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Faculteit Industriële Ingenieurswetenschappen
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Masterthesis

A conceptual approach to retrofit modular concepts into batch reactor setups at Janssen through a data-analysis of the operation records

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Prof. dr. ir. Leen BRAEKEN

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Michiel van Bussel
Scriptie ingediend tot het behalen van de graad van master in de industriële wetenschappen: chemie

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Preface

This thesis marks the end of my academic carrier as a master's student in Chemical Engineering Technology. Consequently, I would like to take this opportunity to thank several people who contributed to this thesis.

First of all, I would like to express my greatest gratitude to Mr. Dennis Van Gool for guiding me through this research and sharing his extensive expertise on pharmaceutical manufacturing. Working together with Mr. Dennis Van Gool has taught me new insights into solving problems as an engineer through a conceptual approach. Subsequently, I would like to thank Janssen Pharmaceutica directly for giving me the opportunity to conduct my thesis.

Furthermore, my sincere appreciation goes to Prof. dr. ir. Leen Braeken for providing me feedback whenever I requested it, for her remarks which have improved this thesis and for keeping me positive during challenging times. In addition, I would like to thank all my teachers of the Faculty of Chemical Engineering Technology of UHasselt in cooperation with KU Leuven of campus Diepenbeek for teaching me the basic and specific facets in the field of chemical engineering.

At last, I would like to express my appreciation to all my family, friends and my girlfriend for supporting me and elevating me to the position I am today.

Hasselt, June 7 2021

Michiel van Bussel

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Glossary

API	Active Pharmaceutical Ingredients
BRIC	Brazil, Russia, India, and China
CapEx	Capital Expenditures
EM	Equipment module
P&ID	Piping and Instrumentation diagram
R&D	Research and Development
R021	Glass-lined reactor 21
R022	Glass-lined reactor 22
R023	Glass-lined reactor 23
R025	Glass-lined reactor 25
R026	Glass-lined reactor 26
R027	Glass-lined reactor 27
R031	Glass-lined reactor 31
R032	Glass-lined reactor 32
R033	Glass-lined reactor 33

Abstract

At present, a major part of the batch reactors at the multipurpose plant of Janssen in Geel is fully equipped with a similar setup of static process equipment. However, future trends in the pharmaceutical industry have heightened the need for more complex and flexible manufacturing capabilities.

An upcoming investment at Janssen prompts the opportunity for this thesis to investigate modular concepts for nine reactor setups to realize a more flexible design, higher equipment utilization and additionally reduce the upcoming investment cost for new equipment.

In this thesis, a data-analysis of records from the reactor's operating system is performed to locate potential modularization options. The data is analyzed in Excel through mapping all operational phases per reactor by examining the duration and frequency of executions of all operational phases of the year 2020 as an approach to evaluate the equipment utilization.

Results of this thesis indicate potential modularization options for distillation, reflux and separation. The small number of separations facilitates the use of an external modular separation system. In addition, the potential implementation of modular condenser systems is feasible due to the lower utilization of the condensers in four reactors. Consequently, two modular equipment setups are proposed respectively following an asset optimization mindset and an asset reduction mindset.

Ultimately, a cost reduction of respectively 6.63% and 1.54% is observed relative to the complete revamp of the equipment.

Abstract in Dutch

Een groot deel van de batchreactoren in de multipurpose plant van Janssen in Geel is uitgerust met een identieke opstelling van statische procesapparatuur. Maar door nieuwe trends in de farmaceutische industrie verhoogt de behoefte aan complexere en flexibelere productiefunctionaliteiten.

Een aanstaande investering bij Janssen maakt het mogelijk om modulaire concepten van negen reactoropstellingen te onderzoeken met het oog op een flexibeler ontwerp, een hogere benuttingsgraad en bovendien een daling in de investeringskost voor nieuwe apparatuur.

Deze masterproef analyseert daartoe data uit het besturingssysteem van de reactor om potentiële, modulaire opties te lokaliseren. De analyse is uitgevoerd in Excel waarbij alle operationele fasen per reactor in kaart gebracht zijn op basis van duur en frequentie met als doel een benadering van de benuttingsgraad van diverse apparaten.

De resultaten wijzen op een potentiële modularisatie bij destillatie, reflux en scheiding. Het kleine aantal scheidingen vergemakkelijkt het gebruik van een extern modulair scheidingssysteem. Daarnaast is de implementatie van modulaire condensorsystemen haalbaar vanwege de lagere bezetting van de condensor in vier reactoren. Hierbij worden twee modulaire configuraties voorgesteld, respectievelijk volgens een optimaliserings- en een reductie standpunt van de apparatuur.

Uiteindelijk wordt een kostenbesparing van respectievelijk 6,63% en 1,54% waargenomen in vergelijking met een complete vervanging van de apparatuur.

1 Introduction

1.1 Context

Janssen is a pharmaceutical company of Belgian origin that was founded by Dr. Paul Janssen. It has been part of the Johnson & Johnson group of companies since 1961 [1]. The core activities of Janssen are research into the development and production of new drugs in five therapeutic areas: cardiovascular and metabolism, infectious diseases, neuroscience and oncology [2].

The chemical production site of Janssen in Geel (Belgium) produces approximately 60% of the active pharmaceutical ingredients of drugs (API's) for the pharmaceutical companies of Johnson & Johnson worldwide. This implies a production of approximately 200 tons of active pharmaceutical substances per year which is done in a multi-purpose high volume Small Molecules API plant that consists of four separate production plants [3].

Besides the production of API's, the site also plays a strategic role as a launch and growth site at which chemical development of new API's and increasing their production volumes takes place. Moreover, innovation, lean production, and sustainability are key aspects within Janssen. For this purpose, Janssen invests annually in new technologies and installations at the site in Geel to produce more with the same resources, be more sustainable and create a future-proof plant design [3]. Each production plant at the site in Geel has a general layout of four levels, as illustrated in Figure 1.

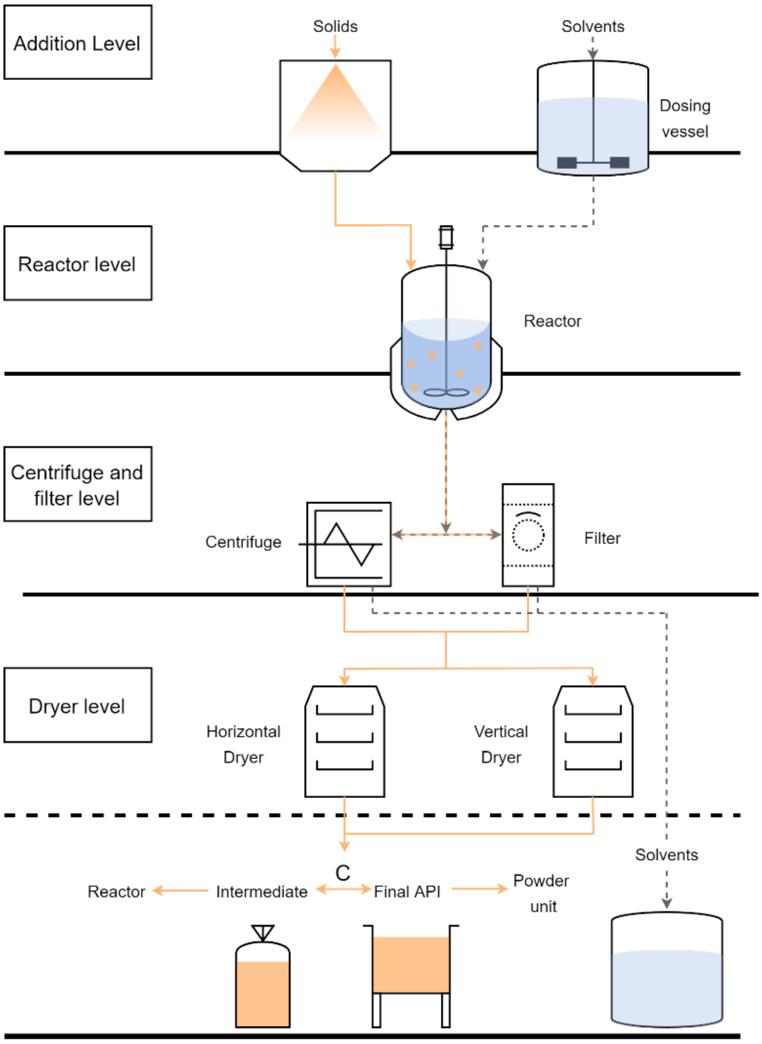


Figure 1: General layout of different levels of API production on plant 3 at Geel [4].

Solid chemical compounds and solvents are added on the top level from where they move to the reactor level on the second floor to produce the desired API's or intermediates. Subsequently, separation and purification of the API crystals take place at the centrifuge and filtration level. Finally, API's are discharged to the dryer level on the ground floor.

Almost all reactors at the site are batch reactors consisting of either stainless steel or with a glass-lined surface. The specific reactor level of plant 3 at the site in Geel consists of eight bays, as illustrated in Figure 2.

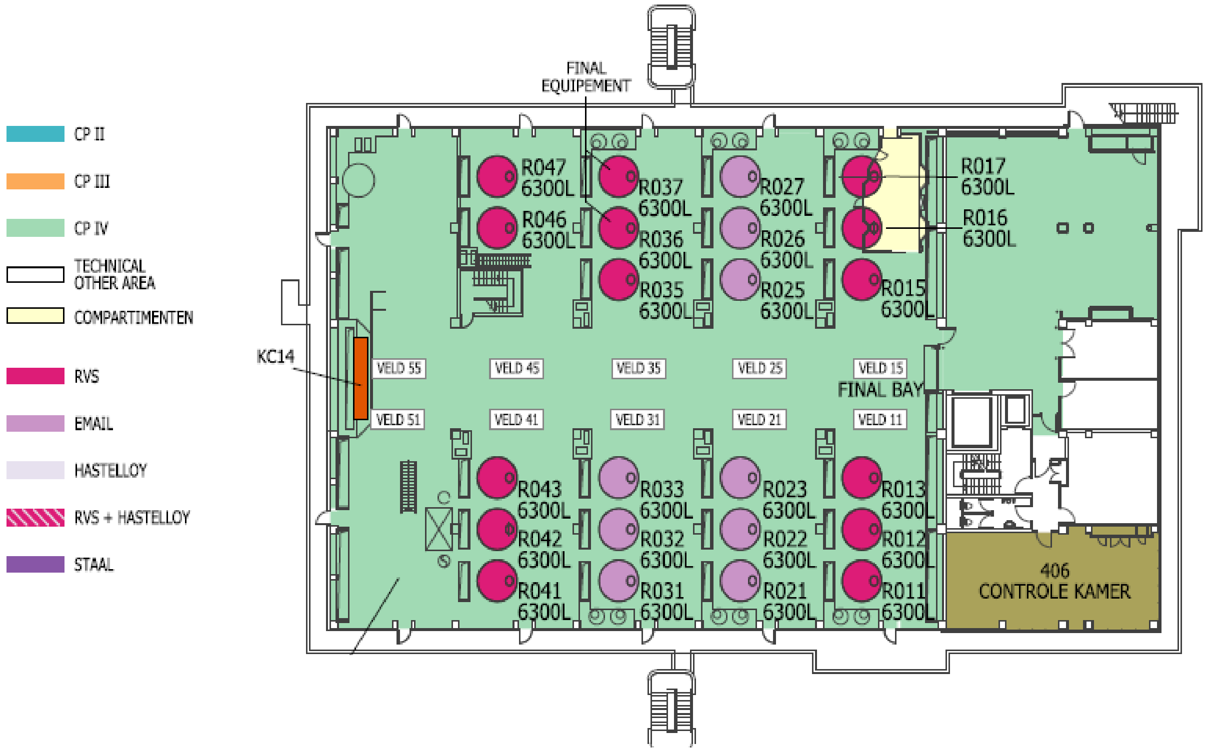


Figure 2: Floor lay-out of reactor level at plant 3 at Geel [5].

As can be seen from Figure 2, the reactor level is organized in separated rows of three reactors which is referred to as a bay. The bay is a physical demarcation of a part of the plant in which a bay consists of three reactors, two centrifuges and half a dryer that are located to each other similar to the levels in Figure 1. Moreover, a complete bay is used during the production campaign of an API and is thus the main viewing perspective of the production planning of API's [5].

Furthermore, all reactors of the same type are almost identical in setup and only have minor differences in connected equipment. The nine glass-lined reactors of bay 21, 25 and 31, which are represented in pink in Figure 2, are within the scope of this thesis. A general overview of a glass-lined reactor with equipment at plant 3 is shown in Figure 3.

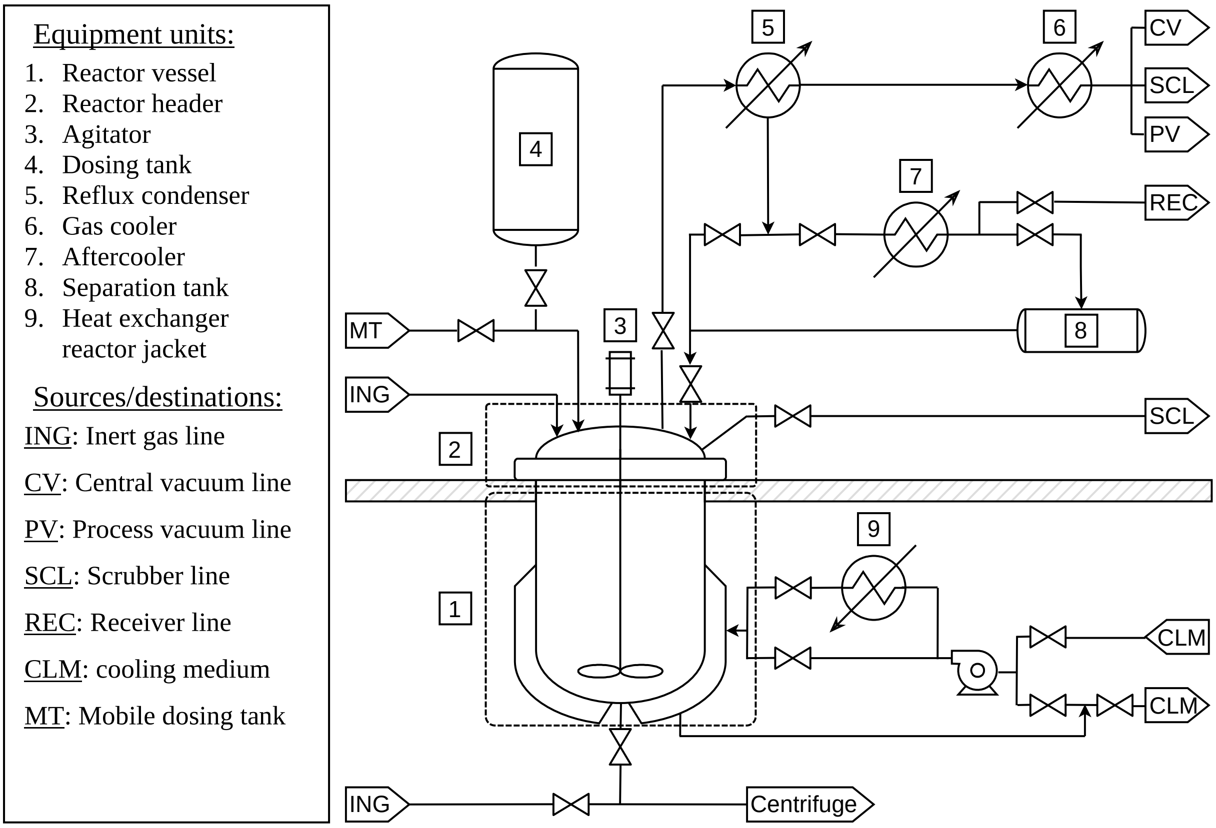


Figure 3: General setup of a glass-lined reactor with standard equipment at plant 3 in Geel [6].

Almost all the equipment units are connected through a static design to the header of the reactor and consequently stay connected during the lifecycle of the reactor. Each connected equipment unit adds a functionality – in other words a capability – to the reactor. Typical examples of capabilities are heating, stirring, refluxing, distilling, liquid-liquid separation, etc. A detailed design in the form of a P&ID of a glass-lined reactor that includes all the inputs to the header of the reactor is given in Appendix A. During this thesis, a reactor including its attached equipment will be referred to as a reactor setup.

1.2 Problem definition

A long-term incentive of this study results from the internal future technology roadmap of Janssen to maintain a future-proof manufacturing plant by introducing new technologies and keeping capabilities of process installations up-to-date with market demands.

This results from the fact that future trends in the pharmaceutical industry have heightened the need for more complex manufacturing capabilities that are preferably flexible to support upcoming trends in product ranges and the market. As the chemical industry in Europe gradually endures more global competition, speed and flexibility are becoming more important capabilities for manufacturing to maintain a competition advantage. Furthermore, new trends in the chemical industry such as diversification and increasing specialization of the product range are being noticed, leading to shorter product lifecycles and consequently smaller product volumes. In addition, the rise of Industry 4.0 with an increasing interconnection between customer and production will demand a reduced time to market and a more flexible production set up to adapt to more volatile markets and product needs. In conclusion, flexible and cost competitive development methodologies and production technologies are needed to ensure future-proof manufacturing and be a successful company within the chemical industry [7].

However, the current batch reactor setups at Janssen, being a generic multi-purpose setup, have similar processing capabilities with limited flexibility to introduce new processing capabilities. Nevertheless, this is not an ideal long-term vision of a competitive design for the future.

A short-term incentive of this study is the intention to invest in a revamp of the header of the glass-lined reactors in plant 3 in bays 21, 25 and 31. This intention results from a safety remediation and solving reliability issues. At present, almost all glass-lined reactors at plant 3 are fully equipped with an identical setup of connected static equipment. A complete revamp of the reactor headers and equipment according to the static reactor design would imply a high investment cost or CapEx of the planned investment. Therefore, more cost-efficient reactor designs to revamp the reactor headers and equipment should be examined with the intention to reduce the CapEx of the planned investment.

1.3 Research objectives

The main purpose of this study is to examine if it is beneficial to introduce modular designs to the glass-lined batch reactors and reactor equipment in plant 3 in order to realize a more flexible design, use the reactor equipment more efficiently by using less equipment for the same reactor setups and additionally reduce the upcoming investment cost for new equipment.

In addition, this study aims to identify and map the intensity of use of the glass-lined reactors and their equipment during operation while developing a first template in Excel which is preferably applicable for a future investigation of other reactors at the plant.

Ultimately, several high-level reactor setups with modular design concepts will be proposed. The results of this study could then serve as a preliminary study and provide insights into the possible design concepts in the upcoming investment of Janssen to revamp the headers and attached equipment of the glass-lined reactor in plant 3.

1.4 Methods

First, a preliminary internship is conducted to learn about the Janssen site in Geel and the API-process. Furthermore, a guided self-study of process manuals, P&ID's and API-manufacturing recipes is performed to learn more about the central role of the reactors in the plant and their required capabilities imposed by the process. A first approach is to map the relevant capabilities of a reactor using API-manufacturing recipes. The latter is important to identify opportunities for the general modularization design concepts of the reactor equipment.

Second, a technical study of the specific P&ID's of the glass-lined reactors at plant 3 is performed in combination with a process manual of the basic operations, basic functions and operational phases related to the reactor header. Through this process, the used reactor equipment per operational phase is investigated and evaluated on the P&ID's to get a good visual understanding of the general equipment utilization.

Third, data from the reactor operating systems of nine glass-lined batch reactors of one year is extracted and exported to Excel. The data analysis is done by examining the duration and frequency of executions of operation phases, and the time allocation of the process in all individual reactors. This is done by filtering data through logic functions in Excel. Moreover, the intensity of use of the reactor equipment during operation is mapped per reactor as an approach to evaluate the equipment utilization during one year of operation. Based on the results of the equipment utilization, several high-level design concepts with modular equipment modules are made. Ultimately, a comparison of the proposed designs is done to evaluate the investment costs relative to the cost of the upcoming investment.

1.5 Layout

In the second chapter of this thesis, the challenges and future trends in the chemical and pharmaceutical industry that heighten the need for more complex and flexible manufacturing capabilities are presented. Furthermore, the basic concept of modular plant design along with its advantages, gaps and challenges will be presented in this chapter. Subsequently, chapter 3 will focus on the material and methods. Here, the extraction and developed method of the data-analysis of the operational records will be introduced. Chapter 4 will discuss the results of the data-analysis and conclude the most interesting results for modularization. From the results of chapter 4, two high-level reactor setup designs will be proposed in chapter 5. In addition, chapter 6 will present a financial evaluation of the two high-level reactor setup designs to the cost of the upcoming investment. Finally, the last chapter provides a conclusion of this thesis and an outlook for future work.

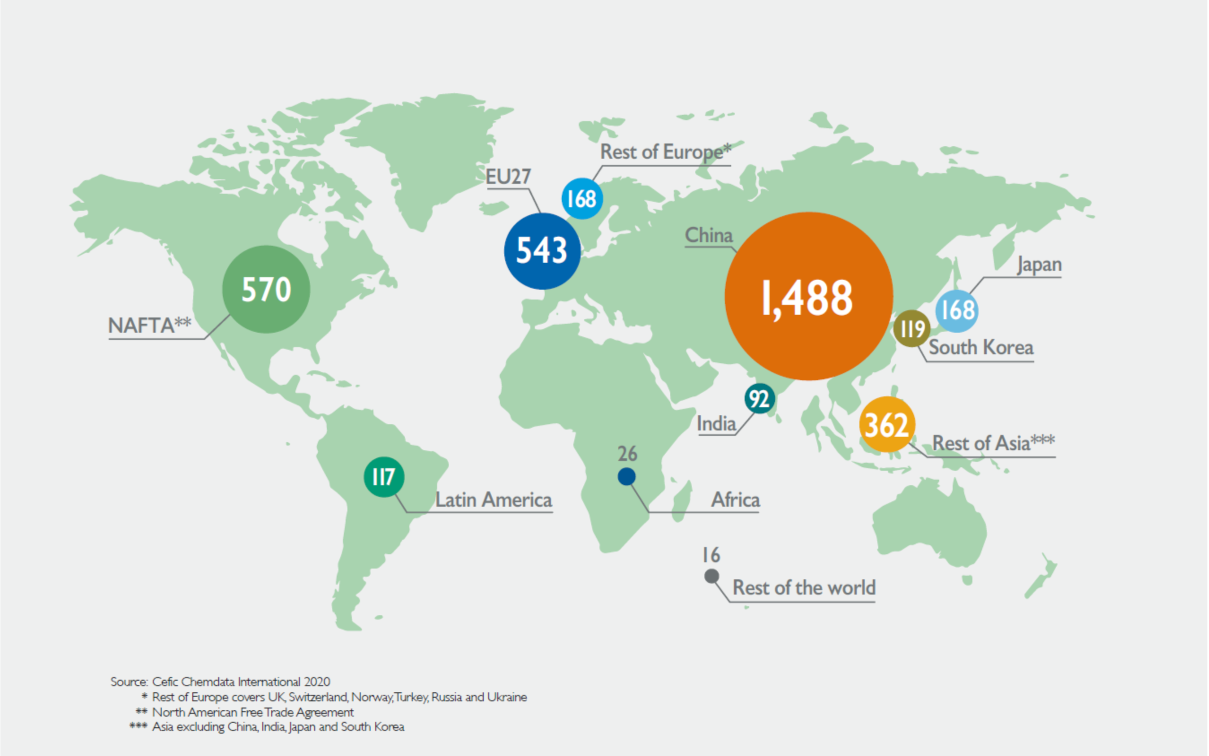
2 Literature study

2.1 Challenges and future trends in the chemical industry

Prospects for the competitive position of the European chemical industry are becoming increasingly uncertain. This uncertainty is mainly caused by an increasing global competition from outside of Europe and the emergence of several new trends of products. Moreover, three main trends can be noticed in the fine chemicals and pharmaceuticals [8].

