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Analysis and visualization for optimization of the production flow of a pharmaceutical pilot plant with high product variety

Bachelor's thesis in Mechanical Engineering

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CHALMERS UNIVERSITY OF TECHNOLOGY
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PREFACE

This report is the result of a Bachelor's thesis (15 credits) for two students at Chalmers University of Technology, as a part of the program Mechanical Engineering. As a first step towards continuous production, AstraZeneca Gothenburg and FCC (Fraunhofer-Chalmers Centre) have started a collaboration. This thesis is the first interaction between these two collaborators. The project has been carried out at AstraZeneca Gothenburg at one of their department's from January 2016 to June 2016 commissioned by for FCC.

We have enjoyed our time at AstraZeneca Gothenburg and FCC. This Bachelor's thesis has been very educational for both of us.

We would like to thank our supervisors and co-supervisors for great support throughout the project: Catarina Dudas at FCC, Åsa Fast Berglund at Chalmers University of Technology and Staffan Folestad at AstraZeneca. Special thanks to our co-supervisor Gunnar Haeffler at AstraZeneca who has been more than helpful and showed great interest and dedication.

We would also like to thank the friendly personnel at the department at AstraZeneca for their collaboration.

Gothenburg, June 2016

Anna Ingelström and Clara Klang

SAMMANFATTNING

AstraZeneca, tillsammans med andra läkemedelsföretag, använder sig i största utsträckning av batch-tillverkning i sin produktion. Det finns idag möjlighet att istället tillverka läkemedel med kontinuerlig produktion, men då vanligtvis avgränsat till en produktvariant. Tillsammans med FCC (Fraunhofer-Chalmers Centre) har ett samarbete startats för att se över möjligheterna att kunna producera flera olika produktvarianter med hjälp av kontinuerlig produktion.

En avdelning med flera olika produktvarianter på AstraZeneca Göteborg, som tillverkar kapslar och tabletter till kliniska studier, har valts som studieobjekt. För att tillverka kapslar och tabletter krävs att ett flertal processteg genomförs, hur många och vilka beror på vilken produkt som tillverkas. För att FCC och AstraZeneca Göteborg ska kunna göra en rättvis framtida analys har en empirisk studie utförts på en av avdelningens tillverkande enheter. Studiens mål har varit att visualisera och beskriva nuläget och att identifiera potentiella förbättringsområden i produktionsflödet.

I den empiriska studien har data samlats in för 11 projekt/tillverkningar under en vald tidsperiod, med vidare analys av två av dem. Som komplement har en tidsstudie genomförts på ett projekt utanför tidsperioden, där ett fåtal processteg undersöktes. Skriftlig dokumentation, intervjuer, en observation samt ett frågeformulär har använts under datainsamlingen.

Resultaten antyder att avdelningen har potential till att öka sin effektivitet genom att standardisera, visualisera och öka sin driftsuppföljning.

Förutom teorier rörande olika typer av produktionsprocesser och layouter presenteras även kort om Lean och läkemedelsbranschens läge idag.

Nyckelord: Läkemedelsföretag, visualisering, Lean, effektivitet, driftsuppföljning, standardisering

ABSTRACT

AstraZeneca, and other pharmaceutical companies, primarily use batch manufacturing in their production. Today it is possible to produce drugs with continuous production, but typically limited to one product variant. AstraZeneca Gothenburg and FCC (Fraunhofer-Chalmers Centre) have started a collaboration to examine the possibility to use continuous production for multiple product varieties.

A department with high product variety at AstraZeneca Gothenburg, which manufactures capsules and tablets for clinical studies, has been selected for the study. To produce capsules and tablets several process steps are required. How many and which ones depends on the product. In order to make a fair future analysis of continuous production, an empirical study has been conducted at one of the department's pharmaceutical pilot plants. The study's goal has been to visualize and describe the current state at the pilot plant and also to find ways to optimize the production flow.

In the empirical study data has been collected for 11 projects/manufactures over a selected time period, with a further analyze of two of them. A time study was performed on a few number of process steps for a project outside the time period. Written documentation, interviews, an observation and a questionnaire have been used to collect data.

The results advocate that the department has the potential to increase their efficiency by standardizing, visualization and production follow-up.

In addition to theory of different process types and layouts, Lean and changes in the pharmaceutical industry are also presented in the report.

Keywords: Pharmaceutical companies, visualization, Lean, efficiency, production follow-up, standardization

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Definition list

Continuous production – a flow production method that manufacture products without interruption. Can also be called a continuous process or a continuous flow process

Continuous flow –the product or batch does not have any waiting time between process steps

Efficacy – capacity for producing a desired result or effect

Efficiency – accomplishment of or ability to accomplish a job with a minimum expenditure of time and effort

Variation – the act, process, or accident of varying condition, character, or degree

Variety – a number of different things, especially ones in the same general category

Contamination – the rooms are called contaminated when no other projects can use the rooms, a.k.a. occupied. Due to strict handling of the material, there may not be any "real contamination", but the pure risk of having any material that could cross contaminate another product in the room excludes the possibility to handle more than one product at a time.

Batch - a quantity of goods or material produced in a single manufacturing run

API – Active Pharmaceutical Ingredient

CIP – Cleaning In Place

DB – Delbatch

DP – Drug product

EBR – Executed Batch Record

GMP – Good Manufacturing Practice

IBC – Intermediate Bulk Container

IM – Intermediate Material

LAF – Laminar Air Flow

LC – Line Clearance

MBR – Master Batch Record

MIMS – Manufacturing Information Management System

OSD – Oral Solid Dosage

QA – Quality Assurance

SB – Subbatch

SHE – Safety, Health and Environment

SOP – Standard Operating Procedure

TH – Toxic Hazard

WIP – Wash In Place

1 INTRODUCTION

The background, aim and delimitations for the empirical study are presented here. An overview of the thesis is included and will guide the reader through the sections of the report.

1.1 Background

The pharmaceutical industry is today in a high degree based on batch manufacturing and has been conservative when it comes to changing that approach. Its main focus is following performance objectives: good quality including safety, efficacy and traceability. There has been a change in the market: the era of blockbuster medicines is over which has led to higher competition and lower margins (Mascia, 2013). There will be a high demand of mass customization and more personalized products in the future. Large pharmaceutical companies will now need to add flexibility (e.g. in product variety) and cost effectiveness to their performance objectives. This puts pressure on the manufacturing, i.e. it needs to be more flexible and more effective, and has led to an interest for new manufacturing methods. One way forward is a switch to higher degree of continuous processes. Earlier studies (Wilburn, 2010) (Mascia, 2013) (Lakerveld, 2013) have spoken of continuous production and its upsides which is lowered costs and shorter throughput times, but the limitations in product varieties with this method have not been mentioned, see figure 1.1.

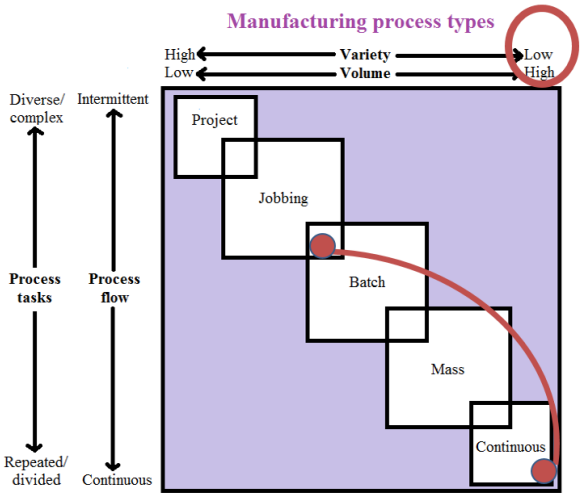

Figure 1.1. From batch to continuous process

As a first step towards continuous production AstraZeneca Gothenburg and FCC (Fraunhofer-Chalmers Centre) have started a collaboration. This study is the first interaction between these two collaborators and will continue in two PhD-works. The study will investigate the secondary production of a pilot plant belonging to AstraZeneca. AstraZeneca is a global pharmaceutical company with 57 000 employees around the world. The pilot plant manufactures drugs for clinical studies and is today mainly dominated by batch manufacturing. The plant has a high flexibility and many product varieties, which is a situation representative for future demands also on big scale manufacturers (commercial mass producers).

An empirical study will describe the pilot plant's current way to manufacture drugs and the resources needed when manufacturing pharmaceuticals with a high level of product variety. The study will also investigate the efficiency of the pilot plant's current manufacturing and data collected will be used when suggesting ways to increase the efficiency at the pilot plant, without changing current batch manufacturing methods. Lean (see 3.3) is an approach that have proven to be useful in many operations to increase efficiency, and to show where

improvements can be made. The result of the study will be used in the continued work towards continuous production for AstraZeneca Gothenburg and FCC.

1.2 Aim of the study

The aim of this study is to describe and visualize the current state at the pilot plant. This includes analyzing the efficiency in the manufacturing of solid oral dosage forms to clinical studies. The current state will enlighten the complexity and limitations of producing multiple product varieties for pharmaceutical manufacturers. The current state will also enlighten where changes can be made for optimization of the production flow at the manufacturing site.

The following questions are to be answered:

- What current resources are needed to ensure good quality, safety, flexibility and traceability?
- What opportunities/approaches exist for further increasing the pilot plant's efficiency from re-engineering the production flow without changing current batch manufacturing methods?

1.3 Delimitations

The following limitations are made:

- Investigate the manufacturing of pharmaceuticals to clinical studies at the department responsible for the manufacturing of drug products at AstraZeneca Gothenburg

The department has a high product variety and flexibility and will represent future customer demands on big scale drug manufacturers (commercial mass producers).

- Investigate the secondary production (not the production of API)

It is most likely that other pharmaceutical companies have a different secondary production and ways of producing solid oral dosage forms to clinical studies, this spectrum has not been included in this study.

- Only focus on two solid oral dosages forms, tablets and capsules, manufactured at a pilot plant at the department studied

Only tablets and capsules are chosen to be investigated because the variety at the department is high. The most common drug delivery method today is solid oral dosage forms.

- Not focus on technical manufacturing methods

Manufacturing methods and their purpose will be described but excluding details on their technical functionality. A more detailed description was not seen as necessary for the empirical study.

- Not focus on manpower shortage

The employees at the studied department do not work only with manufacturing in the pilot plant, they have different assignments, e.g. manufacturing in other facilities and research.

- Only collect data for a period of five months excluding the time study. The reason was that the time study needed to be carried out in real time.
    - Only focus on the used rooms, machines and equipment

In order to determine the overall efficiency in the manufacturing a period that would give a reasonable spread of batch sizes, drug product varieties and stops in production was chosen.

- Only collect data from the projects within the time period

Technical tests, i.e. not manufacture for use in clinical studies are not included.

- Only further analyze two projects within the time period
- The time study will not include all process steps

1.4 Overview of thesis

The report is divided into six chapters.

Chapter 1: Introduction

In the first chapter the background to the study is explained. In this chapter is also the aim of the study with questions to answer found. The last part of the chapter features the limitations of the study.

Chapter 2: Methodology

In the second chapter, the data collection methods, analysis tools and time study used are described, both what they are, when they can be used and how they have been used in this study. Validity, reliability and different types of characteristics of data is presented. Lastly, the research approach is described.

Chapter 3: Theoretical reference frame

The third chapter consists of the theories that the empirical study is built upon. The chapter starts with an explanation of the changes in the pharmaceutical industry. Then the chapter follows with the different types of processes and layouts. Lastly there is a section about Lean including resource efficiency, Lean production, and the DMAIC-cycle.

Chapter 4: Empirical study

The fourth chapter presents the empirical study. For the reader who is familiar with the department and know how solid oral dosage forms are manufactured, sections 4.1, 4.2 and parts of 4.3 can be excluded. Section 4.4 is where the current state is explained regarding the variety in the manufacturing, the complexity of a project and the results from the time study.

Chapter 5: Discussion

In the fifth chapter, there is a discussion about the choice of methods and theories. Thereafter, the subjects' efficiency, production follow-up and standardization are discussed. The discussion include suggestions for the department and how the theoretical reference frame is linked to the results of the study.

Chapter 6: Conclusion

Finally, in the last chapter, the answers to the questions in the aim are summarized.

2 METHODOLOGY

This chapter describes the methods that have been used during the study. A more detailed description on what has been done when and why is also found in this chapter.

2.1 Validity and reliability

Validity and reliability are two well-known concepts when collecting and assessing data. Validity means how correct the reality is compared to the collected and assessed data whereas reliability is how well multiple tests agree with each other. High validity is accomplished if there are no or little systematic faults and the random faults are minimal. High reliability is accomplished if the results of the tests have minimal difference. It is important to know in which situation the results are valid, that relevant data is studied and that surveys are done in a reliable way. A consequence of high validity is high reliability whereas high reliability is not necessary a consequence of high validity (Bohgard, 2010, p. 480). There are two common aspects on validity, external and internal. External validity is accomplished if the result from the study can be generalized to other situations whereas internal validity is accomplished if the result for a specific situation is valid or not (Akademin för ekonomi samhälle och teknik, 2014).

In this study the results will differ from one project (see 4.2.1 and 4.3.1) to another but also if the same project from different time periods would be analyzed. A time study was executed to receive missing data, in order to give reliable results.

2.2 Characteristics of data

Methods for collecting data can be divided into four groups which are categorized by their characteristics. The characteristic groups are their opposites and are as follow: empirical or analytical, objective or subjective, qualitative or quantitative and expert or participative. It is possible to use one or more of them but some combinations are not possible. A good study need to use multiple characteristics and methods (Bohgard, 2010, p. 481).

Depending on the origin of the data, it can be an empirical or analytical study. If the data is taken from the reality it is empirical and if the data is taken from a simulated reality it is analytical. For example an empirical study is done if a physical object, e.g. an operator is studied when in progress whereas an analytical study is done when no physical object is observed, e.g. when an operator's knowledge about the procedure is collected (Bohgard, 2010, p. 481).

The collected data can be objective or subjective. Objective data is collected through direct measurements where a person’s experience and thoughts are not taken into account. For example an observation on how often something is done or how many heartbeats per second a person has. Subjective data is collected through a verbal or written study about people's thoughts and experiences. For example by evaluating how long time a specific element takes to accomplish (Bohgard, 2010, p. 482).

Depending on the result of the data it can be qualitative and quantitative data. If the data results in numbers it is most likely called quantitative. Qualitative data respond to questions as what, who, how, when and where and will result in a description and a comprehension about a certain subject (Bohgard, 2010, pp. 482-483).

If the data is expert or participative depends on how active the user is during the execution. Highly participative is when the users are highly involved in the method and low participative, also called expert, is when they are not involved, instead it is the executor (Bohgard, 2010, p. 483).

The result of this work is an empirical study where both qualitative and quantitative data have been collected. Throughout the study, the degree of participation has been high and therefore enabled subjective data to complement the objective data.

2.3 Data collection methods

During the empirical study, four types of data collection methods have been used: written documentation, questionnaire, interview and observation (Bohgard, 2010, p. 484). The different methods have been used throughout the whole study to gather the relevant information to reach the aim. Written documentation and interviews are the ones that have been used the most.

Written documentation

A literature study is one type of written documentation based on previously documented results. This method is used to collect needed information that is already available in the literature. The information can be found at multiple places, for example on Internet, in books, in articles, checklists and guidelines (Bohgard, 2010, pp. 490-491).

In this report information has been collected to the theoretical reference frame and the empirical study. The theoretical reference frame is based on information found in student literatures, Internet and documents received from the department studied. The empirical study is based on information found on the company's webpage and in PowerPoints, guidelines and other documents given by the department, e.g. EBR, SOP, MIMS and logbooks for rooms and equipment. The data (times and dates, process step, etc.) from the EBRs and MIMS-reports were compiled in an excel-document. See section 4.2 for information about the documents received.

Questionnaire

A questionnaire is a subjective method with no personal contact between the respondent and the creator of the questionnaire (Bohgard, 2010, pp. 488-489).

This method was used to receive information about some of the equipment in the pilot plant from the persons responsible of the equipment. An excel-document were composed with each equipment on separate rows. The needed information was left blank for the persons responsible to fill in. What to fill in was described by the columns. This document was sent to them by email and was sent back when they had filled it in, see appendix 1 for the document sent out.

Interview

Interview is a method that can be used in many different types of projects to get a wider understanding on how people reason and think. The result are therefore subjective. Depending on the structure of the interview the collected data can be qualitative or quantitative. There are three types of interviews; structured, semi-structured and unstructured. The aim decides which one to use. A semi-structured interview is a mix between a structured and unstructured interview (Bohgard, 2010, pp. 485-487).

In a structured interview the questions are predetermined by the interviewer. The interviews are quite short and the people interviewed are many more than in the other two types, therefore the result is quantitative (Bohgard, 2010, p. 486).

In an unstructured interview the questions are much more open, which makes it possible for the person who is being interviewed to talk freely about their opinions and can themselves decide what the interview should cover. This method is used when the interviewer has a slight idea about what him/her want to know (Bohgard, 2010, p. 486).

In this study, interviews have been held with some of the employees at the department, as a complement to the documents received. The interviews have taken place at AstraZeneca throughout the study. Some weeks there have been more interviews than others. The structure of the interviews has been both unstructured and semi-structured. The lengths of the interviews have been different every time. The first four interviews were unstructured and were held to obtain a better understanding on how the department work. Table 2.1 demonstrates the type of interviews that have been held and the persons who have been interviewed. It also indicates the approximate length and reason for the interviews. The interviews are listed in the same order as they were held.

Table 2.1. The interviews held throughout the empirical study

Type of interview	Who	About	Length
Unstructured	The Functional planner	Planning	1 h 30 min
Unstructured	Lean expert*	Old studies	1 h
Unstructured	Lead operator 1	Lead operator tasks	1 h 35 min
Unstructured	Lead operator 1	Manufacturing methods	1 h 30 min
Semi-structured	Team manager	Data collection	1 h
Semi-structured	Lead operator 2	Project A	1 h 15 min
Semi-structured	Lead operator 3 + Operator 1	Project B	1 h 20 min
Semi-structured	Lead operator 4 + Operator 1	Project X	1 h
Semi-structured	Lean expert + Team manager	Time study	1 h 15 min

* The Lean expert was involved in a Lean project 2010 to map the utilization at the newly built pilot plant with the help of a time study. The Lean expert is also associated principal scientist (APS) and GMP technical expert.

Observation

An observation is an objective method to study a situation or person without interference. The method is used to receive information about what people actually do and not only what they think they do. The result can be both qualitative and quantitative. An observation can be held in both a fictitious and an actual environment and can be indirect, direct or participant. In a direct observation the observer is present and it is important to not interfere whereas an indirect observation can be made by collecting the data through videotaping. In a participant observation the observer is a part of the group and do the same things as the rest of the group. The observer should be well versed in the subject (Bohgard, 2010, pp. 484-485) (Nationalencyklopedin, 2016).

In this study an observation was made to relieve the time study of an actual environment. The result was qualitative and the observation was conducted directly. The start- and end time for every activity was written down and also the activity that was executed. During the observation questions were asked to get a better understanding of why some things were done.

Other

In addition to the four data collection methods, further questions have been asked by email to clarify minor uncertainties. The empirical study is also based on information collected in the

hallway as a consequence of random small chats with some of the employees at the department studied.

2.4 Meetings

During the empirical study, there have been a follow-up meetings with the concerned parties approximately once a month. The meetings have been held to obtain a good relationship between the parties and as a sounding board. At the first two meetings, tours on the manufacturing site were given, where valuable information about the manufacturing was acknowledged.

The Team manager (see 4.2.2) has been available for small meetings (approximately five minutes) during every visit at AstraZeneca Gothenburg. The result of the meetings has been guidance and discussions.

2.5 Time study

A time study is when you divide a work procedure into different simplified activities and measure the length of the activities. The time can be measured with a stopwatch or as in this empirical study where the start time and end time was written down (Nationalencyklopedin, 2016).

The time study was executed to get a deeper understanding about what is actually happening during a project and to know how much time that actually is used to reach the end result. The purpose of the time study was to find out the set-up time, up-time and cleaning time but also disturbances. The time study was made on project X. With the help from two interviews and by analyzing an old time study at the pilot plant, two documents and one tutorial were made. The first document was a sheet which was put in every used room with the aim to know when the room was occupied by the project and if another project would be able to enter. The second document was a more detailed sheet which also was put in every used room. In this sheet the operators were supposed to write down all the activities that were made. Each activity was written on a separate row with a specific start- and end time. If there were any disturbances they were supposed to be written down as well. These sheets are found in appendix 2, note that they are written in Swedish. The tutorial was written to let the operators know the reasons of the time study and what to consider when filling in the sheets. There were also examples of data to fill in presented. The tutorial with examples is found in appendix 3, note that they are written in Swedish. As a compliment to the time study an observation were made for one of the manufacturing days. The data collected was compiled in flow charts and in pie diagrams (see section 4.4.3).

2.6 Analysis

The study has mostly been focusing on collecting and visualizing data. Conclusions have been drawn through the use of different methods of presenting the data.

Pie diagram

A pie diagram is a chart which show the proportion of, in this case, time use of different tasks. A pie diagram is quick to compile and is easy to understand (Smartdraw, 2016).

In the empirical study pie diagrams have been used to illustrate which rooms that have been used and the different process steps that have occurred in those rooms. The length of the activities have been documented and sorted accordingly: set-up time, up-time, cleaning time and disturbances. Four types of pie diagrams have been made. One to illustrate how much time a used room have been occupied, one to illustrate the rooms a certain process step has taken place in and one to illustrate the activities in the room. If any disturbances occurred, this were also presented in the pie diagrams. The fourth pie diagram illustrate how much of the time each process step actually took in proportion to each other. To make the pie diagrams, it was important to know which activities that have been made and the lengths of the activities.

Work hours in the pilot plant differs from day to day, so assumptions were needed for the analysis. Both 8 hours and 24 hours was used as a guide, but due to the CIP (see 4.2.5) sometimes running at night, 24 hours was used when making the analysis.

Flow chart

A flowchart is an illustration with the order of operations to complete a task. There are many different kinds of flow charts, for example block diagrams, work flow charts, and activity diagrams (Smartdraw, 2016).

In the empirical study, flowcharts have been used to illustrate which process steps that needs to be done to complete a product and to visualize the order of the activities and flow in the manufacturing. The flowcharts in the empirical study have been adjusted to suit the aim.

Spaghetti diagram

According to Smartdraw: *a spaghetti Diagram allows a critical analysis of the movement of material of people within the workspace. The goal is to eliminate transit waste* (Smartdraw, 2016). No spaghetti diagram was executed in the empirical study.

