRCE_i , TV_1, TV_2, \ldots TV_i) \quad (V)$$

The technical variables TV_i selected to determine the total conversion costs are:
- Train size, reactor volume
- Batch size
- Cycle time
- Change-over time
- Plant operating hours
- Plant utilization
- Minimal campaign size

In the following discussion the parameters of cGMP Building 40 were utilized to perform the calculations with the presented model.

Fig. 3 shows the correlation between the capacity utilization and the campaign size for three different reactor sizes at standard conditions. While for instance a 2 to campaign is too small to be run in a 6.3 m^3 train, a 0.63 m^3 train utilizes 9% and a 2.5 m^3 train only 3% of its capacity. The maximum capacities for the three

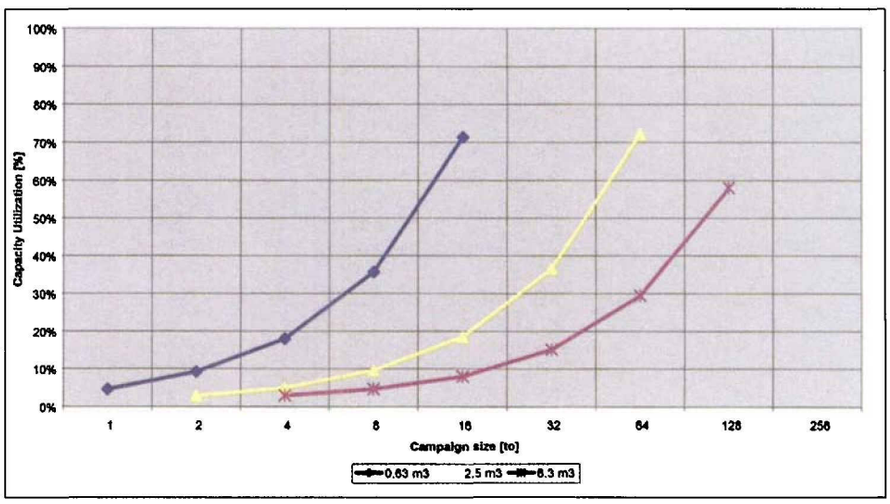


Fig. 3. Capital utilization *vs* campaign size. Parameter: reactor volume

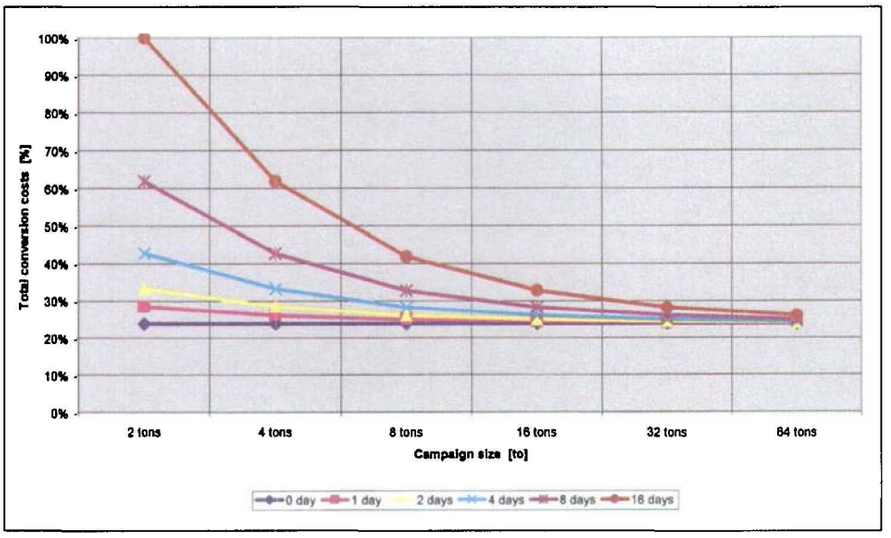


Fig. 4. Total conversion costs *vs* campaign size. Parameter: change-over time – normalized (2 to campaign; 16 days change-over time = 100%) (2.5 m^3 train)