2.1.1 Market competition

In the first place, the chemical industry in Europe gradually endures more global competition, especially from Asia. One cause is the shift in the production of base chemicals from Europe and North America to emerging economies in BRIC countries and other parts of Asia. This is illustrated in Figure 4 which displays the world chemical sales of 2019 [9].



Source: Cefic Chemdata International 2020
* Rest of Europe covers UK, Switzerland, Norway, Turkey, Russia and Ukraine
** North American Free Trade Agreement
*** Asia excluding China, India, Japan and South Korea

Figure 4: World chemical sales in 2019 in Billion (€) [9].

The figures presented by the European Chemical Industry Council (Cefic) in Figure 4 show the large share of the Chinese chemical industry in the world chemical sales [9]. This competition is enhanced by large Asian companies that provide chemical-related activities and are often controlled and funded by their government [10], [11]. Moreover, the increasing growth of the Asian chemical industry is stimulated by lower production costs, lower taxes, different environmental and safety standards, different product legislation and approval, and the increase in skilled personnel in Asia [12], [13]. Furthermore, emerging markets in other parts of Asia and Latin America are gaining a significant contribution to the world chemical sales through which they are becoming attractive for chemical companies to invest in [14].

An important part of the European chemical industry that plays a critical role in reinstating and maintaining the competitive position of the European chemical industry in an evolving global chemical market is the pharmaceutical industry.

Nevertheless, the pharmaceutical industry is facing similar challenges such as the increasing shift of economic and research activities from Europe to fast-growing markets in BRIC-countries. The latter is enhanced by the rise of difficulties in regulatory requirements of products, high R&D costs, and higher fiscal austerity [15], [16].

2.1.2 Customer-oriented production

The first trend is a more customer-oriented production approach. This leads to an increasing diversification and specialization of the product range [17], [18]. Consequently, stock availability and delivery time of final products are becoming key selling points for manufacturers [19].

Furthermore, the investment risk for manufacturers to expand their product range and for bringing new innovative products into new markets increases. Therefore, it is of increasing importance that newly developed products are beneficial for the customer. This is called the customer value of a product. The customer value represents the acceptance of new products onto the market by customers. Conventionally, products are released onto the market through a product push marketing strategy: products are pushed to the customer by active marketing, e.g., by making the product's presence prominent at a shop [20]-[22]. Currently, a shift in the market is observed at which customers are demanding for more personalized products. Due to the increasing demand of more personalized products, the product push strategy is becoming of less importance. A graphical representation of this trend-shift is shown in Figure 5 [20], [21].

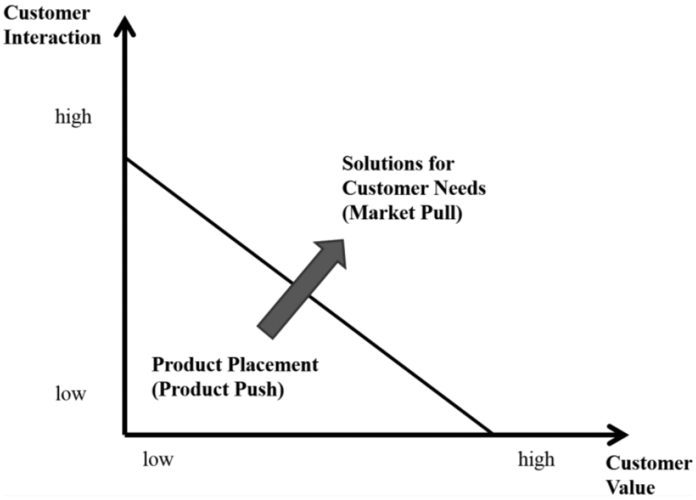


Figure 5: Shift from product pull to market pull due to a customer-oriented production [8, p. 2]

The demand of products by the customer is called the market pull. As a result of the demand of more personalized products, the customer value increases which leads to a more customer-oriented production. Consequently, a high interaction between the customer and the production is needed to acquire specific customer demands and thus achieve the highest possible customer value [20], [21].

Ultimately, the upcoming of Industry 4.0 with an increasing interconnection between customer and production will further increase the customer-oriented production approach [23]. In addition, the customer-oriented production approach is further fueled by the rise of personalized drugs in the pharmaceutical sector. Herewith, drugs are tailored based on the specific needs of individuals or a small group of patients in contrast to common drugs that are intended to treat a large group of patients [24]. Consequently, more complex and flexible manufacturing capabilities and thus production technologies are needed to adapt the current API production process to the production of personalized drugs [25].

2.1.3 Product life cycles

The second trend is a decrease of duration of product life cycles and thus production volumes. This is a result of the diversification and increasing specialization of the product range [18], [26], [23]. The interpretation of the duration of the product life cycle, is the time between the first idea and the retirement of a product [27]. Within the last 40 years, a decrease of 50% of the duration of product life cycles in the fine chemicals and pharmaceuticals has already been noticed [28].

Moreover, the pharmaceutical industry is characterized by a long time-to-market of products. The time-to-market is the duration from the first concept of a product until the first product is released onto the market [29]. This long time-to-market results from the fact that the research and development of new drugs is a time-consuming, expensive, and uncertain activity. The phases of the R&D process of drugs is shown in Figure 6 [15].

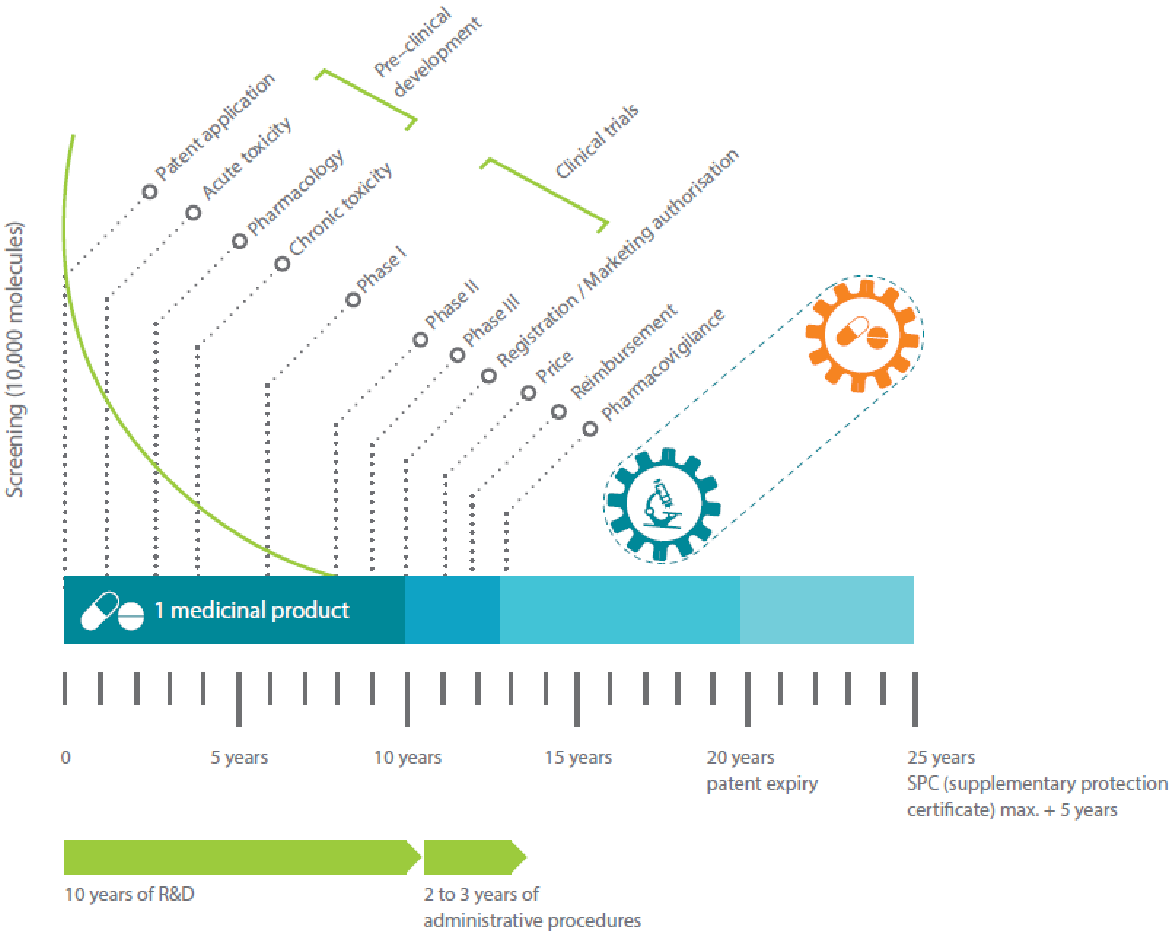


Figure 6: Phases of research and development process of new drugs [15, p. 6]

On average, 12 to 13 years of time-to market applies for drug production at which solely one or two products out of roughly 10 000 synthesized potential drug molecules will make it to the market. Consequently, high R&D costs are inherent for the research-based pharmaceutical industry. It was estimated by DiMasi et al that the average R&D cost of developing a new drug in 2014 was 1.926 million euro [30]. In addition, pharmaceutical companies have a patent term of 20 years for a newly developed drug, starting from the date the patent was filed [31]. After the patent expires, other pharmaceutical companies are allowed to produce generic forms of the drug. which result in a price-drop of the drug.

This means that pharmaceutical companies that bring newly developed product onto the market only have a small window of opportunity of approximately seven years to gain full profit of the drug and recover the high costs made during R&D phases [32].

In summary, the decrease of product life cycles and the long time-to-market of products in the pharmaceutical industry results in a decrease of the lifetime of product-specific production plants. Ultimately, this poses a risk for investment of new production capacity due to rule of thumb that the amortization period of a production plant must not exceed the lifetime of the production plants and thus the product life cycle [8].

2.1.4 Volatile markets

The last trend is partly a result of the differentiation and shorter life cycles of products, which is the emerging of volatile markets in combination with the demand uncertainty [18], [26]. The increasing volatile demand patterns result from fragile economic situations at which the higher value segments of the chemical industry, i.e., fine chemicals and pharmaceuticals, are most affected. In addition, a rising demand in developing economies, such as BRIC countries and other parts of Asia, requires the local presence of production facilities to fulfill this increasing demand [14]. Additionally**,** chemical production is increasingly becoming subject to decreasing margins and moderate growth due to fluctuations of raw material and energy prices [33]. This volatility is due to the rising interconnection of local economies caused by the globalization of the world economy. As a result, the world economy is becoming more sensitive to local crises such as the European debt crisis [14], [34].

2.1.5 Scope for future improvement

In order for the European chemical industry to compete with the increasing global competition and changing market trends, actions have to be undertaken. One action to achieve a competitive advantage is to focus on high technology products and high value engineering for which new innovative production and plant technologies are required [10], [11], [13], [35]. However, strengthening the competitive position of the European chemical industry through innovation by re-investing in current production plants encompasses a major investment risk. Therefore, it is especially important that new innovative production and plant technologies reduce the investment risk. Furthermore, the changing market trends are requiring shorter delivery and development times – in other words reduced time to market – and a flexible production set up to adapt to the more volatile markets and consumer requirements [23], [36].

An overview of the challenges, aims and methods for the present situation of the European chemical industry is produced by Bieringer et al. [23]. This overview is given in Figure 7.

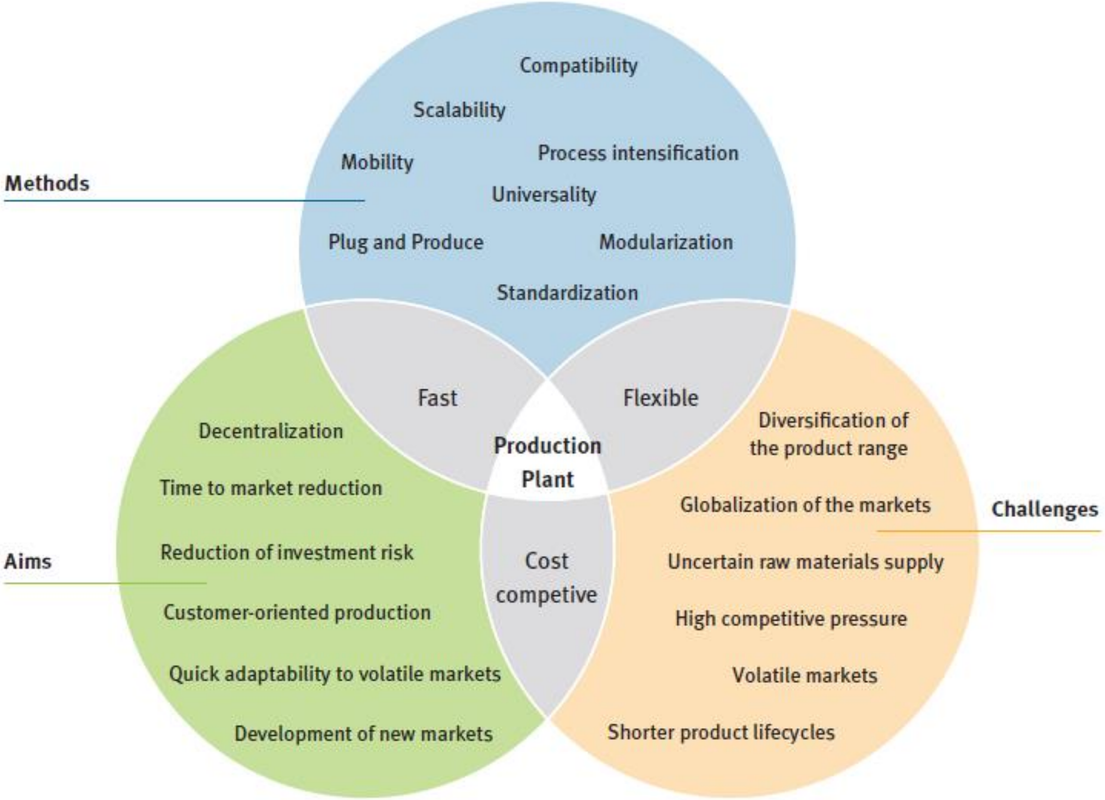


Figure 7: Methods, aims and challenges of reconfigurable production plants [37]

As can be seen in Figure 7, several potential methods to achieve the aims and overcome the imposed challenges are presented. These include the implementation of modularization into chemical production plants by creating scalable, mobile and compatible processes and hereby create universality of process components through standardization. Furthermore, intensification of process apparatus creates a new step forward into the use of innovative technology. Ultimately, it can be concluded that flexible and cost competitive development methodologies and production technologies are needed to ensure future-proof manufacturing and be a successful company within the pharmaceutical industry [23].

2.2 Types and characteristics of conventional chemical production plant concepts

In general, production plants in the chemical industry can be categorized into three fundamental types: multipurpose plants, multiproduct plants, and single-product systems plants [38].

First, multipurpose plants can be described as a system consisting of flexible elements which are mutually linkable. Therefore, the plants can produce a wide range of products with different requirements at which the production is mainly order-related and small volumes are produced. Disadvantages could arise at duration of changeovers of the plant which can be time-consuming and thus expensive [38], [39]. The duration of changeover – in other words batch changeover time – is the time needed to convert and adjust a given process between two different product batches [40].

Second, multiproduct plants can be seen as a special form of multipurpose plants at which they have the same basic lay-out but with a more product specific design [39]. Here, multiple products are produced in a set of equipment items one at a time in sequential product campaigns. The following product will be produced in the same set of equipment at which additional equipment can be connected to meet the product requirements [41]. The disadvantage of time-consuming changeover times of multipurpose plants is here not present [39]. Moreover, multipurpose and multiproduct plants are primarily operated in discontinuous batch mode.

Here, a single batch can be seen as a fixed quantity of material or product that is produced during a specific interval of time [42]. Consequently, it is simple to deal with product changes and apply various process conditions. The main downsides can be designated to long idle times during product charge and discharge, a low level of automation, and extensive heat exchanging processes. In addition, energy recovery is suboptimal and the cyclical heat exchange stresses the equipment. This results in relatively high operating costs. In conclusion, multipurpose and multiproduct plants can be inefficient regarding the use of raw material, capacity utilization and energy consumption [8], [43].

The last type of production plant concept is referred to as the single-product, single-purpose or mono system plant. Primarily, it is designed to produce only one product in large product volumes at which they are set up to continuously operate at an optimal operating point [8]. Moreover, this dedicated plant is built through a customized method with exclusively designed equipment [44]. It has advantages in terms of low idle times, uniform product quality and higher energy efficiency [8]. Nevertheless, the main disadvantage is the lack of flexibility in product range for which only limited solutions with high costs are available due to the inherent complex changeovers of the plant [38], [39], [45]. In addition, high investment costs and longer design and engineering times arise due to the nonconventional custom solutions for optimal operation and the significant size of the plant [8], [44]. As a result, a long time-to-market is inherent for the production plants [46]. In summary, single-product plants are characterized as efficient in terms of operations and inflexible in terms of product range.

In fact, the three fundamental types of production plants are each characteristic for a different branch of the chemical industry, which is illustrated in Table 1. In addition, a summary of the above-mentioned characteristics is implemented Table 1.

Table 1: Overview of the characteristics of bulk vs. fine chemical production [47]

Characteristics	Bulk chemical	Fine chemical	Pharmaceutical
Volume (tons/year)	$10^4 – 10^6$	102 – 104	$10 – 10^3$
Price ($/kg)	< 10	> 10	> 100
Added value	Low	High	Very high
Processing	Continuous	Batch-wise	Batch-wise
Plants	Single-purpose	Multi-purpose	Multi-purpose
Flexibility	Low	High	High
Safety and Environmental efforts	Relatively low	High	Relatively Higher

As can be seen in Table 1, the fine chemical and pharmaceutical sector mainly uses multi-purpose plants for production. On the contrary, continuous single-purpose plants are used for bulk chemical production [47]. In addition, each sector has differences in production volumes, product prices, added value of products, etc. [47]. At last, issues applicable to all production plant concepts are the time- and cost-consuming scaling-up strategies and lengthy planning times of the production site and additional facilities [8]. The chief outcome is that the properties of the conventional production plant concepts will no longer meet the previously described requirements of the market [8], [48]. As a result, innovative production plant concepts are needed that combine flexibility and efficiency, can be applied quickly and thus can follow the emerging volatile markets with a more specialized product range [8]. More specifically for the pharmaceutical sector, existing production plants and supply chains have to be adapted to be more efficient and flexible which is especially difficult for research-driven pharmaceutical enterprises resulting from the complicated interrelation between operational problems, capacity planning and risk management of new drug development [49], [50].

2.3 Modular plant concepts

One of the most promising approaches to achieve efficiency and flexibility in a chemical production plant is by applying modular concepts to the design of the plant [51]. The basic concept of modularization is based on the general idea to decompose a complex system into simple components with well-defined interconnections. The components are rearrangeable and form altogether a new configurable process [35]. Modularization is already widely applied in equipment and instrument production industries for instance automotive, electronics and aviation industry [52], [53]. To date, the concept of modularization is seldom implemented into chemical production plants [54]. However, modular plants are placed first in the list of top five trends by the world forum of the process industries ACHEMA [55]. Therefore, it can be concluded that modular plant concepts are becoming of particular interest in the chemical and pharmaceutical industry [13].

2.3.1 Advanced vision of modular plant concepts

An advanced vision of modular plant concepts can be pursued by building a new production plant from the ground up and applying modularization to all three levels of production: process apparatuses, plants and logistics. This enables three main types of manufacturing flexibility: volume flexibility, process flexibility and location flexibility [56], [57]. This principal is illustrated in Figure 8.

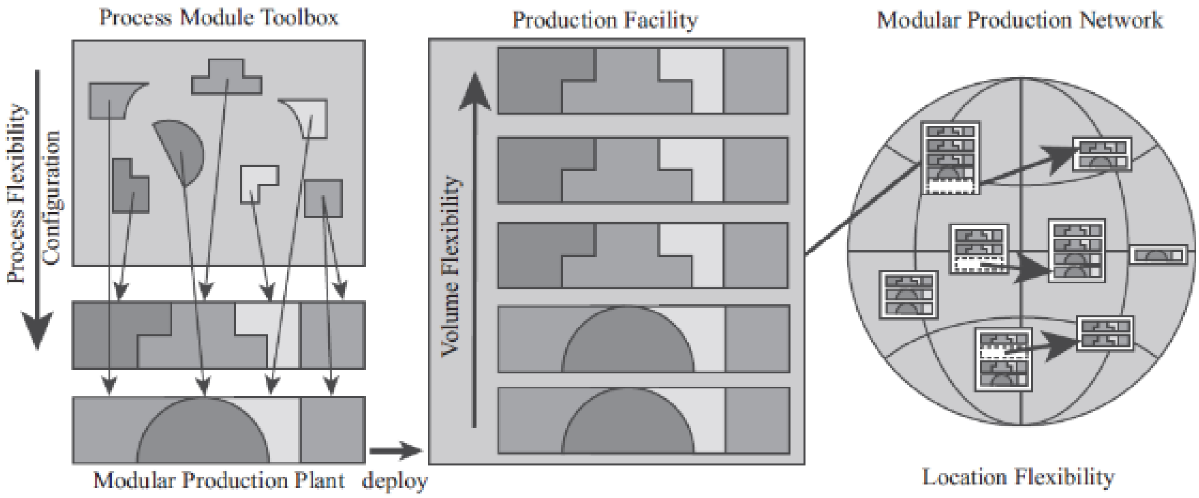


Figure 8: Schematic overview of modularization on all levels of the production network [57, p. 958]

First, individual process modules can be selected from an available process module toolbox and configurated to form a modular production plant. The modular process modules comprise of process equipment with standardized interfaces. Characteristic to this advanced vision is that a modular plant is assembled into transportation containers [57]. This is similar to the modular plant concepts of the F^3-factory project [58]. It is inherent to this modular concept to have the ability to adjust existing production plants during the planning horizon of production. This ability is defined as process flexibility. This can be done through altering production plants by exchange, removal and addition of process modules and thus create production plants with different production capabilities and capacities. As a result, the quantity of feasible products can be adjusted [57]. The process flexibility is dependent of the different possible combinations of process modules and thus depends on the different process modules which are available at the plant [8].

Second, different combinations of modular production plants are then combined and installed together to create a production facility with a specific capacity.

