Inventory and management of process wastewater streams in a pharmaceutical production plant in Finland

M.Sc. Thesis in Chemical Engineering

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Abstract

Pharmaceuticals and their effects on the environment have become continually a more and more interesting topic. Even though only 2% of all European API (Active Pharmaceutical Ingredient) discharges are from the pharmaceutical manufacturing plants, the Finnish environmental permit regulates reducing the amount of APIs released from the pharmaceutical industry into wastewater by various regulations. It is extremely important to understand the amount and location of the generated API discharges of the manufacturing processes in order to minimize the environmental risks caused by APIs. This study includes an inventory of the pharmaceutical wastewater. The inventory is based on the calculation of API losses and also it presents the locations and unit processes where API discharges are generated. After the sources and amounts of API discharges have been clarified, the entry of pharmaceuticals into process wastewater can be controlled by technical and practical solutions. When API discharge levels are known, it is possible to carry out a more detailed risk assessment of pharmaceuticals, which can be used to ensure that API discharges are below the maximum daily discharge limits.

In this study, the quantity and the quality of pharmaceutical wastewater are determined. The inventory of lost API masses are calculated by using process data from PI-sheets (Process Instruction Sheets). Based on the inflows and outflows, accumulated mass or product in the equipment is calculated by proportioning masses to the API concentration. The sufficiently of wastewater collection was qualitatively monitored by discrete samplings of wastewater of the Granulator 3. The concentration differences before and after cleaning processes of the Granulator 3 were detected from the results of wastewater samples. Based on the sample results, at least x% of accumulated API4 was led to the wastewater treatment plant from the cleaning program of Granulator 3. The results of the accumulated mass and the quality data from wastewater samples were used for defining estimated daily discharges. The estimated daily discharges and Predicted No-Effect Concentration values were used for risk assessment for all APIs of tablet and injection departments. Based on the sampling results and risk assessment, wastewater collection of rinsing phases of Granulator 3 is sufficient. Also, smaller sources of API discharges were studied by visual observing the effectiveness of pre-rinsing and taking samples from the rinsing water of weighing tools.

Keywords: Active Pharmaceutical Ingredient (API), Inventory, Risk assessment, Risk Quotient (RQ) and Wastewater

Preface and acknowledgements

This Master's thesis in process chemistry was implemented for Orion Corporation. Because my study and work background have focused on the area of environment, I was indescribably happy about getting this topic. This thesis has been challenging, because the topic requires understanding of the functionality of the whole plant and also the outside of the plant what comes to the risk assessment. I'm glad that I was able to do this and learned a lot of new things during my work that I can certainly utilize in the future. I also hope that my work will provide information to others interested in pharmaceutical wastewater.

However, this work would not have been possible without my supervisors, co-workers and support network. I'm so thankful for my supervisor Ville that you offered me this topic and you have supported me with a positive attitude during the whole process. In addition, I would like to thank Otto for specialist advices in the environmental field. I also want to say big thanks to Emilia for peer support, memes, chocolate and helping me with practical things. In addition to the supervisors, I'm grateful to several different stakeholders and co-workers who have helped me during the whole process. On behalf of the Åbo Akademi University, I would like to thank Professor Leena Hupa for providing the possibilities to do this and Johan Werkelin for active and positive ways for supervising, flexibility and giving great ideas. I'm also grateful for my dear family and friends for their support, encouragement and helping. Last but not least, I want to thank my partner for his endless support, love and caring during my whole study time.

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Abbreviations

AF	Assessment Factor
A.O.P.	Advanced Oxidation Process
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical
BCF	Bioconcentration Factor
CIP	Cleaning In Place
DDD	Defined Daily Dose
EC10	Effect Concentration of 10%
EC50	Effect Concentration of 50%
EMA	European Medicines Agency
EOx	Electrochemical Oxidation
FBG	Fluidized-bed granulation
FM	Facility Maintenance
HSWG	High Shear Wet Granulator
MEC	Measured Environmental Concentration
nmCRPC	Non-metastatic castration-resistant prostate cancer
NOEC	No Observed Effect Concentration
OEB	Occupational Exposure Band
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentrations
PI	Process Instruction
PNEC	Predicted No-Effect Concentration
PW	Purified Water
RC	Roll Compaction
REACH	Registration, Evaluation, Authorization and restriction of Chemical substances
RQ	Risk Quotient
TSG	Twin-Screw Granulation
vPvB	very Persistent and very Bioaccumulative
WW	Wastewater
WWTP	Waste Water Treatment Plant