2.7 Research approach

The study's focus, along with mapping the pilot plant, started out as finding ways to improve the planning and capacity at the pilot plant. If there was a way to predict how long a project would take to manufacture, it would prevent disturbances and release more resources. Due to setbacks in finding information needed to make any conclusions on how to improve the planning, focus shifted to emphasize the importance of measuring processes and production follow-up.

Firstly four interviews were held to give an understanding of the subject and an indication of where to start. This led to the decision to investigate a specific time period and the projects within that time period. Sections 4.1, 4.2 and 4.3 have been gathered throughout the study with the aim to understand section, 4.4. The data collection methods described in section 2.3 were used to collect the data. The product variety in the pilot plant during the period (see

4.4.1) was documented with help from the Functional planner (see 4.2.2). In order to find out the pilot plant's up-time during the period EBR's (see 4.2.1) and MIMS-reports (see 4.2.5) were used to find out when, where and how long the process steps (see 4.3) had taken for each project during the time period. The data was compiled in an excel-document where each project had their own sheet. This was a wide approach and would be of importance when improving the planning. After the mapping, it was found that the time used for each process step in the EBR's was not reliable enough. To dig deeper and to get more reliable data logbooks of the rooms and equipment (see 4.2.3 and 4.2.4) were collected.

Due to the amount of work needed, it was decided to only investigate two projects further. See section 4.4.2 for information about project A and project B. Various flowcharts for each project were made to visualize the flow within the project. One of the two projects was more thoroughly described. Interviews were held in order to approximate the set-up time for all process steps and to approximate the cleaning and run times for the processes that did not have MIMS. The interviews did not give the data needed, i.e. information was scarce. The interviews showed that the time-use for a process step was not known and that how long it should take was not stated. This is where the focus of the study shifted. It became obvious that it was needed to find out how long time process steps actually takes.

A time study was executed for one on-going project and its result is found in section 4.4.3. The time study was executed in order to show, without assumptions, how much time the rooms were occupied, the activities in them, and the length of the activities. Focus was on set-up time, up-time and cleaning time. The results were presented with both pie diagrams and flow charts.

As a part of the empirical study, a questionnaire was sent out and information about the equipment used during the time period was collected. The result of the questionnaire can be found in the tables in sections 4.2.3 and 4.3.

3 THEORETICAL REFERENCE FRAME

In order to make this study, information from different sources has been collected. To make a similar study or to continue where this study left of, there must be a knowledge about the incitements for this study as well as an understanding of the product and process.

3.1 Changes in the pharmaceutical industry

The pharmaceutical industry has experienced a tremendous change the past few years. The blockbuster model that has given the pharmaceutical companies growth and high revenue is now said to not fit the market anymore (Carroll, 2009) (Malik, 2007) (Nisen, 2013).

The blockbuster model is a business strategy which means to put all efforts to find a drug that will be a best seller. This is enabled by making the drug suitable to all patients. These drugs traditionally treat one condition and fit the average patient. Drugs are sold with high margin and most of the profit is obtained during the time the company still has patent on the drug. When the patent expires, the same drug can be produced and sold by others, often at a lower price. The competition is higher and it is not profitable enough (as it used to be) to slightly improve a drug and sell it as a new patent. The chance of producing a blockbuster drug is lower today.

The blockbuster model is now changing and many blockbuster producers have patents that have or are about to expire. The new focus is on personalized drugs that is more patient orientated and can treat many conditions (PwC, 2011). We will see many new products on the market, and high margin products will be significantly lower. It is crucial to be able to produce drug products at low cost. This affects the whole industry both research, supply chain and the manufacturing.

The years of low competition, high margins and high profit have enabled the pharmaceutical industry to not focus on cost efficiency to the same degree as in other industries. PwC have had a serie of reports, called “Pharma 2020- Which path will you take?”, published 2007-2011 which summarize the upcoming challenges and actions that pharmaceutical industry face in order to cut costs and be competitive. The reports implicate the need for improved supply chains, new techniques, and new demands in the manufacturing of drugs. Research and development need to operate with a lower budget due to lower margins and it affects the manufacturing to clinical studies. The demand for improvements in capacity and throughput time is rising in order to decrease time to market, and thereby increasing the time the product can be sold under patent (PwC, 2011).

The production is mainly restricted to batch manufacturing today, but continuous production as an alternative to bring down costs in the manufacturing has been studied. Earlier studies (Wilburn, 2010) (Mascia, 2013) (Lakerveld, 2013) have shown that it is possible to produce drugs this way and that it has many advantages to traditional batch manufacturing. A business case from 2010 (Wilburn, 2010) implicate a cost reduction with continuous production over traditional batch manufacturing. The business case did not mention changeovers and only one drug product was taken into account.

Pharmaceutical companies have implemented some concepts and tools of Lean (more about Lean in section 3.3) but still struggles with applying continuous flow in their organization and manufacturing. Knowledge management and viewing manufacturing as an important part of the products value chain are said to be of major importance (Shanley, 2010) (PwC, 2011) .

3.2 Process types and layouts

There are five different types of manufacturing processes which are based on a volume-variety spectrum: project, jobbing, batch, mass and continuous processes. To this processes there are four types of basic layout types: fixed-position, functional, cell and product layout (Slack, 2013, pp. 101-102, 193). Figure 3.1 illustrates the different types of manufacturing processes and which variety, volume, process flow and process tasks they represent. Figure 3.2 illustrates which manufacturing process type that is suitable for a certain basic layout type. Figure 3.3 (page 14) illustrate the layout of each layout type and which is used when regarding variety and volume.

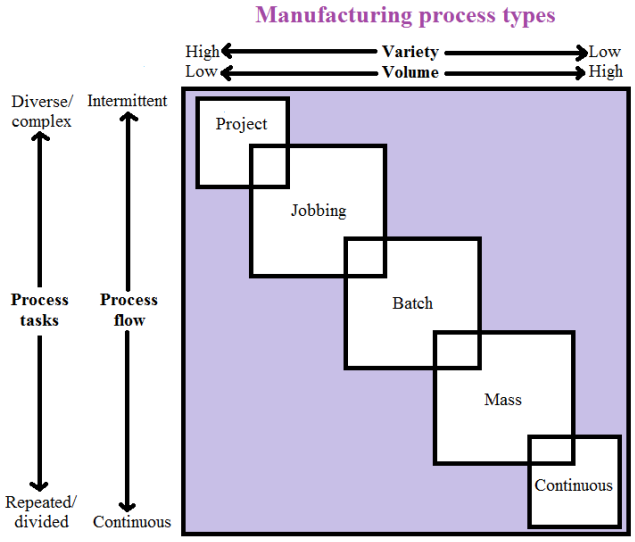

Figure 3.1. Manufacturing process types, adapted from Slack et al. (2013, p. 102)

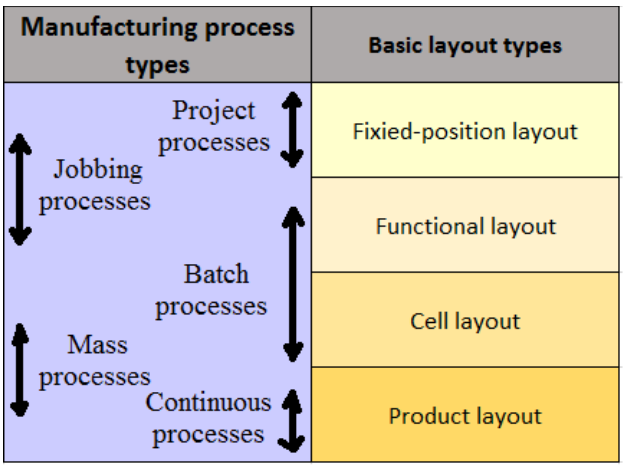

Figure 3.2. Manufacturing process types & basic layout typed, adapted from Slack et al. (2013, p. 194)

Project process

Slack et al. (2013, p. 497) define a project as *a set of activities with a defined start point and a defined end state, which pursues a defined goal and uses a defined set of resources*. The complexity and variety is high whereas the volume is low, because it is only one object that is being manufactured. The resources needed in a project process are more or less exclusively devoted to it. An example of a project process is large fabrication operations (Slack, 2013, pp. 102-103).

Jobbing process

The jobbing process is more or less the same as a project because the variety is high and volume is low. The same job can occur again but it is not necessary. The resources needed in a jobbing process are not exclusively devoted to the specific job and can therefore be used in other jobs. An example of a jobbing process is a special designed machine (Slack, 2013, p. 103).

Batch process

BusinessDictionary define a batch as *a quantity of goods or material produced in a single manufacturing run* (BusinessDictionary, 2016). A batch process pass through the same sequence of operations to reach the end result. The batch size can be small and similar to the jobbing process but also large and repetitive and similar to the mass process. An example of a batch process is cooking different dishes to a dinner (Slack, 2013, pp. 103-104).

Mass process

The mass process have a high volume with little variety difference. All the products pass through the same process even if there are some differences between the products. An example of a mass process is an automotive plant where all the cars are manufactured in a single line (Slack, 2013, p. 104).

Continuous process

The continuous process have the highest volume and lowest variety of the five manufacturing process types. The process are rarely to stop and have a continuous flow where the product always is in motion therefore changeovers are unlikely. An example of a continuous process is a petrochemical refinery (Slack, 2013, p. 104).

Fixed-position layout

As figure 3.3 illustrate the resources move to the product which is in a fixed position. There are multiple reasons to why the product is not to be moved. One reason is that it is too large and another is that the product is too delicate. Example of resources are personnel, machines and materials. This layout is suitable for both project and jobbing processes. An example of a process with a fixed-position layout is a shipbuilding which is too large to be moved (Slack, 2013, p. 194) (Mattsson, 2013, p. 29).

Functional layout

In a functional layout the resources are situated at one place and the products are moved between them as needed. This makes the different products taking different routes within the layout. Similar resources are located together because it can be more convenient or will improve the utilization. This layout is suitable for both jobbing and batch processes. An example of a process with a functional layout is a supermarket (Slack, 2013, pp. 194-196) (Mattsson, 2013, p. 29).

Cell layout

In a cell layout the resources needed to manufacture a certain product are located in the same cell. The resources in the cell can either be organized as a functional or a product layout. It is possible to use one or more cells in the manufacturing. This layout is suitable for both batch and mass processes. An example of a process with a cell layout is a maternity unit in a hospital (Slack, 2013, p. 197) (Mattsson, 2013, p. 29).

Product (line) layout

As figure 3.3 illustrates, and the name implies, this layout is a line with different operations located in sequence and the products are manufactured in this sequence. The layout give a good flow where the same type of products are being manufactured. This layout is suitable for both mass and continuous processes. An example of a process with a product line is an automobile assembly (Slack, 2013, pp. 197-198) (Mattsson, 2013, p. 29).

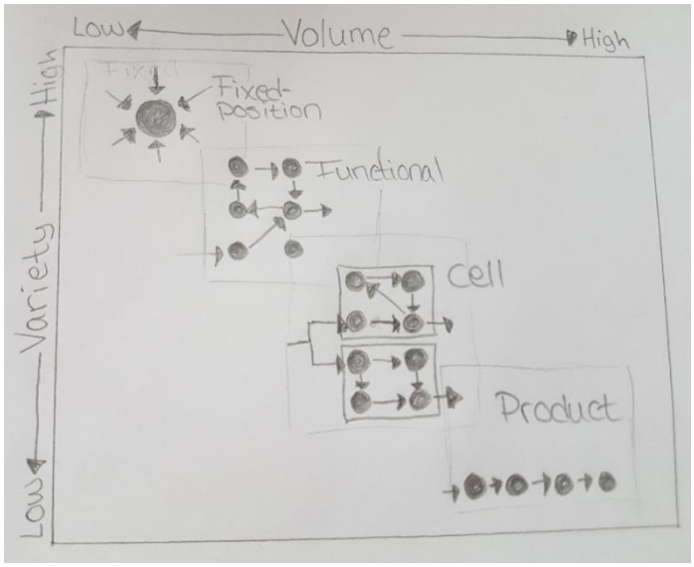

Figure 3.3. Basic layout types, adapted from Slack et al. (2013, p. 202)

3.3 Lean

There are many approaches on how to manage and improve operations. To stay competitive it is important to make continuous improvements.

Resource efficiency

Resource efficiency is the traditional form of efficiency and is measured by utilization. Utilization of a resource is calculated by comparing the used time with the available time. Low utilization means that the resources are not used to maximum extent and therefore derives an unnecessary cost to the company. Resources can be both personnel and machines. Focus for resource efficiency is on increasing the time the resource is used and thereby increasing the productivity (Modig, 2012, pp. 7-11). This, on the other hand, can lead to overproduction and sub optimization (Bergman, 2012, pp. 462-463).

Lean production

Lean production is a philosophy that has its origins from the Japanese automotive manufacturer Toyota. The philosophy was introduced to the west as Lean production in the 90's after results showing that Toyota was significantly better than competitors - both in quality and productivity (Womack, 1990).

Lean production is summed up by 14 principles and can be categorized after the 4P model. The 4Ps are Philosophy, Processes, People and Problem solving. This study has focused on the second P which is Processes, where principles 2-8 can be found. Lean production focuses on a swift and even flow by eliminating waste in their processes (Liker, 2004, p. 13).

Principle 2: Creating flow

Lean focuses on flow efficiency and it is measured by taking the total value adding time and divide it with the throughput time (Modig, 2012, p. 26). Slack et al. (2013, p. 100) define throughput time as *the average elapsed time taken for inputs to move through the process and become outputs.* The flow efficiency can be improved by reducing the work in progress, reduce cycle times or by adding more resources where needed (Bergman, 2012, p. 463). To improve the flow efficiency Lean speaks about seven wastes. By aiming to eliminate the activities that does not add value the flow and throughput time can be improved.

Liker, J. K. (2004, pp. 28-29) define the seven wastes of lean as:

Overproduction - Producing more than needed at the time

Waiting - The products are not being processed and instead are waiting to be processed

Transport - Movement between the processes

Over processing - The processes may not be producing exactly as they should

Inventory - Having more in stock than is needed

Motion – Unnecessary movement of the operator that does not involve the product

Defects - Producing defective products or rework

As mentioned, the Lean philosophy focus on a swift and even flow. It is a way of working smarter - not harder. By eliminating waste and aiming for a fast one-piece flow, quality and throughput time can be improved (Liker, 2004, pp. 87-101).

Principle 3: Use Pull systems

The purest form of pull is a one-piece flow without inventory produced on-demand. Production orders are not based on projected customer demand and pull systems are preferable to avoid overproduction (Liker, 2004, pp. 104-112).

Principle 4: Level out workload

Liker, J. K. (2004, pp. 113-125) refers to Muda, Muri and Mura. Muda is the seven wastes and only focusing on them can give bad results therefore Muri and Mura also needs to be considered. Muri means overburdening people or equipment beyond natural limits and can result in safety or quality problems. Mura means unevenness and is a result from an uneven production schedule and uneven volumes. Unevenness creates waste and an important way to avoid unevenness is reduced set-up times for changeovers and standardization.

Principle 5: Stop the process

Build a culture that fix problems as they occur in order to get quality right the first time. It is of importance since the problem may repeat itself tomorrow and to avoid defects continuing downstream. Design for quality, standardized task and involving team members are the key (Liker, 2004, pp. 128-139).

Principle 6: Standardize tasks

Standardized work is essential for continuous improvement and employee empowerment and consist of setting a standard for time required for processes, the sequence of doing things and how much inventory to have. The standards need to have a balance between specific rules and still provide flexibility and room for innovation. The standards should be improved by those who do the work (Liker, 2004, pp. 140-148).

Principle 7: Use visual control

Visualization is used to make problems visible and to support a good flow. 5S is a common tool used to visualize and eliminate waste. Without visualization it is hard to distinguish deviations and a fire-fighting way of work occurs. Visual control is a way of easily finding deviations from the target and can be a chart or methods integrated in the process, i.e. Kanban's (Liker, 2004, pp. 149-153). Visualization makes it possible for everyone to see what has been and is being done at the production site and also if there have been any problems (Slack, 2013, p. 475).

Principle 8: Only use reliable, tested technology

The processes that are to be used must be tested. A new technology can be difficult to standardize and implement without affecting the flow. Stability, reliability and predictability are therefore important (Liker, 2004, pp. 160-168).

DMAIC-cycle

The DMAIC-cycle is an improvement cycle with five stages. The first stage D stands for define and in this stage the problem or problems are defined. They are defined to know what process that needs to be improved and often a formal goal is set. The next stage M stands for

measure and in this stage the process is measured and described to know if there really is a problem (Slack, 2013, p. 584). This mean that what you do not know you cannot change, namely to measure is to know and is confirmed by a quotation from a lecture held by William Thomson Kelvin (1889, p. 73):

I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of Science, whatever the matter may be.

In stage A, that stands for analyze, the measurements are analyzed in order to find the root causes of the problem or problems. The fourth stage I stands for improve and in this stage the process are improved. This is done by developing ideas and testing solutions. If the solutions tend to solve the problem or problems they are implemented and later formalized and the results are measured. The last stage is C, which stands for control, it is here the process are controlled to see that the results are sustained. It is important to know that when a cycle is finished the cycle starts again and so it continues (Slack, 2013, pp. 584-585).

4 EMPIRICAL STUDY

In this chapter there is a description of how the secondary production of solid oral dosage forms for clinical studies is manufactured today at the pilot plant. Section 4.1 consists of a short description about what clinical studies and solid oral dosage forms are. Section 4.2 consists of general information about the department studied. Section 4.3 gives information about what a project is and the different process steps when manufacture the solid oral dosage forms. In the last section, 4.4, the current state is described. The information found in this chapter is based on interviews and documents given by the department studied.

4.1 Clinical studies and solid oral dosage forms

The department is responsible for manufacturing drug products for clinical studies. Clinical studies are trials on patients or on healthy persons that need to be done before a drug product can be released on the market. The aim of clinical studies is to see the effects and risks with a new drug product. Historically it typically takes eight to twelve years to put a new drug on the market, i.e. from idea to approved medicine. There are three phases to pass before a new drug product can be released and this decides the spectrum of how much to manufacture. In Phase I there are approximately 20 studies with a total of 400 healthy persons. In Phase II there are 2-4 studies with a total of 800 patients, these patients have the condition the drug product are trying to cure or ease. In Phase III there are multiple studies with at least 5000 patients. (Nationalencyklopedin, 2016) (AstraZeneca, 2016).

At the pilot plant, oral solid dosage (OSD) forms are manufactured. There are different types of OSDs, two of them are tablets and capsules. They will be further described. Tablets and capsules are a convenient way of drug delivery for the patient. The manufacturing process has been developed over 100 years and is well defined. A tablet/capsule consists of multiple ingredients. Some only have the active substance and a filler, but it is often more complex. Ingredients that give the OSDs the wanted characteristics and make the production easier are frequently added. It is easy to adjust the active content in capsules and therefore prompted to be good for future demand on personalized pharmaceuticals.

Active substances

API: Active Pharmaceutical Ingredient, the drug that will help the patient

Inactive substances (excipients)

Fillers: To increase bulk volume in order to produce a tablet of practical weight

Disintegrants: To facilitate rapid breakup and disintegration of the tablet

Binders: To bind powder particles together during wet granulation (see 4.3.2.4.2) and increase the tablet strength

Lubricants: To prevent adhesion of powder to the surfaces of punches and dies and to facilitate tablet ejection from the die

Glidants: To reduce interparticulate friction and to improve flowability of the powder

Wetting agents: To aid wetting and dissolution of the drug

Coating Liquid: Gives a cast over the tablets that makes them easier to swallow

Capsule shell: Made from e.g. gelatin.

Color and flavor: Helps to identify and separate the drug

4.2 General information about the department

This section will give an understanding of the department studied and its way of working, guidelines in production, people responsible, equipment needed and how the manufacturing site (a.k.a. pilot plant) for solid oral dosage forms is built.

4.2.1 The department's way of working

AstraZeneca Gothenburg has about 2400 employees and approximately 50 are currently working at the studied department. Approximately 30 of those work at the pilot plant where the empirical study took place. They work day-shift and the manufacturing is therefore mainly performed daytime, if necessary, there are possibilities to manufacture on weekends or evenings. The department manufactures inhalation products, non-sterile liquids, parenterals (injectables), and OSDs. Therefore, many different skills are needed. This empirical study will only investigate OSDs, which are manufactured in a facility referred to as the pilot plant. Manufacturing the drug is the key delivery for the department. However, the department is also providing important input to the research and development of pharmaceuticals. Formulations need to be adjusted and process steps need to be optimized. The quality and safety of the drug is very important. Technical tests are done at the site before manufacture to ensure that it is possible to produce the drug in the wanted quantity. These tests require time from both personnel and equipment. The technical tests are made to ensure that the manufacturing will be right at the first time.

It is also a lot of paperwork before a drug can be manufactured and a lot of work after the manufacturing is done. An information flow process chart (swimlane plot) was made for a Six sigma project a few years ago, see figure 4.1. This shows that the work done before and after manufacturing takes up a major part of the time. The Six sigma project focused on minimizing the time loss outside the manufacturing.

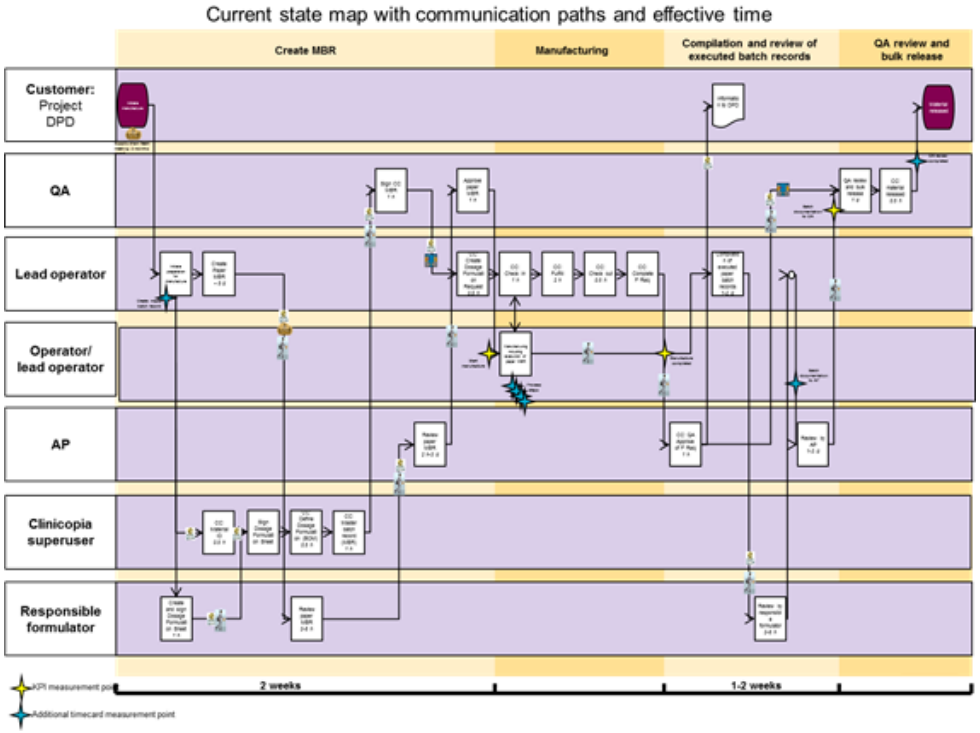

Figure 4.1. Information flow process chart over the department

Every product that is manufactured at the pilot plant belongs to a unique development project and the manufacture of that specific product may be repeated over time depending on the clinical studies. A manufacture within a project consist of finalizing the secondary production of a drug product. The ways of carrying out a manufacture could be described as a **project** in itself, but that "project" must not be mixed up with the development project and is usually referred to as a manufacture rather as a project. The drug product of a project can for example be tablets of different strengths. The products corresponding to a project contains the same API although excipients may and strength may differ. More about it in section 4.3.1.