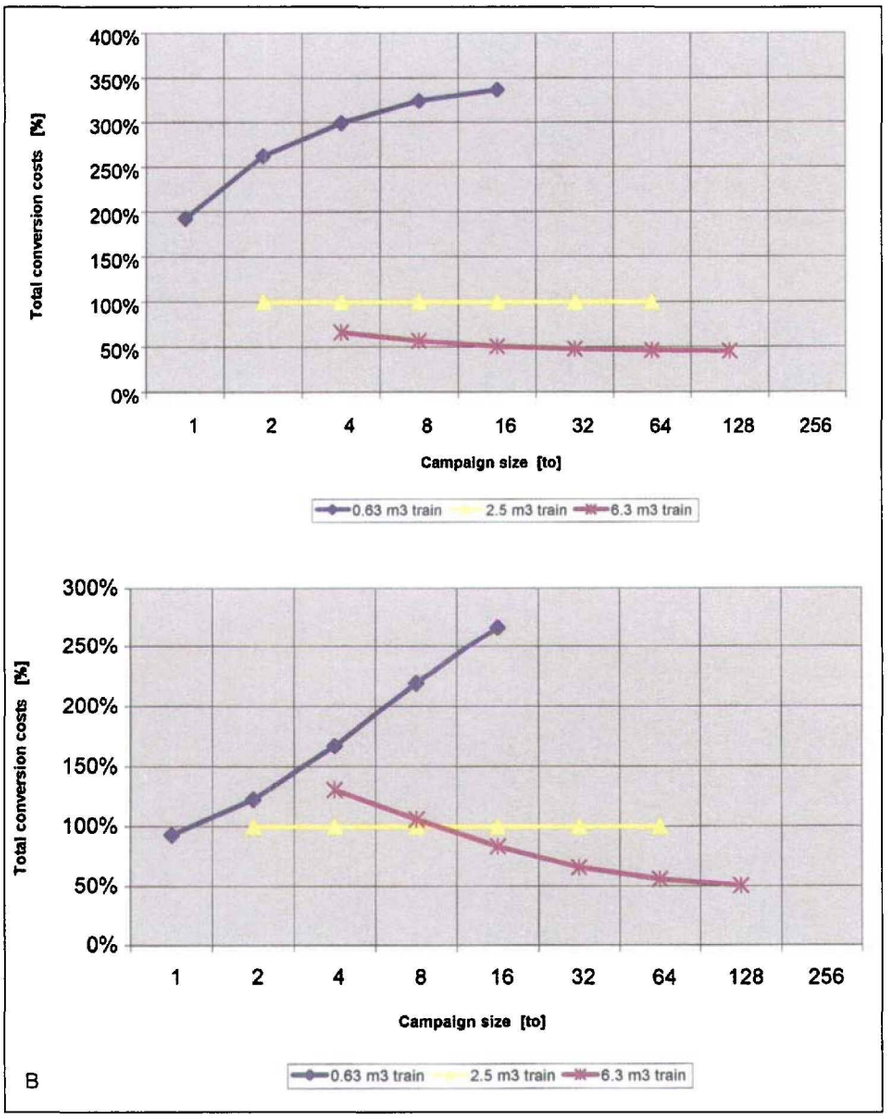


Fig. 5. Total conversion costs *vs* campaign size. Parameter: reactor volume – normalized (2.5 m^3 train). A = standard conditions; B = modified standard conditions

train sizes 0.63 m^3, 2.5 m^3 and 6.3 m^3 are 20 to, 90 to and 220 to (at standard conditions).

The dramatic impact of the change-over time for equipment cleaning on the total conversion costs is illustrated in Fig. 4. Example: Due to unexpected difficulties during the cleaning operations the change-over time increases from originally 2 to 8 d. For a 4 to campaign at standard conditions this variation will result in an increase of the total conversion costs by 50%. Knowing the drastic impact the change-over time has on the performance of a plant, it must be a top priority for the manager to have programs in place which will enable efficiently organized cleaning operations.

An impressive demonstration as to how the campaign size and the reactor volume dictate the total conversion costs of a product is given in Fig. 5A and Fig. 5B. While in Fig. 5A standard conditions are applied, in Fig. 5B selected technical variables were changed (batch size, cycle time and change-over time). It is part of good business practice to make sure the marketing representatives, the production planner and of course the customers are fully aware of these strong interdependencies.

The chemical processing capacities of five cGMP multipurpose facilities were investigated (Fig. 6). In the benchmarking process special consideration was given to the capital investment costs. The data used in the comparison were published over the course of the last three years [5]. Fig. 6 reveals that the differences in the specific capital investment costs per train are significant. The most expensive train (case 2) is more than twice as costly than the most economic one (case 5). The differences between the specific capital investment costs per reactor volume are even larger: one meter cube reactor in case 4 costs six times as much than in case 1 or case 5. The cases 1 and 5 are in good agreement with Pollack [6], who estimated the specific capital investment costs per meter cube reactor volume to approximately $ 1Mio. The cGMP multipurpose plant B40 is represented by case 5.