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Introduction

Sustainability - an important part of the pharmaceutical industry

Orion Corporation is a Finnish pharmaceutical industry company, which researches, develops, manufactures and markets human and veterinary medicines as well as Active Pharmaceutical Ingredients (APIs). The product category has increased widely since 1917, and currently the main therapeutic areas of pharmaceutical research are oncology, neurological and respiratory diseases. Although Orion has grown as an international company, all the manufacturing plants are located in Finland. Orion has production and research operations in Espoo, Turku, Kuopio, Salo, Oulu and Hanko. In the manufacturing processes, sustainability plays a very important role. Orion has built its own sustainability agenda, which includes four different areas: patient safety and ensuring the reliable supply of medications, manufacturing products in an environmentally sustainable way, responsibility of Orionees and ethics and transparency of the business (Orion Oyj, 2021a; Orion Oyj, 2021b; Orion Oyj, 2021c).

Nowadays environmental protection and climate change mitigation are important values for the pharmaceutical companies, and this is one of the reasons why Orion has also included manufacturing products in an environmentally sustainable way in its own sustainability agenda. This means among other things that API discharges should be known and managed in an efficient and sustainable way. Possible API discharges are generated when production equipment and tools are cleaned after the manufacturing processes of pharmaceuticals. Limits for the API discharges to the wastewater treatment plant are not regulated in the Finnish law, and the requirements for API discharges are mainly regulated in the environmental permit. By calculating risk assessment for all manufactured APIs, it is possible to ensure that pharmaceuticals can be manufactured without endangering the environment.

In this study, the theory of the pharmaceutical manufacturing processes and cleaning processes are reviewed, because those are important from the wastewater generation point of view. The chemistry of a few interesting APIs and the risk assessment calculations are also included as a background for the experimental study. In the method section, the sampling procedure of the wastewater is described, and data of the API discharges for the year 2020 is calculated and the sources of the APIs discharging are presented.

The motivation of the study

In Finland, the wastewater from households and industries are transported to a wastewater treatment plant, where the wastewater is processed before leaving as an effluent to water systems. Because the wastewater treatment process is not designed to remove APIs from the wastewater, most of the harmful APIs end up in the environment, e.g. Baltic Sea. Even though estimated API discharges from the pharmaceutical industry are rather small, approximately 2% of the total European API discharges, it is important to minimize API discharges in the manufacturing processes, because some APIs have severe impacts to the environment already in small concentrations. Rest of the API discharges comes from the use of the customers, hospitals and animals and improper disposal of expired products (Bio Intelligence service, 2013; Larsson & G. D., 2014; Orion Oyj, 2021).

This study is part of Orion's production wastewater management program. The study is beneficial for the company, because by having knowledge about the quantity of waste fractions and their sources, environmental risks are easier to minimize and to manage also in exceptional situations. The inventory system is also usable for the production to manage the API discharges, among the other systems, and it seeks to increase an emission-minded thinking into the day-to-day operations of the production. The inventory of the discharged APIs also enables optimization of the separately collected wastewater and planning for the at-source API wastewater treatment in the future.

The objectives of the study

The objective of this study is to investigate which unit processes, equipment or spaces generate API discharges to the wastewater stream and calculate the annual mass flows for the API losses based on production data from the pharmaceutical production plant. On the basis of this research data, an inventory system was constructed in a uniform way to manage API discharges. The requirements for the inventory system are that it is easy to access, update and also utilize in other manufacturing plants. In addition to the quantity knowledge of APIs, the split factors between collected and non-collected wastewater from granulators are required to be clarified with wastewater sampling. At the same time, the most practical sampling methods are studied. In addition to the inventory system and wastewater sampling, technical solutions for wastewater management (e.g. valves, pipes, changes the cleaning processes) as well as the instructions and possible changes in procedures for operators are suggested during the thesis.

In order to aim for zero API discharges in a pharmaceutical industry plant, the amount and location of the generated API discharges should be known in order to suggest different technical solutions. In this study, annual mass flows of API residues are calculated in three different departments in the pharmaceutical production plant. These include the tablet, inhalation and injection departments. The time period for the API discharges inventory is the production year 2020. Figure 1 shows a schematic overview of the wastewater generation and transportation in the manufacturing process of pharmaceuticals.