The work is done in **teams** with operators chosen based on their skills and availability. The teams consist of about five to ten operators. The operators have different skills and do not necessarily follow the manufacturing from start to end. Each process step has different operators responsible. A process step need at least two operators (see further down under GMP). The personnel is highly educated, almost every one of them have an academic degree and the personnel have a high sense of responsibility. The department is positive to changes and progress. The operators have other assignments at the department besides manufacturing, so working hours in the manufacturing differ from day to day and person to person. Education, e.g. learning new process steps, is done during manufacturing and when running technical tests. Most work is done in pairs and learning subsequently from each other is possible without calling in a third party. Twice a year there is a time period set aside for training on the machines and equipment, but these skills need to be used frequently not to be forgotten. The operators are usually experts on one or a few machines and have basic knowledge on additional ones. It is common that the operator focuses on one machine/process step for a certain period of time and thereby supports several projects rather than following the manufacture of one project from start to end.

There are many guidelines so called **SOP's**, Standard Operating Procedures, to follow for the department, as in any modern production. When handling pharmaceuticals, there are higher demands than e.g. manufacturing food products. Pharmaceuticals demand an absolute clean process, and cannot allow traces of previously manufactured products. SOP is available for multiple machines and activities in manufacturing. The documents describe how to set-up, run and prepare a changeover. It can also describe how to take samples in the right way. It is a standardized document with points to follow which ensures that the work is done smoothly and that steps are not forgotten. SOPs are used to comply with both GMP and SHE. There may be differences in some manufacturing steps in ways of working depending on different toxic hazard classifications.

The department has to follow **GMP**, Good Manufacturing Practice, to assure safety and efficacy, e.g. the purity of the products need to be on point. GMP is guidelines that say that the equipment and the environment need to be clean, processes must be documented, quality defects must be investigated and the product must be traceable. All operators have been trained to work according to GMP. Most work in the manufacturing need to be done in pairs due to the GMP standard since many steps must be double checked by a second person. "Is the scale calibrated properly? Does the substance weigh XX mg?" These are examples of things that needs to be signed by two operators.

Some substances are toxic in large quantities. The operators work according to strict **SHE,** Safety, Health and Environment, rules. This entails many routines for the employees to follow such as using safety masks. The level of safety gear depends on the toxic hazard (TH) classification of the substances handled and the containment of the process step. TH has a company internal gradation 1-5, were inactive raw materials typically have 1-3 and active typically have 2-5. Many substances that are used in the drugs are new and the hazards with handling the substances are not yet defined. These substances are given the highest safety procedures until the risks are fully known.

Visual planning. To optimize the manufacturing there are daily meetings, improvement groups, a visual information board and various improvement projects. Disturbances, e.g. broken equipment, of the past week and coming week are discussed thoroughly once a week. After a project is finished a **Lessons Learned** meeting is held by the operators active in the project to avoid similar mistakes when/if the same drug is going to be produced or when using the same processes for different projects.

MBR, Master Batch Record, is a document that works as a recipe with compulsory steps that needs to be carried out to make the final product. When the MBR is filled in, it is called an **EBR**, Executed Batch Record, and work as a receipt on the product's quality. The EBR is a paper sheet that is filled in by hand and when complete they are scanned and uploaded to AstraZeneca's database. All the use of material, rooms and equipment for each process step needs to be documented. Responsible operators for each process step are also included. At the beginning of a process step, there is a need to do a Line Clearance (see 4.2.6 for more information about LC). There is no need for LC in certain cases if the room will not be contaminated, e.g. a contained IBC (see 4.2.4) will only use the floor scale in a room. The end time visible in the EBR's is not set by when a process step is finished with a room, but when

the paperwork for the product is finished, and when multiple rooms is used for a process step the time used in each room is not shown.

A project can have one or more outputs. An output can be an intermediate product and/or an OSD form with a specific strength. Each output has its own MBR with a designated **lot-number** that differs every time the project is recurring with an increasing number. Each MBR also have a **DP-** or **IM-number**, which one it is depends of the result/output. DP is short for drug product and IM is short for intermediate material. If a project will result in only one output, it will have one MBR, with its designated lot-number, and one DP-number (see EBR project E and I, no information about this is included in this thesis). This is when the intermediate is manufactured and all of it will be used in the output of the project. This DP-number will be used next time the same project with the same output will be recurring. If a project will result in different outputs, each output will have its own MBR, with its designated lot-number and also a DP- or IM-number. The manufacturing of the intermediate to the OSD form will have an IM-number and each OSD strength will have a DP-number. This DP- and IM-number will be used the next time the same strength and intermediate will be manufactured. If you within the project are not able to make the whole batch of a strength at the same time, you need to have a new MBR (see EBR project B, no information about this is included in this thesis). If not all of the intermediates are used directly after the manufacturing they will be stored and used later (see EBR project F, no information about this is included in this thesis). Traceability is very important in the pharmaceutical industry and therefore it is important to have different numbers (lot, IM and DP).

The manufacturing is made in batches. The batch size, i.e. quantity, depends on the size of the clinical study which is dependent on the development phase of the drug. The batch size may, however, be limited by equipment capacity and several batches may be required for the study. During the time period studied no phase III projects were made in the pilot plant (see table 4.11, page 38). Every MBR has a specific batch-size. If the MBR has an IM-number the unit is gram (g) and if it has a DP-number the unit is units. The batches sometimes need to be divided into subbatches. This is because of multiple reasons: the formulator recommend a certain batch-size, limitation of the equipment capacity, limitation of the equipment availability and limitation of IBC-containers (see figure 4.5, page 30).

The complexity and variety of a project is high and the volume is relatively low. A project is recurring during the clinical study phases which can last for a long time. This means that the manufacturing is a batch process towards a jobbing process.

4.2.2 Organization and planning

The **Functional planner** takes care of the global plan, in other words exactly when a project will be manufactured. The plan stretches six months ahead. The Functional planner has responsibility for planning all the production at the department, not only OSDs. OSDs are mainly made in the pilot plant and does generally not compete for equipment or rooms with other drug production. Map over the pilot plant can be found in section 4.2.3.

Today there is up to four OSD projects and one technical trial manufactured at the site at the same time. Each project is assigned a time slot and a team of operators. The manufacturing takes various time to finish. Some projects finish in a week or two and some projects take much longer. This is mostly because of how many batches and subbatches that are needed e.g. how much drugs that are ordered and the complexity of different process steps. How much time to schedule for a project is not defined but based on earlier experiences and by communication with the responsible Lead operator (see further down). The time slot is made with excess to make sure there is room for errors. The Functional planner tries to avoid queues to equipment and rooms by not scheduling two similar projects in manufacturing at once. More about differences in projects can be found in section 4.3.1. The number of operators is based on the size and complexity of the project.

The **Team manager** is in charge over improvement projects, employees and together with the Functional planner making sure that the manufacturing goes smoothly as planned. Operators continuously give feedback to the Team manager.

The **Lead operator** is the operator who is responsible for a specific manufacture (project). The first step is to plan the manufacturing and make a MBR. The MBR needs to be reviewed by QA (see further down) and the responsible formulator (see further down). The Lead operator is in charge over a team of operators and make the detailed time schedule and book rooms and equipment. The rooms and equipment are booked in one system and two dispensing rooms are booked in an Outlook calendar which allows shorter booking slots than possible in the main booking system. The Lead operator needs to collect knowledge from multiple instances and persons. The Lead operator is usually also working as an operator during manufacturing. Most of the rooms and equipment are booked a few weeks before manufacturing start.

The **Operator** has responsibility over one or more process steps in manufacturing. This work can be setting up, cleaning and running machines, dispense/weigh ingredients, make tests to ensure the quality, fill in the MBR, take samples and/or package the OSDs. The operators have other assignments besides manufacturing at the pilot plant. Other assignments can for example be improvement projects, updating documentation, examining and follow-up deviations in the manufacturing.

The **Technical operator** help with easier tasks at the site to ease operators' work. They do not have the education that is needed for advanced pharmaceutical production.

The rooms are cleaned by educated **Cleaning personnel** whom work at an external company. When the cleaning takes place depends mostly on the GMP standards, e.g. weekly for most of the process rooms, but the cleaning can be made more frequently if needed. The cleaning is ordered by the operators. The Cleaning personnel clean the rooms thoroughly by GMP standards. There can be no production or CIP (see 4.2.5) running in the room during cleaning and it needs to be visually clean and empty of material before start.

Maintenance, an outside source is called upon when there is disturbances with the equipment or rooms. The site has a high reliability but such problems are still likely to occur.

QA (quality assurance) approve the MBR and every change done to the process procedure. They have responsibility to check and assure that the quality is inside tolerance limits.

The **Formulator** makes a list of ingredients/composition and supplies a manufacturing method. All changes made to the manufacturing method must be agreed upon by the formulator.

The **Supply Chain Team (SCT) Rep** checks if excipients, API, packaging components are available and with correct status. They make sure that the BOM (bill of materials) is correct.

The **AP (authorized person)** makes a pre check of documentation before QA approval to minimize the risk of errors.

The **Excipient coordinator** is responsible for securing all excipients that are needed for a project, and make sure the excipients are available on manufacturing start.

4.2.3 Map over the pilot plant

The production site reminds a lot of a lab that has been up-scaled and the production is batch based. The rooms, equipment and machines are built for batch manufacturing. Figure 4.2 is a map over the pilot plant. There are 21 process rooms in which the solid oral dosage forms are made, two of the process rooms are not included in the map. Each room roughly represent a manufacturing step. To enter almost each room, an airlock has to be passed to minimize air exchange between the room and the corridor. The reason is to minimize the risk of cross-contamination. The rooms are built with good ventilation and ensures a contained process by securing the air flows between process rooms and between the rooms and the corridor. All of the rooms have not been used during the time period and are therefore not described in section 4.3. In some of the rooms, it is possible to clean some of the equipment parts. Most of the rooms have scales that are been used throughout a project, see table 4.1 for scales used during the time period and time study.

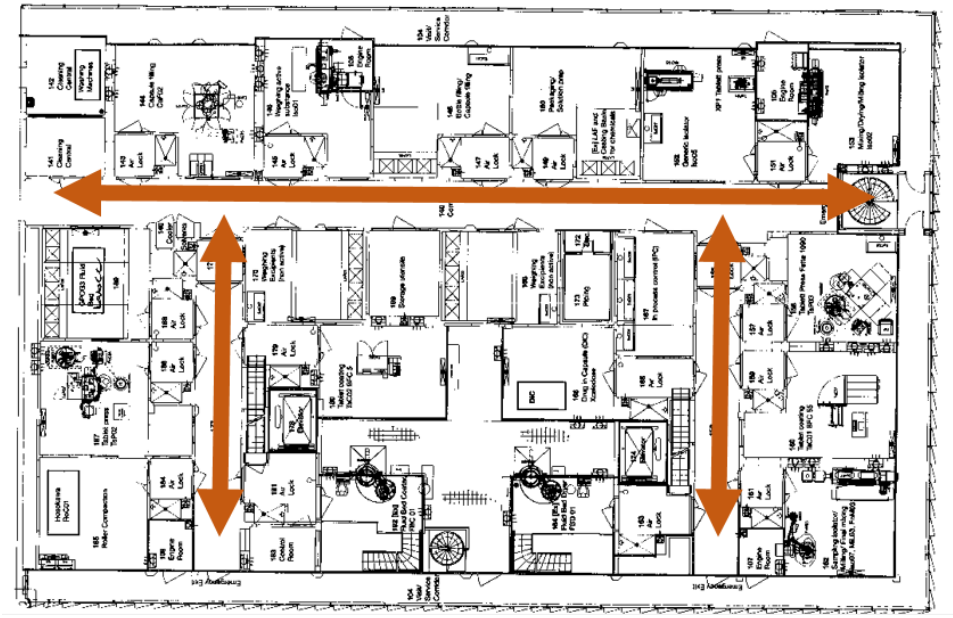

Figure 4.2. Pilot plant

The site has one main corridor that always needs to be passed. To this corridor two small corridors are connected. Each corridor represents a “train”, where a train represent a batch size possible to manufacture within the train. The three sizes are 1-3 kg, 10-12 kg and 18-20 kg (the red arrows in figure 4.2). Each train has a cell layout with a functional layout in each cell.

Table 4.1. Amount of scales and what type of scales the rooms have

Room	**Scales**	**Room**	**Scales**
144	1 analytical, 1 floor, 3 precision	168	1 analytical, 1 floor, 1 precision
146	1 industrial	170	1 analytical, 1 floor, 1 precision
152	1 analytical, 1 precision	180	1 analytical, 1 precision
158	1 analytical, 1 floor, 1 precision	185	1 precision
160	1 analytical, 1 floor, 1 precision	187	1 analytical, 1 floor, 1 precision
162	1 floor, 1 industrial	189	1 analytical, 1 floor, 1 precision
164	None	276	1 floor
166	1 analytical, 1 precision		

There are also some important areas that do not appear on the map. For example the scullery and storage is not included since they are in another part of the building. There is also a middle storage at the ground floor of the pilot plant where IBCs and material are stored.

Every room in the pilot plant has a logbook in paper form that needs to be filled in to know what and when something has been done in the room. These logbooks are very general and the things that need to be filled in are: start date with one signature, the activity executed in the room, the lot-number, the project name, if there is a risk for contamination in the room due to open handling of material, and finally an end date with a signature. Cleaning activities are also logged in the logbooks by the Cleaning personnel. The logbooks are kept in the rooms until full and are then moved to an archive in the pilot plant.

4.2.4 Information about equipment

There are equipment that are either fixed in the room or mobile. If they are mobile they can be moved and set-up in the pilot plant when they are needed. Then there are equipment that can be called parts which are mobile and need to be set on the machine or the IBC every time they are needed. Examples of parts are mills, vessels and high containment (HC)-valves for material transfer. Each equipment has an ID that needs to be filled in the MBR to secure traceability.

Every equipment has a paper logbook that needs to be filled out by hand. Information to be filled in depends on the equipment, but here are some examples: project name, start- and end date when used and if contained use. The logbooks are kept with the equipment until full and are then moved to an archive.

Tools are needed in order to set-up the machines and every room with a machine therefore has a toolbox. The content of the toolbox depends on the room and if some of the tools have been moved.

In most of the rooms there are boxes with a list about what the box should contain, accordingly to 5S. Which items that should be in the boxes differ from box to box. During the observation, it was learnt that the items in the boxes are not always corresponding to the list on the box. Example of items are earplugs and timekeeper.

There are disposable articles which can be found in one of the storages. Examples of disposables are: plastic bags, gloves and overalls.

IBC, Intermediate Bulk Container, is used in the manufacturing of a product. There are five different sizes of the IBC's: 10, 20, 40, 80 and 160L. Which IBC size that will be used depends on the size of the batch/subbatch and the equipment used, for more information see tables for each process step in section 4.3. The amount of IBC that needs to be used during a project depends on the accessibility and the size of the project. To almost every process step there needs to be two IBC-containers for every subbatch. One that holds the raw material that will be charged to the machine and one that the processed raw material will end up in. The IBCs need to be booked in advance and also have logbooks.

4.2.5 Supporting programs/systems

SmartSupplies, is a computer system for managing planning, material and distribution (PDM). In every process step some things need to be done in rooms that is not visible at the map above, as earlier mentioned. What and how many things that need to be picked up depend on the project and the process step. All raw material needs to be picked up from an automatic storage and retrieval system (AS/RS). All equipment parts are not always attached to the machine/equipment and therefore some parts need to be picked up. This is also done through the AR/RS.

CIP, Clean In Place, is an automatic cleaning program that some of the equipment have. The program makes it possible to clean the equipment with no or minimal use of human power. The length of the CIP depends of the program you will use and which equipment you will clean. Sometimes the CIP-program are programmed to have a stop during the process so that the operators will do a manual activity before the CIP-program starts again. When the CIP is running no one is allowed to be in the room, due to the risk of leakage. There are three CIP skids: 1, 2, 3. Which one that will be used depends on the pipes the equipment are connected to. You cannot have two CIP-programs connected to the same skids running at the same time, in other words two CIP2 programs cannot be running at the same time.

WIP, Wash In Place, is another type of cleaning program. This process is a semi-automatic cleaning process and an operator should be present at all time. A WIP-program cleans the equipment to a degree safe for further manual cleaning but not clean enough to avoid cross contamination from one batch to the next.

MIMS, Manufacturing Information Management System, is a system that collects all the batch data for those machines that are connected to the system which result in a MIMS-report. Examples of data are the recipes used as well as actual process parameter values over time. The MIMS-report also consists of a resume where you among other things can find the start- and end time for the MIMS running, the recipe for the program in other words the steps (BOP = basic operation) and the time elapsed for each step in the recipe. The MIMS are running from when you start it until you manually stop the process. This tends to show that some programs are running for a really long time, e.g. CIP. To find the real end time of the CIP you have to open the report and look for the step Finish.

To most of the machines there are **run sheets** to be filled in during the machine is processing. This procedure is necessary for equipment not connected to MIMS or other automatic logging systems and is also used for collecting complementary data from equipment connected to MIMS. In the run sheets are data about the product written down.

4.2.6 Changeovers

Between projects there needs to be a changeover. The changeover is mainly cleaning the machines but it also include set-up. The cleaning is very advanced and it is important that there is no traces left of any substance. The substances are classified after their ability to be cleaned and which toxic hazardous classification they have. This demands different routines for the cleaning process.

When a project is finished in a room the operators make sure that the room is visually clean and one of following options are made:

- If the equipment has a CIP-program it needs to be manually prepared and connected to the cleaning system. Depending on the equipment, the Cleaning personnel is called for cleaning of the room either before or after equipment cleaning. When the Cleaning personnel have cleaned the room before the CIP-program, it is done so the room can be accessed without wearing the highest level of safety gear such as safety masks, which complicates the manual work. If the machine is contained the operators will not be under any risk entering the room. When the CIP is running, no one is allowed to enter the room. It is favorably if the CIP-program is running during night to utilize the time the personnel are not on site. The length of the CIP-programs can be found in the tables in section 4.3.
- If the equipment has a WIP-program, it also needs to be manually prepared and connected to the cleaning system. Sometimes when the WIP is running an operator needs to be in the room, to monitor and perform some manual steps. The equipment is usually either designed for CIP or WIP.
- Equipment without automatic cleaning needs to be cleaned completely manually.

After the program is finished, the operators manually finish the cleaning. There is no need to verify the result of the cleaning if a validated cleaning method has been used. If there is no validated method for the specific substance, there is a need to test if there is any traces of the substance left. This is determined by CV-restrictions, cleaning validation.

Some machines have parts that are removed and cleaned further in the scullery. All IBCs and utensils are also cleaned thoroughly using validated methods to assure the cleaning result.

When a project has multiple subbatches, there is a less thorough cleaning for the machines between the subbatches for some process steps. If CIP is used, this is called a CIP campaign recipe since the subbatches are said to be part of a so called manufacturing campaign. The substances used are the same for all subbatches so it will not contaminate the new batch in the same way as when changing project. The cleaning is done to ensure that the machine will function properly and that the same result as the first batch is obtained. This is a shorter cleaning program than a full cleaning, see tables in section 4.3 for which equipment that have CIP campaign. If there are many subbatches, a normal CIP is used every other time.

It is common that the set-up is done approximately one day beforehand and not in one sequence. It is also common that the cleaning process is not started directly after the activities in the room is finished.

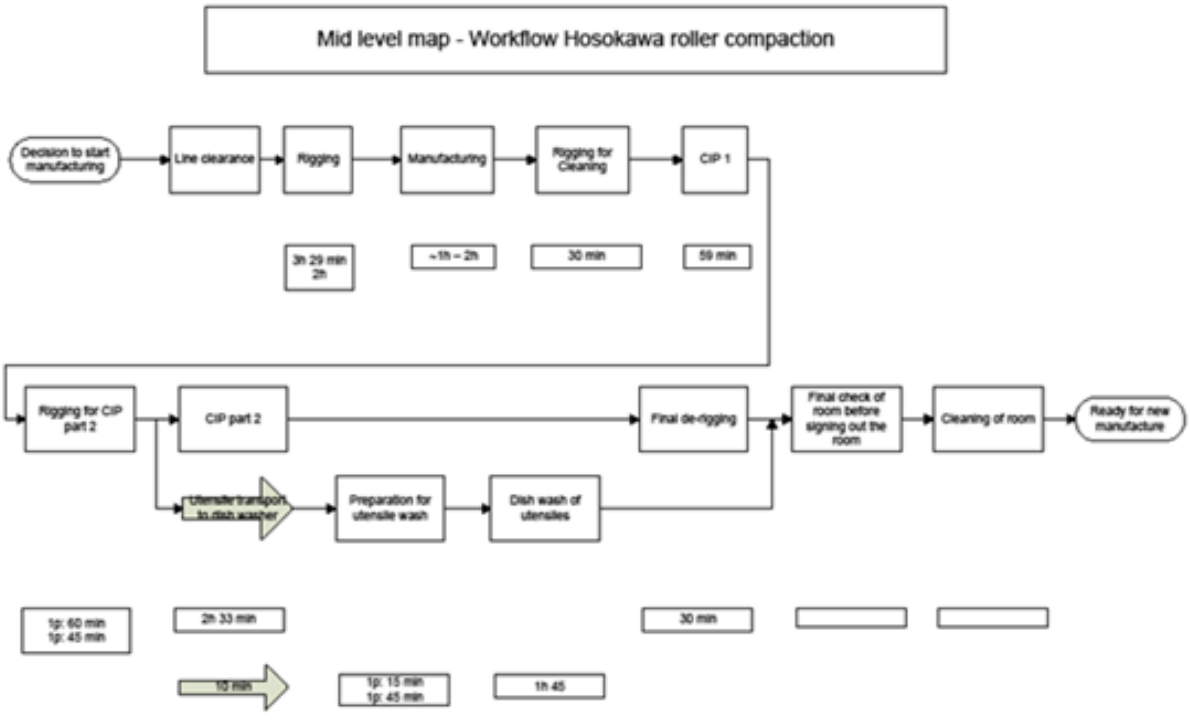

Figure 4.3. Workflow for dry granulation of one batch, including changeover

When starting a new project the room must have a **Line Clearance** (LC), i.e. a check that it is okay to enter the room and start the process and use the machines in it. This is to ensure that the room is cleaned and that no material or documentation form pervious projects have been left. The equipment that will be used does also need to be LC. Scales are calibrated and

operators set-up the machines. These activities are filled out in the EBR in the beginning of each process step. If a room already has been LC in an earlier process step within the project, a new LC does not have to be done, but a comment in the EBR has to be made.