At this level, modular design enables flexibility in terms of volume, which can be seen as the possibility of the capacity of existing facilities to be started up, deactivated, reactivated and the opportunity to expand and contract this capacity. In general, this can be done by adjusting the number of production plants and thus the production volume or production capacity. In the literature, this is frequently defined as modular capacity [57].

Lastly, the modular production network comprises of various production facilities which consist of different compositions of modular production plants. In general, the modules represent the lowest level of production entity in the modular product network and the production facilities the highest level [57]. Moreover, the different levels are characterized by a mutually dependency. For example, the full potential and advantage of modular equipment can only be realized together with modular plants and contrariwise [8]. Consequently, the multiple levels of modularization provide different degrees of flexibility in the tactical planning of the modular production network.

The last flexibility that is enabled by modular design in the production network is location flexibility. This is the ability to relocate and exchange modular production plants between different production facilities. This results in the opportunity to relocate available production capabilities and capacities on a tactical decision level or in the ideal case even locate whole production facilities in close proximity to customers or suppliers [57]. The modular production plants enable great tactical flexibility of production in comparison to centralized production of conventional large-scale plants [57]. The principal through which production facilities are geographically dispersed is known as a decentralized production network [57]. A comparison between centralized and decentralized production networks is illustrated in Figure 9.

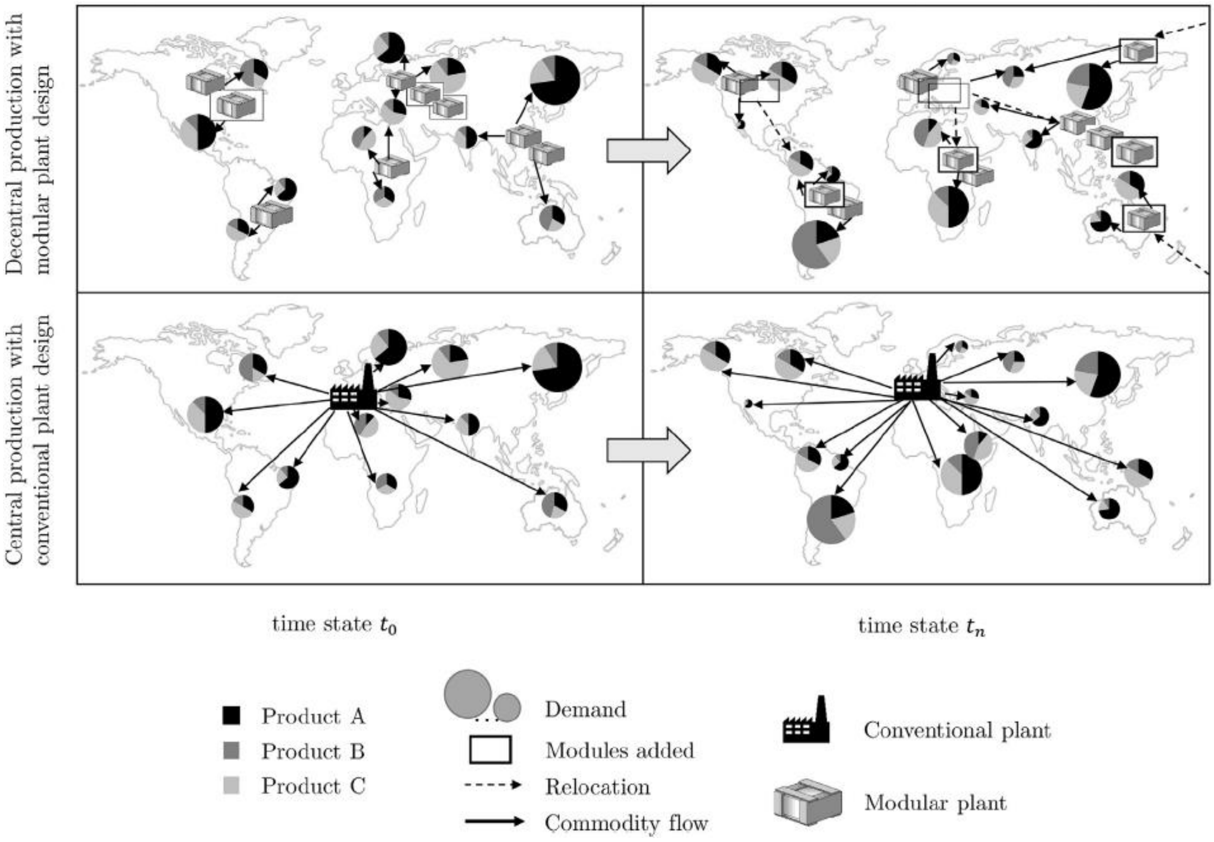


Figure 9: Differences in flexibility of conventional and modular production networks [57, p. 959]

First, a high degree of decentralization in combination with the utilization of a large number of modular plants is present in the modular production network during the state t_0. After a certain period of time t_n, changes in product demand have arisen by which the modular production network responds with a number of relocations of modular plant. In general, it can be concluded from Figure 9 that a modular production network diverges radically from a conventional plant network in terms of structure and flexibility. Hereby, it is important to mention that dedicated planning models are needed to support tactical planning of modular production networks for decision-making in terms of number, type of production plant and location [57].

Ideally, this facilitates that modular production plants can be located in close proximity to the customer and other resources such as raw material and energy suppliers. This allows for a rapid adaptation of the production to the customer requirements, a reduction in material flow within the network, a reduction in transportation costs, a greater availability of resources and a lower energy cost [43], [13], [57], [8]. Furthermore, decentralization enables just-in-time production which can lead to lean production, a reduction of inventory levels and thus faster fast response times to customer inquiries. In addition, modular plants facilitate the production of more customized products in combination with lower production volumes and thus leading to a higher customer orientated production [8], [57].

In conclusion, modular production networks represent a competitive advantage for the new upcoming differentiation and volatile markets through their high level of customer orientation [59]. As a result, changes in markets can pursued geographically as well as in time [8]. Furthermore, the most substantial issue concerning the implementation of the advanced vision of the modularization concept is that almost every step of the planning and design of a chemical production facility is affected [23]. This results from the aspect that the advanced modular vision radically diverges from the conventional plant concept [8]. Here, the advanced vision is solely given as an informative visualization of the full capabilities of the implementation of modular concepts on all levels of production.

2.3.2 Modularization at equipment level

For the specific case of Janssen that concerns the implementation of modular concepts into the reactor setups of the glass-lined reactors, the advanced vision of modular plant concepts is far beyond the scope. A more entry-level modularization applicable to Janssen is the modularization at the process apparatuses level, i.e., modular equipment.

In order to apply modularization into an existing plant process, a detailed analysis of the process is necessary. As previously mentioned, modularization is based on the general idea to decompose a complex system into simple components with well-defined interconnections [35]. To illustrate this concept, the modularization of a fictional, conventional chemical process is given in Figure 10.

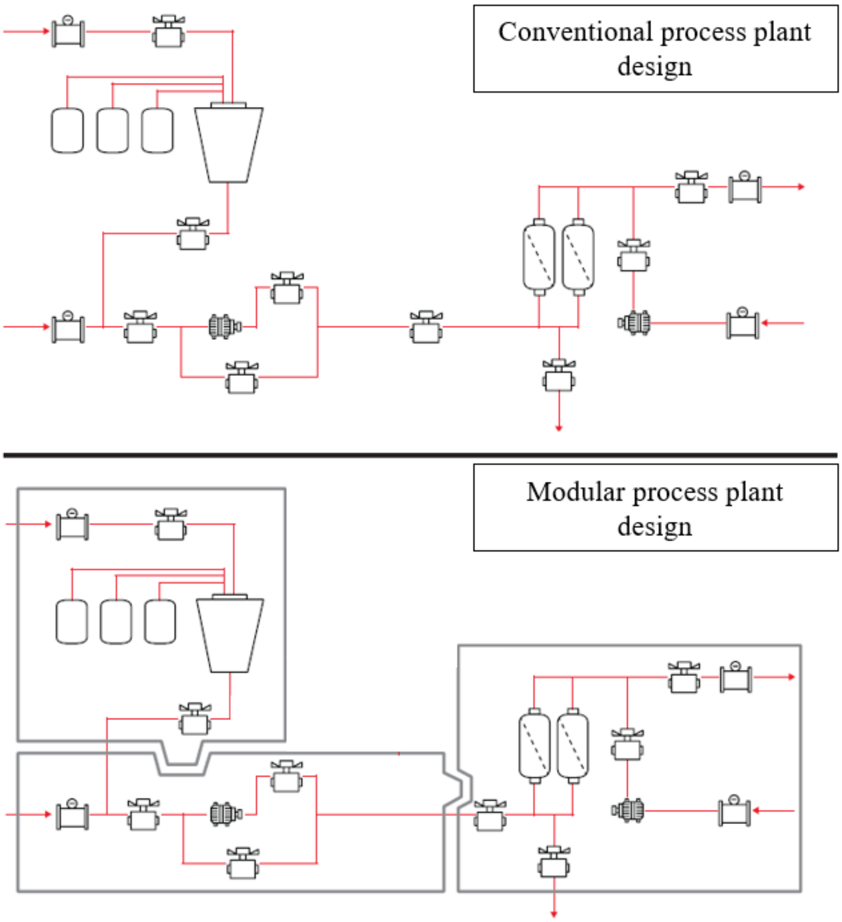


Figure 10: Concept of modularization at equipment level of a fictional plant concept [60, p. 5]

First, all plant components have to be analyzed concerning their function in the process and their relationship with each other. After this, components can be divided into assignable functional groups which embody the fundamental steps – in other words unit operations – of the process, e.g., reaction, separation, purification, mixing or storage. The functional groups are called the modules in the modular nomenclature. The classification criteria by which the modules are grouped always remains the same [35]. Furthermore, the size of the modules is determined by the scope of the project. It is inherent to modular design that the modules can be detached from the rest of the plant without having any influence on their group functionality. This is referred to as 'Plug-and-Produce'.

Moreover, various concepts of modules are already used in the process in the form of skids that are manufactured at the equipment manufacturer's facility and transported and integrated into the customers plant infrastructure [14]. While the concept of modules is thus not state of the art, it remains a central issue within modular engineering due to the lack of a generally accepted definition of a module [61].

Within the modular concept, the interpretation of modules being a segment of the plant is extended to the idea that a module itself can consist of smaller modular equipment that in turn consists of even smaller modular components. In literature, various interpretations of a module in modular concepts are described. A summary of the interpretations is given in Table 2.

Table 2: Different interpretations of modules in modular concepts

Definition of modular modules	Research project or author
Mobile unit	Jameson [62]
Main equipment item including its local pipe installation	Burdorf et al. [63]
A mobile ISO container equipped with standardized connectors, process equipment designed as sub-modules fitting into the ISO container structure, and a fixed backbone facility that supplies auxiliary utilities and services.	F^3-factory [58]

From Table 2, a general trend of increasing detailing of the definition of modular modules can be noticed. In order to implement modularization into a process, it is necessary to find an appropriate definition of a module for a given project. Nevertheless, most definitions of a module are not suitable for the specific case of this research because they approach a module as being a main equipment with auxiliary apparatuses covering a unit operation, such as a whole reactor equipped with a reflux system, heating and cooling system, etc. A more detailed approach is proposed by Uzuner in a Table 3 [64].

Table 3: Aggregation levels of a modular process and plant hierarchy proposed by Uzuner [64]

Process Hierarchy	Plant Hierarchy
Process	Plant Module
Unit Operation	Plant Section Module
Unit Function Element of Unit Function	Equipment-Module Building Group or Part Module
Sub-Element of Unit Function	Sub-Building Group or Building Group for Part Module

In this approach, the embodiment of a unit operation is encapsulated in a plant section module. This is for example the realization of a reaction task in a reactor module equipped with condensers, heating and cooling system, agitator, pressure control, etc. One level below the unit operation the unit function of a process is situated. Here, the unit function can be seen as solely the reactor and is defined as an equipment module. To Uzuner's accordance, equipment modules are modules with an identical functional range. This aggregation level can be used to describe less complex functions, e.g., pressure control, heat exchangers, condensers or other auxiliary components. [64], [65]. Consequently, this definition of a module is applicable to the modularization of the reactors and the connected equipment at Janssen.

2.4 Advantages of modular equipment concepts

2.4.1 Flexible and efficient equipment utilization

The main advantage of modular equipment is that it enables simple and fast exchangeability of individual modular equipment units through the ‘Plug-and-Produce’ method. Consequently, the high exchangeability of modular equipment allows the more efficient use of equipment and thus results in a higher equipment utilization [8].

2.4.2 Reduction of project schedule time

A distinct advantage of modular equipment over conventional static process equipment is the capability of modular equipment to be easily prefabricated at the facility of the equipment manufacturer in a controlled fabrication environment at which all necessary components for equipment construction are available [18], [66], [67]. This eliminates construction inhibition due to work permits or waiting for construction materials and equipment. Moreover, interruption of the plant site is minimalized as a result of off-site prefabrication of modular equipment. More specific, it reduces potential hazards and safety risks associated with field construction activities of construction contractors. Furthermore, for projects that cover construction of new equipment in an existing chemical production facility of the customer, prefabrication of modular equipment minimizes production interruption – in other words downtime or shutdown – of adjacent production processes. As mentioned above, this downtime is caused due to safety precautions for potential hazards and safety risks of nearby construction activities. The statements mentioned above results from the inherent ‘Plug-and-produce’ feature of modular equipment which enables fast installation of the modular equipment on the chemical production facility of the customer [13], [66], [67].

In summary, modular equipment reduces the scheduled time of construction projects which result in a shorter time-to-market due to the faster construction and implementation of the modular equipment in the customer’s production facility and minimization of production shutdown [66]. Consequently, a reduction of costs related to production shutdown and the faster financial gain due to an earlier production start-up of the installed modular equipment create a financial advantage for modular equipment projects in comparison to static equipment projects [13].

2.5 Gaps and challenges for a modular approach

Beside all the advantages, there are still various business challenges and technology gaps in order to successfully implement modular equipment concepts into the chemical and pharmaceutical industry.

2.5.1 Standard interfaces for process control and automation

The first major challenge of modular units is the engineering of automation and process control for process modules in production facilities. This is because the implementation of modularization would involve significate changes in comparison to the fixed distribution structure of conventional process control systems [68], [69]. Moreover, the objective of modular equipment and production modules is to be used following a Plug-and-Produce method. Therefore, it is necessary that the control system is compatible with the Plug-and-Produce system and is able to communicate independently with an individual module. Furthermore, the simplicity of this method is of great importance because it would otherwise require specialized employees [68].

To present day, the foremost problems which obstruct the exchangeability of modules through a Plug-and-Produce method are the lack of acceptance of the process control systems for the automation of modular units and the lack of standard interfaces from the module to the control system. This means that control systems of current plants are not prepared for the implementation of modular modules [68]. A proposed solution in literature that could deliver the necessity of flexibility and stability is structured peer-to-peer architecture. However, a standard that accounts for automation has thus far not been developed [69].

2.5.2 Development of modular equipment modules

Another major challenge for modularization is the development of modular equipment for flexibility. As it is the intention to exchange modular equipment between different unit processes, equipment modules should have a wide operating window to offer their flexible usage. This is contrary to the design of conventional static equipment that is mostly tailor-made and optimized for a specific process and thus has a single operating point within a narrow operating window. Consequently, a parallel numbering-up strategy would be necessary to enlarge the operating window in case equipment modules are used with narrow operating window. Hence, equipment modules with a large operating window have to be developed to avoid the inefficient use of multiple equipment modules in parallel [70].

2.5.3 Business Models and Product Service Systems

As modular concepts in the chemical industry are state of the art, new business and service models are needed. These are needed to determine the most appropriate modular plant design to meet the requirements of the customer [23]. Furthermore, a possible business model and product service has been proposed by Lier et al. [71]. As a result of the implementation of modular equipment into process plants, an opportunity is created for a provider that could offers physical modules in combination with module services. A proposed business model for this provider is the rental or leasing of the modules with corresponding services such as maintenance, replacement, construction and dismantling. This business model is further supported by the inherent scale-up strategy for capacity adjustment of modular production plants at which numerous modules are used and exchanged [8].

2.6 Conclusion of literature and reflection on current situation at Janssen

It can be concluded from the literature that the implementation of modularization into the reactor setups of the nine glass-lined reactors at the site in Geel will be a hybrid solution of a modular concept in which mainly the equipment of the reactor will be modularized and the static reactor will be preserved.

This will require an in-depth analysis of the functions of the equipment attached to the reactor and the relations between them. Furthermore, the existing production process will become more flexible due to the convenient exchange of modular equipment through the ‘Plug-and-Produce’ methodology. In theory, this makes it possible to use the equipment more efficiently in comparison to static equipment. From a financial point of view, this would result in a lower investment cost because possible less equipment modules are needed to replace the static equipment. However, the financial point of view is not the most important driver to implement modularization.

In short, the most substantial driver is that the exchangeability of modular equipment increases the allowance to adapt the production process more flexible and introduce new equipment technologies to achieve more complex production capabilities in future. Ultimately, this facilitates the creation of a future-proof production plant of Janssen in Geel that is able to adapt to the increasing market competitions and upcoming trends such as the rise of personalized drugs in the pharmaceutical sector.

3 Materials and methods

First, the basic structure of the reactor operating system is explained. Afterwards, the used method of the data extraction and analysis is presented. Moreover, the used method for the data extraction and analysis is applied by default to the extracted data of all nine reactors of the three bays in Excel. Hence, displaying the used method with all the data would imply nine extensive data tables with an average of 4000 rows per data table. Therefore, it is opted that the used method is described by means of an elaboration of the method on a small amount of example data.

3.1 The reactor operating system

The operating system of the batch reactors at Janssen follows the ANSI/ISA S88 batch process control standard. The S88 is an international standards and terminology for batch control at which it mainly strives to serve as a design philosophy for product procedures and equipment of batch processes. The S88 concept is based on the key principle that the product-dependent production procedure is separated from the equipment-depend control system by utilization four main models: the process model, the physical model, the procedural control model, and the activity model [72].

The process model describes the activities of the chemical and physical modifications of the raw materials into the desired product. Important to mention is that it does not include the concept of equipment. Furthermore, the physical model divides the process plant into sections of hardware with a hierarchic structure. In this structure, the plant is defined as the process cell that is broken down into smaller process units. Moreover, the process units are segmented into smaller equipment modules (EM's) and control modules. The equipment modules are each capable of performing a single function in the process or in other words a minor process activity. Hereby, the control modules mainly consist out of pumps, valves and meters. In brief, the physical model describes the equipment used to perform the process in which the batch reactor is considered as a process unit and the required process functionality is covered at the level of the equipment modules [72]. To illustrate this model, an example of a physical module of a glass-lined batch reactor is given in Figure 11.

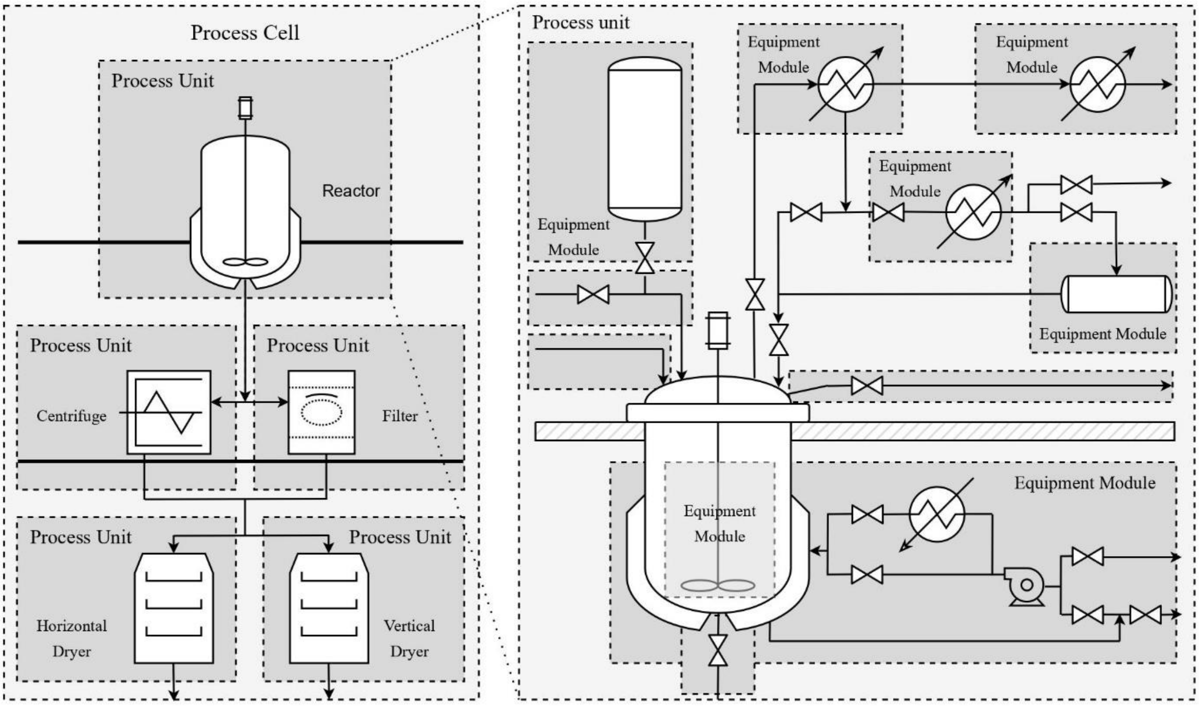


Figure 11: Example of a physical module in the ANSI/ISA S88 batch process control standard

Subsequently, the method to produce a specific product in the available equipment is defined in the procedural control model which is linked with the physical model and process model. In this model, a similar hierarchy is present. First, the procedure to make a specific product consists of unit procedures which are linked to the used process units. In turn, the unit procedure can be divided into smaller parts which are defined as operations. Finally, the operations can be divided into phases. As a result, a hierarchy within the procedure is created that shows the general and detailed links in the process [72]. To illustrate this principle, a fictional example of a PFC (Procedural Function Chart) applicable to the operating system of the glass-lined reactors at Janssen is shown Figure 13.

At last, it can be noted that a closely linked relation between the physical model and the procedural control is present. This relationship is given in Figure 12.