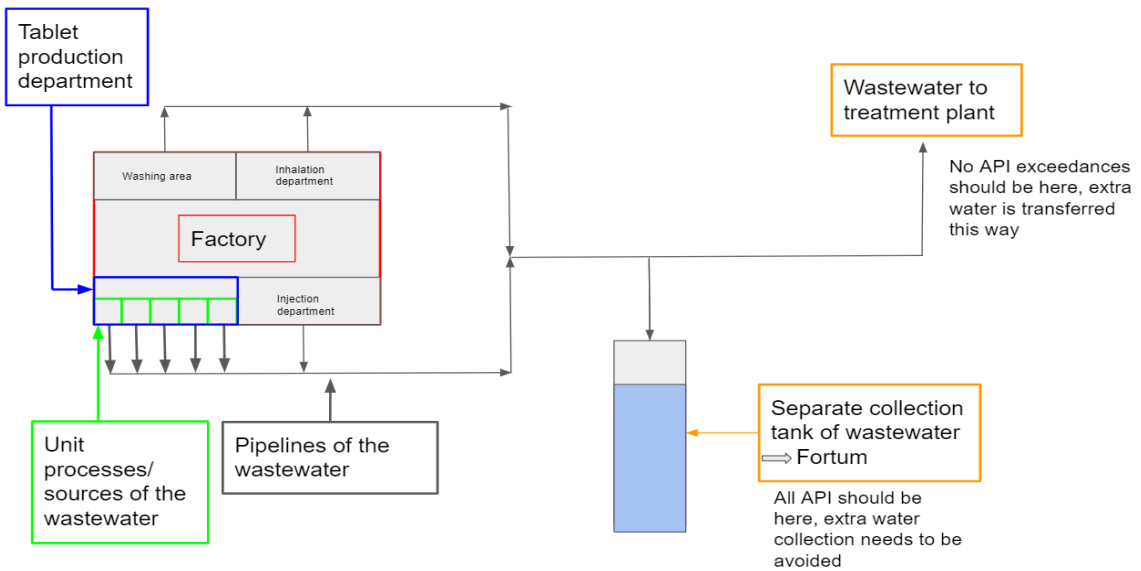

Figure 1. A schematic overview of the wastewater generation in the manufacturing process of pharmaceuticals.

Background

Tablet manufacturing process

The tablet manufacturing process consists of several unit processes. Figure 2 shows that the first unit process is the weighing process, where raw materials of the tablets are weighed to the containers. After the weighing process, raw materials are transported to the granulators or compactors where the mass manufacturing takes place. Mass manufacturing process produces granules which are easy to press to the tablet form in the tableting phase. After pressing granules to the tablet form, those are coated with a coating solution to improve physical and chemical properties of the final product. The final process phase is to package the tablets to the packaging before delivering products to the customers (Pharmapproach, 2021). From the wastewater inventory point of view, the main focus is on the mass manufacturing process, because it can be assumed that most API discharges are generated in that unit process. Appendix 1 shows that API discharges from the coating process correspond to the API7 concentration of x-y tablets. Some API discharges are also generated in the weighing unit process. In addition to those sources, minor API discharging sources from the other unit processes are also possible. Those are the reasons why this study is mainly concentrated on the weighing and mass manufacturing unit processes.

Figure 2. The unit processes of the tablet manufacturing processes. This study focuses on the weighing and mass manufacture unit processes.

Mass manufacturing

Granulation is a well-studied unit process in the pharmaceutical industry field. It is commonly used in manufacturing of tablets and capsules, which can be supplied in a solid form (Hansuld & Briens, 2014; Prakash, Julu, & Seong, 2019). The target of the granulation process is to improve the important properties of raw materials for tableting, like flowability and compressibility of powders (De Simone, Caccavo, Lamberti, d'Amore, & Barba, 2018). The granulation process can be classified into two major techniques, wet and dry granulation. In wet granulation, enlargement of the powder particles occurs. Liquid binder is

added to the powder and due to the reactions, new bonds between particles are formed. Uniformly mixing process during wet granulation is an essential process phase. In dry granulation, liquid binder is not required, because functionality of the dry granulation process is based on the agglomeration of the fine particles under the mechanical pressure from compression of the rolls. The dry granulation process is suitable for sensitive components of pharmaceutical manufacturing because no heat or liquid is required (Charinpanitkul, Tanthapanichakoon, Kulvanich, & Kim, 2008; Pishnamazi et al., 2019).