Figure 4.3 illustrates the workflow for the dry granulation of one batch. The figure is from a Six sigma project at the department. It includes the set-up ("rigging" in the figure), LC, and the work executed after the manufacturing.

Outside every manufacturing room there is an air lock, which is a small room that connects the corridor to the manufacturing room. At every door towards the hallways there are two different types of **triangle** signs. One used for hazardous substance and one for less hazardous substance. These indicate the status of the room: work in progress, cleaning desired or cleaned. Cleaning is done after virtually all activities and depending on the room and what is done in the room it needs to be cleaned within 7 or 21 days, due to GMP standards even if there has been no activity in the room.

4.3 Manufacturing of solid oral dosage forms

General information on how solid oral dosage forms are manufactured at the pilot plant, important equipment and their location and general differences between projects will be found in this section. A process step starts with a capital letter whereas the activities within a process step start with a small letter.

NOTE: The equipment presented in the tables in this section are the ones used in the projects. There are more equipment but they have not been used during the time period or time study and further information about them are therefore not given.

4.3.1 General differences between projects

The flexibility is high at the pilot plant. It is flexible both in volume, product mix and innovation, e.g. introducing new technology. This enables a high variety in projects. Most correct is to say that every project manufactured is unique, but there are some similarities for categorizing the projects.

4.3.1.1 Differences in volume and varieties

Every product that is manufactured in the pilot plant is a unique project. There are differences in both ordered volume and ordered product variety within a project. The department needs to be very flexible when it comes to batch sizes, in particular since decisions about required amount may come late.

When manufacturing a drug product, the intermediate is sometimes made for the whole project with the same strength. It is common that multiple subbatches are needed. The intermediate is then used to manufacture OSD forms, and the strength of the form is adjusted by the amount of intermediate. This results that tablets with a higher strength are larger and

that capsules with a higher strength are heavier. A strength can use one or more subbatches. The different strengths are not allowed to be mixed.

Following differences are there for projects (see figure 4.4):

- The total ordered volume can vary
- The number of different tablet (or capsule) strengths can vary
- The number of tablets (or capsules) of a certain strength can vary

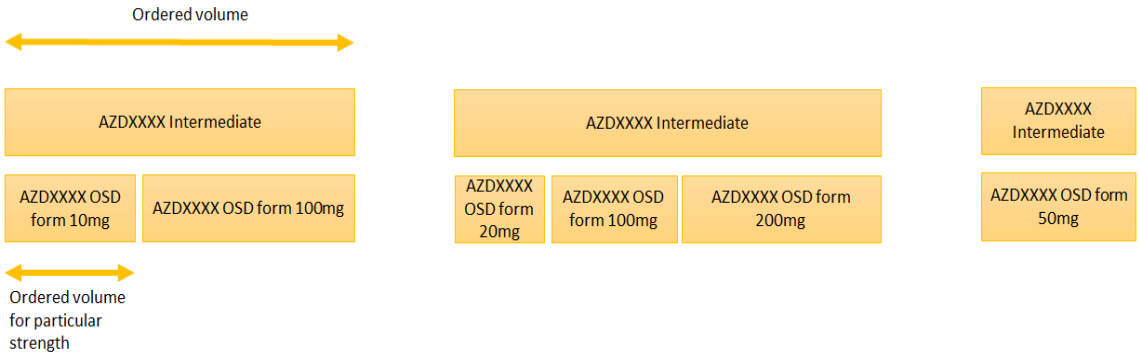

Figure 4.4. Three different versions of a project

4.3.1.2 Differences in manufacturing methods

The high variety of projects demands different methods in the manufacturing of OSDs. Which process steps, equipment and parameters to use depends on the recipe. The process steps are flexible and have different activities, e.g. the Blending step sometimes include sieving and sometimes the blending needs to be done twice.

When manufacturing tablets, there are some general steps that most projects have in common. The steps are Dispensing, Blending, Granulation, Final blending, Tablet compression, Tablet coating and Sampling, bulk packaging and labeling, see figure 4.5. Note that Granulation is not a necessary process step for all projects, since tablets may be compressed directly from a powder blend. Another important thing to note is that the mixture is called granules after the granulation step, before the Final blending step, and figures 4.5, 4.6, 4.8, 4.10 and 4.12 can be misleading. The Final blending step is often included in the MBR for the intermediate and is therefore illustrated as a step to finish the intermediate.

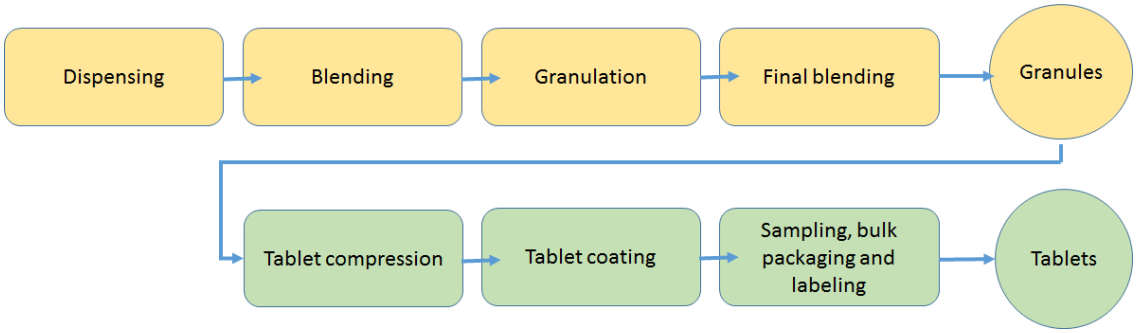

Figure 4.5. General process steps for manufacturing of tablets

For capsules, the following steps are the ones most projects have in common. The manufacturing process differs from manufacturing tablets in the last process steps. Instead of compressing the mixture into tablets, granules are made to fill capsules. The steps are Dispensing, Blending, Granulation, Final blending, Capsule filling and Sampling bulk packaging and labeling, see figure 4.6. Note that Granulation is not a necessary process step for all projects since capsules may be filled with a powder blend.

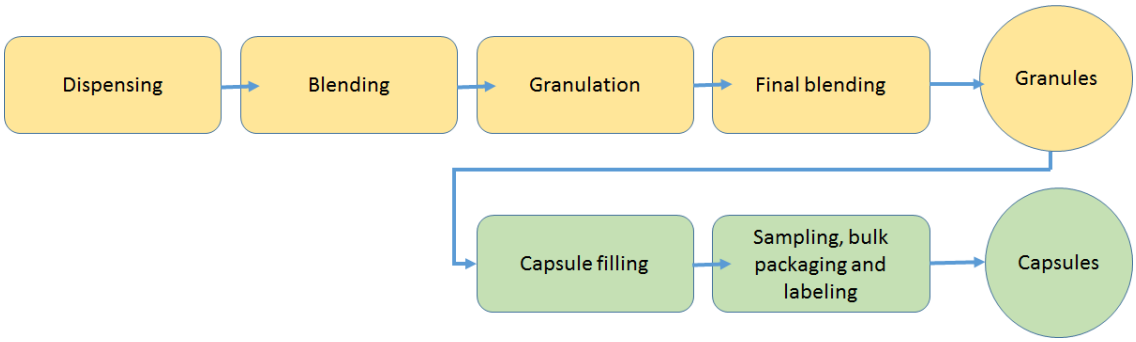

Figure 4.6. General process steps for manufacturing of capsules

4.3.2 Manufacturing of intermediate

The intermediate can be powder or granules. If it is manufacturing of a powder blend, it does not include the granulation process step, see figure 4.7 page 33.

4.3.2.1 Dispensing

The first process step when manufacturing OSD forms is to dispense the API and excipients. This is made in an isolator or/and in a room with good ventilation such as LAF ceiling (Laminar Air Flow ceiling ventilation). It is important to not contaminate the substances but also to protect the operators. Dispensing is recurring throughout a project, for example coating liquid is dispensed later in the manufacturing.

The number of activities a process step have depends on the complexity of the project. If a substance will be weighed and placed in a plastic bag until next process step there is no need for instructions and the dispensing list in the EBR only needs to be filled in. In other cases, for example if you need to sieve before weighing a substance, the substance is not allowed to be exposed to light for a longer time or if the substances will be added one at the time to an IBC, these steps needs to be written down as activities in the MBR. How long time the dispensing takes depends on the amount and number of raw material needed for the project and also how many subbatches there will be.

Table 4.2 gives information about the rooms and equipment that have been used, which substances they can handle, if the equipment's are connected to MIMS and if they can take all IBC sizes. It also says how long time, if any, it takes to set-up, run, manually clean and perform the CIP.

Table 4.2. Rooms and equipment used for dispensing

Room	Equipment	Substance	Set-up time	Run time	Manual cleaning	CIP	IBC	MIMS
146	Iso01	API	1-2 h	1 h – 7 d	2-5 h	2 h	10-40 L	Yes
162	Iso07	API	1,5 h	1 h – 7 d	2-3 h	1 h	All	Yes
168	LAF ceiling	Excipient	N/A	N/A	N/A	N/A	All	No
170	LAF ceiling	Excipient	N/A	N/A	N/A	N/A	All	No
189	LAF ceiling	API/ Excipient	N/A	N/A	N/A	N/A	All	No

4.3.2.2 Blending

The second process step is to blend the mixture. This can be done by hand or, when operating a big batch, by a blender. This results in a fine powder blend. The blending can be made all at once or be divided into different steps. In this process step the IBC might already been charged with material in the process step Dispensing. If not, the material is added here according to the recipe.

Table 4.3 gives information about the rooms and equipment that have been used, if the equipment's are connected to MIMS and if they can take all IBC sizes. It also says how long time, if any, it takes to set-up, run, manually clean and perform the CIP.

Table 4.3. Rooms and equipment used for blending

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP	IBC	MIMS
162	FnM03	10 min	2-10 min	N/A	N/A	All	Yes
168	By hand	N/A	N/A	N/A	N/A	All	No
170	By hand	N/A	N/A	N/A	N/A	All	No

4.3.2.3 Sieving

This is a separate step when a large volume needs to be sieved before the granulation step. It is not done in every project. The step is usually done with an automatic machine instead of doing it manually which saves a lot of time. Some substances need to be sieved before weighing. This is usually performed by hand in the Dispensing step.

Table 4.4 tells where the sieving has taken place, which equipment that has been used, the length of the set-up, run, manual cleaning and CIP. The table also tells if the equipment can take all IBC sizes and if it is connected to MIMS.

Table 4.4. Rooms and equipment used for sieving

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP	IBC	MIMS
152	Quadro Flexsift S10	2h	5-30 min	4 h	No	10-80L	No

4.3.2.4 Granulation

The granulation is an important process step to ensure a good distribution of the active substances and make the mix more processable, e.g. flowing better. Some projects do not need granulation and go directly from powder blend to tablet compression.

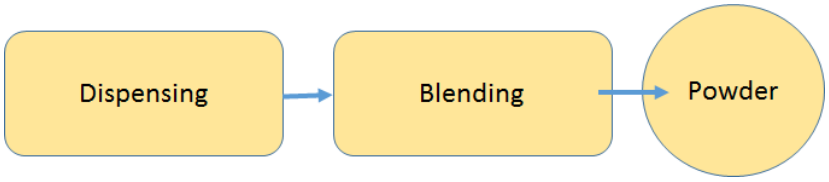

Figure 4.7. General process steps for manufacturing of powder

The granulation can be made in mainly two different ways, by Wet granulation or Dry granulation. Wet granulation demands a compulsory subsequent step (Drying). It all depends on the method prescribed by the formulator if granulation will be done and if so which method of the two that will be used. See figure 12 for the difference between Dry granulation and Wet granulation.

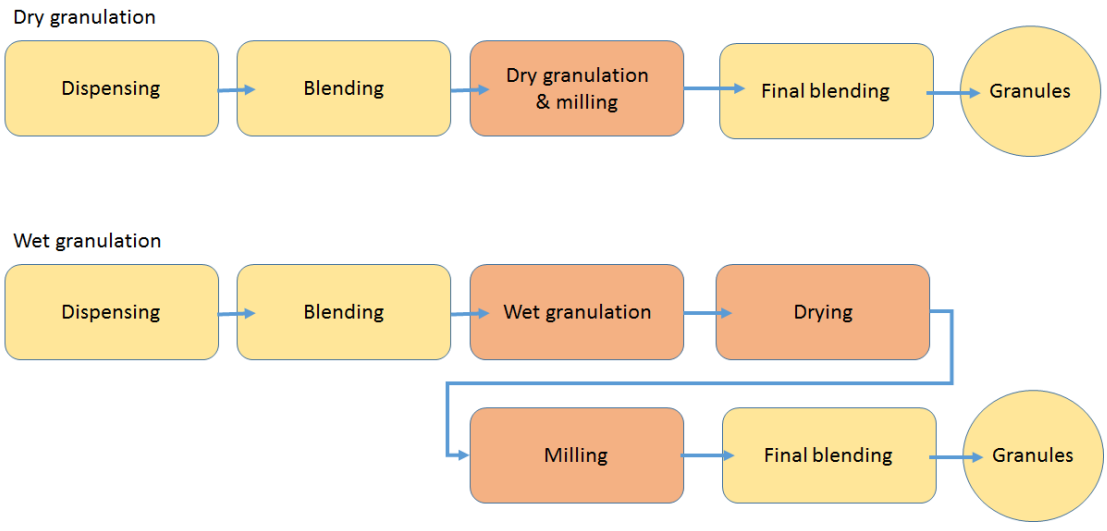

Figure 4.8. Difference between a Dry granulation and a Wet granulation project

4.3.2.4.1 Dry granulation

The powder is compressed with high pressure into ribbons that are subsequently milled to granules. This is made in a roller compactor and the process is also called roller compaction.

Table 4.5 gives information about the room and equipment that has been used, if the equipment is connected to MIMS and if it can take all IBC sizes. It also say how long time it takes to set-up, run, manually clean and perform the CIP.

Table 4.5. Rooms and equipment used for dry granulation

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP	IBC	MIMS
185	RoC01	3-4 h	1-4 h	~5 h *	4 h	40L lower	Yes

* including washing machine time

4.3.2.4.2 Wet granulation, Drying and Milling

Liquid and potentially a binder are added to the powder under high shear forces. This makes the powder bind and make granules. After wet granulation, there needs to be a drying and milling process. This ensures that it is not any moisture left in the granules.

Table 4.6 gives information about where and which equipment that have been used for wet granulation, drying and milling. The table also says if the equipment's are connected to MIMS and if they can take all IBC sizes. It also says how long time, if any, it takes to set-up, run, manually clean and perform the CIP.

Table 4.6. Rooms and equipment used for wet granulation, drying and milling

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP normal	CIP campaign	IBC	MIMS
162	Mil03	30-60 min	3-15 min	30 min	3 h	2 h 30 min	All	Yes
164	FBD01	1-2 h	2-5 h	N/A	25 h	12-14 h	All	Yes
276	HSM03	2 h	10-40 min	1-2 h	25 h	12-14 h	All	Yes

4.3.2.5 Final blending

After granulation, a second blend to the mixture is necessary to ensure a good homogeneity. Also, lubricants are added to improve the flow in the tablet press. Sometimes other raw materials than lubricants are added to the batch as well after the granulation. Same equipment

as in the Blending step is used and the data is the same as for the Blending step, see table 4.3 page 32.

4.3.3 Manufacturing of tablets and capsules

There are mainly two types of OSDs, tablet and capsules, to be made. They are further described below.

4.3.3.1 Tablets

In the manufacturing of tablets there are usually three steps that needs to be made. The last two are made if the tablets are to be coated.

4.3.3.1.1 Tablet compression

The intermediate is poured into a machine (a tablet press) which then compresses the mixture into tablets. The pilot plant has many different tablet presses, three of them have been used in the projects.

Table 4.7 gives information about the rooms and equipment that have been used, if the equipment's are connected to MIMS and if they can take all IBC sizes. It also says how long time, if any, it takes to set-up, run, manually clean and perform the WIP.

Table 4.7. Rooms and equipment used for tablet compression

Room	Equipment	Set-up time	Run time	Manual cleaning	WIP	IBC	MIMS
152	TaP01	2-6 h	~1-8 h	~6-8 h	1-2 h	Manual feeding	No
158	TaP03	4-8 h	~2-5 h	~24 h	~2 h	Yes	No
187	TaP02	2-6 h	~1-8 h	~6-8 h	30 min – 1 h	All	No

4.3.3.1.2 Preparation of coating liquid

In this process step, the coating liquid is prepared. This is done by dispensing the specific coating liquid substance into a plastic bag. The dispensing is sometimes a process step of its own in the EBR, but are most of the time included in the process step Preparation of coating liquid. The dispensing takes place in one of the ventilated rooms. The substance will later be blended with a fluid in a vessel. This can be done in either one of the ventilated rooms or the room where the tablet coating will take place.

4.3.3.1.3 Tablet coating

The coating of the tablets is the last step. Most tablets have coating, since it e.g. makes the tablets easier to swallow. It is also esthetically more pleasing and there may be additional functional aspects such as protecting the content of the tablet. The tablets are dispensed to a drum that rotates at the same time as coating liquid is evenly sprayed. There are different sizes of drums to the equipment's.

Table 4.8 gives information about the rooms and equipment that have been used, if the equipment's are connected to MIMS and if they can take all IBC sizes. It also says how long time, if any, it takes to set-up, run, manually clean, and perform the CIP and WIP.

Table 4.8. Rooms and equipment used for tablet coating

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP	WIP	IBC	MIMS
160	TaC01	2-4 h	2-7 h	N/A	4 h	2 h	Depends on the weight	Yes
180	TaC02	1-2 h	2-6 h	2-4 h	N/A	N/A	N/A	No

4.3.3.2 Capsules filling

The manufacturing process differs between the two options, tablet or capsules, in the last process steps. Instead of compressing the mixture into tablets, the intermediate is made to fill the capsules. The granules make it easy to adjust the active content in the capsules, by filling different amounts, and is therefore prompted to be good for continuous flow production and future demand on personalized pharmaceuticals.

Table 4.9 gives information about the rooms and equipment that have been used, if the equipment's are connected to MIMS and if they can take all IBC sizes. It also say how long time, if any, it takes to set-up, run, manually clean, and perform the CIP and WIP.

Table 4.9. Rooms and equipment used to capsule filling

Room	Equipment	Set-up time	Run time	Manual cleaning	CIP	WIP	IBC	MIMS
144	CaF02	8 h	N/A	20-40 h	N/A	N/A	Yes	No
166	DiC	30 min	300 h	4-5 h	N/A	N/A	No	No

4.3.3.3 Sampling, bulk packaging and labelling

When the OSDs are manufactured, they need to be weighed, packaged and labeled, and handed over to the function responsible for final packing and distribution. Analytical tests such as content uniformity are done on samples from the batch and results are sent to the QA department. The products are mostly put into aluminum bags with approximately the same amount in each, the last bag excluded. When the products are put into the bag, the bag is sealed with the help of a sealing equipment. Each bag need to be labeled. You will get the label by performing “pack containers”, for each bag, in SmartSupplies. The bulk product is then moved to a storage location and the material handlers are notified.

This process step does not need a special equipment or room to be accomplished. The room just needs space and a scale. For example, one Lead operator prefers to use room 144 because there are good benches and windows for the day light. Table 4.10 gives information about which rooms that have been used for the projects, more information about the projects in section 4.4.1.

Table 4.10. Rooms used to perform Sampling, bulk packaging and labeling

Room	Projects
144	F
168	B, C, D, G, H, J
170	A, B, D, I, J
180	E
187	I

4.3.4 Other

Common for each process step is that there is always a step where you need to weigh the IBC’s used in the process. This is done both when the IBC is empty and not yet used, when the IBC have contents in it and again when the IBC have been emptied. This is done to make sure that there are no or little leftovers and to be able to calculate material loss in the different process steps. Such calculations are done for most of the process steps. This is done when time is given, and the time needed and the room used are therefore not found in the EBR.

4.4 Current state

The current state will focus on describing the variety in the pilot plant and how it affects the manufacturing. To understand the complexity of a project, there will in this section be a closer description of two projects and a time study of one project that was on-going during the empirical study.

4.4.1 Variety in the manufacturing

During the chosen time period there were 11 projects. One of them had started before the time period and one did not finish until after the time period. In addition there were also technical tests, which are not considered in the empirical study.

Table 4.11 shows the variety of projects during the chosen time period, regarding main process, phase, batch size, OSDs, slot time, outputs and strengths. It gives an insight of how complex the variety at the pilot plant is. During this period, it was many lager projects that needed many subbatches to finish. In this work, the project are called A, B, C, etc.

Table 4.11. Information about the 11 projects

Project	**Main process**	**Phase**	**Batch size (kg)**	**OSD forms**	**Slot time (days)**	**Outputs IM+DP**	**Strengths**
A	Dry	II	80,8	Tablets	26*	1+2	2
B	Wet	II	90	Tablets	103**	1+4	3
C	Pellet coating	I	0,376	Capsules	30	2+4	4
D	Powder	I	15,9	Tablets	27	1+3	3
E	Powder	II	5	Tablets	19	0+1	1
F	Pellet coating	I	N/A	Capsules	15	1+N/A	N/A
G	Wet	I	24+37	Tablets	28	2+2	2
H	Powder/dry	II	76+50000 units	Tablets	24	2+1	2
I	Wet	II	26500 units	Tablets	24	0+1	1
J	Powder	II	13	Tablets	18	1+2	2
K	Wet	II	20	Tablets	28+	1+1	1

*EBR finished later
**Started before time period and had problems with the manufacturing
+ Finished after time period

Figure 4.9 shows when and in what order the projects have been manufactured during the time period. It does not say which rooms that have been used or if there have been any collisions regarding rooms or equipment. Table 4.11 and figure 4.9 are based on data given by the Functional planner.