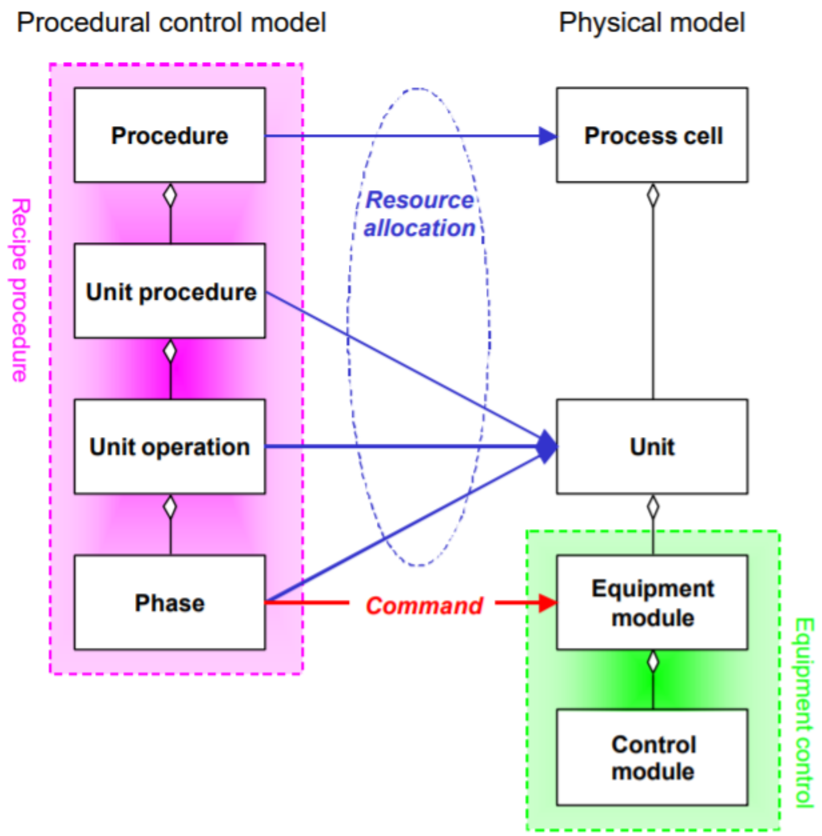


Figure 12: Relation between the procedural model and the physical model [72, p. 12]

In this relationship, the behavior of equipment control is specific in the process cell. These are for example agitation, temperature control and liquid transfer. As mentioned before, the procedural control model contains the description of the production procedure which is called the recipe procedure. Within the recipe procedure, phases are used to command the state of the equipment modules, i.e., define setpoints and select basic control sequences in the equipment modules. In addition, it is possible that multiple equipment modules are needed to perform a certain phase [72].

Ultimately, it is opted to perform the data extraction and analysis in the upcoming subchapter on the level of phases because it is the lowest level of the operational records and it is directly linked to the used equipment modules of the reactor. However, this creates a high level of detail which increases the complexity of the data analysis to analyze overlying processes.

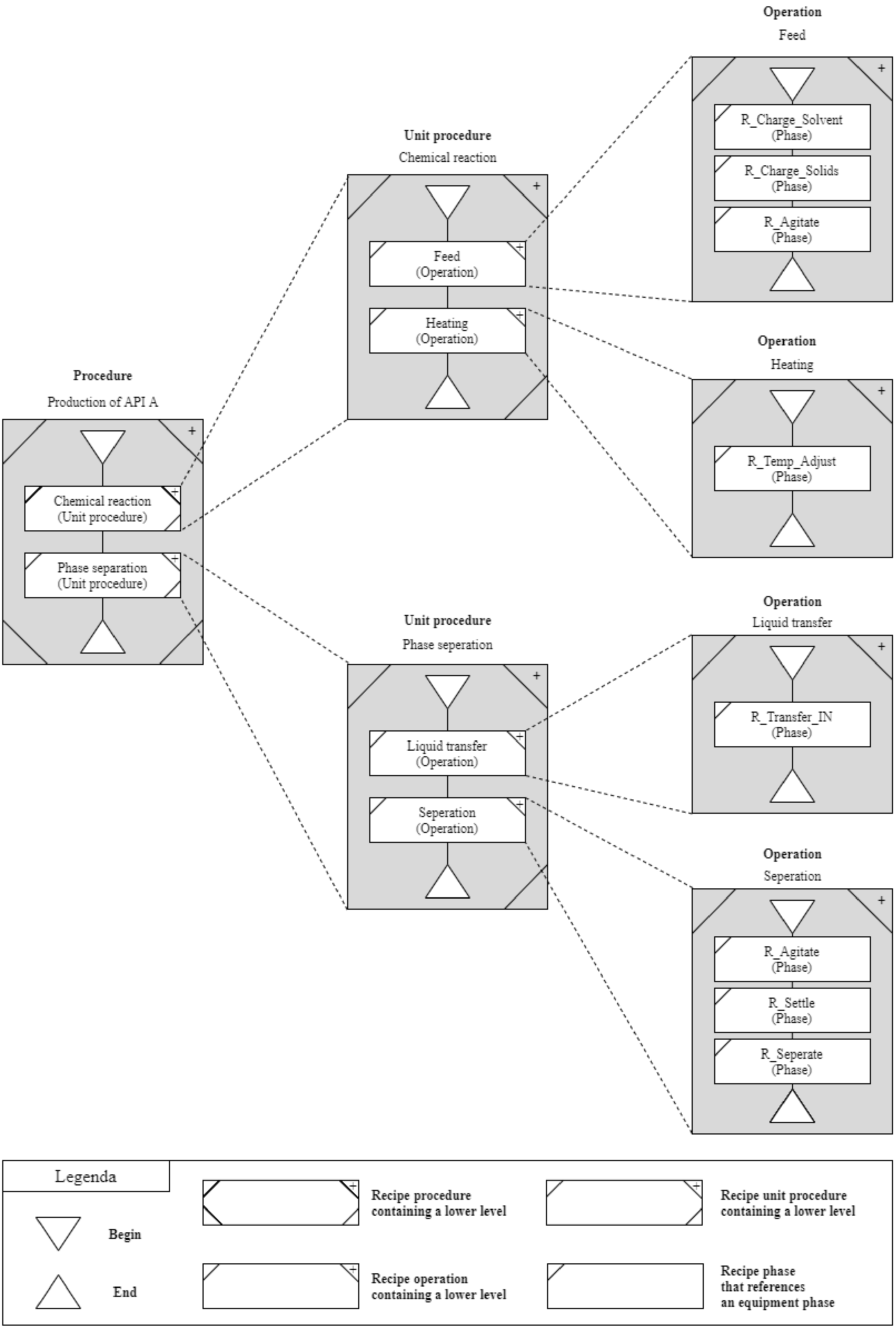


Figure 13: An example of a PFC of a fictional production procedure of an API [72], [73]

The specific reactor phases that are present within the operating system of the glass-lined reactor of Janssen are shown in Table 4.

Table 4: Reactor phases and their corresponding physical actions

Phase	Process Action
R_CHARGE_SOLV	Charging liquids into the reactor from any container
R_CHARGE_SOLIDS	Adding solids into the reactor
R_CHARGE_RT_CND	Dosing to reactor via dosing tank or via mobile dosing tank or container
R_TEMP_ADJUST	Start temperature control, change command, change set point, change alarm limits
R_AGITATE	Start agitator, change agitator set point, optionally with nitrogen flow
R_INERT	Inertizing reactor with nitrogen flow
R_AERATE	Aerating reactor with oxygen flow
R_LEAKCHECK	Performing leak test under pressure or under vacuum
R_SETTLE	Allowing reactor contents to settle for a defined period of time
R_SAMPLE	Sampling from reactor, optionally via bottom tap
R_TRANSFER_IN	Filling of reactor from another reactor or receiver through bottom or top valve
R_TRANSFER_OUT	Draining reactor content to any destination, filtering, decomposing
R_SEPARATE	Separation of reactor contents to any destination
R_RECIRC	Circulating reactor content over reactor via e.g., a high shear mill or a plate filter
R_DISTILL	Distilling reactor content over water separator or to another receiver
R_REFLUX	Refluxing reactor content
R_SETUP	Preparing device at start and end of batch
R_CLEAN	Cleaning of reactor
R_CLEANING_RELEASE	Release of all individual components of EM's during cleaning
R_PROMPT	Sending out a question to the operator to make a decision
R_DECISION	Taking a reactor decision
R_RELEASE	Release of reactor

The phases of Table 4 are further used and examined in the data-analysis of the operational records in the upcoming subchapter.

3.2 Data extraction from the reactor operating system

The extracted data consists of the operating records on the level of phases of the nine glass-lined reactors from 2020. An example of the extracted data is given in Table 5. Hereby, a sequence of three chronological records is each cut out from the original data file of reactor R022 of 2020 at which each row represents one record of the executed phase of the reactor at a specific moment. It is important to mentioned that the four sequences of three chronological records do not correspond with the original data sequence because they are each cut out from the original data to give a decent representation of the used method with a greater variety of results. This is done because only a small amount of data can be used for this brief representation of the used method.

Table 5: Example of the extracted reactor operating records of reactor R022 in 2020

Reactor Phase	Start time (Date + hh:mm:ss)	End time (Date + hh:mm:ss)	Duration (hh:mm:ss)	Event path
R_CHARGE_SOLV:1-1	10-01-20 21:35:33	10-01-20 21:51:07	0:15:35	[RT001202G3-08_0007_20718302_I20AB0192_1]\UP_RT001202G308_R1:1-1\OP_R_CHARGE_SOLV_VACUUM_NKC:3-1
R_INERT:1-1	10-01-20 21:51:08	10-01-20 22:03:46	0:12:39	[RT001202G3-08_0007_20718302_I20AB0192_1]\UP_RT001202G308_R1:1-1\OP_R_INERT:2-1
R_CHARGE_SOLIDS:1-1	10-01-20 22:03:47	11-01-20 08:55:45	10:51:58	[RT001202G3-08_0007_20718302_I20AB0192_1]\UP_RT001202G308_R1:1-1\OP_R_CHARGE_SOLIDS:1-1
R_DISTILL:1-1	02-03-20 02:45:51	02-03-20 03:14:30	0:28:39	[RT003854G3-01_0002_20727120_I20CD0836_1]\UP_RT003854G301_R1:1-1\OP_R_DISTILL_VACUUM_RECEIVER_JACKT:1-1
R_DISTILL:1-1	02-03-20 03:14:30	02-03-20 10:20:26	7:05:56	[RT003854G3-01_0002_20727120_I20CD0836_1]\UP_RT003854G301_R1:1-1\OP_R_DISTILL_VACUUM_RECEIVER_DELTA:1-1
R_TEMP_ADJUST:1-1	02-03-20 10:20:26	02-03-20 10:21:25	0:00:59	[RT003854G3-01_0002_20727120_I20CD0836_1]\UP_RT003854G301_R1:1-1\OP_R_TEMP_ADJUST_IDLE:2-1
R_SETTLE:1-1	06-04-20 17:18:00	06-04-20 18:32:38	1:14:38	[RT003066G3-04_0015_20732167_I20DB1273_1]\UP_RT003066G304_R1:1-1\OP_R_SETTLE:1-1
R_SEPARATE:1-1	06-04-20 18:32:38	06-04-20 19:48:38	1:16:00	[RT003066G3-04_0015_20732167_I20DB1273_1]\UP_RT003066G304_R1:1-1\OP_R_SEPARATE:1-1
R_AGITATE:1-1	06-04-20 19:48:38	06-04-20 19:51:39	0:03:01	[RT003066G3-04_0015_20732167_I20DB1273_1]\UP_RT003066G304_R1:1-1\OP_R_AGITATE:10-1
R_REFLUX:1-1	28-05-20 11:09:51	28-05-20 11:48:27	0:38:36	[SU220002G3-01_0000_20739966_CLEANING_1]\UP_SU220002G301_R1:1-1\OP_R_REFLUX_DELTA_T:1-1
R_TEMP_ADJUST:1-1	28-05-20 11:48:27	28-05-20 11:54:24	0:05:57	[SU220002G3-01_0000_20739966_CLEANING_1]\UP_SU220002G301_R1:1-1\OP_R_TEMP_ADJUST_DELTA_T:1-1
R_REFLUX:1-1	28-05-20 11:54:24	28-05-20 12:37:49	0:43:25	[SU220002G301_0000_20739966_CLEANING_1]\UP_SU220002G301_R1:1-1\OP_R_REFLUX_DELTA_T:2-1

The first column contains the executed phases of the reactor operating system. The following columns contain respectively the start and end time, the duration, and the event path of the executed phases. Moreover, the event path is a code that consists of the unit procedure, the batch number, the reactor's recipe number and operation. An example of the composition of the event path is given in Figure 14.

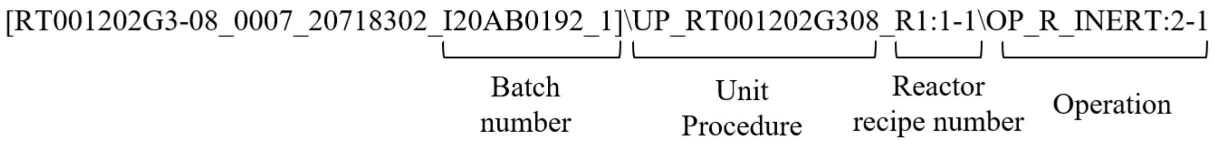


Figure 14: The composition of the information in the event path

From each row of the data, the batch number, unit procedure and reactor recipe number were extracted from the event path to separate columns through a combined function in Excel. Furthermore, a final column was added in which the unit procedure of each record was analyzed and categorized as productive, cleaning or other. Here, productive is seen as the state of the reactor that is processing the API or intermediate, or other steps that are directly related to the production of the API or intermediate. Moreover, the cleaning state is seen as the physical cleaning of the reactor or attached equipment at which the reactor is not available for production related steps of the API or intermediate. Finally, the 'other' category consists of events such as tests of the reactor, maintenance or special storage of compounds.

The function that is used in Excel for the categorization searches for specific text strings in the code of the event path that is linked to one of the defined categories that is mentioned above. The specific text strings are given in Table 6.

Table 6: Defined time allocation categories and their corresponding text strings in the event path

Category	Text string in event path
Productive	RT, RR, ZR, HT
Cleaning	SU, VR, reinigen
Other	TEST, UNDEFINED, STOCKAGE, AFSLINGEREN

In addition, a column is added in which the idle time of the reactor is calculated by formula (1).

$$Idle\ time\ (n) = End\ time\ at\ timepoint\ (n) - Start\ time\ at\ timepoint\ (n+1) \tag{1}$$

The idle time is calculated by the subtraction of the end and start time of two consecutive records. In Table 7, the result of applying the categorization, batch number subtraction and idle time calculation to the example data of Table 5 is given.

Table 7: Extraction, categorization and calculation of idle time of example records of reactor R022

Batch number	Unit procedure	State of reactor	Idle time (hh:mm:ss)
I20AB0192	RT001202G308	Productive	0:00:01
I20AB0192	RT001202G308	Productive	0:00:01
I20AB0192	RT001202G308	Productive	1217:50:06
I20CD0836	RT003854G301	Productive	0:00:00
I20CD0836	RT003854G301	Productive	0:00:00
I20CD0836	RT003854G301	Productive	846:56:35
I20DB1273	RT003066G304	Productive	0:00:00
I20DB1273	RT003066G304	Productive	0:00:00
I20DB1273	RT003066G304	Productive	1239:18:12
Cleaning	SU220002G301	Cleaning	0:00:00
Cleaning	SU220002G301	Cleaning	0:00:00
Cleaning	SU220002G301	Cleaning	0:00:01

In Table 7 above, the latter mentioned extracted information is visible per data point. From the column of the idle time, it can be seen that small idle times are present during the execution of phases of a unit procedure for a specific batch number. Moreover, it can be deducted that larger idle times are present between the changeover of two consecutive batch numbers. The presence of large changeover times, in this context idle times, for multipurpose batch reactor plants is mentioned in section 2.2. However, the large idle times in Table 7 do not correspond with actual idle times in the original data file because the data is cut out from the original data to give a decent representation of the used method. Nevertheless, the actual larger idle times between batch changeovers are in the range of several to 20 hours with some exceptions within the range of approximately 20 to 1000 hours. In general, the evaluation of the idle time gives an overall understanding of the global time allocation of the reactors as it is not in the scope of this research to conduct an in-depth investigation of the productivity of the reactors. Ultimately, the data of Table 5 and Table 7 used for further data-analysis in the upcoming section of this research.

3.3 Data analysis of the reactor data

3.3.1 Global time allocation of reactors

A global time allocation is made from the extracted data of the reactor.

First, a calculation is performed of the total time duration of the categories of Table 6 in the reactor, i.e., productive, cleaning or other. In order to conduct this calculation, following function in excel is used which is presented in formula (2).

$$SUMIFS(sum\_range; criterion\_range; criterion1\ [criterion\_range2, criterion2], \dots) \tag{2}$$

The Sumifs-function makes a summation of all the values in the sum range that meet the single or multiple specified criteria in the corresponding criteria range. Moreover, the function is used as follows for the de time allocation in the reactor of the categories: productive, cleaning and other.

$$SUMIFS(duration\ column; state\ of\ reactor\ column; category\ (productive, cleaning\ or\ other))$$

Here, the function makes a summation of all the rows of the column duration of Table 5 for the cases that the state the reactor in Table 5 is assigned as productive, cleaning or other. Consequently, this yields the duration per category.

Second, the total idle time of the reactor is calculated. Here, a distinction is made between the usable and non-usable idle time. The usable idle time is calculated with following formula (3).

$$SUMIF(range, criterion, [sum\_range]) \tag{3}$$

The Sumif-function makes a summation of the values in a range that meet a specified criterion. In addition, a supplementary summation range can be specified and used. Applying this function to determine the usable idle time gives following formula.

$$SUMIF(idle\ time\ column; idle\ time \geq mean\ time\ of\ batch\ in\ reactor)$$

As a result, all idle times in the idle time-column of Table 7 that are greater than the mean batch time in the batch reactor are summed. Within the context of this thesis, the usable idle times responds to the larger idle times that could be used for potential production optimization as it is theoretically possible to produce another batch with a batch time equal to the mean batch time. Moreover, the mean batch time of each reactor is calculated by taking the average of the duration of all batches excluding the idles times and cleaning. The method of calculation of the mean batch time in each reactor is not given because it is of minor importance.

Furthermore, non-usable idle time responds to relatively small idle times, several minutes to hours, that are smaller than the mean batch time of the reactor. This is calculated with formula (4).

$$SUM(idle\ time) - SUMIF(idle\ time; idle\ time \geq mean\ time\ of\ batch\ in\ reactor) \tag{4}$$

In this formula, the non-usable idle time is calculated by subtraction of the total summation of the 'idle time'-column minus the summation of the usable idle time.

In summary, a visualization of the method of the global time allocation of a reactor is applied to the real dataset of reactor R022. This is given in Table 8.

Table 8: An example of the used method of time allocation of the reactor applied to reactor R022

Reactor activity	Duration (hh:mm:ss)	Duration (%)
Productive	3182:56:32	36,24
Cleaning	1224:49:08	13,95
Other	0:24:50	0,00
Usable Idle time	3403:10:37	38,75
Non-usable idle time	971:38:52	11,06
Total time spend over 1 year	8782:59:59	100,00

In Table 8, the absolute duration and percentual duration of the reactor activities are given. Through this method, a brief overview of the global time allocation of the reactor is made which is applied to all nine reactors in the excel-file.

3.3.2 Duration and frequency of operational phases in a reactor

A second part of this data-analysis consists of the determination of the duration and frequency of executions of the phases by the reactor operating system for each reactor during the year 2020. An example of this mapping is given in Table 9. This table originated from the real data in the Excel file of reactor R022 during one year of operation because applying the method to the example data of Table 5 would not give a complete representation of the used method.

Table 9: Example of mapping duration and frequency of all phases of a reactor for one year

Phase	Frequency of executions	Absolute duration (hh:mm:ss)	Relative duration (%)
R_CHARGE_SOLV	327	290:28:32	6.59
R_CHARGE_SOLIDS	45	58:58:36	1.26
R_CHARGE_RT_CND	103	82:57:06	1.78
R_TEMP_ADJUST	478	244:17:49	5.24
R_AGITATE	423	199:45:47	4.28
R_INERT	174	54:43:34	1.17
R_AERATE	10	13:52:59	0.30
R_LEAKCHECK	25	15:27:07	0.33
R_SETTLE	51	93:02:39	2.00
R_SAMPLE	33	44:22:05	0.95
R_TRANSFER_OUT	282	753:20:22	16.15
R_TRANSFER_IN	73	214:48:52	4.61
R_SEPARATE	46	32:17:21	0.69
R_RECIRC	0	0:00:00	0.00
R_DISTILL	177	375:56:52	8.06
R_REFLUX	45	40:23:17	0.87
R_SETUP	110	1:30:54	0.03
R_CLEAN	66	927:45:59	19.89
R_CLEANING_RELEASE	41	255:32:38	5.48
R_PROMPT	200	580:08:29	12.44
R_DECISION	391	382:02:30	8.19
R_RELEASE	71	1:59:39	0.04
Sum	3171	4663:43:08	100.00

Firstly, the frequency of executions of the phases is determined by formula (5) in Excel.

$$COUNTIF(range; criterion) \tag{5}$$

The Countif-function counts the number of cells that meet a specified criterion. To determine the frequency of executions, the function is used as follows.

$$COUNTIF(Phase\ record\ column\ of\ one\ reactor\ ; specific\ Phase)$$

Here, the applied function evaluates each record of the phase-column of a complete dataset of one reactor in Excel which is similar to brief example of the phase-column in Table 5. Subsequently, the function then counts all phase records that contain equal the inserted phase of Table 9. Consequently, the total frequency of executions of one specific phase is calculated for the specific reactor for one year of operation. Applying this to all phases results in the ‘frequency of executions’-column in Table 9.

Secondly, the absolute duration of each phase is calculated. This is done through the Sumsifs-function that is previously explained in formula (2), which is applied as follows.

$$SUMIFS(phase\ duration\ column\ of\ one\ reactor; phase\ record\ column\ of\ one\ reactor; specific\ phase)$$

The applied function makes a summation of the phase duration cells of one reactor by evaluating if the corresponding phase in the phase column of the reactor is equal to the inputted, specific phase in the function. As a result, a summation of the duration of each specific phase is made. This is represented as the absolute duration of the phase in Table 9 which is referred to as the total operating time of the reactor. In addition, the relative duration of each phase is calculated by the ratio between the individual duration of the phase and the summation of the duration of all the phases. Finally, this method prompts the results given in Table 9. As previously mentioned, this method is applied by default to the data of all nine reactors of the three bays.

3.3.3 Duration and frequency of operational phases in a bay

In a third part of the data-analysis, the determination of the duration and frequency of executions of the phases of all the three reactor per bay are analyzed during the year 2020. The data-analysis of a bay is taken since the planning of the reactors for production is done from this bay perspective. As previously stated, a complete bay is used during the production campaign of an API and is thus the main viewing perspective of the production planning of API’s in the reactors.

The data-analysis from a bay perspective is done by adding the durations and frequencies of all the three reactors in the bay, which result from applying previous method explained in 3.3.2 to the three reactors of the bay. The summation of the durations and frequencies of the three reactions in the bay is then compared relative to the total duration and frequency of the bay during the year 2020. An example of the data-analysis of the total duration of all executed phases from the bay perspective of bay 21 is given in Table 10. Here, the total duration of all executed phases in bay 21 is defined as follows in formula (6).

$$Total\ duration\ bay\ 21\ = Total\ duration\ R021 + Total\ duration\ R022 + Total\ duration\ R023 \quad (6)$$

The total duration of the reactor is equal to the sum of the absolute durations of the phases of one year in the reactor of which an example is present in the bottom row of the absolute duration column in Table 9.