Fig. 7 shows that the sensitivity of both the capital investment costs and the direct labor costs on the total conversion costs is approximately 2:1. This means that either a reduction of the capital investment costs or the direct labor rate by 50% will result in a reduction of the total conversion costs of approximately 25%.

It is assumed that the location of the cGMP multipurpose plant B40 in Prat-

Criteria	Units	Case 1	Case 2	Case 3	Case 4	Case 5
Description of cGMP multipurpose plant:						
Total number of trains	-	2	8	5	6	4
Total number of reactors per train	-	3.0	3.3	3.0	3.2	2.8
Total reactor volume	m^3	24	54	22	17	46
Average reactor volume	m^3	4.0	2.1	1.5	0.9	4.2
Capital investment key figures:						
Capital investment per train	Mio $	11	23	17	14	10
Relative capital investment per train	-	1.1	2.3	1.8	1.4	1.0
Capital investment per m^3 reactor volume	Mio $	0.9	3.4	3.9	4.9	0.9
Relative capital investment per m^3 reactor volume	-	1	4	5	6	1

Fig. 6. Benchmarking – capacity *vs* capital investment costs of cGMP multipurpose plants

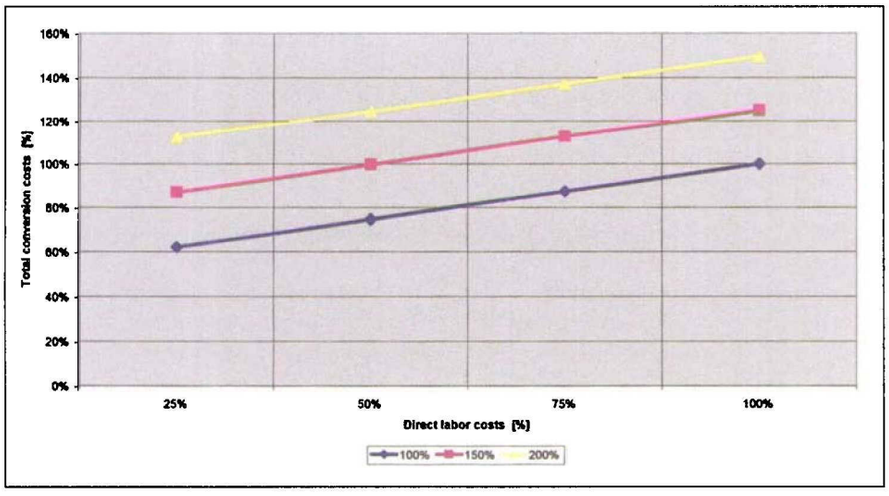


Fig. 7. Total conversion costs *vs* direct labor costs. Parameter: capital investments costs

teln, Switzerland will result in direct labor costs toward the top of the range. A possible impact on the overall efficiency of the operations due to highly skilled operators, low absenteeism rates *etc.*, as is common in Switzerland however, is not considered in the following comparison.

It is rather evident that a relatively small employer cannot have an influence on the labor rates at his site. On the other hand, practical experience learns that the capital spending can and must be controlled. The cases in Fig. 6 show that the variations in capital spending for plants with comparable capacities can be drastic and can exceed the maximum possible variations of the local direct labor rates by far.

Conclusion

The niche player in a high labor cost environment is able to offer chemical manufacturing services successfully under the following conditions:

- The technical capabilities of the cGMP multipurpose plant have to match the customer's requirements: the marketing has to identify 'the best fit'.
- The cGMP multipurpose plant must be based on a lean and efficient plant design and operation concept.

Received: October 10, 2000

[1] Definition of *fine chemicals*: Chemically defined substances of various complexity, consumed by a highly specialized industry. In this presentation the focus is generally put on fine chemicals for the pharmaceutical industry, however other, analogous applications are also included.
[2] S.A. Friedrich, 'Was ist 'core', und was ist 'non core'?', *io management* **2000**, *22* (Nr. 4), 18–22.
[3] C. Hume, B. Schmitt, 'Proceed with Caution', *Chemical Specialties* **2000**, May/June, 21–28.
[4] S.C. Stinson, 'Pharmaceutical Fine Chemicals', *Chem. Eng. News* **2000**, July 10, 63–80.
[5] E. Habegger, private notes, **1997–1999**.
[6] P. Pollack, *Chimia* **1998**, *52*, 243.