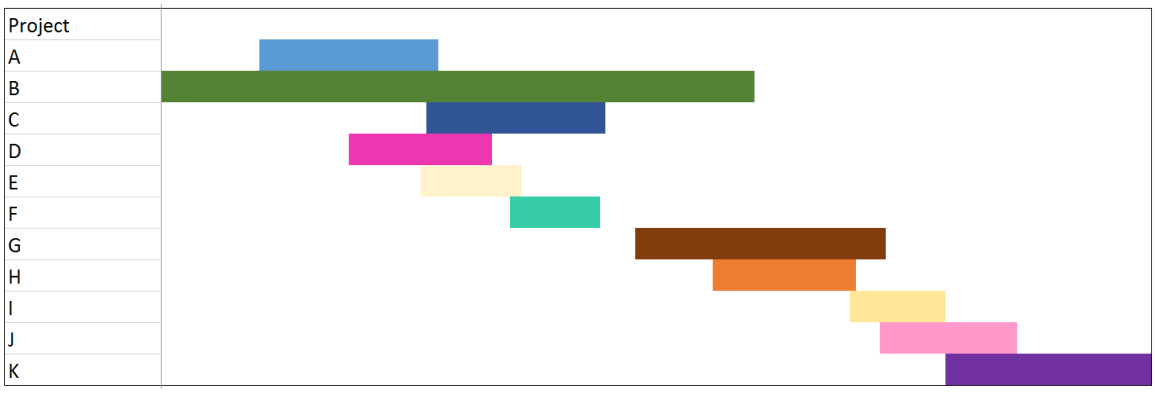

Figure 4.9. Overall view of the projects

4.4.2 The complexity of a project

As earlier mentioned, every project is unique. Both in volume and number of different strengths, as well as in manufacturing methods needed (see 4.3). This section will show the differences and similarities between two projects (project A and B) manufactured during the time period in order to visualize the need of flexibility when manufacturing many varieties. The two projects have successfully been manufactured at the pilot plant before. All activities in a process step are not visible in the flow charts or description, i.e. the project descriptions should be read as a simplified picture of the reality. There is always something unexpected that will happen and this section will try to visualize it. When things have not turned out as planned, there is a comment about it. Project A is more thoroughly described than project B.

NOTE: During the manufacturing of project A and B, different scales and different rooms were used, all of them are not mentioned in figure 4.10 and 4.12, pages 40 and 44. Another important thing to note is that the mixture is called granules after the granulation step, before the Final blending step, and figures 4.10 and 4.12 can be misleading. The Final blending step was included in the MBR for the intermediate and is therefore for project A and B illustrated and described as a step to manufacture the intermediate.

4.4.2.1 Project A - a dry granulation project

Project A is a dry granulation project in phase II and the manufacture resulted in two strengths of tablets, 80 mg and 200 mg. The project was made within the given timeslot, not done earlier or later. Some extra testing needed to be done to clarify that the tablets were fulfilling specifications. Because of the equipment used for dry granulation the manufacture needed to be divided into four subbatches.

The manufacturing of the granules were made in four process steps in the following order: Dispensing, Blending, Dry granulation and Final blending. The manufacturing of the tablets were made in following four process steps: Tablet compression, Tablet coating and Sampling, bulk packing and labelling. The batch size were approximately 81 kg and had to be divided into four subbatches. Figure 4.10 illustrates the process steps needed and the main rooms used during the eight process steps. It also shows where the subbatches have been submerged,

more details is found in sub sections 4.4.2.1.1 and 4.4.2.1.2. Figure 4.11 illustrates in what sequence the process steps have been executed for the subbatches.

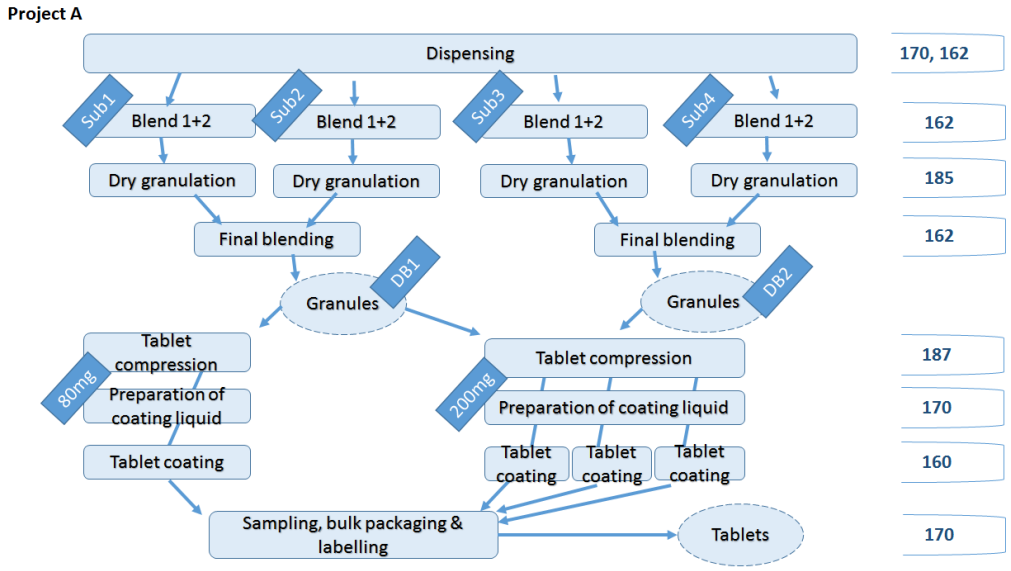

Figure 4.11. Flow chart project A: process steps, subbatches and rooms

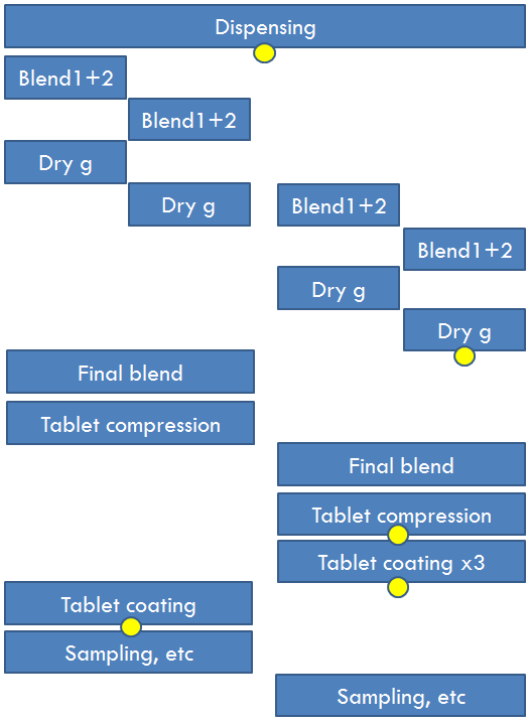

Figure 4.10. Flow chart project A: sequence, the yellow dots represent a CIP or WIP

4.4.2.1.1 Manufacturing of the intermediate

Dispensing

According to the LC in the EBR, the Dispensing step took place in two different rooms (room 170 and room 162). The excipients for all subbatches were dispensed one at the time using the

precision scale in room 170. The dispensing was executed the first day of the manufacture. The substances were put into different plastic bags until able to add to IBC-container. The team had booked four IBC 80L, but since project B were using all of the IBC 80L none IBC 80L were available at the start of the project. One IBC 80L got available the third day and another the fourth day. These were the only ones that the team could get. The lack of IBC's made a slight delay to the project because the content of SB1 and SB2 first had to be put into two different IBC 80L and then let them pass through process step three before being reused by SB3 and SB4.

The API was dispensed in room 162 using the industrial scale in the isolator (iso07). The dispensing took place on the third day of the project and the API for each subbatch was put into suitable containers until it was possible to add to IBC-containers. The API and excipients were added to the IBC accordingly to the EBR. SB1 was added the third day, SB2 was added the fourth day, SB3 and SB4 were both added the eleventh day. The IBC's was weighed before adding the raw material and this was done using the floor scale in room 162.

Blending

According to the LC in the EBR, the Blending step took place in room 162 and room 170. The blending were made in two steps for each SB. Not all raw material was added before the first blend was run. One ingredient was added after the first blend was finished and before the second blend was executed. When the blending was completed the IBC's were weighed using the floor scale in room 162. Samples for technical use were taken after both blending programs for SB1.

Dry granulation

According to the LC in the EBR, the Dry granulation step took place in room 185, 187 and 162. The RoC01 was set-up the seventh day of the project. Before the dry granulation started, the IBC-containers that the granules would be submerged to, was weighed. For SB1 and SB2, the floor scale in room 170 was used. Room 170 was not written in the EBR since no LC was needed. For SB3 and SB4, the floor scale in room 187 was used. The dried granules for every subbatch were collected into an IBC 40L with the exception that SB2 also used an IBC 10L. For SB1 there were problems with the granules. When the process was stopped and the empty IBC 80L was weighed, it was discovered that the IBC was not completely empty. Therefore it was used in the granulation of SB2 and in end of the granulation there was a need to switch to an IBC 10L.

During the dry granulation, a RoC run sheet was filled in approximately every 20 minutes and tests were made until stop of process. After the dry granulation, the IBC's were weighed again, both the 80L and the 40L. For SB1 the floor scale in room 187 was used. SB2 was by mistake not weighed, but data for the empty IBC 80L from the Dispensing step for SB4 could be used. For SB3 and SB4, the floor scale in room 162 was used. The filled and later empty IBC lower 10L was weighed on the floor scale in room 162. In the end of this process, some calculations needed to be done. These calculations could be done directly after granulation or at a later time.

Final blending

According to the LC in the EBR, the Final blending step took place in three rooms: 187, 162 and 168. SB1 and SB2 were submerged into one IBC 160L (DB1) and SB3 and SB4 was submerged into another IBC 160L (DB2). Before the submerging, the empty IBC's was weighed. DB1 used a floor scale in room 187 and DB2 used a floor scale in room 162. After the submerging, the same scales as above were used to weigh the IBC's again. In the Final blending step, one excipient was added and the amount had to be calculated and weighed before added. DB1 used a precision scale in room 187 and DB2 used a precision scale in room 168. Samples for technical use were taken from IBC 160L DB1 but not for DB2. After this, Performed Pack Containers in Smart Supplies was done and labels were printed. These steps were made for both batches at the same time. Finally, the actual amount of lubricated granulate was calculated. When both DB1 and DB2 were done, the total amount of lubricated granulated was written down.

4.4.2.1.2 Manufacturing of the tablets

As figure 4.11 page 40 illustrates the manufacturing of the two strengths of tablets started with Tablet compression for 80 mg. Thereafter the Tablet compression for 200 mg was executed. The dispensing in the process step Preparation of granulation liquid was performed for 80 mg right before 200 mg. The preparation of coating liquid and the process step Tablet coating were performed first for 200 mg and later for 80 mg. The process step Sampling, bulk packaging and labelling was performed the same day with start of 80 mg and then 200 mg. As figure 4.10 page 40 illustrate was 80 mg manufactured with DB1 and 200 mg with both DB1 and DB2.

200 mg: This strength had a batch size with approximate 200 000 units and was therefore divided into three subbatches when the process step Preparation of coating liquid and Tablet coating were made.

80 mg: The batch size was approximately 100 000 units.

Tablet compression

According to the LC in the EBR room 187 was the only room used to perform the Tablet compression step. Firstly, the total amount of the granules for both DB was noted and charged to the machine. The machine was started and parameters were tuned until the outcome was within acceptable prescribed range. A metal check was set-up before the continuous compression could start. Every day, before and after start of compression, the test disks were tested. During the compression. In Process Controls (IPCs) were made. A compression run sheet was filled in every 30 minutes and the tablets fraction weights were filled in. The IPC-test is done in room 167 and there is no need to do a LC before entering and therefore was this not written in the EBR. During the process relevant process adjustments and data were noted. If there were any rejects in the metal check these were passed through the check again. In this case there was one reject (for 200 mg) that did not pass the second run but, it was within the acceptable range so no further investigation was needed. After the process was stopped, calculations were made.

Preparation of coating liquid (including dispensing)

According to the LC in the EBR, the dispensing of the coating liquid took place in room 170. The dispensing of coating liquid was supposed to start the 22nd day but for some reason was delayed one day. The dispensing for both strengths took place right after each other using the same precision scale in room 170. Only one weighing was needed for 80 mg but two for 200 mg, the second one was enough for SB2 and SB3.

According to the LC in the EBR, the Preparation of the coating liquid took place in room 170 for DB2 and room 160 for DB1. For 200 mg, the preparation of coating liquid was executed for the three subbatches at the same time.

Tablet coating

According to the LC in the EBR, only room 160 was used to perform the Tablet coating step. The equipment used was TaC01 with a 25 kg sized drum. The step started with calculating how much coating liquid that was needed. Thereafter, the set-up of the equipment was performed and parameter settings were set. Before starting the machine, the tablets were charged. During the coating process, observed values were filled out in a coating run sheet. After the coating was stopped, the tablets were weighed and calculations were made. Due to too much increased weight for the tablets in SB2 and SB3, QA had to be contacted. Between the strengths, simplified cleaning was made, due to campaign manufacturing.

Sampling, bulk packaging & labelling

According to the LC in the EBR, only room 170 was used to perform the Sampling, bulk packaging and labelling. The packaging was performed with a sealing equipment. Firstly, an AQL testing was made, thereafter sampling for QC testing. For 200 mg, they had to do two AQL testings. Thereafter, the bulk packaging and labelling started. An appropriate amount of tablets were put into aluminum bags. After every full bag, a label was attached to the bag before filling a new bag. The amount in each bag was filled out in a table in the EBR. The label was printed after performed “pack containers” in SmartSupplies. The bulk product was then moved to a storage location and the material handlers at the function responsible for final packing and distribution were notified. Lastly, a calculation of accountability was made.

4.4.2.2 Project B - a wet granulation project

Project B is a wet granulation project in phase II and the project resulted in three strengths of tablets, 50 mg, 25 mg and 10 mg. This project did not completely follow the time schedule, due to malfunction of HMS03 and FBD01. All 50 mg tablets and 25 mg tablets were made in time as well as some 10 mg. The rest of the 10 mg tablets were not done until approximately two months later.

The manufacturing of the granules was made in six process steps in the following order: Dispensing, Blending, Wet granulation, Drying, Milling and Final blending. The manufacturing of the tablets was made in following four process steps: Tablet compression, Preparation of coating liquid, Tablet coating and Sampling, bulk packing and labelling. The batch size was 90 kg and because of the process steps Wet granulation and Drying, the

manufacture needed to be divided into six subbatches. Figure 4.12 illustrates the process steps needed and the main room used during the process steps. It also shows where the subbatches have been submerged. Figure 4.13 illustrates in what sequence the process steps have been executed for the subbatches.

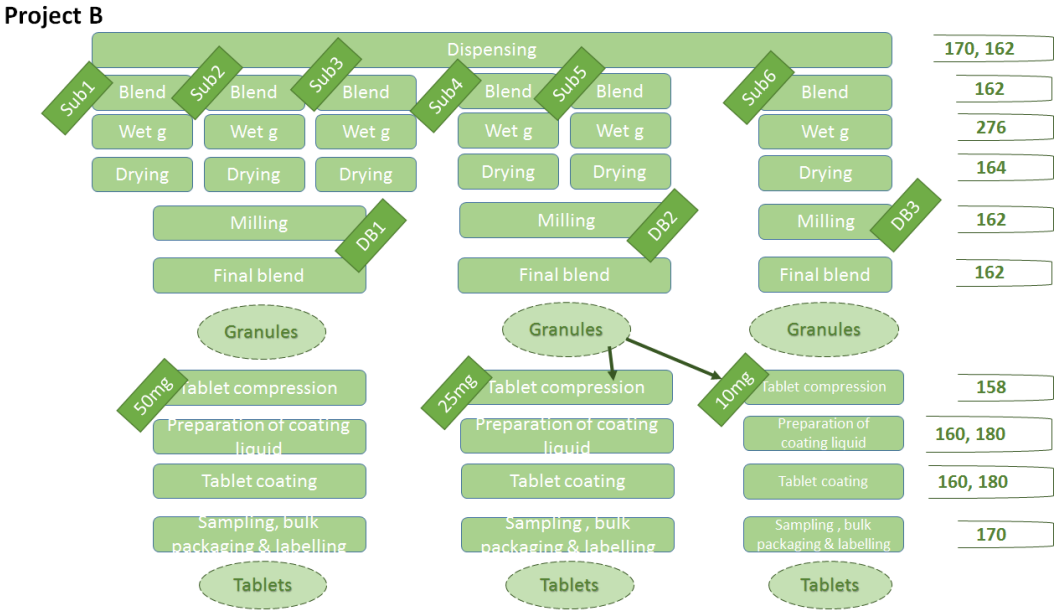

Figure 4.12. Flow chart project B: process steps, subbatches and rooms

All six subbatches were prepared at once, one raw material at a time. The API was dispensed at last, and it was done in Iso07 in room 162. The raw material was put into six IBC's. The subbatches were put through Blending, Wet granulation and Drying and then put into six new IBC's. The IBC's could not be reused without being cleaned, even though it was the same project and strength. The reuse was not possible because it is not according to GMP since it can change the characteristics of the batch (especially after wet granulation). The subbatches were then submerged before Milling (see figure 4.12). Three new IBC's were needed when collecting the milled granules.

The milled granules were weighed and lubricant liquid was dispensed accordingly before the Final blending. Each IBC passed through the subsequent steps, one after the other, and resulted in three different strengths of tablets. The IBC's were emptied into TaP03 and a metal check was at the outlet. The coating liquid could be prepared after the compressed tablets had been weighed. The coating liquid was later used when coating the tablets in room 160 and 180. Sampling, bulk packaging and labelling step was the last process step.

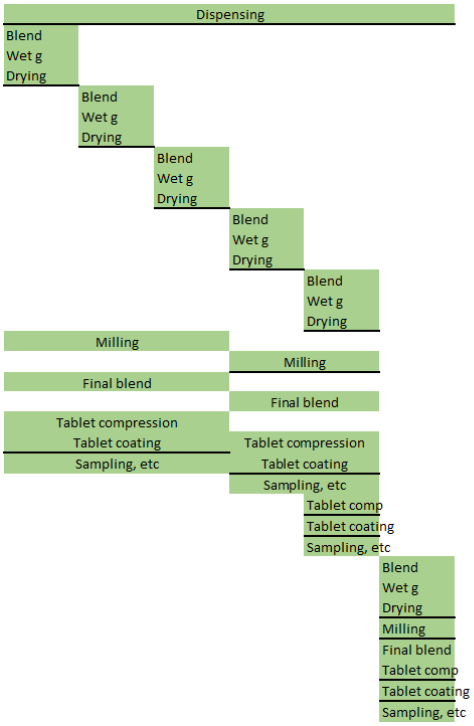

Figure 4.13. Flow chart project B: sequence, the fat lines represent a CIP or WIP

Figure 4.13 shows the sequence in which the process steps have been performed. The project started with dispensing all raw materials for all subbatches. The isolator (Iso07) needed to be cleaned after use. The first five subbatches were put through the process steps Blend, Wet granulation and Drying one after another. Between each subbatch there needs to be a CIP running for the HSM03 and FBD01. Between SB1 and SB2, SB3 and SB4 there was a campaign CIP-program. Between the other subbatches there was a full CIP-program.

The sixth and last subbatch was not started as planned because of a malfunction in HSM03 and FBD01. It was decided to set aside granules from subbatches four and five to make up for the loss of subbatch six to manufacture a small amount of 10 mg tablets.

The Milling process was done carried out after the five subbatches had passed through the first process steps. The Milling process submerged subbatch one, two and three into one large batch (batch one). No cleaning was needed before milling subbatch four and five (second batch in the Milling process). Due to the need for traceability and according to GMP, the batches could not be in the same process room at the same time. When the two batches were milled, the MiL03 was cleaned. Lubrication and Final blending was done next, starting with batch one. Same for Tablet compression step, first batch one, then batch two. When batch two was being compressed into tablets, batch one was already on the next process step, Tablet coating. The TaC01 was cleaned after every batch. The two strengths were sampled, labelled and bulk packaged at different times.

The granules set aside to make up for the loss of subbatch six were then used to make tablets with the third strength. The same steps as above were used but another coating machine was used. The tablet press (TaP03) and the tablet coater (TaC02) were cleaned. When the HSM03 and FBD01 were functioning again, the sixth subbatch was manufactured as planned.

4.4.2.3 Both projects

With the data from the EBR's, MIMS-reports and logbooks for the rooms it was possible to make a schedule for when the rooms were used by project A and project B, see figure 4.14. The blue color represents project A and green represents project B. Room 158, 164, 180, 189 and 176 were only used for project B and room 185 and 187 were only used for project A. Room 160, 162, 168 and 170 were used by both projects. In room 160 and 162, the projects used the same room the same day. Project A was using room 160 before project B entered. Room 162 holds equipment for both dispensing and blending and the two activities can be performed at the same time if the processes are contained. This enabled that the blending process could be carried out for project B during the dispensing of API for project A. As can also be seen in the figure, the projects have been in several rooms at the time. Project A occupied four rooms at the most, whereas project B occupied five rooms at the most.

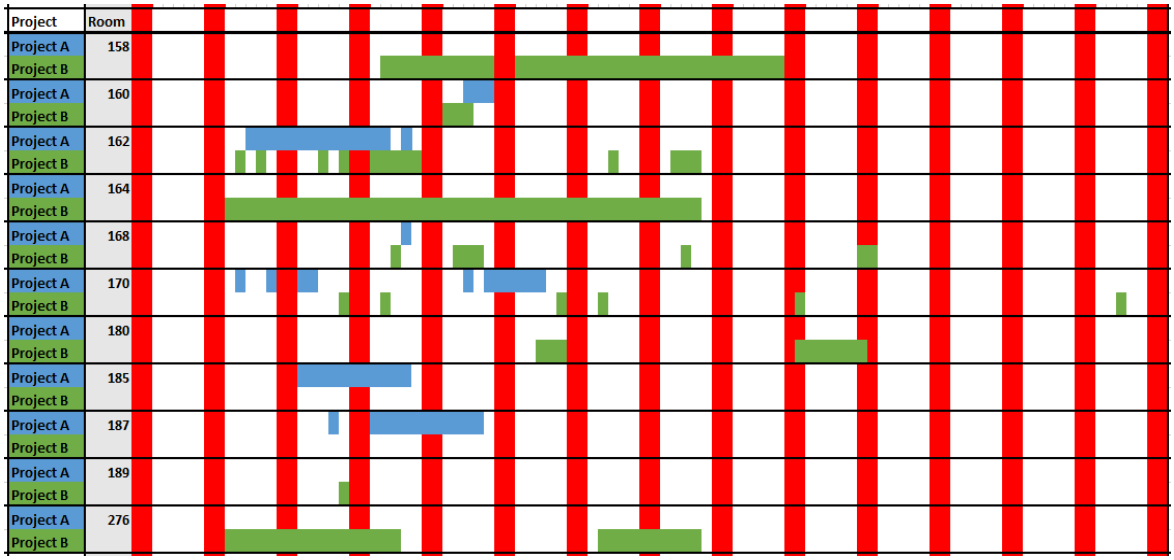

Figure 4.14. Room used for project A and B

The Dispensing step was executed in the same way for both projects. Both projects had thereafter a Blending step, where project A was blended twice and project B once. Thereafter, both projects had separate paths until it was time for Final blending. Project A only had one process step whereas project B had three. After the granulation and final blending the projects had the same path: Tablet compression, Preparation of coating liquid, Tablet coating and finally Sampling, bulk packaging and labelling.