From formula (6), the relative duration of the phase from a bay perspective is calculated through formula (7).

$$Relative\ duration\ of\ phase\ in\ bay\ 21\ = \frac{Absolute\ duration\ of\ phase\ in\ reactor}{Total\ duration\ of\ all\ phases\ in\ bay\ 21} \quad (7)$$

In this formula, the absolute duration per phase is divided by the total duration of all phases in bay 21 that was calculated through formula (6). The result of applying this method for the real data of the reactors R021, R022 and R023 of bay 31 is given in Table 10.

Table 10: Example of the total duration and frequency of bay 21 during the year 2020

Reactor Phase	Relative duration of phase (%)			Total relative duration of phase (%)
	Reactor R021	Reactor R022	Reactor R023	Bay 21
R_CHARGE_SOLV	1.87	1.97	2.59	6.42
R_CHARGE_SOLIDS	1.24	0.40	2.09	3.73
R_CHARGE_RT_CND	1.22	0.56	1.19	2.96
R_TEMP_ADJUST	1.86	1.65	2.96	6.48
R_AGITATE	1.46	1.35	2.57	5.38
R_INERT	0.35	0.37	0.47	1.19
R_AERATE	0.06	0.09	0.11	0.26
R_LEAKCHECK	0.08	0.10	0.23	0.41
R_SETTLE	0.00	0.63	0.33	0.96
R_SAMPLE	0.01	0.30	0.02	0.33
R_TRANSFER_OUT	4.39	5.10	5.96	15.45
R_TRANSFER_IN	1.10	1.45	0.82	3.37
R_SEPARATE	0.00	0.22	0.18	0.40
R_RECIRC	0.00	0.00	0.00	0.00
R_DISTILL	4.86	2.54	3.60	11.00
R_REFLUX	0.46	0.27	1.22	1.96
R_SETUP	0.01	0.01	0.01	0.03
R_CLEAN	3.95	6.28	6.75	16.98
R_CLEANING_RELEASE	1.85	1.73	1.41	4.99
R_PROMPT	3.44	3.93	2.99	10.36
R_DECISION	2.31	2.59	2.39	7.29
R_RELEASE	0.02	0.01	0.02	0.05
Total duration of all phases	30.53	31.57	37.90	100.00

The method described above is also applied to the frequencies of the reactor in the bay. As this identical, the elaboration of the method applied to the data of the frequencies will not be given. Ultimately, the results of applying this method to all nine reactors of the three bays is presented in the upcoming chapter of this thesis.

4 Results and discussion of the data-analysis of the reactor data

In this research the assumption is made that possible restrictions for reactor and equipment scheduling due to the genuine production planning are not take into account for the interpretation of the results and the development of the high-level designs. This will be referred to as the conceptual assumption of this thesis. In accordance with Janssen, the effect of the production planning on the equipment utilization is considered to be beyond the scope of this research. Consequently, the simultaneity of execution of the phases and thus the simultaneous utilization of equipment of all reactors is not evaluated and not taken into account for the results of this research.

4.1 Global time allocation of the reactors

The first result of the data-analysis of the extracted operation record is a global time allocation of the reactors. This is done to gain a profound comprehension of the overall view of the activity of the reactors during one year of operation. The results of the time allocation of all nine reactor are given in Figure 15.

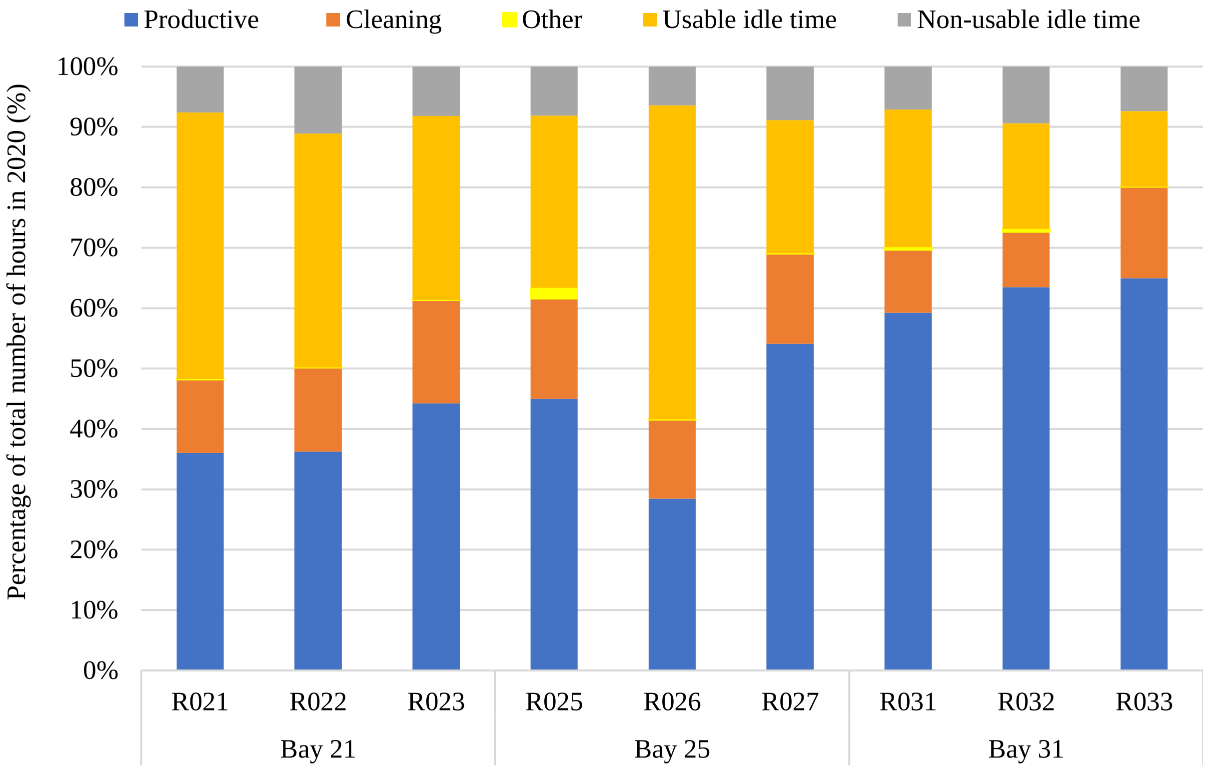


Figure 15: Time allocation of all nine glass-lined reactors in bay 21, 25 and 31 of the year 2020

It can be inferred from Figure 15 that high percentages of productivity, and thus low percentages of idle time, are present in the reactors of bay 31. Here, the reactors are productive for 63% on average of the total number of hours in 2020. Otherwise, a lower productivity is seen in bay 21 with an average of 39%. Consequently, higher percentages of usable idle time are visible in this bay with an average of 38%. In addition, the lowest productivity is present in reactor R026 in bay 25 in which 52% of the total number of hours in 2020 is occupied by usable idle time. On average, bay 25 has a percentage of productivity and usable-idle time of respectively 43% and 34%. Moreover, the non-usable idle time is approximately constant for all reactors with a mean percentage of 8%. Furthermore, it is noticeable that cleaning is equally performed throughout all nine reactors with an average of 14% of the total number of hours in 2020. Lastly, only a relatively small percentage of the category ‘other’ is present in reactor R025 but it is almost neglectable for all the reactors in comparison the other categories.

Overall, the results indicate that a potential of capacity is not used in the reactors of bay 21 and bay 25. This results from the high percentages of productive time are achievable in the reactors of bay 31. This can be mainly be related to the fact that bay 31 is used to produce API's or intermediates with a long reaction time which results in longer durations of phases and thus a higher productivity after one year of production. As results, a higher total percentage of 'productive', 'cleaning' and 'other' is observed in the reactors R027 and R031 until R033. Consequently, a higher utilization of the equipment is expected in the specific reactors because the equipment is solely actuated during activities 'productive', 'cleaning' and 'other'. Nonetheless, all nine reactors are equipped with the same process equipment and thus have the same capacity. Therefore, it can be concluded that in theory usable capacity is present in the reactors with a lower percentage of productive than the reactors of bay 31. Mainly, this concerns reactors R021 until R026. In addition, the variations in the time allocations of the reactors result from the inherent variable production character of a multipurpose plant at which the development of the production planning mainly focusses on the requirements of the product and not on the optimal use of equipment.

4.2 Duration and frequency of phases from a reactor perspective

First, the results of the duration and frequency of the phases of one reactor are broadly described as an outline to the results from a bay perspective. In Figure 16, the relative duration and frequency of all the executed phases in reactor R021 during the year 2020 are given from a reactor perspective.

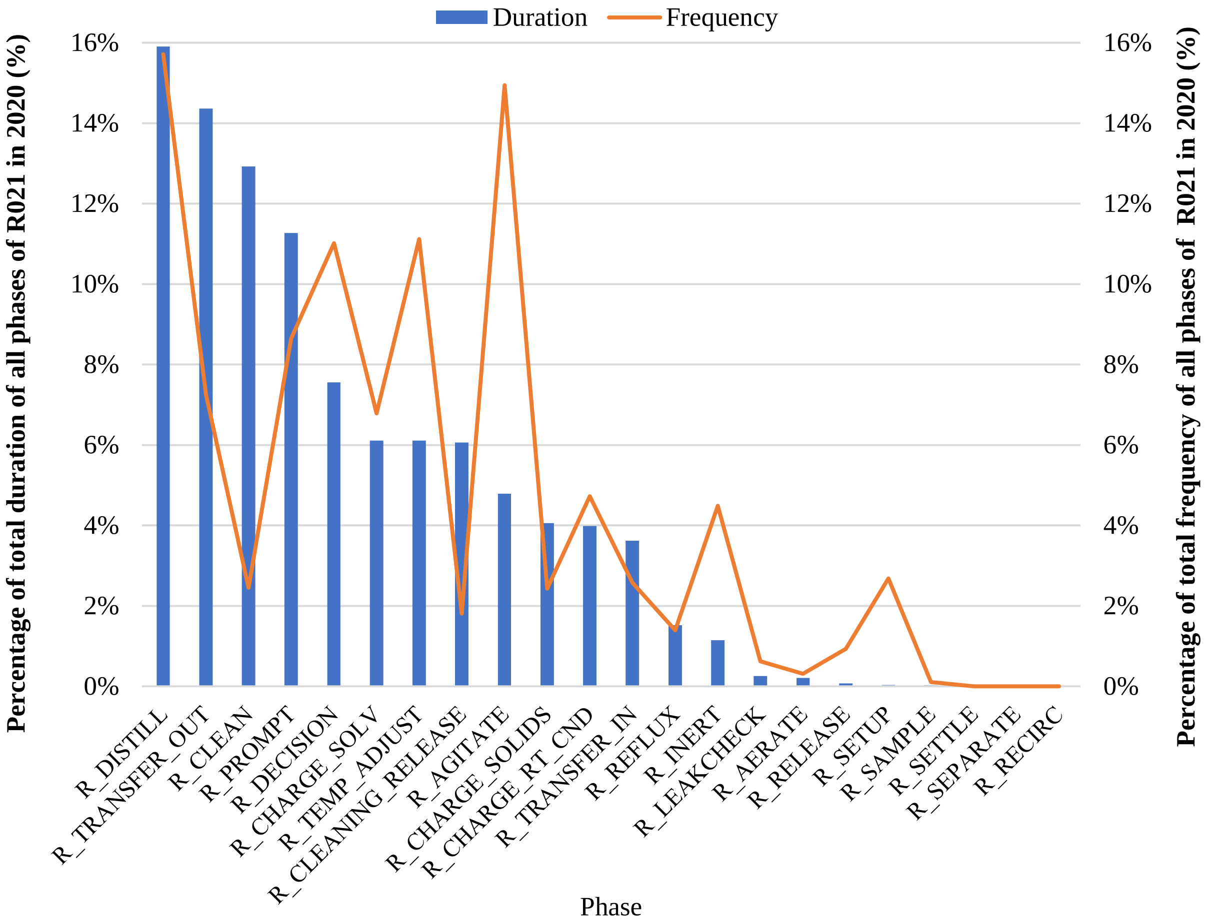


Figure 16: Relative duration and frequency of the phases executed in reactor R021 in 2020

In Figure 16, the phases are ranked following a declining order of relative duration and are expressed relative to the percentage of the total duration of all phases executed in a reactor in 2020. In general, this results in a ranked utilization of the phases of the reactor during one year of operation from which several main observations can be deducted.

Through this, the time consumption of all phases in a reactor can be evaluated and compared, with very high time consumptions and frequencies indicating key phases and very low time consumptions of phases indicating potential opportunities for optimization in the form of modularization.

In addition, the frequency of the executions of the phases is also displayed in Figure 16 with the intention to gain a broader view of the phase utilization and include the intensity of phase execution. Furthermore, the evaluation of the duration and the frequency gives an insight into the relationship between each other and thus an approximation of the duration per execution of a phase. However, an in-depth analysis of the phases from a reactor perspective will not be given as it was opted to do this from a bay perspective because it is a common perspective within the production plant of Janssen due to the multi-purpose lay-out and production planning.

4.3 Duration and frequency of phases from a bay perspective

4.3.1 Bay 21

Moving further from the reactor perspective, the duration and frequency of the phases are viewed from a bay perspective which is mentioned in 3.3.3. For bay 21, this is shown in Figure 17. Here, the relative duration and relative frequency of the phases in the reactors of bay 21 during the year 2020 are given.

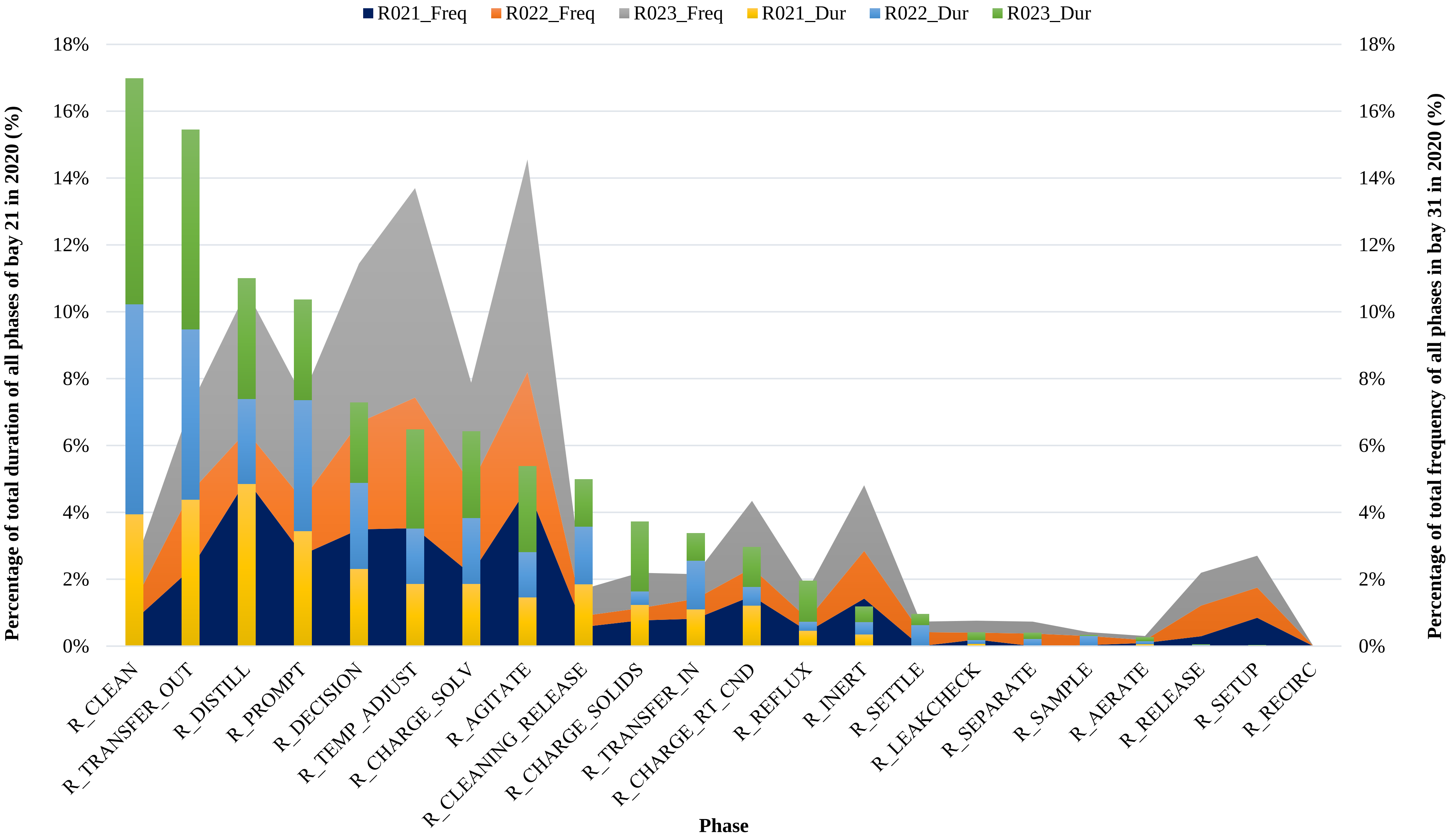


Figure 17: Relative duration and frequency of all phases executed in the reactors of bay 21

In Figure 17, the phases are ranked following a declining order of relative duration and are expressed relative to the percentage of the total duration of all phases of bay 21 consisting of reactors R021, R022 and R023 during the year 2020. In addition to a very low total time consumptions of the phases, great differences between time consumptions of the same phase in different reactors can also indicate potential modularization opportunities.

First, it can be seen from Figure 17 that the phases with the longest duration consists of ‘R_Clean’ and ‘R_transfer_out’ which have a time consumption of respectively 17% and 15.5% in the bay. The operation for cleaning, ‘R_Clean’, has a high time consumption in the bay but a relatively low frequency of execution. Consequently, this indicates an approximation that the operation ‘R_Clean’ has a high duration per execution. This is rather logical due to the labor-intensive character of cleaning that was observed during to preliminary internship of this thesis. In addition, the long duration can also be explained by the common situation that the reactor stays in the cleaning operations due to a lack of time and situations when no purpose can be found for the reactor at that specific time.

Similarly, the phase ‘R_transfer_out’ has a relatively high time consumption in the bay which can be explained by the fact that emptying the 6000 L of maximal reactor content to different destinations is time consuming. In addition, a higher frequency of executions is observed.

After the two phases, a drop of 4.5% in duration is observed in Figure 17 for the following phase. Here, the phase ‘R_Distill’ has a time consumption of 11% of the total duration of all phases in the bay. Moreover, the relative frequency and duration become approximately proportional to each other. In addition, it is visually noticeable that the proportion of the phase in reactor R022 is smaller compared to R023 and R021. Here, a time consumption of 2.54% is present in R022 in contrast to the 4.86% and 3.60% of respectively reactor R021 and R023.

Between the following phases ‘R_Prompt’ and ‘R_Decision’, a decrease of 3% in duration is present. However, these phases are not used to command specific physical equipment modules of the reactor and are therefore not important to locate potential modularization options. Similar phases that belong to this group are: R_cleaning_release, R_Release and R_Setup. Nonetheless, the phases are still displayed and used to give a complete view of the mapping of all phases of the reactor.

Subsequently, it is observed that phases ‘R_temp_adjust’ and ‘R_agitate’ have the highest frequencies of phase execution. This is expected as these are essential phases within batch reactor operation.

The phase from ‘R_reflux’ down to ‘R_aerate’ can be seen as a segment of relatively low time consumption as their time consumption is situated below 2%. The phases have a time consumption that is approximately 8.5 to 65 times lower than to the highest duration ‘R_clean’ in the bay. Hereby, the phase ‘R_recirc’ is not mentioned because it is not executed throughout the year 2020 in bay 21. Furthermore, the low time consumption of the phases in this segment indicates the possibility to optimize the corresponding equipment. Herewith, the low utilization facilitates the opportunity to replace the current fixed equipment by modular equipment modules. Within this segment, solely the phases ‘R_reflux’, R_settle’ and ‘R_separate’ represent potential options for modularization as the phases command an enclosed group of equipment of the reactor. The other phases ‘R_inert’, ‘R_leakcheck’, ‘R_sample’ and ‘R_aerate’ are rather pointless to modularize as they are general functionalities created by the attachment of utility lines the reactor.

4.3.2 Bay 25

For the reactors of bay 25, the relative duration and relative frequency of the phases during the year 2020 are shown in Figure 18

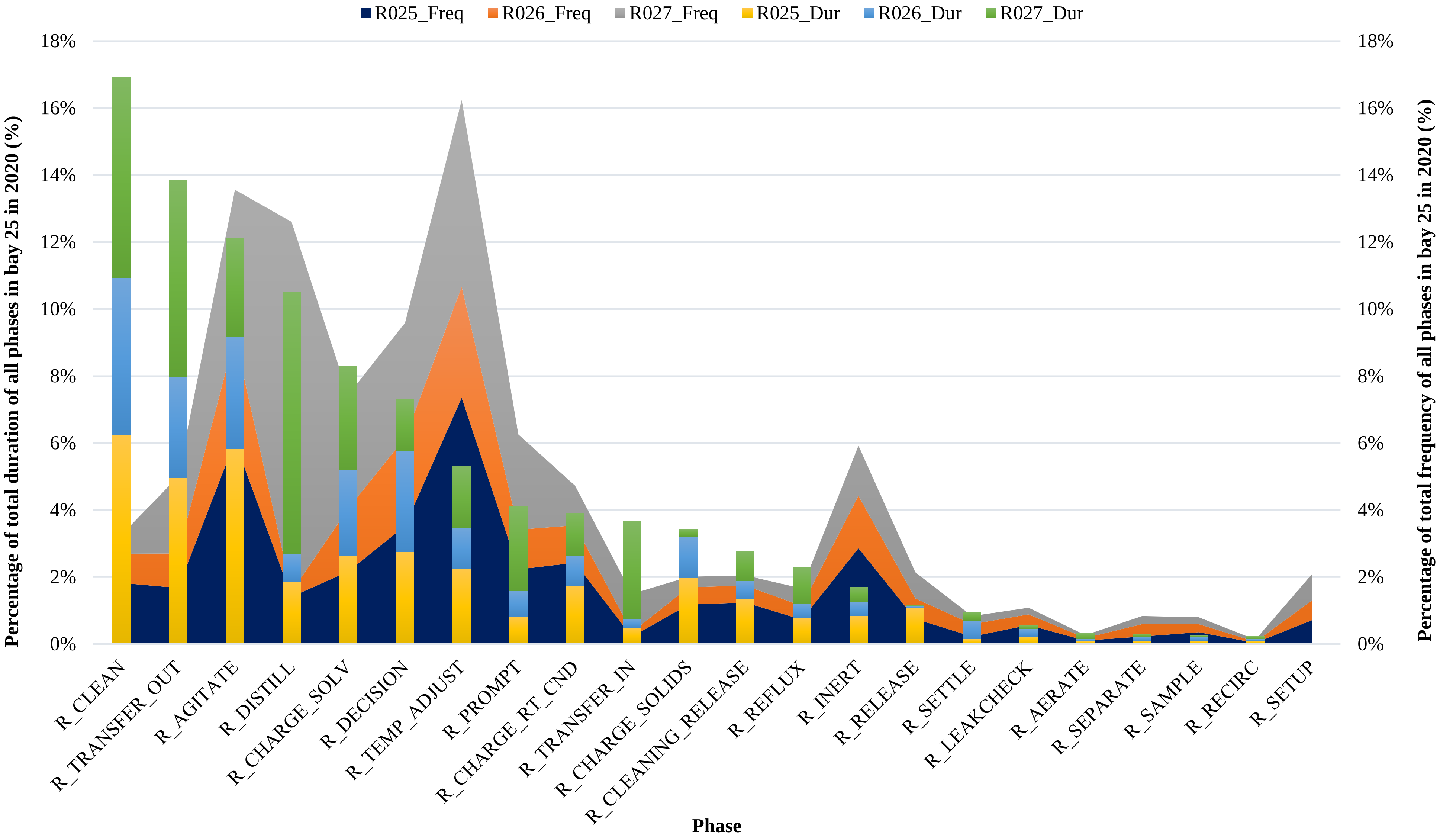


Figure 18: Relative duration and frequency of all phases executed in the reactors of bay 25

From Figure 18, it is apparent that the longest phase in this bay is ‘R_Clean’. This finding is similar to bay 21 in Figure 17. However, the ranking of phases through a descending order in this bay consists of a different composition. In this bay, ‘R_agitate’ has a much higher time consumption of 12.1% than in bay 21. Consequently, ‘R_Distill’ is placed one position lower on the ranking compared to bay 21. Here, ‘R_Distill’ counts for 10.5% of the total duration of all phases of the bay. The most interesting aspect of the phase ‘R_Distill’ in this bay is the large difference in the duration and the frequency between the reactors in this bay. Reactor R025 until R027 have a relative duration of respectively 1.9%, 0.8% and 7.8% of the total duration of all phases in the bay. Hence, this large difference in the utilization of the equipment corresponding to the phase ‘R_Distill’ gives a first indication of potential modularization options of this bay.