4.4.3 Project X

The text in this section is based on the MBR for the project, the last two interviews displayed in table 2.1 and the time study (both the sheets and the observation). Note that the pie charts are based on 24-hours and they do not tell the length in minutes, instead percentage is used. The sheets were filled in by different operators who might not all have filled in the same way, since they have not had the same appreciation when dividing a process into different activities.

Project X was a wet granulation project with the result of two different strengths of tablets. Aside from different batch size project X is the same project as project G (which occurred during the time period). The manufacturing of the intermediate was, due to the API, divided into two different batches. The first batch was divided into two subbatches for the following process steps: Blending, Sieving, Wet granulation and Drying. The results of the two subbatches were tablets of the same strength (100 mg). The second batch was divided into five subbatches for the following process steps: Blending, Sieving, Wet granulation and Drying. The result of the five subbatches were tablets of the same strength (50 mg). See figure 4.15 for the overall manufacturing process plan for the manufacture of intermediate, made by Lead operator 4 for project X.

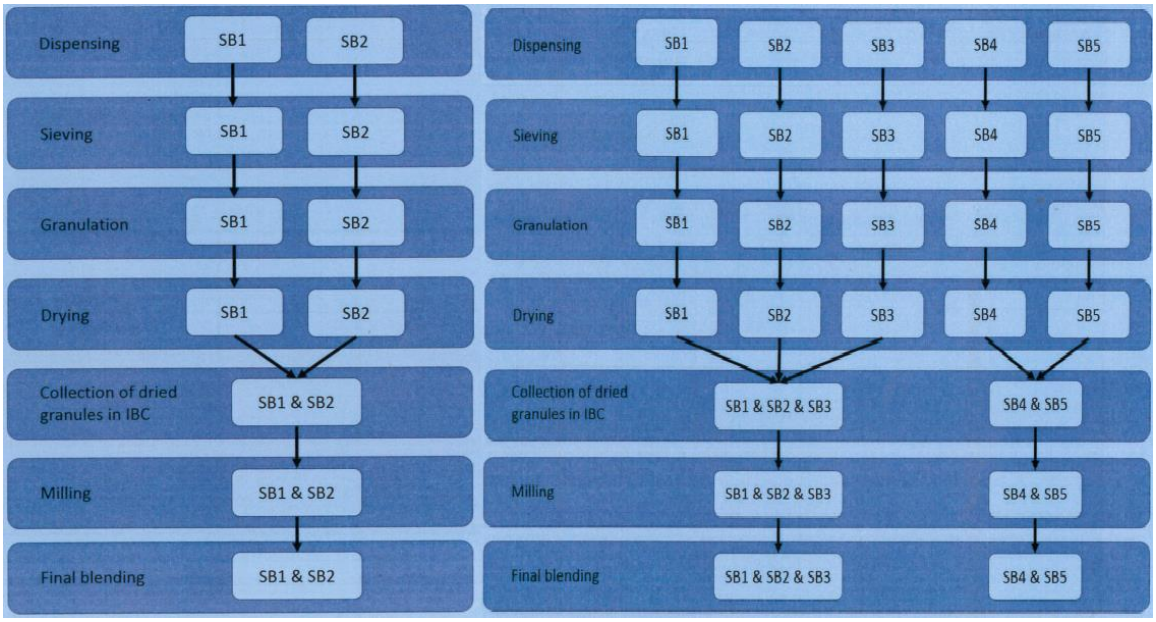

Figure 4.15. Overall manufacturing plan for project X

Only data for the first two weeks (day 1 to day 14, see figure 4.17 page 48) was gathered. This means that the manufacturing of tablets was not included. The orange rectangles in figure 4.16 represent the process steps gathered. It were the Dispensing for all subbatches, the Blending for four subbatches and the sieving for three subbatches. The Wet granulation and Drying of the first two subbatches were also included. The CIP-program for HSM03 and FBD01 needed after SB2 was not included in the time study.

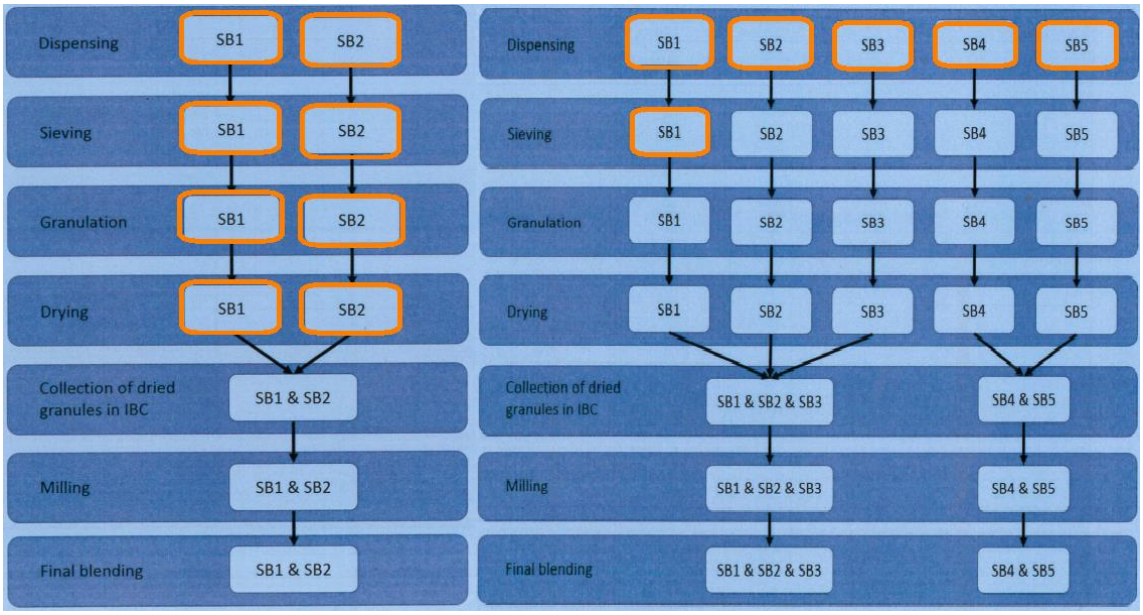

Figure 4.16. Overall manufacturing plan with the process steps executed in orange color

4.4.3.1 Rooms contaminated/occupied

The first day of the project was a Friday and room 120 (not included in the map in figure 4.2) was used to take out material needed for the Dispensing step. This room can be used by other projects at the same time, and was therefore not further investigated. This was the only activity executed this day.

For the first five process steps a total of six rooms have been used: 146, 152, 162, 164, 170 and 276. Four of the rooms have been used for only one process step, meanwhile two of them have been used for 2-4 process steps, see figures 4.18-4.23. The rooms are called contaminated when no other projects can use the rooms, a.k.a. occupied. Due to strict handling of the material, there may not be any "real contamination", but the pure risk of having any material that could cross contaminate another product in the room excludes the possibility to handle more than one product at a time.

Figure 4.17 illustrates the days the rooms have been contaminated/occupied and if they have been used for more than one day. Room 146, 152, 164 and 276 were still in use after day 14 when the time study ended.

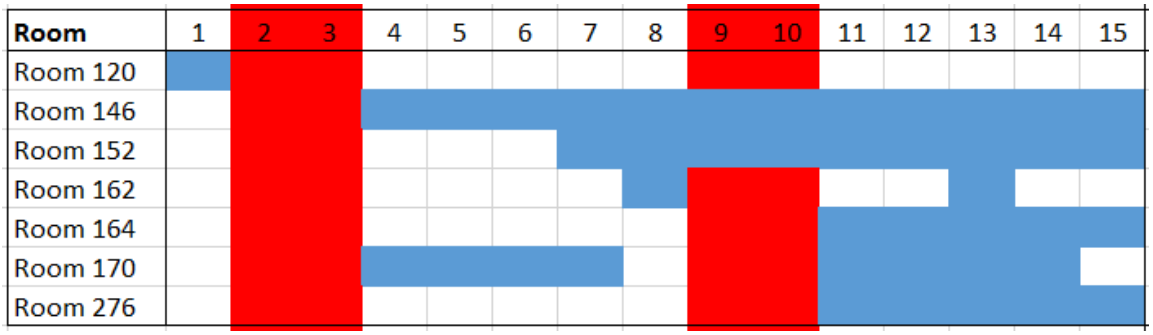

Figure 4.17. Days the rooms have been contaminated for project X

Room 146

Room 146 was used 5,12 % of the total time it was contaminated/occupied, see figure 4.18. Of that time 3,52 % was used for the Dispensing step whereas 1,66 % was used for the Blending step. As mentioned in section 4.3.2.1 room 146 has an isolator, which was used to dispense the API. The Dispensing step was carried out for all subbatches. According to the MBR the API was added into IBC's in the Blending step, i.e. the Blending step was also a part of room 146. The Blending step was executed for the first four subbatches.

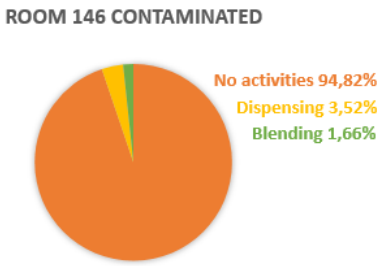

Figure 4.18. Room 146 contaminated

Room 152

Room 152 was only used for one process step, Sieving, see figure 4.19. There were activities during 4,61 % of the total time the room was contaminated/occupied. As mentioned in section 4.3.2.3 room 152 is the room that is used to sieve the raw material with an automatic sieve. The Sieving step was done for the first three subbatches.

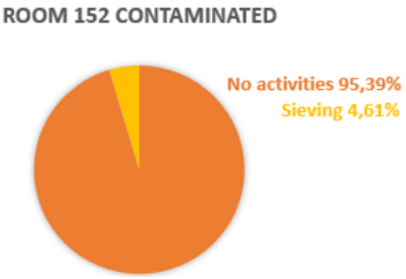

Figure 4.19. Room 152 contaminated

Room 162

Room 162 was used 100 % of the total occupied time, and was used for the Blending step, see figure 4.20. The reason for this was that the content of the IBC's were contained at all time, which allows several projects to work in the room at the same time. The Blending step was done for the first four subbatches.

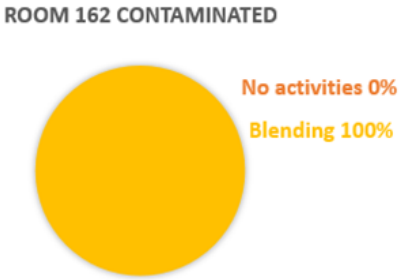

Figure 4.20. Room 162 contaminated

Room 164

Room 164 was only used for one process step, Drying, see figure 4.21. There were activities during 51,40 % of the total contaminated/occupied time. The reason that this room had more activities than the others (except room 276) was that the CIP and cleaning for SB1 are included here. The Drying step was performed for the first two subbatches.

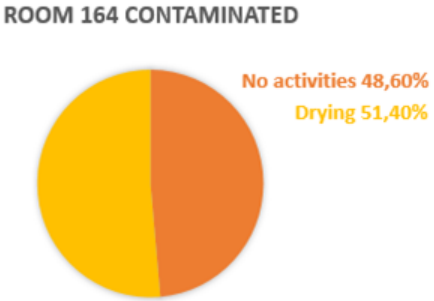

Figure 4.21. Room 164 contaminated

Room 170

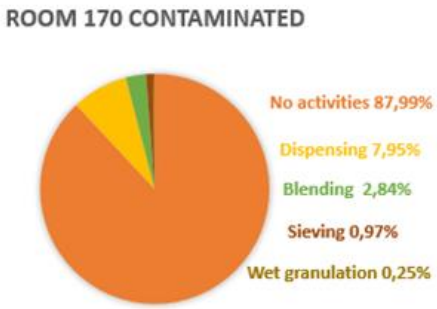

Figure 4.22. Room 170 contaminated

Room 170 was used 12,01 % of the total time the room was contaminated/occupied, see figure 4.22. The most of that time (7,95 %) was used for the Dispensing step. This is expected, since the room is mainly used to dispense raw material. The Blending step used 2,84 % of the time. The reason for this is the same as in room 146, i.e. adding raw material into IBC's. The excipients were added before the API. The Sieving step used 0,97 % of the time. In the Sieving step the empty IBC had to be weighed before sieving and then weighed again after the step. Due to no existing floor scale in room 152 this was performed in an available and suitable room, in this case room 170. The Wet granulation step used 0,25 % of the time. Normally no other room than room 276 is needed for the Wet granulation step but due to wrongly dispensed amount of excipient to the wet granulation liquid in the Dispensing step, the excipient needed to be dispensed again.

Room 276

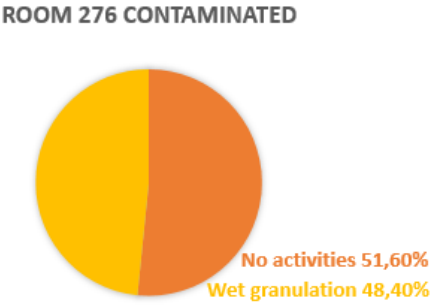

Figure 4.23. Room 276 contaminated

Room 276 was used for one process step, Wet granulation, see figure 4.23. There were activities during 48,40 % of the total contaminated/occupied time. The reason that this room had more activities than the other (except room 164) was that the CIP and cleaning for SB1 are included here. The Wet granulation step was performed for the first two subbatches.

4.4.3.2 Rooms used and the different process steps activities in those rooms

In this section pie diagrams illustrate the rooms that have been used for the five process steps. The Drying step was the only process step that did not used more than one room. There are also pie diagrams that illustrate the activities executed for every process step in these rooms. The different activities are set-up, up-time, cleaning and disturbances. Note that some of the process steps were performed at the same time, this is not illustrated in the pie diagrams. These pie diagrams illustrate how much of the total process step time that have taken place in the rooms.

Dispensing

The Dispensing step was executed in two rooms, room 146 and room 170, see figure 4.24 pie diagram 1. The dispensing for all seven subbatches was made at the same time. The API was dispensed in room 146 and used 46,46 % of the time whereas the excipients were dispensed in room 170 and used 53,54 % of the time. The excipients were dispensed one at a time and it took several days to complete. The dispensing of the API also took several days to complete.

According to pie diagram 2 in figure 4.24 the up-time was accounted as 78,19 % of the time used in room 146 for the Dispensing step. The dispensing was executed at four different times. The rest of the time, 21,81 % was accounted as set-up time. The set-up of the equipment was executed at two different times. Picking up the API was not included because it was not found in the activity sheet for room 146. During the time period no disturbances occurred and no cleaning was executed.

In room 170, as pie diagram 3 in figure 4.24 illustrates, most of the used time (82,24 %) was accounted as up-time. The dispensing was executed three different days and during those days one disturbance occurred, 1,51 %: an excipient was dropped on the floor and cleaning was needed. The set-up time was counted as 13,40 % of the time. This time included picking up the raw material and disposable articles, print out labels and general prepare before the dispensing of the excipients. The cleaning that occurred was manual cleaning for the day and it was accounted as 2,85 % of the time.

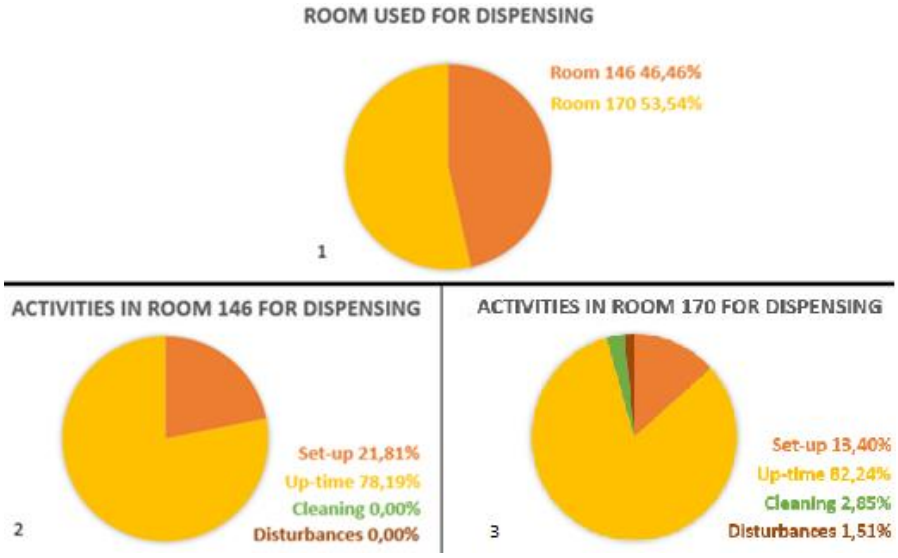

Figure 4.24. Rooms used for the Dispensing step & the activities occurring in these rooms

Blending

The Blending step took place in three rooms, see pie diagram 1 in figure 4.25. Most of the time (48,04 %) took place in room 146. Room 170 was used 41,76 % of the time and room 162 10,20 % of the time. The blending took place in room 162 using the FnM03 but adding the raw material in the IBC's were included in this process step and therefore room 146 and 170 were also used.

The pie diagrams number 2, 3 and 4 illustrate that the up-time was 100 % in all three rooms. During the period, four subbatches were blended and for them there were no disturbances occurring. No cleaning occurred due to there was no need for cleaning of the equipment and the rooms between the subbatches. The FnM03 in room 162 does not need to be set-up before use and room 146 and 162 was before the Blending step already set-up, due to the Dispensing step.

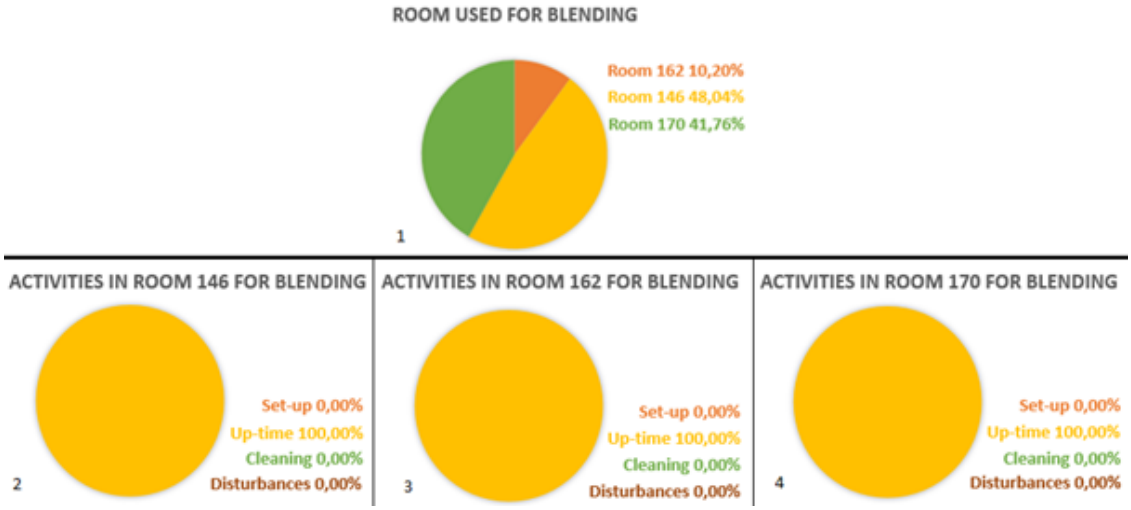

Figure 4.25. Room used for the Blending step & the activities occurring in these rooms

Sieving

The Sieving step took place in two rooms, room 152 and room 170, see pie diagram 1 in figure 4.26. Most of the time (86,56 %) took place in room 152 and the rest (13,44 %) took place in room 170. This is expected since the automatic sieve is located in room 152. As a reminder from section 4.4.3.2.5 room 170 was used due to no existing floor scale in room 152.

Pie diagram number 2 in figure 4.26 illustrate that of the time used for the Sieving step there was no cleaning performed. The equipment and room did not need to be cleaned between the subbatches. Most of the time used (56,60 %) was accounted as set-up time. The set-up took three days to complete and during that time two disturbances occurred (21,49 %). The first disturbance was longer than the other and occurred because of CV-restrictions. During that time the operators picked up some equipment that was needed. The next disturbance was that the operators had to go and get a sieving-net that was not found where it should be located. The up-time was accounted as 21,91 % of the time and was executed during three different times.

Room 170 was used to weigh the IBC's before and after the sieving. The IBC's with the subbatches were contained at all time when weighed and therefore no cleaning was needed. The scale did not need any set-up and it did not occur any disturbances for the Sieving step in the room. The only activity that was executed was weighing which was accounted as up-time, thereby 100 % up-time, see pie diagram 3 in figure 4.26.

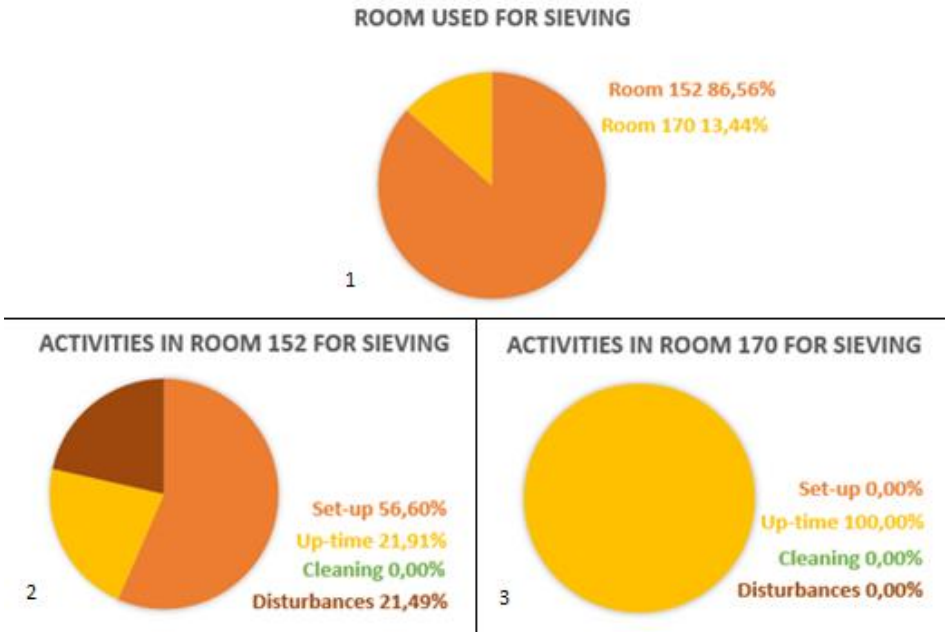

Figure 4.26. Room used for the Sieving step & the activities occurring in these rooms

Wet granulation

The Wet granulation was executed in two rooms, room 276 and room 170, see pie diagram 1 in figure 4.27. Most of the time (99,12 %) took place in room 276 and the rest (0,88 %) took place in room 170. As earlier mentioned room 170 was used due to the incident when the wrong amount of the excipient to the granulation liquid for SB2 was dispensed.

Pie diagram number 2 in figure 4.27 illustrates that of the time used for the Wet granulation step in room 276 most of the time (66,48 %) was accounted as cleaning time. This included preparation before the CIP-programs, the CIP-program for SB1 and change of filter during the program and a cleaning verification for SB1. The cleaning verification was needed to be made because of the use of a new campaign CIP-program the CIP-program was not yet fully validated. The CIP for SB1 could not start until another CIP, using the same pipe was complete and was accounted as a disturbance. The second largest time was disturbances. There were one disturbance during the set-up where the operators could not find a part but it also included helping with the Sieving step. When the wet granulation of SB2 was supposed to start there were two disturbances. First the IBC containing SB2 was not found, then at the beginning of the wet granulation-process the valve between HSM03 and FBD01 accidentally was opened. The reason for this was that the same button is used for opening the valve and changing to manual speed. The disturbances was accounted as 16,29 % of the total time. The up-time was accounted as 8,68 % of the time and it included making granulation liquid and the wet granulation-process.

As earlier mentioned it was necessary to dispense the excipient to the granulation liquid for SB2 again, this occurred in room 170 and was counted as a disturbance, see pie diagram 3 in figure 4.27.

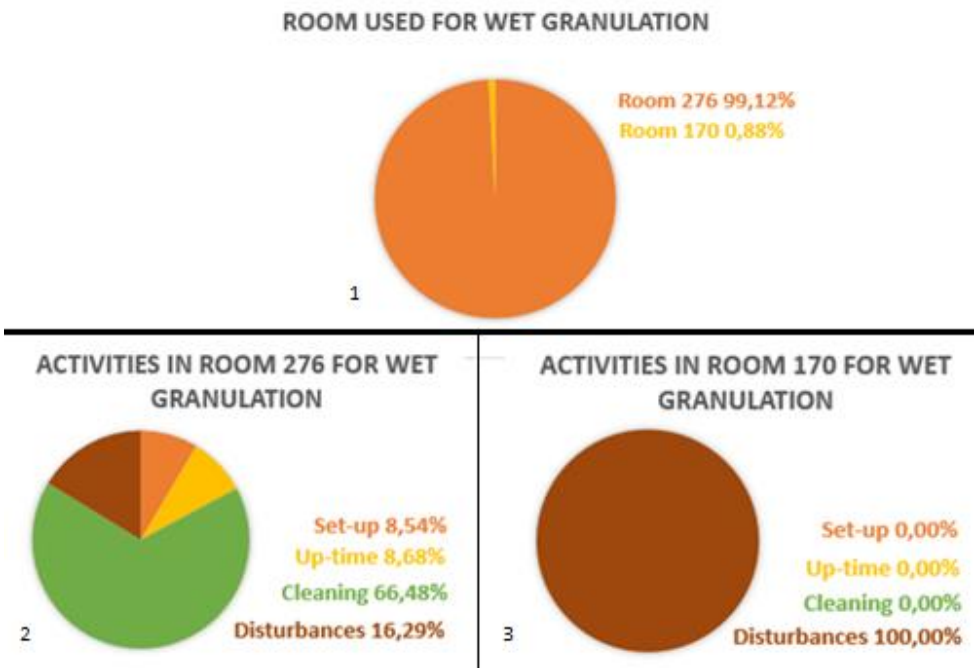

Figure 4.27. Room used for the Wet granulation step & the activities occurring in these rooms

Drying

The Drying step took place in room 164, see pie diagram 1 in figure 4.28. The activities during that time are illustrated in pie diagram 2 in figure 4.28. Most of the time (55,45 %) was used for cleaning. The cleaning included the setting of CIP-program for both SB1 and SB2, and the CIP-program for SB1 and the cleaning performed by the Cleaning personnel after the CIP for SB1. Cleaning verification was also needed due to campaign CIP-program. As mentioned earlier the CIP for SB1 could not start directly and was accounted as a disturbance, in this case shorter than for the Wet granulation step in room 276. Other disturbances that occurred were that the wet granulation for SB2 could not start as planned because of a need to clearance from QA, waiting time due to incorrectly dispensed excipient to the granulation liquid and the opening of valve between HSM03 and FBD01. These disturbances were accounted as 14,45 % of the time. The up-time was accounted as 12,85 % of the time. The set-up was accounted as 8,17 % of the time and was only made at the beginning of this process step and included LC, pick up of disposable articles and weighing of the IBC.

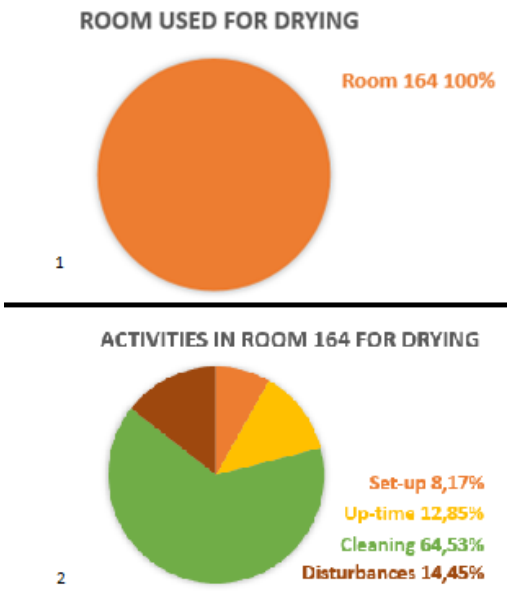

Figure 4.28. Room used for the Drying step & the activities occurring in these rooms

4.4.3.3 Process steps proportion

Figure 4.29 gives an indication about how much time each process step actually took in proportion to each other. Note that the CIP for HSM03 and FBD01 is accounted for twice, one time to the Drying step and one time for the Wet granulation step. The Dispensing step that was carried out for all subbatches used 16,79 %, the Blending step that was done for the first four subbatches used 7,68 % and the Sieving step that was done for the first three subbatches took 8,18 %. Most of the time, 32,54 % and 34,81 % respectively, was used for the Wet granulation and Drying step.

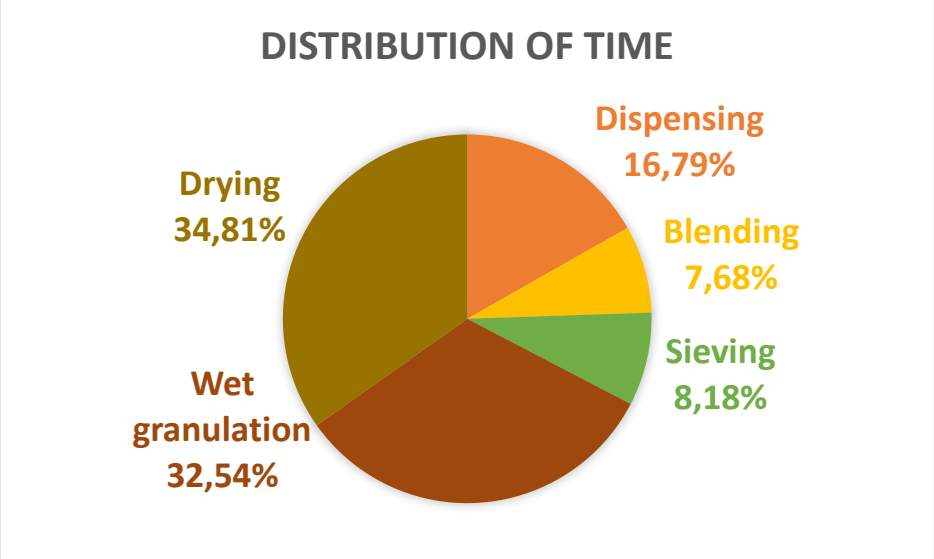

Figure 4.29. Distribution of time for the five process steps

As section 4.4.3.2 advocate the five process steps were executed in 1-3 different rooms. Depending on the process step, the time was used for different activities. For the Dispensing step, most of the time was accounted as up-time and for the Blending step 100 % of the time was accounted as up-time. For the Sieving, Wet granulation and Drying step it was different. The Sieving step in room 170 had 100 % up-time whereas in room 152 most of the time was used for set-up. The wet granulation and drying used an equipment that is connected to each other and the process took similar time, the pie diagrams are therefore almost identical for them. Most of the time for the two process steps was used for cleaning. The set-up was only performed once for the equipment and it occurred in the beginning of the process steps. The Dispensing, Blending and Sieving steps had no need for a cleaning between the subbatches whereas the Wet granulation and Drying step needed it.

4.4.3.4 Observation

There was an observation executed for the wet granulation and drying process for SB2. This gave a greater understanding of how many things there are to consider. It was acknowledged that there are many small activities that occur within an activity.

To enter the pilot plant you have to get undressed and wash the hands thoroughly, then put on new clothes that are provided and then again wash your hands and finally apply alcogel on the hands. This took about 10 minutes.

There were waiting time for the operators, especially in room 164. When full safety gear is used you do not want to leave the room, therefore there were limited ways of communication. When a disturbance occurred the operators had to get answers/clarification from both QA and the Lead operator before starting the process again.

5 DISCUSSION

This chapter will start with a discussion about the use of applied methods and theories. Thereafter, there is a discussion with recommendations regarding the efficiency, the need for production follow-up and the need for standardization at the pilot plant.

5.1 Applied methods and theories

As mentioned in the research approach focus has changed during the empirical study due to the setbacks in finding information needed. This has been a reoccurring problem during the collection of data: finding reliable data to do a valid analysis. The results of the projects during the time period and the project in the time study is valid but if the same projects at a different time period would to be analyzed the result would be different.

The methods used throughout the empirical study have been helpful but not always the best, both because of the difficulty to find data and choice of method. There were an idea at the beginning of the project to use a simulation program to visualize the flow and utilization of the equipment and resources at the pilot plant, but flowcharts and excel-compilations were later considered as enough. It was decided not to not include a spaghetti diagram in this study. However such diagram would be useful too illustrated how much the operators and/or batches move in or between process rooms.

The data collection methods have all been useful, in particular the written documentation. The expectation was that the EBR's, MIMS-reports and potentially the logbooks for the rooms and equipment would give more exact times to analyze, but unfortunately they did not. It was not because of the method but for the lack of data that needed to be collected. It was also discovered during the empirical study that collecting data from a period which had passed was not the best approach to detect limitations or how much of the time given that actually was used. To do this a time study was needed and therefore executed.

The time study was a successful method with the result as hoped. More data to analyze and present could have been possible if the time study had started earlier and followed entire project X, but this was not possible due to time limitations. There was a difficulty to have the operators to fill in the activities and times the exact same way, even though a tutorial was handed out. When compiling the data from the time study some of the sheets were more detailed than others. An example when the times were not identical was when the waiting time for the CIP to start in room 164 was shorter than in room 276 although the same time was expected.

The observation during the time study gave a better understanding about how many small activities there are. It was difficult to see and understand the activities due to a limited view and scarce knowledge about the process.

Flowcharts and pie diagrams have been very useful to illustrate the pilot plant: the different process steps, the sequence they have been executed in, their length, etc. The pie diagrams would have been more reliable and valid if the sheets would have been filled in the exact way

but it would also give a much larger workload on the operators and probably would have distracted them.

The theories have been helpful when deciding which data to look for. Lean is an approach that have proven to be useful in many operations to increase efficiency, and show where improvements can be made. The different process types and layouts have not been used more than describing the layout of the pilot plant and tell what kind of manufacturing process the pilot plant use. A greater understanding of today's changes in the pharmaceutical industry has been useful in order to understand why improvements are needed.

5.2 Efficiency

As section 4.4.3.1 advocates the overall efficiency of the rooms is low, when examined from a 24-hours view. The rooms were occupied much longer than they needed to be. There are several reasons for this and not all of them have been discovered nor will they be discussed here. It was only room 162 that was used 100 % of the contaminated/occupied time, but that was because the process does not need any cleaning, i.e. several projects can work in the room at the same time. Room 164 and room 276 were the rooms that almost 50 % of the contaminated/occupied time were used for activities. The high degree of utilization is mostly because of the CIP but also since the rooms not were used from the start of the project (see figure 4.17 page 48). Room 146 and 170 were used at the start of the project and the pie diagram includes all subbatches for the Dispensing step. An important aspect to note is that the pie diagrams only display the efficiency based on data from the first 14 days and that four rooms still were in use when the time study ended.

To improve the efficiency, there are two ways to go, resource efficiency or flow efficiency. No matter which one the department choose to focus on, measuring is important, see section 5.3. One is measured by utilization and the other one is measured by throughput time. The study has focused on flow and time-use, and standardization is an important way to improve, see section 5.4. Both throughput time and utilization can be helped by measuring the time a room has been contaminated/occupied/used for each process step. By trying to maximize the time the resources are used the utilization can be improved and by minimizing the non-value adding time the throughput time can be improved.

The way the pilot plant is built and projects are organized, puts the focus on resource efficiency, which means projects are planned so that equipment will be used to maximum extent. When the pilot plant has many projects active in the production, queues occur. This implicates that the pilot plant have resource limitations and many possible bottlenecks in the production, which becomes visible when many projects are active at the site at the same time. The manufacturing has a natural pull from the clinical studies to be supplied and the limitations of being able to build stock make throughput time of more importance to free resources to other projects.

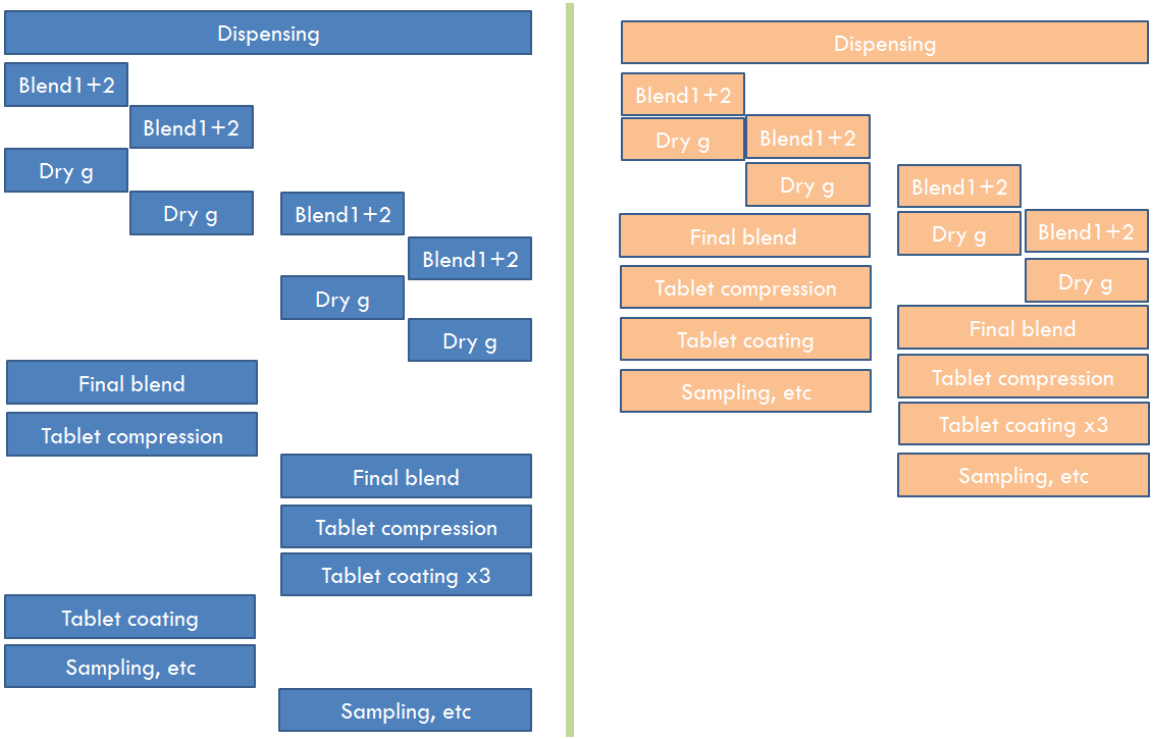

Figure 5.1. Project A today and project A without increasing the number of changeovers

Today there is a lot of waiting and manual work to the process. To increase the efficiency there are a few aspects to focus on in the manufacturing to achieve a reduced throughput time and better flow. The left side of figure 5.1 illustrates in what sequence the manufacturing of project A was made in whereas the right side illustrates how it could look if the process steps were executed with a continuous flow. The right side would decrease the throughput time of a project and the time a room is contaminated/occupied. This would enable more active projects. It is important to decrease the time a room is contaminated/occupied since no other projects can enter, and as the pie diagrams in sub sections 4.4.3.1 and 4.4.3.2 show, most of the contaminated/occupied time is not value adding time. The right side has not taken into account that other projects might use the equipment needed, personnel shortage or other reasons for delays. This kind of comparison and visualization is important to make, it evokes many questions and it becomes clear where improvements need to be made.

During the empirical study, there have been indications that there might be too few IBC-containers at the pilot plant. This has been notified both from the interviews and the EBR's for project A. A further investigation can be made with focus on if the IBC-containers are utilized enough, if better planning can help or if new IBC-containers need to be purchased.

5.3 Production follow-up

Today the follow-up for the product is very strict while the follow-up for the production is limited. There is information on the throughput time for the whole project, but not for certain rooms or process steps. The empirical study advocate that the logbooks for the rooms and equipment not are detailed enough to tell what actually has been done in the room. This has made it difficult to analyze and visualize.

As section 3.3 advocates measuring and production follow-up is essential to make improvements. A visualization of the pilot plant will make it possible to see problems, e.g. collisions between projects with respect to rooms and equipment. To make this possible at the pilot plant, a lot more data needs to be collected before any major decision should be made. Data can be collected and analyzed in the same way as this study, with the exception that it should focus on a larger scale and more aspects need to be taken into account.

The time study should be continued to visualize entire project X but also involve other projects at the pilot plant. An entire visualization of project X was not possible due to time limitation. A longer period of time could be investigated to get a better view over the different types of projects at the pilot plant. The focus should still be on set-up time, up-time and cleaning time. A suggestion would be to do a more thorough observations and clock each step in order to find out what the value adding time is and where changes can be made. As section 2.3 indicates the observer should be well versed in the subject before the observation takes place.

The data collected today does not exactly tell why it looks like it does and reasons to this need to be investigated further. For example, data does not tell if there are or will be any collisions, if IBC-containers will be booked or if the rooms are occupied. More interviews can be held with people within the department to obtain a greater understanding on how things are done, but mostly to clear up the why's.

Disturbances occur and it is something that the pilot plant is trying to avoid. Collisions is a disturbance that delay the projects. The Functional planner tries to avoid collisions when giving a project a timeslot, but it is not completely avoidable. Today the Functional planner needs to know many things by heart, which is learnt by trial and error. The schedule program does not warn if a room or equipment has a risk to become overbooked. This gives a high faith of the Functional planner. Therefore a good idea could be to develop a planning tool that detects overbooking (collisions). For this, standardized times for every step/activity need to be calculated, see section 5.4. The times gathered in the time study give a good indication. Missing items are also a disturbance.

There have been indications from both the time study and interviews that equipment and tools not always have been where they should. To go and look after missing items or things that always are used in a room takes time from the production. This wasted time can be eliminated if there is a list in every room that say what things that should always be in a room. To make sure that the rooms are complete according to the list there can be someone to check the room before it will be used, for example the technical operators. A suggestion is to improve and follow up on the already implemented 5S project.

It feels a bit old fashion that the EBR's and logbooks are in paper form and filled in by hand. If the EBR and logbooks were to be digitalized, it would be easier to search in the documents and it would minimize the risk that data would get lost. If the documents would to be digitalized, it needs to be taken into account that the documents needs to be able to be signed. The traceability needs to be very high and the documentation needs to be correct and in most cases two people needs to sign the documents. A connection between the digitalized EBR's

and logbooks with the MIMS-reports would make it possible to see the performance of the process.

5.4 Standardization

Today there is a need for high flexibility in the manufacturing due to differences in volume, product variety and variety in demand. The empirical study has shown that the pilot plant has many different resources available to manufacture a wide range of products, both in manpower and in equipment.

As stated in section 3.2, a continuous flow will be received by having a lower variety and more repeated process tasks. This could be solved by more standardization. Finding similarities is the key when standardizing. As mentioned earlier, every project is more or less unique. At the moment, the production is batch based towards jobbing and the organization and pilot plant is designed accordingly. The department works in project form and this have many advantages when the manufacturing need a certain knowledge. As proven there are many process steps and different manufacturing methods within the process steps. The process steps are not as simple as e.g. turning, they are much more complex mostly because of the high demand on quality and traceability of the products. This was assumed from the beginning but has been confirmed during the empirical study. Some projects have more process steps than others, but the order of the used process steps is more or less the same. The equipment used are also more or less the same for every project.

The number of subbatches are of importance when setting up a project, this mostly affect the workload and time use. This is due to the changeovers between subbatches. It becomes difficult to oversee when and how long time the changeover will take since the number of tasks that have the chance of being delayed are multiplied. A problem that was discovered is that the manufacturing start with one batch size which is often divided into subbatches. These subbatches are later submerged to fewer batches and these are later dedicated to different strengths of OSDs. Project A and B had a similar batch size, project A was divided into four subbatches whereas project B was divided into six subbatches. The equipment and formulation was the reason for this. Then later, the subbatches were submerged to one or more batches before being dedicated to a certain strength. The strengths were then divided into subbatches, see figures 4.10 and 4.12 in section 4.4.2. This implies that there is an unevenness (Mura) in the production and it can be reduced by standardization and reduced set-up times for changeovers.