Other interesting phases of Figure 18 that indicate a difference in duration between the reactors in the bay are ‘R_Temp_adjust’, ‘R_Charge_rt_cnd’, ‘R_Transfer_in’ and ‘R_Charge_solids’. Firstly, ‘R_Temp_adjust’ has a duration in reactor R026 that is approximately 30% to 50% shorter compared to reactor R027 and R025. However, due to the fact that this phase still has a considerable frequency of execution it would be impractical to modularize the equipment system of this phase. Moreover, cooling and heating should also be present in a batch reactor in terms of safety for keeping the temperature in the reactor within controlled and safe limits. The same result is seen for the phase ‘R_Charge_rt_cnd’ that has a similar shorter duration in reactor R026 which is 30% to 50% shorter compared to reactor R027 and R025. Nevertheless, the duration and frequency are still relatively large compared to the shortest phases. Secondly, a noticeably smaller duration of the phase ‘R_Transfer_in’ is present in reactor R026 and R025. The equipment related to the ‘R_Transfer_in’ phase mainly consists of piping and instrumentation to transfer products, API’s or intermediates in the liquid state to the reactor from other destinations such as another reactor, centrifuge, etc. Therefore, the modularization of the phase would imply the disconnection of the transfer-in pipe to the reactor which wouldn’t achieve an added value to the reactor setups as it is an essential functionality of a reactor. Finally, the small duration of the phase ‘R_Charge_solids’ of reactor R027 in Figure 18 indicates a potential option for modularization. Similarly, the equipment of the phase ‘R_Charge_solids’ is essential for the API production in the reactor and is thus not further discussed for modularization.

Similar to bay 21, the segment of Figure 18 that comprises of the phases with the lowest durations consists of the same phases. The phases that are of main interest in this segment are: ‘R_reflux’, R_settle’ and ‘R_separate’. Likewise, this is generally due to the low time consumption of the phases in the bay and thus a low utilization of their corresponding equipment which makes them potential candidates for modularization. The total duration of the phases is respectively 2.3%, 1.0% and 0.3% of the total duration of all phases of bay 25.

For the phase ‘R_reflux’, this is further facilitated by the lower duration in reactor R026 relative to reactor R025 and R027. Furthermore, it is observed that the highest share of duration of the phase ‘R_Settle’ is present in reactor R026. In addition, the duration of the phase ‘R_separate’ is very small compared to the other phases in the bay.

4.3.3 Bay 31

In Figure 19, the relative duration and relative frequency of the executed phases in bay 25 during the year 2020 are shown.

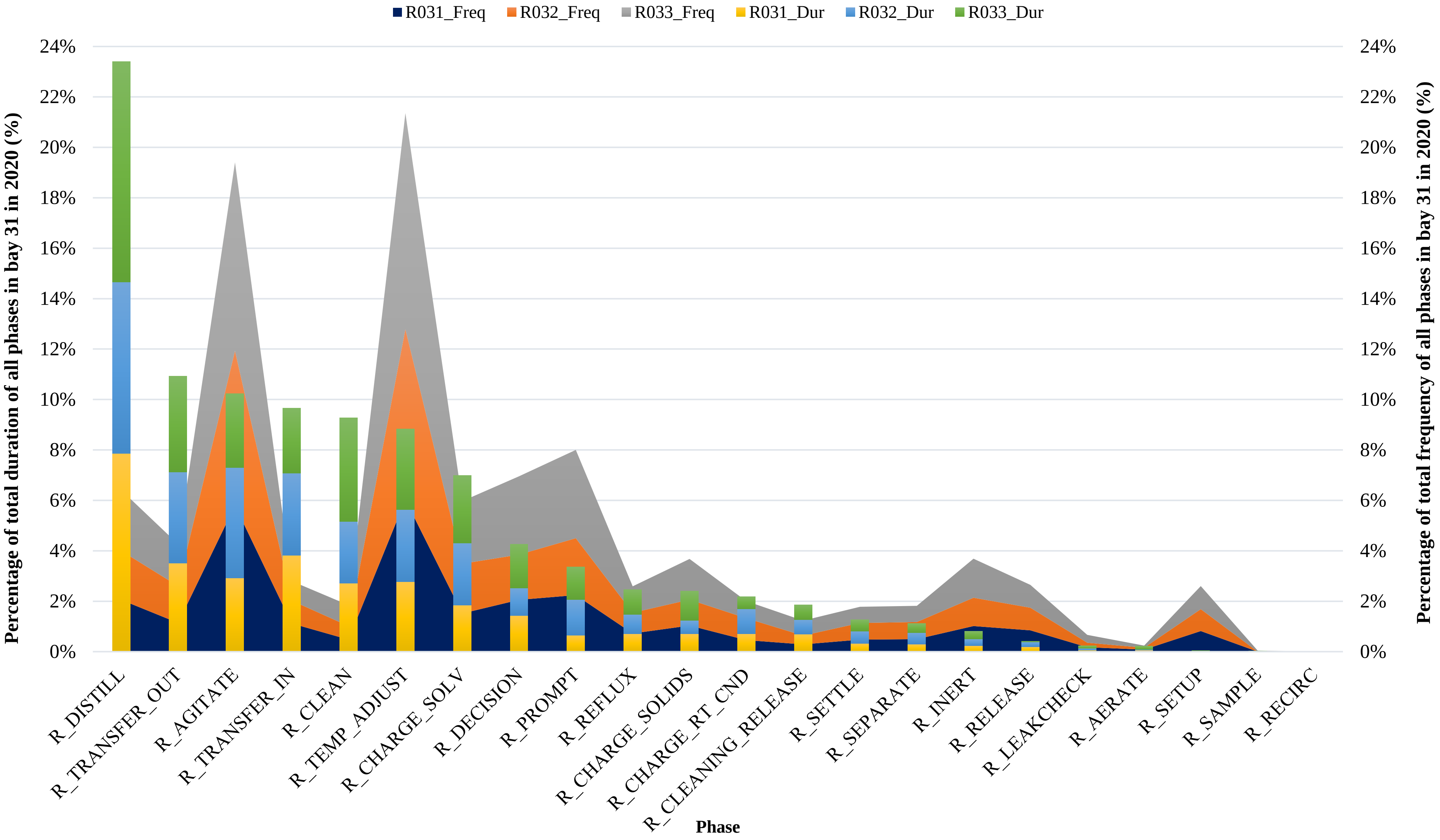


Figure 19: Relative duration and frequency of all phases executed in the reactors of bay 31

As can be seen from Figure 19, the most predominant result is the high duration of the phase ‘R_Distill’. In this bay, the phase accounts for 23.4% of the total duration of all phases at which it holds the highest duration. This is different than in bay 21 and bay 22 where the highest phase is ‘R_Clean’. Furthermore, the duration with the second highest duration in the bay 31 is ‘R_Transfer_out’. However, this phase account for 10.9% and thus has a time consumption of roughly half the duration of ‘R_Distill’.

Subsequently, the segment with the lowest durations of phases consists of a larger share of phases than in bay 21 and 25. As previously mentioned, particularly interesting phases in this segment are: ‘R_reflux’, R_settle’ and ‘R_separate’. Similarly, their low utilization of corresponding equipment makes them potential candidates for modularization.

4.4 Conclusion of potential modularization options from the data-analysis

The results of the data-analysis of the relative durations and frequencies of the phases from the perspectives of the bays indicate several potential modularization options for equipment corresponding to the phases. During the analysis of all the phases in the three bays, the potential phases for modularization were selected based on their relatively low time consumption. The selected phases consist of reflux, separation and settle which have a relatively low time consumption in all nine reactors. In addition, several phases were omitted due to the essential preservation of their related equipment. Moreover, the phase ‘settle’ and ‘separate’ will from this point be referred to as solely ‘separation’ as the two phases are linked to each other by means that they are consecutively executed to perform a separation operation in the reactor. This will make it more convenient for the modularization of the two phases. More about this assumption will be mentioned in the upcoming chapter. Furthermore, the large difference of the duration of the phase ‘distill’ in bay 21 and bay 25 showed potential options of optimization for reactors R022, R025 and R026.

Finally, it is opted to focus solely on the phase distillation, reflux, separation. In addition, this decision is assisted by two supplementary considerations.

The first consideration is based on the aspect that the phases distillation, reflux and separation facilitate a more convenient segmentation of the corresponding equipment into individual modular equipment modules. This segmentation is visualized in Figure 20.

Equipment units:

1. Reactor vessel
2. Reactor header
3. Agitator
4. Dosing tank
5. Reflux condenser
6. Gas cooler
7. Aftercooler
8. Separation tank
9. Heat exchanger reactor jacket

Relevant specifications:

- Condenser surface:
  - Condenser: 10,35 m^2
  - Gas cooler: 3,1 m^2
  - After cooler: 3,9 m^2
- Reactor volume:
  - 6000 L

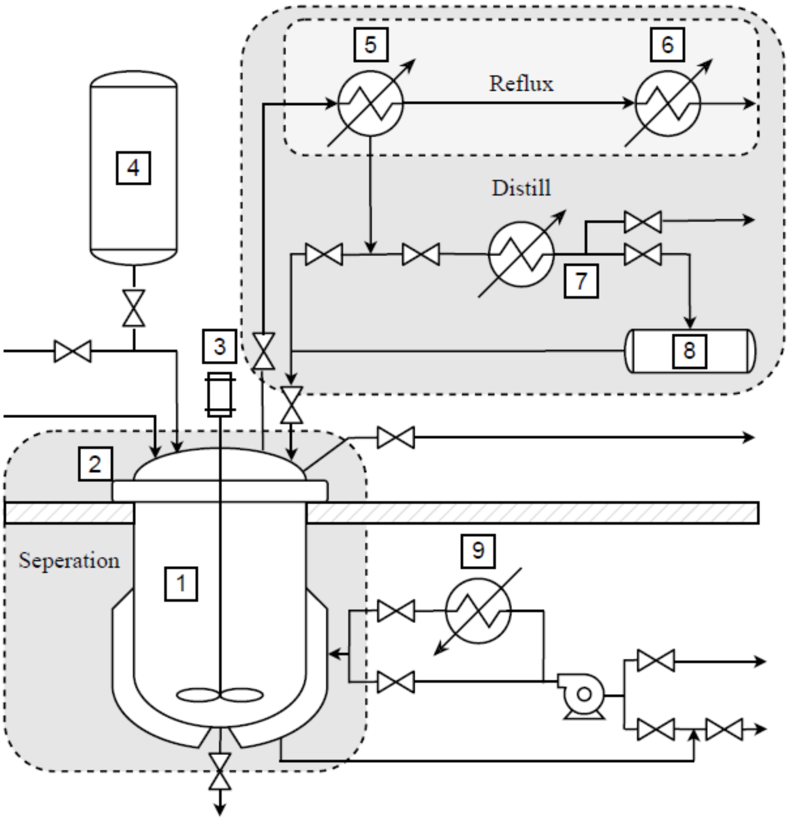


Figure 20: Visualization of the segmentation of the equipment corresponding to the phase distill, reflux and separate

During the distillation phase the gas cooler, reflux condenser and after cooler are used. Consequently, all three condensers of the condenser setup are being utilized. Subsequently, the execution of the phase for refluxing results in two out of three condensers being operated which are the after cooler and reflux condenser. As a result, the condenser system can easily be segmented into modules with specific functionalities and separated from to reactor. However, an overlap of utilization is present for the reflux condenser and gas cooler as both condensers are actuated during the ‘reflux’ and the ‘distill’ phase. This creates a necessity to review both phases with respect to each other for the utilization of the condensers.

At last, the phase ‘separation’ implies a liquid-liquid separation or extraction that is performed in the reactor. This means that the reactor vessel itself is thus utilized during a separation. Segmenting the equipment used during a separation would imply the segmentation of reactor vessel including the agitator. However, the reactor vessel itself is the main asset for the API production and thus cannot be physically segmented and separated from the reactor setup. Although, one possibility to modularize the phase separation is to introduce an external separation unit.

The second consideration to focus on the phases mentioned above results partly from the upcoming high intensity CapEX investment of Janssen to revamp the header of the reactor and connected equipment. Moreover, it was stated that achieving a reduction of the upcoming investment cost for new equipment is a secondary objective of this thesis. As the optimization of the condenser setup through modularization has a direct impact on the cost related to this investment, an opportunity is created to realize a possible cost reduction. In addition to the latter, the possibility of a cost reduction through an optimized modular condenser setup design would generate more interest for future implementations of modular concepts into the equipment of the production process at Janssen.

5 High-level reactor setup designs with modular concepts

The crux of the matter is to realize a more flexible design, higher equipment utilization and additionally reduce the upcoming investment cost for new equipment. To achieve an optimized utilization of the equipment and a more flexible design, the proposed high-level reactor setups are designed in accordance with the equipment utilization and modular equipment is implemented. As stated before, the equipment utilization is indicated by the duration of the related phases.

5.1 Modularization of distillation, reflux and separation

For the configuration of the high-level conceptual reactor designs, the phases distillation, reflux and separation are evaluated. Hereby, an evaluation of the phases 'distill' and 'reflux' is adequate for a realistic representation of the utilization of the condensers. However, a complete separation process in the reactor consists, besides the phase 'separate', of multiple consecutive executions of different phases. Due to the complex layered structure of production procedures, as illustrated in Figure 13, difficulties arose to find a standardized sequence of code that fully represented the complete separation process in the reactor. An evaluation of the phase sequence of the phase separation resulted in the conclusion that the phase 'R_Settle' is always followed by the phase 'R_Separate' during a separation process in the reactor. Moreover, it was observed that the phases 'R_Settle' and 'R_Separate' have the greatest time consumption of the separation process. Therefore, it was opted to make an assumption in which the duration of the phases settle and separate are added up and multiplied by two as an approximation for a realistic duration of the separation process in the batch reactor. This assumption was confirmed to be valid by Janssen and a further validation was deemed to be irrelevant. Additionally, it is observed that in rare cases the phase 'R_Settle' is executed for purposes beside separation. However, they are considered to be neglectable.

In Figure 21, the time consumption of the phase distillation, reflux and separation of all nine reactors are compared to specify the compositions of the high-level reactor setup designs.

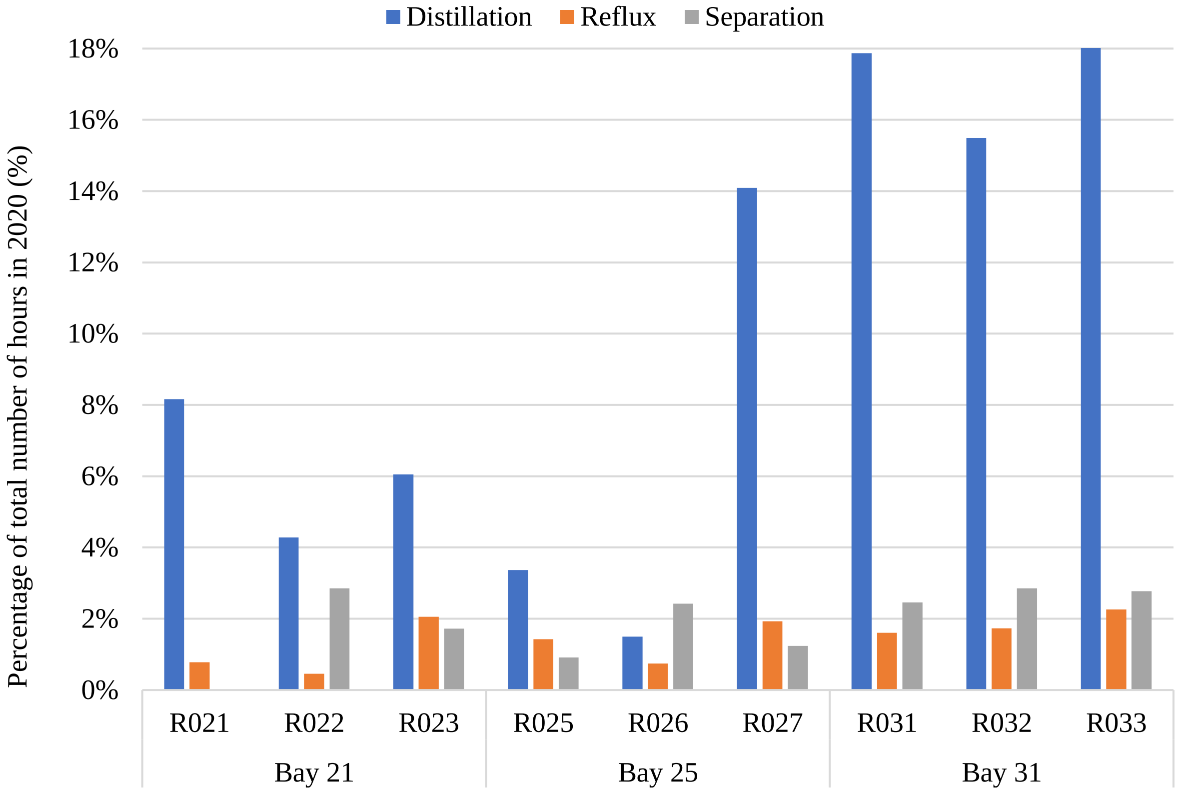


Figure 21: Relative duration of phases distillation, reflux and separation in all reactors in 1 year

As can be seen in Figure 21, the total duration of the phase distillation, reflux and separation in all nine reactors of the three bays are compared to each other to make propositions for the high-level reactor setup designs. Different from the other figures given in chapter 3, the total duration of the phases in the reactors are compared relative to the total amount of hours in the year 2020. This is done to give a decent overview of the proportionality of the time consumption of the phases and to compare them between all reactors. Furthermore, three main results are concluded from Figure 21. First, a relatively small share of separation in the total reactor phase is present. Separation accounts on average over all reactors for 1.9% of the total numbers of hours in 2020 with no separation in reactor R021 in 2020. In addition, a higher bay average of 2.7% is present in bay 31 compared to the 1.5% in bay 21 and bay 25. This relatively low time consumption of separation facilitates an opportunity to extract the phase from the reactor to perform it externally. Moreover, the low time consumption implies the theoretical possibility to pursue this concept in terms of production scheduling constraints. As a result, the use of an external modular separation system could in theory make an average of 1.9% per year in each reactor available.

Second, a relatively low time consumption of the reflux phase can be noticed which is uniformly executed throughout all reactors with an average over all reactors of 1.4%. In addition, the largest relative duration is noticeable in reactor R033 with a total of 2.3% of the total numbers of hours in 2020. The lowest percentage of reflux are present in reactor R021, R022, R026 and R027, which are respectively 0.8%, 0.5% and 0.7%. Consequently, the relatively low execution of the phase reflux empowers the vision that it is possible, in accordance with the conceptual assumption, to configure the reflux equipment into a more optimized and reduced modular setup.

Finally, a relatively higher execution of distillation is observed in reactors R021 and R027 until R033. In bay 21 and 25, a bay average of 6.2% and 6.3% is present compared to the 17.8% of bay average in bay 31. This implies a time consumption of distillation in bay 31 that is almost three times higher than the time consumption of bay 21 or 25. Ultimately, the relatively large difference in time consumption of the phase distillation, and thus in the utilization of three condensers per reactor, indicates the potential application of an optimized or reduced configuration of the condensers on the reactors R022 until R026 in which modularization is applied to create more flexibility. Although, the condenser utilization is related to both the execution of the reflux phase and the distillation phase and thus must be reviewed with respect other each other. This is necessary because a higher duration of the phase distill in the same reactor would refute the argument that an optimized condenser setup can be achieved due to the observation of a low duration of the reflux phase in the reactor. This results from the fact that the distillation phase indicates the use of all three condensers out and the reflux phase only two out of three condensers. Therefore, the distillation phase is prioritized over the reflux phase for the evaluation of the condenser utilization. The highest optimizations of the condenser systems in these reactors are possible in R026 in which a summation of the duration of the phase ‘distill’ and ‘reflux’ leads to a total condenser usage of 2.2%. Furthermore, a moderate utilization of the condensers is present in R022 and R025 with a total summation of distillation and reflux of respectively 4.7% and 4.8% of the total time consumption of 2020. In reactors R021 and R023 a higher total percentage of distillation and reflux is present of respectively 8.9% and 8.1%. Ultimately, these are still low percentages compared to the high percentage of R027 and all reactors of bay 31 which all exceed a total summation of distillation and reflux of 16%.

For the reactors of bay 31, the duration of the phase distillation indicates a utilization of the condenser that is too high the apply a reduced modular condenser setup. Following on the conclusions of the three phases, two high-level reactor setups with modular equipment are designed in accordance with the observed equipment utilization to achieve an optimized utilization of the equipment. In addition to the asset optimization mindset for the equipment, an asset reduction mindset is pursued to additionally reduce the upcoming investment cost for new equipment.

5.2 Design I: condenser optimization based on the condenser utilization

The main purpose of the first design is to introduce a configuration of the condenser setups of the reactor that is optimized according to results of the time consumption. This high-level design is given in Figure 22.