A suggestion would be to find an optimal batch size, one that works for every project and equipment. The pilot plant needs to be flexible due to the clinical studies but it makes it difficult to have a more continuous flow. There needs to be a change to get a more standardization.

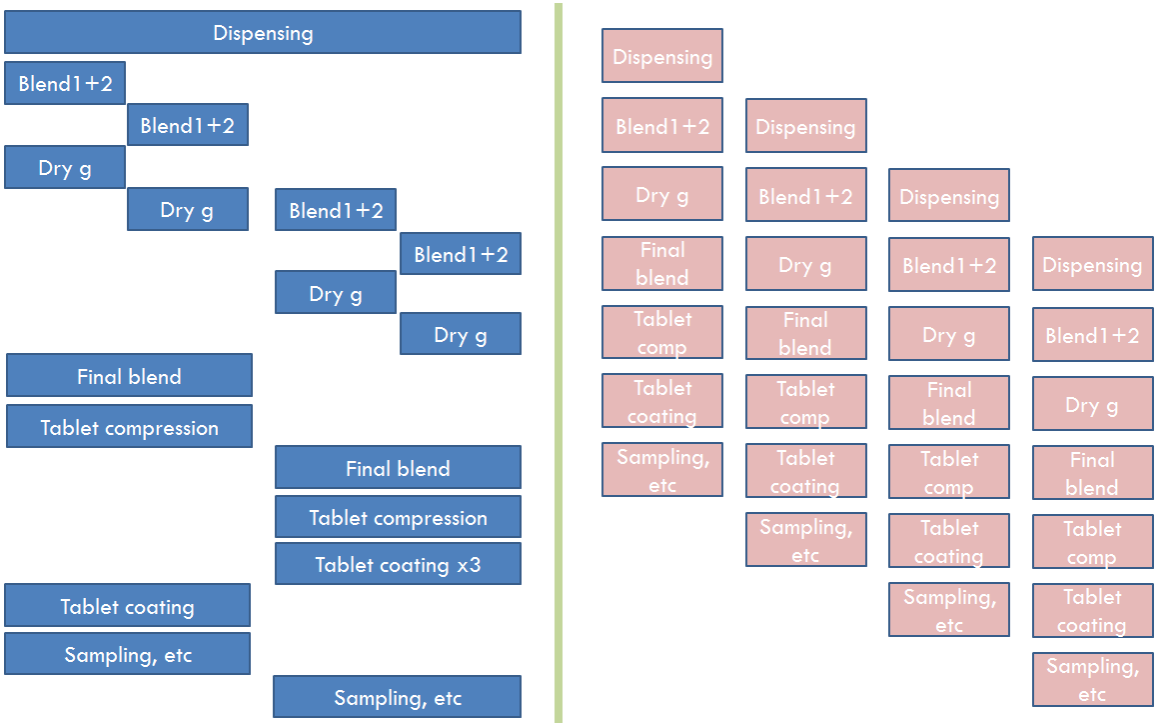

Figure 5.2. Project A today and project A with increased number of changeovers

The left side of figure 5.2 illustrates in what sequence the manufacturing of project A was made, whereas the right side illustrates how it could look like if the process steps were executed with a continuous flow with the same batch size at all times. This would increase the number of changeovers and therefore demand shorter set-up and cleaning processes. It might not be possible at the plant today, partly because of the high demand on safety and uniform quality but also because the way the organization traditionally plan their projects. It would be interesting to investigate how the manufacturing would be affected if a project with many subbatches and different strengths were divided into smaller projects. Would the planning become easier?

Following questions are to be asked:

- Can it be worth to divide a project with multiple subbatches to several small projects?
- Can it be worth to divide a project with multiple strengths to several small projects?
- What are most preferable: less active projects (and less subbatches) and as a consequence less queues or more active projects and as a consequence higher resource utilization?

The projects have had multiple subbatches and it has been hard to follow the projects through the site. Interviews showed that the time used for a process step could vary and that how long each process step should take was not stated. The pie diagrams in sub section 4.4.3.2 together with the tables for each process step in sub section 4.3 gives an indication on how much time to actually dispose. Today the set-up time for each equipment differs depending on if there are to be any extra parts and the person performing the set-up. The cleaning depends on the raw material, equipment and if it is a campaign or not. The up-time depends on the batch size and the formulation. By standardizing these times planning would be easier.

6 CONCLUSION

The empirical study should by now, both described and visualized the current state at the pilot plant. Several areas for improvement lightened and clarified, such as changeovers, variety in products and volumes, flow, time use, activities that are needed and the demands.

The first question has been answered in section 4.1, 4.2 and 4.3. To sum it up in a few sentences: the manufacturing demand advanced rooms and equipment, the tasks are diverse and demand personnel with a high level of knowledge and there are numerous standards and functions in the manufacturing for the department to correct after.

The second question is tougher to answer. The results in this study is based on just a few projects and during a limited time period in the pilot plant's manufacturing but it reveals many of the difficulties there are to pharmaceutical manufacturing. The result shows that factors affecting projects are many. Today there is a need for high flexibility in the manufacturing due to differences in volume, product variety and variety in demand. This makes it hard to know how long time a project will take to finish and to know what resources that will be in risk of being used by other projects. This makes it hard to plan ahead, creates an unstable flow in the manufacturing. To know how long time each process steps take, and aiming to reduce throughput time is important in order to avoid collisions between projects and queues. The overall utilization of the equipment and rooms can be improved. Particularly the lack of visualization, production follow-up and standardization was identified as important ways to improve the pilot plant's efficiency.

REFERENCES

Akademin för ekonomi samhälle och teknik, 2014. *Validitet.* [Online]
Available at:
http://www.mdh.se/student/minastudier/examensarbete/omraden/metoddoktorn/metod/validitet-1.29071
[Accessed 3 Juni 2016].

AstraZeneca, 2016. *Jakten på nya läkemedel.* [Online]
Available at: http://www.astrazeneca.se/forskning/jakten-p-nya-lkemedel
[Accessed 11 May 2016].

Bergman, B. &. K. B., 2012. *Kvalitet från behov till användning.* 5 ed. Lund: Studentlitteratur AB.

Bohgard, M. e. a., 2010. *Arbete och teknik på människans villkor.* 2 ed. Stockholm: Prevent.

BusinessDictionary, 2016. *Batch.* [Online]
Available at: http://www.businessdictionary.com/definition/batch.html
[Accessed 11 May 2016].

Carroll, S., 2009. *Goodbye blockbuster medicines; hello new pharmaceutical business models.* [Online]
Available at: http://www.pharmaceutical-journal.com/opinion/comment/goodbye-blockbuster-medicines-hello-new-pharmaceutical-business-models/10966185.article
[Accessed 26 May 2016].

Lakerveld, R. e. a., 2013. *Model-based Design of a Plant-Wide Control Strategy for a Continuous Pharmaceutical Plant,* Wiley Online Library: American Institute of Chemical Engineers.

Liker, J. K., 2004. *The Toyota way - 14 Management Principles from the World's Greatest Manufacturer.* New York: McGraw-Hill.

Malik, N., 2007. *Has the Era of Blockbuster Drugs Come to an End?.* [Online]
Available at: http://www.biopharminternational.com/has-era-blockbuster-drugs-come-end
[Accessed 26 May 2016].

Mascia, S. e. a., 2013. *End-to-End Continuous Manufacturing of Pharmaceuticals: Integrated Synthesis, Purification, and Final Dosage Formation,* Wiley Online Library: Angewandte Chemie.

Mattsson, S.-A. J. P., 2013. *Material- och produktionsstyrning.* 1 ed. Lund: Studentlitteratur AB.

Modig, N. a. Å. P., 2012. *Detta är lean.* 2 ed. Halmstad: Stockholm School of Economics Institute for Research.

Nationalencyklopedin, 2016. *Klinisk prövning.* [Online]
Available at: http://www.ne.se/uppslagsverk/encyklopedi/lång/klinisk-prövning
[Accessed 11 May 2016].

Nationalencyklopedin, 2016. *Observation.* [Online]
Available at: http://www.ne.se/uppslagsverk/encyklopedi/lång/observation
[Accessed 12 May 2016].

Nationalencyklopedin, 2016. *Tidsstudier.* [Online]
Available at: http://www.ne.se/uppslagsverk/encyklopedi/lång/tidsstudier
[Accessed 11 May 2016].

Nisen, M., 2013. *Novartis CEO: The Age Of Massive Blockbuster Drug Is Over.* [Online]
Available at: http://www.businessinsider.com/future-of-pharmaceutical-blockbusters-2013-3?r=US&IR=T&IR=T
[Accessed 26 May 2016].

PwC, 2011. *Pharma 2020: Supplying the future - Which path will you take?, .*: Pharmaceuticals and Life Sciences.

Shanley, A., 2010. *Toyota's Meltdown: Lessons for Pharma on its Lean Journey.* [Online]
Available at: http://www.pharmamanufacturing.com/articles/2010/091/
[Accessed 3 June 2016].

Slack, N. B.-J. A. a. J. R., 2013. *Operations management.* 7 ed. Edingburgh: Pearson Education Limited.

Smartdraw, 2016. *Flow chart.* [Online]
Available at: https://www.smartdraw.com/flowchart/flowchart-software.htm
[Accessed 13 May 2016].

Smartdraw, 2016. *Lean.* [Online]
Available at: https://www.smartdraw.com/lean/
[Accessed 11 May 2016].

Smartdraw, 2016. *Pie chart.* [Online]
Available at: https://www.smartdraw.com/pie-chart/
[Accessed 13 May 2016].

Thomson, W., 1889. *Popular lectures and addresses.* 1 ed. London: MacMillian and Co.

Wilburn, K. R., 2010. *Business Case for Continuous Manufacturing of Pharmaceuticals.* [Online]
Available at: https://dspace.mit.edu/bitstream/handle/1721.1/59190/659834956-MIT.pdf?sequence=2
[Accessed 26 May 2016].

Womack, J. P. J. D. a. R. D., 1990. *The Machine that Chaged the World.* New York: Rawson Associates.

APPENDIX 1 – Questionnaire

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1						Interval (max and min time)								
2	**Responsible for equipment**	**Process step**	**Room**	**Equipment**	**Set-up-time**	**Process/ run time**	**CIP (normal)**	**CIP (campaign)**	**WIP**	**Manual cleaning time**	**Extra equipment/parts that is able to attach**	**Capacity (Kg)**	**Can theg take all IBC?**	**Other**
3		**Dispensing**												
4	Firstname Lastname	Isolator	146	ISO01										
5	Firstname Lastname	Isolator	162	ISO07										
6			183	LAF ceiling										
7			170	LAF ceiling										
8			168	LAF ceiling										
9		**Blending**												
10	Firstname Lastname	Dry blender	162	FrM03										
11				LAF ceiling										
12		**Granulation**												
13	Firstname Lastname	High-shear mixer	276	HSM03										
14	Firstname Lastname	Fluid bed	164	FBD01										
15	Firstname Lastname	Roller Compaction	185	RoC01										
16	Firstname Lastname	Dry mill	162	MIL03										
17		**Tablet compression**												
18	Firstname Lastname	Tablet comp	187	TaP02										
19	Firstname Lastname	Tablet comp	158	TaP03										
20	Firstname Lastname	Tablet comp	152	TaP01										
21		**Tablet coating**												
22	Firstname Lastname	Tablet coating	160	TaC01										
23	Firstname Lastname	Tablet coating	180	TaC02										
24		**Capsule filling**												
25	Firstname Lastname	Capsule filling	144	CaF02										
26	Firstname Lastname	Capsule filling	166	DiC										
27														
28	Firstname Lastname	**Scales**												
29		in rooms above												
30														

APPENDIX 2 – Sheets for time study

Activity sheet

	A	B	C	D	E	F	G	H	I
1	RUM:	LF			Tidsintervall				
2	Processte	Aktivitet (operatör och process var för sig)	Ev rum	Extra kommentar	Starttid (med datum)	Sluttid (med datum) alt tidsåtgång om tidtagare	Antal personer	Stopp & störningar under tidsintervall	Stopp & störningar utanför tidsintervall
3									
4									
5									

Room sheet

	A	B	C	D
1	RUM	LF		
2	Starttid rum (när rummet inte kan användas av annat projekt)	Sluttid (när rum kan användas till annat projekt)	Kommentar (om rummet har använts av ett annat projekt, t.ex dispensiering samtidigt som blandning)	
3				
4				
5				

APPENDIX 3 – Tutorial for time study

Tidsstudie för projekt A

Bakgrund: Tidsstudien är en del av den nulägesanalys som vi (Anna Ingelström och Clara Klang) utför i from av ett examensarbete.

Syfte:

- Att identifiera hur stor andel av den planerade tiden som utnyttjas.
- Att identifiera vad som görs under den utnyttjande tiden och se störningar/flaskhalsar

Två olika papper behöver fyllas i:

1. Kompletterande rumslogg
2. Aktivitetslogg

1. Kompletterande rumslogg

Vad: En lapp i varje rum (de som används under projektets gång).

Syfte: Vill veta när rummet är kontaminerat av projekt A (dvs när inget annat projekt kan befinna sig i rummet).

Metod:

- Fyll i när rummet blir upptaget (starttid med datum och tid (timme och minut)).
- Fyll i när rummet inte längre är upptaget, dvs någon annan kan gå in och använda rummet (sluttid med datum och tid (timme och minut)).
- Eventuella kommentarer: T.ex. om man varit två projekt i rummet (t.ex. rum 162) samtidigt och hur det har påverkat processen (blivit förseningar, etc).

2. Aktivitetslogg

Vad: Har en *lapp i varje rum* där ni skriver in varje aktivitet och mellan vilka tider aktiviteten utförs.

Syfte: Få reda på hur lång tid varje aktivitet tar och var det utförs

Metod:

Fyll i varje kolumn efter beskrivning och exempel nedan.

Kommentarer till lapp

Processteg:

Namnge vilket processsteg i MBRn som aktiviteten tillhör (dispensering, blending, våtgranuelring, etc).

Aktivitet:

- Aktivitet = När något aktivt sker i rummet. Antingen är det en operatör som gör något (t.ex. riggar, övervakning/körning av maskin) eller så är det utrustningen som gör något (tex CIP, körning maskin). Dessa aktiviteter ska ha egna rader.
- Ny aktivitet --> ny rad med nytt tidsintervall
- **VIKTIGT**. Går man ut ur rummet för t.ex. lunch eller slut för dagen ska man skriva ut sig. När man senare ska fortsätta måste man påbörja en ny rad. T.ex. riggar två olika dagar
- Om flera aktiviteter sker samtidigt i ett rum så ska de stå på olika rader.
- OBS en aktivitet behöver inte ha ett rum (se nedan ev rum)
- Om man t.ex. riggar och spriten tar slut eller man missade att få med ett redskap så finns det två alternativt:

- Alt 1 (se exempel). Skriva på ny rad när man går ut för att hämta något snabbt. Om det blir jobbigt →
- Alt 2 (se exempel). Fyller i det som en störning under tidsintervallet med helst uppskattad tidsåtgång. Detta kan ni då fylla i när ni fyller i sluttiden för aktiviteten vilket gör att ni reflekterar över hur aktiviteten gick.

Exempel på aktiviteter:

- Hämta ut excipient, API eller utrustning (ex på störning under tidsintervall: smartsupplies hängde sig)
- Rigga
- Körning: Våtgranulering, dispensering av excipient 1 eller API 1
- Förstäda (synligt rent)
- Lämna excipient 1 och hämta excipient 2 (om görs vid samma tillfälle).
- Slutstäda/CIP/WIP, kampanj?
- Beräkningar, om görs i rum samtidigt som man maskinen körs kan det stå med i den aktiviteten (helst då med tidsåtgång) men om det sker utöver en annan aktivitet ska det ha en egen rad.
- Fler exempel finner ni i excel-dokumentet.

Tillägg:

- Lägg till vilken subbatch det gäller och mer exakt vad man gjort
- Om ni utför beräkningar utanför rummen (t.ex. senare på dagen): notera hur lång tid det tog och gärna vilken dag det utfördes och spara lappen så vi kan få den senare.
- Om ni väljer att väga/räkna en dag senare får ni gärna skriva varför i stopp och störningskolumnen.

Ev rum:

Inget måste att fylla i denna kolumn

- Om man lämnar rummet för att utföra en annan aktivitet som ändå tillhör rummet (t.ex. hämta ny sked, hämta och lämna excipient, diska av en utrustningsdel) så ska det stå med på denna lapp med tillägg vilket rum man befann sig i (t.ex. hämtade excipient 1 i rum 120).
- Om aktiviteten utförs i det rum som står överst på lappen behöver inget fyllas i här.

Extra kommentar:

Kan vara mer eller mindre ifylld men det som vi vill ska framgå är att om det har tagit längre eller kortare tid att utföra något för att där är en extra utrustningsdel i fallet, extra rengöring pga TH-klass eller kampanj-städning osv. T.ex. en kvarn som också riggas på (och därför tog det en extra timme att rigga), använts en våg som enbart finns i det rummet.

Starttid:

Den tid ni påbörjar aktiviteten (datum, timme, minut)

Sluttid:

- Den tid ni avslutar aktiviteten för dagen (om CIP som körs över natten så skriv in slutdatum och tid när den är klar (när ni stänger av den, kommer vi från MIMS sen att kunna utläsa den exakta sluttiden på programmet men det är inte alltid MIMS fungerar så om ni hittar sluttid för programmet får ni gärna skriva med det här som kommentar)). Om den tar längre eller kortare tid än vanligt så skriv en kommentar om det.
- Om samma dag som start behövs ej datum skrivas med här
- Om ni använder tidtagare så räcker det att ni skriver in vad tidtagaren säger istället för att skriva in sluttid. Dock får man inte pausa tidtagaren för att göra annat och sen starta igen och räkna det som samma aktivitet för detta blir då olika aktiviteter och kräver ny rad

Gällande start- och sluttid så finns det alternativ. Antingen fyller ni i start- och sluttid, eller så fyller ni i starttid och sen tidsåtgången, eller så fyller ni i tidsåtgången och sluttiden. Det beror på vad som passar er bäst.

Antal personer:

Hur många ni var för att utföra aktiviteten (om man kommer och går skriv ner hur många ni var största delen av tiden). Om ni känner för det går det bra med signatur.

Stopp & störningar under tidsintervall

Beroende på hur ni väljer att ha ny rad varje gång ni går ut för att hämta något eller att skriva det i störningar så kommer denna kolumn vara mer eller mindre ifylld.

Viktigt här är i alla fall att reflektera över ev stopp och störningar som skedde under ert tidsintervall. Skriv ner vad de tillfälliga stoppen/störningarna var och ungefär hur långt (utav tidsintervallet) som de tog. OBS! Om det är ett stopp som påverkar alla, så aktiviteten inte kan fortsätta, behöver man skriva in en sluttid och notera vad som hände i kolumnen bredvid.

Stopp & störningar utanför tidsintervall

Ex frågor att besvara:

- Varför utfördes inte något direkt?
- Var någon annan i rummet/IBC som ni behövde/hade bokat?
- Var man tvungen att gå för dagen?
- Slutade maskinen att fungera? etc.
- Kunde inte utföra något pga städ inte varit där ännu.

ÖVRIGT:

MIMS: Behöver få MIMS-rapporter för varje CIP och Körning av utrustning så att vi kan uttyda när maskinen är klar och hur länge den körde efter att den var klar (framförallt aktuellt vid CIP)

Angående skyddsutrustning eller andra upprepade aktiviteter som tar ungefärligen samma tid:

- Om en liknande aktivitet sker ofta (t.ex. ta på skyddsutrustning eller väga IBC-kärl efter granulering), tar ungefärligen samma tid varje gång samt sker i samma kronologiska ordning (utan paus) så kan följande förkortning utföras:
- Skriv ner vad aktiviteten är och sen ev. vilken subbatch det gäller. Skriv ner starttid och sluttid (ev tidsåtgången för aktiviteten). Markera raden med en stjärna.
- När liknande aktivitet sen sker igen så räcker det att skriva vad aktiviteten är, gärna starttid och därefter en stjärna (på så sätt vet vi hur lång tid det tog förra gången och räknar med att det tar denna gång också → vilket gör det enklare för er). **OBS:** Detta förutsätter att aktiviteten som markeras med en stjärna utförs precis innan nästföljande aktivitet annars måste en start och sluttid skrivas med.

Exempel gammal tidsstudie

För att ge mer exempel så bifogar vi en del av tidsstudien från 2010. Den ser inte ut exakt så som vi har tänkt. t.ex. så ska det som är processtid och operatörtid stå på olika rader i vår tidsstudie. Det framgår inte heller om någon aktivitet har skett parallellt och det är det som vi vill med vår tidsstudie.

Det som är röd-markerat är vad vi inte vill ha.

Det som är gul-markerat är ett OK exempel på hur man kan göra med dubbelaktiviteter (såvida det sker samtidigt eller är en liten del av aktiviteten).

Kom ihåg att vi gärna vill ha tidsåtgången om det är någon extra springaktivitet i stora aktiviteten.

Det som inte har någon färg är bra som det är.

Avslutande ord

Vi ska försöka vara med och observera under riggning och körning av våtgranulering och torkning av en subbatch (antagligen SB2). Detta är för att mer kunna se i detalj på vad som verkligen sker.

Vi uppskattar att ni gör detta så detaljrikt ni bara kan men vi har full förståelse för om det kanske inte alltid är möjligt!

Tack för er hjälp :)

Med vänliga hälsningar

Anna Ingelström och Clara Klang

Ni når oss på mejlen

	A	B	C	D	E	F	G	H	I
1	**RUM:**	**187**			**Tidsintervall**				
2	**Processteg**	**Aktivitet (operatör och process var för sig)**	**Ev rum**	**Extra kommentar**	**Starttid (med datum)**	**Sluttid (med datum) alt tidsåtgång om tidtagare används**	**Antal personer**	**Stopp & störningar under tidsintervall**	**Stopp & störningar utanför tidsintervall**
3	ALT1								
4	Tablet Compression	Hämta mtrl till rigg	?		2016-12-05 08:52	09:30	2	Y låg inte på rätt plats så tog lite längre tid (ev extra tidsåtgång)	
5	Tablet Compression	Rigga	187		2016-12-05 09:30	15:20	3		
6	Tablet Compression	glömde den saken	?		2016-12-05 11:11	11:16	1 utav ovan		
7									
8	ALT2								
9	Tablet Compression	Hämta mtrl till rigg	?		2016-12-05 08:52	09:30	2	Y låg inte på rätt plats så tog lite längre tid (ev extra tidsåtgång)	
10	Tablet Compression	Rigga	187		2016-12-05 09:30	15:20	3	Glömde den saken (5 min)	
11									