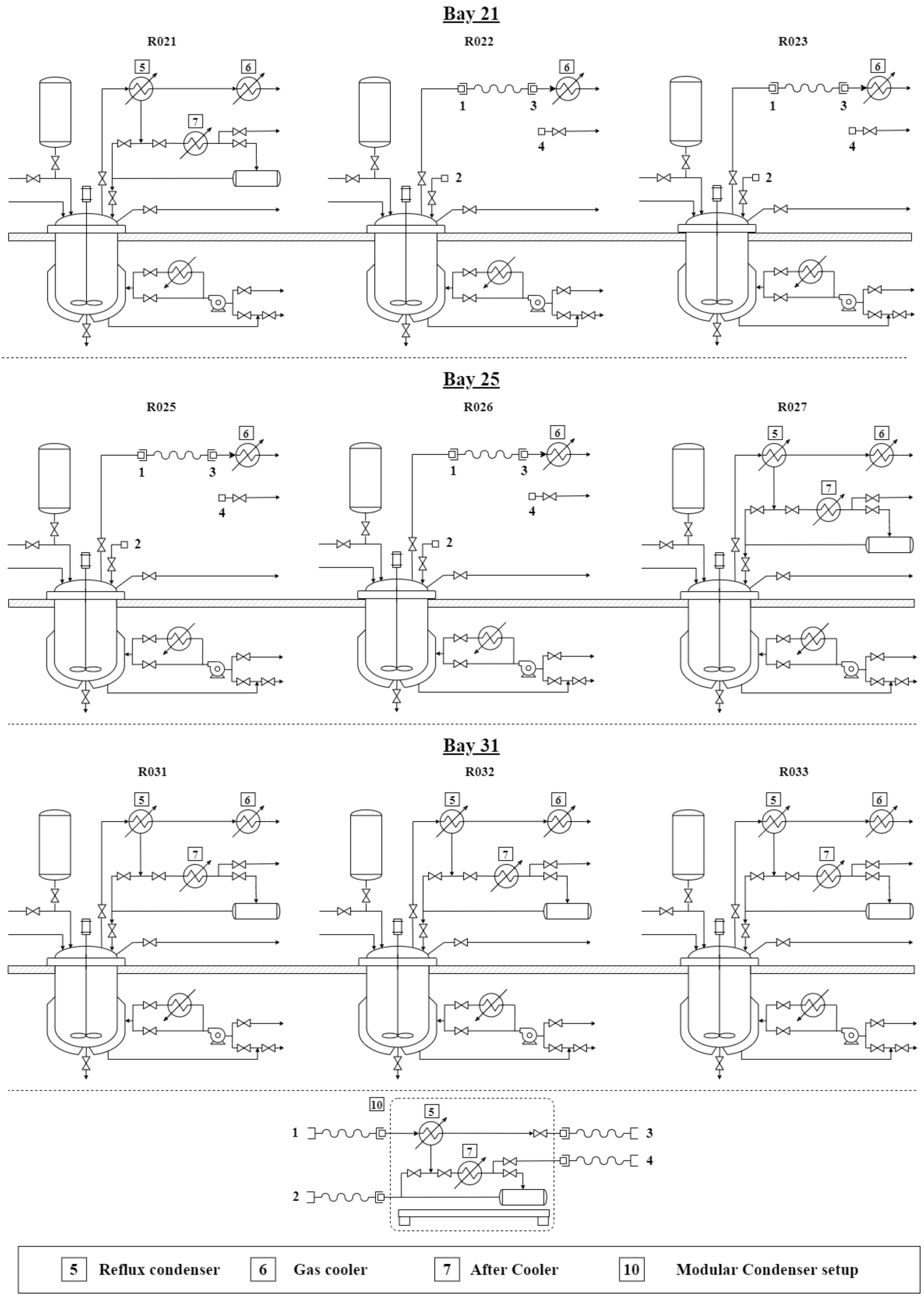


Figure 22: High-level reactor setup design I with a condenser optimization based on the condenser utilization

In Figure 22, the design consists of one fully equipped reactor and two reactors with an optimized condenser setup for bay 21 and 25. In addition, all reactors of bay 31 have a fully equipped fixed condenser setup. The latter is equal to the original static condenser setup. First, the reduced condenser setups in R022 until R026 comprise of solely a fixed gas cooler. This decision results from the relatively low utilization of all three condensers for distillation in these reactors and the low utilization of two condensers for reflux in general. Consequently, the use of solely one condenser with a smaller surface in the reactors is assumed to be sufficient to support all phases except distill and reflux from the conceptual perspective in this thesis. Moreover, the smaller gas cooler is expected to be adequate to form a barrier for possible solvent vapor.

Second, to support the limited numbers of executions of the phases distill and reflux in the reduced reactors, a modular condenser unit is proposed. This modular condenser has a combined surface area for heat exchange of the reflux and after cooler condenser. Hence, connecting the modular unit to the fixed gas cooler condenser on the reactor ensures the reactor being capable of performing the phase reflux and distillation. In addition, the proposed connections between the static condenser and the modular condenser setup are numbered from one to four and displayed on Figure 22. At last, it is proposed that a modular distillation condenser unit is used in both bay 21 and 25 to cover the phase reflux and distill which results in one modular condenser unit.

5.3 Design II: condenser reduction by performing the separation externally

The second design aims to implement an alternative reactor configuration compared to the first design in which the number of condensers is also reduced but no additional modular unit is foreseen. This high-level design is presented in Figure 23.

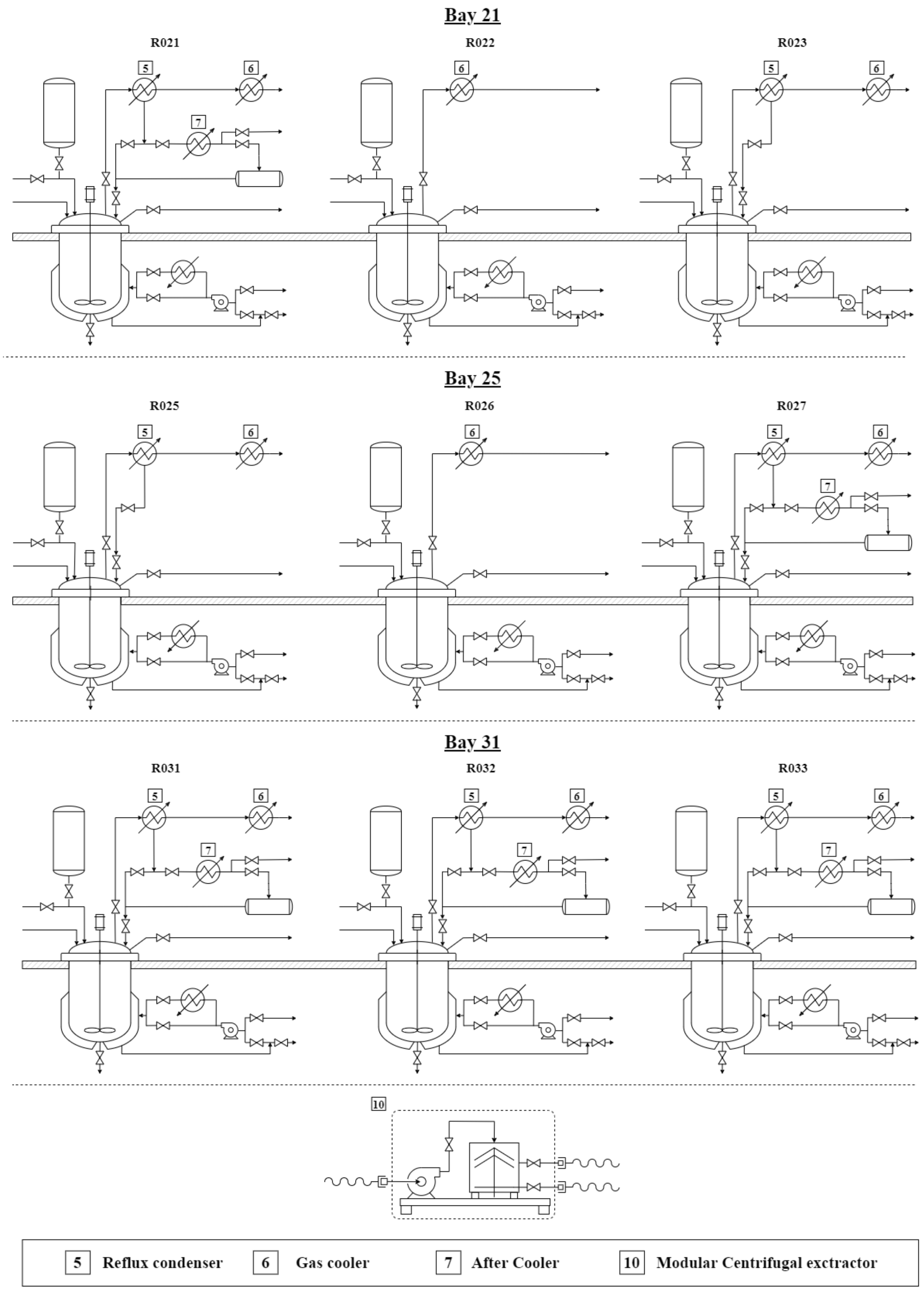


Figure 23: High-level reactor setup design II with a condenser reduction by performing the separation externally

As shown in Figure 23, reactors R022 until R026 have a reduced condenser setup that is in accordance with the relatively low execution of the phase ‘distill’ and ‘reflux’ and hence a lower utilization of the condenser setup consisting of the condensers. However, no additional modular unit is foreseen support the limited numbers of executions of the phases ‘distill’ and ‘reflux’.

Therefore, a conceptual assumption is made that it is possible that the planning of the process can be partially reorganized to centralize the load of the condenser utilization to two reactors in the bay. This conceptual assumption is an implication of the previously made conceptual assumption that restrictions for reactor and equipment scheduling due to the genuine production planning are not take into account for the interpretation of the results and the development of the high-level designs. As a result, the possibility to partially reorganized the planning to centralize the load of the condenser utilization to two reactors in the bay is used as the key principle of this design. Hereby, the different levels of optimization that were mentioned in in 5.1 for reactors R022 to R026 are applied to the condenser systems in this design. Subsequently, it is opted to design bay 21 and 25 with one fully equipped condenser setup to perform distillation, one setup with two condensers to perform reflux and a last reactor with solely a gas cooler setup to manage other phases.

Furthermore, all reactors of bay 31 consist of a fully equipped setup of three condensers due to the high utilization of the condensers. The latter is equal to the original static condenser setup and the setups of bay 31 in design I.

Different from the first design, the second design comprises a concept in which the separation is performed externally to the reactors in a modular separation system. This concept is an outcome of the result mentioned in 4.4 in which a relatively small share of the total duration of all phases of the reactors is observed for separations. From the conceptual perspective in this thesis, the implementation of an external modular separation system makes 1.9% on average per year of each reactor available. Consequently, the additional available time creates more flexibility to adapt the production planning to the modified setup and thus empowers the feasibility to apply a reduced condenser setup in reactor R022 until R026. Ultimately, it was proposed by Janssen to use modular centrifugal extractors to perform the separation externally. A high-level design of a modular centrifugal extractor is given in Figure 23. Because the required number of centrifugal extractor units is not known, an estimation of the required capacity is performed in the upcoming subchapter.

5.3.1 Estimation of the capacity and number of modular centrifugal extractor units

First, an estimation for the required capacity of the modular centrifugal extractor system is performed. The estimation is based on the assumption that the frequency of the executed phase ‘Separate’ represents the number of separations performed during one year of operation. The flow rate is than calculated by formula (8).

$$Flow\ rate = \frac{Number\ of\ separations \cdot Max\ batch\ volume\ (l)}{Total\ duration\ of\ separation\ in\ a\ reactor\ during\ 1\ year\ (h)} \tag{8}$$

In this formula the maximum separation volume is considered to be equal to the maximum allowed content volume of the batch reactor, which is 6000 L. Furthermore, the total duration of separations in each reactor is based on the previously mentioned assumption in 4.4 in which the duration of the phases ‘settle’ and ‘separate’ are added up and multiplied by two as an approximation for a realistic duration of the separation process in the reactor. The result of determining the flow rate for each reactor is given in Table 11.

Table 11: Estimation of the required flow rate of a centrifugal extractor unit for separation

	Bay 21			Bay 25			Bay 31		
	R021	R022	R023	R025	R026	R027	R031	R032	R033
Number of separations in 1 year	0	46	44	34	56	37	77	107	100
Total duration of separations in 1 year (h)	/	250.67	151.18	80.44	212.72	108.49	215.91	250.48	243.58
Mean flow rate of separations (l/h)	/	1101.06	1746.32	2536.03	1579.56	2046.34	2139.80	2563.05	2463.26
Mean flow rate of separations (l/min)	/	18.35	29.11	42.27	26.33	34.11	35.66	42.72	41.05

From Table 11, it can be seen that the highest mean flow rate is present in reactor R025 with a flow rate of 42.72 $\frac{l}{min}$. This value gives an indication of the flow rate that the extractor system has to process per separation for the worst-case scenario with a maximal separation volume of 6000 L.

Second, the numbers of units and the corresponding total investment cost is determined for the external separation unit. In order to perform the separation externally, it was proposed by Janssen to use modular centrifugal extractors. Subsequently, the data of specific centrifugal extractors is used that originates from a quotation and internal cost estimation of Janssen which is given in Appendix B. The data contains information about four available centrifugal extractors with different flow rate ranges from a specific manufacturer. Due to the result of the required capacity estimation for the separation unit, a centrifugal extractor with an operating range of 1 to 80 $\frac{\mathrm{l}}{\mathrm{min}}$ was selected. As the simultaneity of the executions of the separations in all nine reactors is not evaluated, the assumption is made that only one separation is performed at a time per bay due to the multipurpose production planning. According to the estimated flowrates in Table 11, one would infer at first sight that three centrifugal extractors are necessary to perform the separation externally. However, it was opted to use two modular units of each one centrifugal extractor with an operating range of 1 to 80 $\frac{\mathrm{l}}{\mathrm{min}}$ to perform all separations. This decision results from the fact that the chosen type of centrifugal extractors with a maximal flowrate of 80 $\frac{\mathrm{l}}{\mathrm{min}}$ could perform the maximal estimated flowrate of 42.72 $\frac{\mathrm{l}}{\mathrm{min}}$ roughly twice as fast. Consequently, separations could theoretically be performed faster which results in an increase of time for production scheduling. This makes it more feasible to use solely two centrifugal extractor units. In addition, a worst-case scenario is used to perform the estimation of the flow rate which possibly results in an overestimation of the real flowrate. Hence, two modular units of each one centrifugal extractor with an operating range of 1 to 80 $\frac{\mathrm{l}}{\mathrm{min}}$ are assumed to be sufficient in accordance with Janssen.

6 Cost estimation of the high-level reactor setup designs

The total cost estimation of the two proposed reactor setup designs comprises out of two key components: the cost estimation of the condenser setups and the cost estimation of the modular centrifugal extractors. Therefore, a cost estimation of each different type of setup is made to give an overview of the corresponding cost elements, i.e., equipment, piping and instrumentation, automation, and engineering costs. Moreover, the modifications of the process imposed by the implementation of the modular equipment are reviewed through the cost of replacing process piping and internal engineering. Furthermore, the cost estimation of the condenser setups is based on data of a previous cost estimation of Janssen which is given in Appendix C. As previously mentioned, the cost estimation of the centrifugal extractors is based on data of a quotation and internal cost estimation of Janssen which is given in Appendix B. Finally, a cost comparison is made between the two designs and the complete revamp of the original condenser setup of the upcoming investment.

6.1 Cost estimation of the complete revamp of the original condenser setup

6.1.1 Original condenser setup

The upcoming investment of Janssen to revamp the headers of all nine glass-lined reactors includes the revamp of the original condenser system consisting of the reflux condenser, gas cooler and after cooler. Hereby, a cost estimation of the complete revamp of the original condenser setup was previously conducted by Janssen. Janssen's cost estimation is used as a reference to compare the cost estimations of the two proposed designs and is given in Table 12.

Table 12: Cost estimation of a complete revamp of the original condenser setup per reactor

Cost element	Cost (€)
Reflux Condenser (10.35 m^2) After cooler (3.9 m^2) Gas cooler (3.1 m^2)	120,000.00 95,000.00 80,000.00
Hoisting operations	20,000.00
Insulation operations for piping	15,000.00
Replacing glass process piping	150,000.00
Adapting stainless steel service pipes	70,000.00
Instrumentation of process pipes	34,900.00
Instrumentation of Service pipes	15,900.00
Electrical operations	30,000.00
Process automation	30,000.00
Internal engineering	100,000.00
External engineering	50,000.00
Total cost per setup/reactor	810,800.00

From the data of Janssen's cost estimation in Table 12, it can be seen that the major costs are related to the condenser units, replacement of the glass process piping and internal engineering costs. This results from the high amount of piping and instrumentation that is attached between the three condensers and the header of the reactor, and the three condenser units that need to be revamped if the original design is preserved. Finally, the total cost of a complete revamp per reactor is 810,800.00 euro.

6.1.2 Total cost of the complete revamp of the original condenser setup

The cost of a complete revamp of the original condenser setup for all reactors is given in Table 13.

Table 13: Total cost estimation of a complete revamp of the original condenser setup of all reactors

Cost element	Cost (€)
Bay 21	
Static setup of three condensers in R021	810,800.00
Static setup of three condensers in R022	810,800.00
Static setup of three condensers in R023	810,800.00
Bay 25	
Static setup of three condensers in R025	810,800.00
Static setup of three condensers in R026	810,800.00
Static setup of three condenser in R027	810,800.00
Bay 31	
Static setup of three condenser in R031	810,800.00
Static setup of three condenser in R032	810,800.00
Static setup of three condenser in R033	810,800.00
Total cost	7,297,200.00

From Table 13, it can be seen that the estimated cost of a complete revamp of the original condenser setup for all nine reactors is 7,297,200.00 euro.

6.2 Cost estimation of design I

6.2.1 Static gas cooler setup

In the first high-level reactor setup, reactor R022 until R026 are designed with a reduced static condenser setup in which they solely have a gas cooler. An estimation of the total cost of the revamp of the original condenser system in a reactor to one gas cooler setup is given in Table 14.

Table 14: Cost estimation per reactor to revamp the original condenser system to one gas cooler

Cost element	Cost (€)
Gas cooler (3.1 m^2)	80,000.00
Hoisting operations	15,000.00
Insulation operations for piping	10,000.00
Replacing glass piping process	110,000.00
Adapting stainless steel service pipes	50,000.00
Instrumentation process pipes	31,650.00
Instrumentation Service	8,300.00
Electrical operations	20,000.00
Process automation	50,000.00
Internal engineering	130,000.00
External engineering	70,000.00
Total cost	574,950.00

From Table 14, it can be seen that the main costs arise at replacing glass piping process and internal engineering. However, a reduction in cost for piping and instrumentation can be observed compared to complete revamp of the original setup because less piping and components must be revamped due to the reduced setup. Similarly, the cost of the condenser unit has become a smaller part of the total cost per setup. This results in a total cost of 574,950.00 euro per setup.

6.2.2 Modular condenser setup

In addition to the gas cooler setup in reactor R022 until R026 of the first high-level reactor setup design, a modular condenser setup is proposed to support the limited numbers of executions of the phases distill and reflux. The modular condenser setup combines the reflux condenser and the after cooler in a combined condenser system which consist of one condenser with the equivalent heat exchange surface area of the reflux condenser and the after cooler. This is done because the combined condenser unit, available in the cost estimation of Janssen in Appendix C, results in a cost reduction compared to a separate reflux condenser and gas cooler setup. An estimation of the total cost of one modular condenser setup is given in Table 15.

Table 15: Estimation of one modular condenser setup

Cost element	Cost (€)
Condenser (13.6 m^2)	145,000.00
Mobil skid infrastructure	5,000.00
Instrumentation process pipes	31,650.00
Instrumentation Service pipes	8,300.00
Electrical operations	20,000.00
Process automation	50,000.00
Internal engineering	130,000.00
External engineering	70,000.00
Total cost per setup	459,950.00

As shown in Table 15, mainly the cost of the condenser and internal engineering contribute to the total cost of the modular setup. This results from the engineering necessary to facilitate the implementation of the new modular condenser system into the existing process framework following the Plug-and-Produce method that will require many process changes. Moreover, this also results in a higher cost of the process automation because the implementation of modular equipment involves significant changes in the fixed distribution structure of conventional process control systems which is mentioned in 2.5.1 [68], [69]. This results in a total cost per modular condenser setup of 454,950.00 euro.

6.2.3 Total cost of design I

At last, the cost estimations presented in previous parts are combined to make an estimation of the total cost of design I, which is given in Table 16.

Table 16: Total cost estimation of high-level reactor setup design I

Cost element	Cost (€)
Bay 21	
Static setup of three condensers in R021	810,800.00
Static gas cooler setup in R022	574,950.00
Static gas cooler setup in R023	574,950.00
Bay 25	
Static gas cooler setup in R025	574,950.00
Static gas cooler setup in R026	574,950.00
Static setup of three condenser in R027	810,800.00
Bay 31	
Static setup of three condenser in R031	810,800.00
Static setup of three condenser in R032	810,800.00
Static setup of three condenser in R033	810,800.00
Modular condenser setup	454.950,00
Total cost of design	6,808,750.00

From Table 16, it can be seen that the reactors R022 until R026 have a reduction in cost due to their optimized and thus reduced condenser systems. In order to support the limited execution of distill and reflux in the reactors, one modular condenser unit is provided. Reactors R021, R027 and R031 until R033 are revamped to the original condenser system consisting of three condensers. As a result, the cost per reactor is higher. Ultimately, the total cost of design I results in being 6,808,750.00 euro.

6.3 Cost estimation of design II

6.3.1 Static reflux condenser and gas cooler setup

In addition to the condenser setups mentioned in 6.1 and 6.2.1, a condenser setup consisting of a separate gas cooler and reflux condenser is used in the second proposed design. The cost estimation of this condenser setup is given in Table 17.

Table 17: Estimation of the total cost of a gas cooler and condenser setup

Cost element	Cost (€)
Reflux Condenser (10.35 m^2) Gas cooler (3.1 m^2)	120,000.00 80,000.00
Hoisting operations	17,000.00
Insulation operations for piping	12,000.00
Replacing glass piping process	130,000.00
Adapting stainless steel service pipes	60,000.00
Instrumentation process pipes:	33,900.00
Instrumentation Service pipes	13,600.00
Electrical operations	25,000.00
Process automation	40,000.00
Internal engineering	120,000.00
External engineering	60,000.00
Total cost per setup	711,500.00

In Table 17, the main costs arise for the reflux condenser and the gas cooler, replacing the glass piping and engineering. Regarding the costs for glass piping and engineering, a lower cost is observed compared to the complete revamp scenario of 6.1. This results from the fact that less piping and instrumentation needs to be replaced for two condensers in contrast to the three condensers of the complete revamp. Furthermore, a moderate engineering cost is present which consequences from the moderate modifications of the process routing in the process routing study to adapt the existing system to the new setup.

6.3.2 Total cost estimation of the modular centrifugal extractor units

In addition to the condenser setups of design II, two modular units of each one centrifugal extractor with an operating range of 80 $\frac{\mathrm{l}}{\mathrm{min}}$ are selected to perform the separation externally. However, the price of two extractor units with a flow rate of 160 $\frac{\mathrm{l}}{\mathrm{min}}$ was calculated in the cost estimation of Janssen in Appendix B. Consequently, the exponent method for equipment is used to perform an estimation based on the given data. Because no exponent size exponent for centrifugal extractors was found, the rule of six-tenths is applied to estimate the cost of the extractor, which is presented through formula (9) [74].

$$C_B = C_A \cdot \left(\frac{Q_B}{Q_A}\right)^{0.6} \tag{9}$$

In this formula, Q_A and Q_B represent the capacities of the two different unit at which Q_A is the size of the equipment with the known cost and Q_B the size of the equipment with the unknown cost. Furthermore, C_A is the known cost with the corresponding size Q_A. The elaboration of applying this formula to the case of the centrifugal extractor is given in Table 18.

Table 18: Exponent method for equipment costs applied to the centrifugal extractors

	A	B
Extractor capacity Q (l/min)	160	80
cost of extractor C (€/unit)	250 000	164 939

From Table 18, the cost estimation of the centrifugal extractor with a flow rate of 80 $\frac{\mathrm{l}}{\mathrm{min}}$ results in a price of 164 939 euro. Hence, the cost of two centrifugal extractors is 329 877 euro. Finally, an estimation of the total cost of the installation of two centrifugal extractors is performed. As previously mentioned, this is based on the data from a former cost estimation of Janssen. An overview of all costs is given in Table 19.

Table 19: Cost estimation of the centrifugal extractor setup

Cost element	Cost (€)
Two centrifugal extractors units	329,877.00
Two pumps for water and reagent	10,000.00
Three flow meters with flow control valves	30,000.00
Mobil skid infrastructure	10,000.00
Basic control and trending for RPM and flowrate	30,000.00
Piping, valves and connectors for equipment	50,000.00
Qualification	20,000.00
Process engineering	50,000.00
Automation engineering	20,000.00
Prevention studies and inspections	8,000.00
Total cost	557,877.00

From Table 19, it can be seen that the total cost of the two selected centrifugal extractor units is estimated at 557,877.00 euro.

6.3.3 Total cost of design II

Finally, the cost estimations presented in previous parts are combined to make an estimation of the total cost of design II, which is given in Table 20.

Table 20: Total cost estimation of high-level reactor setup design II

Cost element	Cost (€)
Bay 21	
Static setup of three condensers in R021	810,800.00
Static gas cooler and reflux condenser setup in R022	711,500.00
Static gas cooler setup in R023	574,950.00
Bay 25	
Static gas cooler setup in R025	574,950.00
Static gas cooler and reflux condenser setup in R026	711,500.00
Static setup of three condenser in R027	810,800.00
Bay 31	
Static setup of three condenser in R031	810,800.00
Static setup of three condenser in R032	810,800.00
Static setup of three condenser in R033	810,800.00
Modular centrifugal extractor setup	557,876.98
Total cost of design	7,184,776.98

In Table 20, cost reductions can be seen in reactor R022 until R026 due to their optimized and thus reduced condenser systems. As mentioned before, this results from the bay configuration of bay 21 and 25 that consists of one reactor with three condensers to perform distillation, a second reactor with two condensers to perform reflux and a last reactor with solely a gas cooler setup to manage other phases. Furthermore, a complete revamp to the original design with three condensers is performed in all reactors of bay 31 which results in the highest cost per reactor. Subsequently, two modular centrifugal extractors are chosen to perform the separation externally to the reactors. Over all the bays, this corresponds to a total cost of 7,184,776.98 euro for design I.

6.4 Financial comparison between the proposed designs and the original design

At last, the result of the cost comparison between the two proposed designs and the complete revamp of the original design is given in Table 21.

Table 21: Financial comparison of designs to a complete revamp of the original design

Cost	Original design	Design I	Design II
Revamp of static condensers (€)	7,297,200.00	6,353,800.00	6,626,900.00
Modular equipment (€)	/	459,950.00	557,876.98
Total cost (€)	7,297,200.00	6,813,750.00	7,184,776.98
Absolute cost reduction to original design (€)	/	483,450.00	112,423.02
Relative cost reduction to original design (%)	/	6.63	1.54

From Table 21, it can be seen that design I has a lower total cost than design II. This results from the aspect that a greater reduction of the static condensers is achieved due to the optimized setup in which solely a gas cooler is used in reactor R022 until R026. Consequently, less condensers need to be revamped and thus a smaller cost to revamp the static equipment is present in design I. In addition, the implementation of one combined modular condenser unit for design I results in being less expensive than the two proposed centrifugal extractors of design II. As a result, the cost for modular equipment is smaller for design I compared to design II.

Ultimately, a cost reduction of design I and II compared to the cost of the upcoming investment in which a complete revamp of all condensers will be performed is respectively 6.63% and 1.54%. It can be concluded that the implementation of the two designs does not result in substantial cost reductions. Nevertheless, the financial point of view is not the most important aspect. The implementation of the modular equipment adds more flexibility to the existing process through the exchangeability of the modular equipment. However, the effect of an increased flexibility of the existing process cannot be taken into account in the determination of the total cost of the design with modular equipment. Additionally, the modular centrifugal extractors or condensers could be used for other reactors or unit processes which results in a potential saving of a future equipment cost.

7 Conclusion and Outlook

The main goal of this study is to realize a more flexible design, higher equipment utilization and additionally reduce the upcoming investment cost for new equipment by introducing modular concepts into the reactor setups of nine glass-lined batch reactors at Janssen.

In this thesis, a method has been worked out to identify and map the intensity of use of the existing glass-lined reactors and their equipment during operations to locate potential modularization options. This is done by performing a data-analysis of operational records from the reactor operating system. The data is analyzed in Excel through mapping all phases per reactor and by examining the duration and frequency of executions of all phases during the year 2020 as an approach to evaluate the equipment utilization.

Results of the data-analysis of this research have indicated distillation, reflux and separation as potential modularization options. First, a relatively low time consumption of the phase reflux has been noticed which was uniformly executed throughout all reactors with an average over all reactors of 1.4% of the total numbers of hours in 2020. In addition, the largest relative duration is noticeable in reactor R033 with a total of 2.3%. Consequently, the overall low execution of the phase reflux indicates the potential implementation of an optimized and reduced modular setup of the two condensers used for refluxing.

Second, a relatively high time consumption of the phase distillation has been observed for reactors R021 and R027 until R033. In contrast, a relatively low time consumption has been noticed in reactors R022 until R026 of bays 21 and 25. In bay 21 and 25, a bay average of 6.2% and 6.3% is present compared to the 17.8% of bay average in bay 31. This implies a time consumption of distillation in bay 31 that is almost three times higher than the time consumption of bay 21 or 25. Ultimately, the relatively large difference in time consumption of the phase distillation, and thus in the utilization of three condensers per reactor, indicates the potential application of an optimized or reduced configuration of the condensers on the reactors R022 until R026. In contrast, the high utilization of the three condensers in reactors R021 and R027 until R033 impedes the use of an optimized setup and thus results in the preservation of the original design.

Thirdly, a low total duration of separations has been observed for all the reactors during one year of operation. All executed separations account on average over all reactors for 1.9% of the total numbers of hours in 2020. As a result, the overall relatively low time consumption of the separations has facilitated the opportunity to extract the operation from the reactor to perform it externally. Consequently, the use of an external modular separation system could in theory make an average of 1.9% per year in each reactor available.

From the results and the conclusions of the data-analysis, two high-level reactor setups with modular equipment have been designed in accordance with the observed equipment utilization to achieve an optimized utilization of the equipment. In addition to the asset optimization mindset for the equipment, an asset reduction mindset has been pursued to additionally reduce the upcoming investment cost for new equipment.

The first high-level design consists of an optimized condenser setup in bay 21 for R022 and R023, and in bay 25 for reactors R025 and R026. Compared to the original designs of the reactor setups, which comprise of three condensers per reactor, the optimized condenser setups have been designed with solely a fixed gas cooler per reactor. Furthermore, the two remaining reactors R021 and R027 that are located respectively in bay 21 and 25, and all three reactors of bay 31, are designed with three fixed condensers per reactor.

Finally, one modular condenser unit has been implemented into the first design to support the limited numbers of executions of the phases distill and reflux in reactors R022 until R026 with an optimized condenser setup.

The second high-level design is based on an extension of the conceptual assumption that the planning of the process can be partially reorganized to centralize the load of the condenser utilization to two reactors in the bay. Therefore, a bay configuration has been designed for bay 21 and 25 that consists of one reactor with three condensers to perform distillation, a second reactor with two condensers to perform reflux and a last reactor with solely a gas cooler setup to manage other phases. Furthermore, all reactors of bay 31 have been designed with a setup consisting of three condensers due to the high utilization of these condensers. Subsequently, the second design comprises of two modular centrifugal extractors through which the separation is performed externally to the reactors. This has been done to create more flexibility to adapt the production planning to the modified setup and thus empowers the feasibility to apply the proposed condenser setup in reactor R022 until R026.

Ultimately, the cost reduction of the upcoming investment for new equipment by introducing the two proposed designs has been evaluated. A cost reduction of respectively 6.69% and 1.54% has been observed relative to the cost of the upcoming investment in which a complete revamp of all condensers will be performed. As the implementation of the two designs does not result in substantial cost reductions, one should remember that the proposed modular equipment adds flexibility to the existing process through their exchangeability and thus could be used for other reactors or process equipment setups which results in a potential saving of a future equipment cost. At last, the introduction of modular equipment through the proposed designs could increase the allowance to adapt the production process more flexible and introduce new equipment technologies to achieve more complex production capabilities in future.

This thesis has provided new insights into the potential implementation of modular concepts into existing processes by means of a holistic method to located potential modularization options based on an analysis of the operation records. An additional result of the developed method is a template in Excel that could serve as starting point for future investigations to located potential modularization options in other reactors at the plant by analyzing data of the operating system. Furthermore, the results of this study could serve as a preliminary study and provide insights into the possible design concepts to revamp the headers of the glass-lined reactor in plant 3 for the upcoming investment. Similarly, the template in Excel could be used to evaluate other cost scenarios of alternative condenser setups of the nine reactors as a scenario calculator was developed and implemented in the template that calculates the total cost per reactor based on the inputted condenser setup.

Since the effect of the production planning on the equipment utilization was considered to be beyond the scope of this research, further research could assess the effects of the production planning by evaluating the simultaneity of execution of the phases and thus the simultaneity of equipment usage. The addition of the simultaneity of execution to the method used in this study would improve the feasibility of the proposed designs resulting from this method.

In addition, future work could focus on the optimization of the required surface area of heat exchange for the condensers with a low utilization in order to further optimize the condenser setups. Ultimately, this would lead to a further optimization of the reactor designs of this thesis.

At last, the practical challenge that remains after the conceptual designs of the reactor setups with modular equipment in this research is to evaluate the acceptance of the existing automation system to introduce the modular equipment at Janssen.

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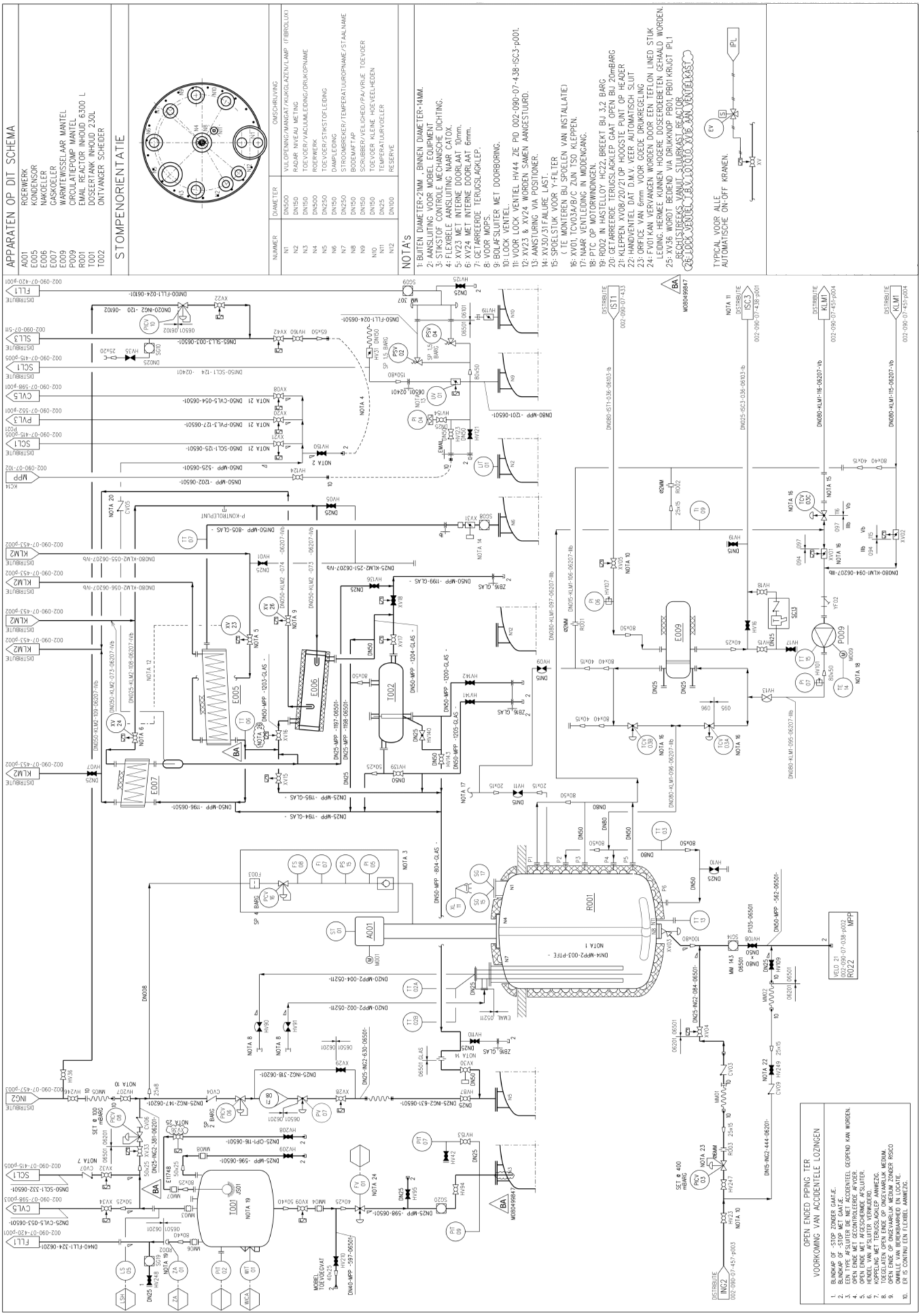
Appendix

Appendix A: P&ID of glass-lined reactor R022 at plant 3 of Janssen in Geel



APPARATEN OP DIT SCHEMA

A001	ROERWERK
E005	KONDENSOR
E006	NAKOELER
E007	GASKOELER
E009	WARMTEWISSELAAR MANTEL
P009	CIRCULATIEPOMP MANTEL
R001	EMAIL REACTOR INHOUD 6300 L
T001	DOSEERTANK INHOUD 230L
T002	ONTVANGER SCHEIDER

STOMPENORIENTATIE

NUMMER	DIAMETER	OMSCHRIJVING
N1	DN500	VULOPENING/MANGAT/KIJKGLAZEN/LAMP (FIBROLUX)
N2	DN150	RADAR NIVEAU METING
N3	DN150	TOEVOER/VACUUMLEIDING/DRUKOPNAME
N4	DN500	ROERWERK
N5	DN250	TOEVOER/STIKSTOFLEIDING
N6	DN150	DAMPLEIDING
N7	DN250	STROOMBREKER/TEMPERATUUROPNAME/STAALNAME
N8	DN150	BODEMAFTAP
N9	DN150	SCRUBBER/VEILIGHEID/PA/VRIJE TOEVOER
N10	DN150	TOEVOER KLEINE HOEVEELHEDEN
N11	DN25	TEMPERATUURVOELER
N12	DN100	RESERVE

NOTA'S

1: BUITEN DIAMETER=21MM , BINNEN DIAMETER=14MM.
2: AANSLUITING VOOR MOBIEL EQUIPMENT
3: STIKSTOF CONTROLE MECHANISCHE DICHTING.
4: FLEXIBELE AANSLUITING NAAR CATOX.
5: XV23 MET INTERNE DOORLAAT 10mm.
6: XV24 MET INTERNE DOORLAAT 6mm.
7: GETARREERDE TERUGSLAGKLEP.
8: VOOR MOPS.
9: BOLAFSLUITER MET DOORBORING.
10: LOCK VENTIEL.
11: VOOR LOCK VENTIEL HV44 ZIE PID 002-090-07-438-ISC3-p001.
12: XV23 & XV24 WORDEN SAMEN AANGESTUURD.
13: AANSTURING VIA POSITIONER.
14: XV30/31 FAILURE LAST.
15: SPOELSTUK VOOR Y-FILTER
(TE MONTEREN BIJ SPOELEN VAN INSTALLATIE)
16: XV01, TCV03A/B/C ZIJN TSO KLEPPEN.
17: NAAR VENTLEIDING IN MIDDENGANG.
18: PTC OP MOTORWINDINGEN.
19: RD02 IN HASTELLOY HC22, BREEKT BIJ 3,2 BARG
20: GETARREERDE TERUGSLAGKLEP GAAT OPEN BIJ 20mBARG
21: KLEPPEN XV08/20/21 OP HOOGSTE PUNT OP HEADER
22: HANDVENTIEL DAT D.M.V. VEER AUTOMATISCH SLUIT
23: ORIFICE VAN 6mm VOOR GOEDE DRUKREGELING
24: FV01 KAN VERVANGEN WORDEN DOOR EEN TEFLON LINED STUK
LEIDING. HIERMEE KUNNEN HOGERE DOSEERDEBIETEN GEHAALD WORDEN.
25: XV36 WORDT BEDIEND VIA DRUKKNOP PB01, PB01 KRIJGT IPL1
RECHTSTREEKS VANUIT STUURKAST REACTOR
26: LOCK VENTIEL T.B.V. LOTOTO XV16 AAN VENTIELKAST

TYPICAL VOOR ALLE
AUTOMATISCHE ON-OFF KRANEN.

OPEN ENDED PIPING TER
VOORKOMING VAN ACCIDENTELE LOZINGEN

1. BLINDKAP OF -STOP ZONDER GAATJE.
2. BLINDKAP OF -STOP MET GAATJE.
3. EEN TYPE AFSLUITER DIE NIET ACCIDENTEEL GEOPEND KAN WORDEN.
4. OPEN EINDE MET GECONTROLEERDE AFVOER.
5. OPEN EINDE MET AFGESCHERMDE AFSLUITER.
6. HENDEL VAN AFSLUITER VERWIJDERD.
7. KOPPELING MET TERUGSLAGKLEP AANWEZIG.
8. TOEGELATEN OPEN EINDE OP ONGEVAARLIJK MEDIUM.
9. OPEN EINDE OP ONGEVAARLIJK MEDIUM ZONDER RISICO
OMWILLE VAN BEREIKBAARHEID EN LOCATIE.
10. ER IS CONTINU EEN FLEXIBEL AANWEZIG.

Figure 24: P&ID of glass-lined reactor R022 [75]

Appendix B: Internal price calculation and information of centrifugal extractors of Janssen

Table 22: Data of a quotation of centrifugal extractors of a manufacturer

Type of extractor	Flow rate (l/min)	L x B x H (cm)	Weight (kg)
CS 50	0.01 – 1	30 x 30 x 60	30
CS 250	1.0 – 80	70 x 70 x 170	400
CS 330	1.0 – 160	105 x 105 x 214	900
CS 400	1.0 – 300	112 x 112 x 230	1400
CS 500	1.0 – 750	120 x 120 x 260	2000

Table 23: Initial cost estimation of Janssen of two centrifugal extractors from the quotation

Cost element	Cost (€)
Two centrifugal extractors units of type CS 330 in SS	250,000.00
Two pumps for water and reagent	10,000.00
Three flow meters with flow control valves	30,000.00
Mobil skid infrastructure	10,000.00
Basic control and trending for RPM and flowrate	30,000.00
Piping, valves and connectors for equipment	50,000.00
Qualification	20,000.00
Process engineering	50,000.00
Automation engineering	20,000.00
Prevention studies and inspections	8,000.00
Total cost	728,000.00

Appendix C: Internal price calculation of a complete revamp of the static condensers

Table 24: Cost estimation of Janssen of the complete revamp of the condenser system

Cost element	Cost (€)
Reflux Condenser (10,35 m^2)	120,000.00
After cooler (3,9 m^2)	95,000.00
Gas cooler (3,1 m^2)	80,000.00
Hoisting operations	20,000.00
Insulation operations for piping	15,000.00
Replacing glass piping process	150,000.00
Adapting stainless steel service pipes	70,000.00
Instrumentation process pipes: Temperature meters (4 pieces) Automatic valves (7 pieces) Automatic drain valves (3 pieces) Manual valves DN50 (7 pieces) Manual valves DN15 (2 pieces) Pressure control valve (1 pieces) Sight glass (1 pieces)	34,900.00
Instrumentation Service pipes (SS): Control valve (2 pieces) Automatic valve (1 piece) Drain valve (3 pieces)	15,900.00
Electrical operations	30,000.00
Process automation	30,000.00
Internal engineering	100,000.00
External engineering	50,000.00
Total cost	810,800.00

Table 25: Cost estimation of Janssen of a revamp to a reduced condenser setup with two condensers

Cost element	Cost (€)
Reflux Condenser (13.6 m^2) After cooler (2.5 m^2)	145,000.00 55,000.00
Hoisting operations	17,000.00
Insulation operations for piping	12,000.00
Replacing glass piping process	130,000.00
Adapting stainless steel service pipes	60,000.00
Instrumentation process pipes: Temperature meters (4 pieces) Automatic valves (7 pieces) Automatic drain valves (2 pieces) Manual valves DN50 (7 pieces) Manual valves DN15 (2 pieces) Pressure control valve (1 pieces) Sight glass (1 pieces)	33,900.00
Instrumentation Service pipes (SS): Control valve (2 pieces) Drain valve (3 pieces)	13,600.00
Electrical operations	25,000.00
Process automation	40,000.00
Internal engineering	120,000.00
External engineering	60,000.00
Total cost	711,500.00

Table 26: Cost estimation of Janssen of a revamp to one combined condenser setup

Cost element	Cost (€)
Reflux Condenser (17.2 m^2)	175,000.00
Hoisting operations	15,000.00
Insulation operations for piping	10,000.00
Replacing glass piping process	110,000.00
Adapting stainless steel service pipes	50,000.00
Instrumentation process pipes: Temperature meters (3 pieces) Automatic valves (7 pieces) Automatic drain valves (1 pieces) Manual valves DN50 (7 pieces) Manual valves DN15 (2 pieces) Pressure control valve (1 pieces) Sight glass (1 pieces)	31,650.00
Instrumentation Service pipes (SS): Control valve (1 pieces) Drain valve (1 pieces)	8,300.00
Electrical operations	20,000.00
Process automation	50,000.00
Internal engineering	130,000.00
External engineering	70,000.00
Total cost	669,950.00