Wet granulation

There are several wet granulation techniques including high shear wet granulation (HSWG), fluidized-bed granulation (FBG) and twin-screw granulation (TSG). Wet granulation methods can be divided into three different phases. The first phase is wetting and nucleation, where a liquid binder is added to the powder and nuclei formation occurs after wetting of the particles. The second phase includes growth and consolidation, where formed granules collide and stick together forming large granules. The last phase of wet granulation is attrition and breakage, where large granules attrite and break into smaller granules (Prakash, Julu, & Seong, 2019). This study concentrates on the HSWG and FBG techniques, because those wet granulation techniques are used in the mass manufacture unit process of the studied plant.

High shear wet granulation

High shear wet granulation (HSWG) mechanism is based on the addition and dry mixing of powders and addition of a liquid binder into the powder mixtures during the mixing. Figure 3 shows that the HSWG includes two rotating parts: an impeller and a chopper. The principle of the impeller is to mix the granulation mass uniformly and the chopper breaks the mass by avoiding formation of too large agglomerates. At the beginning of liquid binder addition, the speed of the impeller and the chopper is lower. When the liquid binder is absorbed, the speed is increased to a product-specific level (Y. Saito, X. Fan, A. Ingram, & J.P.K. Seville, 2010).

The HSWG method has several advantages, such as a good mixing effect, short residence time, high loading rate, high efficiency and also low energy consumption. The process can be run without generating the process dust, because the granulation process is fully closed (A. Kumar, K.V. Gernaey, T. De Beer, & I. Nopens, 2013; G. Luo, B. Xu, Y. Zhang, X. Cui, J. Li, X. Shi, Y. Qiao, 2017; P. Thapa, A.R. Lee, D.H. Choi, & S.H. Jeong, 2017). However, it also has shortcomings, such as chemical degradation of thermally sensitive materials,

mechanical degradation of fragile particles and the formation of clumps caused by over-wetting (M. Börner, M. Michaelis, E. Siegmann, C. Radeke, & U. Schmidt, 2016; M. Cavinato et al., 2011).

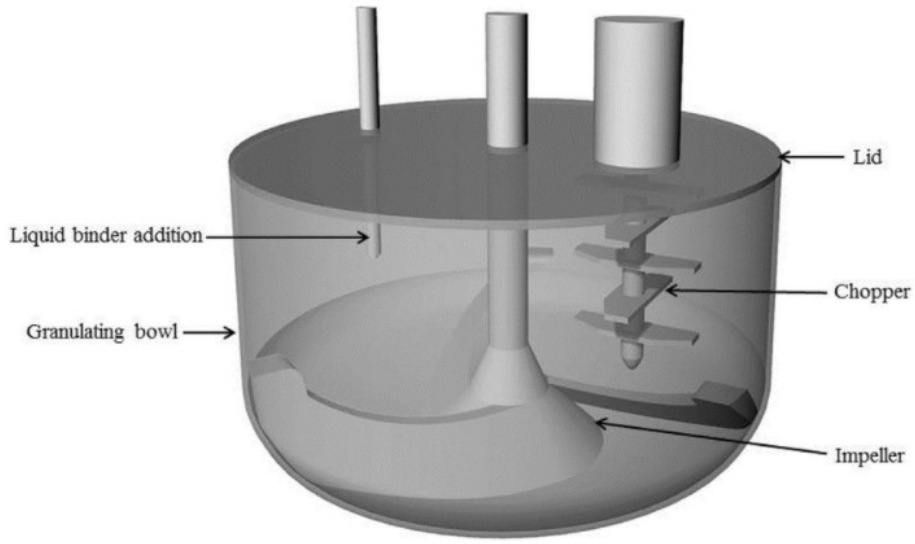

Figure 3. High shear wet granulator includes granulating bowl, lid, impeller, chopper and tube for liquid binder addition (Prakash et al., 2019).

Fluidized-bed granulation

Fluidized-bed granulation (FBG) is a widely used unit operation in the mass manufacturing process of pharmaceuticals. The FBG is a versatile granulation technique because it includes wetting, drying, particle enlarging, shaping, homogenization and separation processes and the production in one unit process phase. Figure 4 shows that at the beginning of the FBG, inlet air is filtered in the air handling unit and added to the product container. Airflow is controlled with the air distribution plate. Because of the added air, dry raw material powder starts to fluidize inside the granulator. In the wetting phase, liquid binder is pumped through the spraying nozzle into the fluidized powder particles by causing nucleation. After the nucleation, wetted particles collide and agglomerate and short-range physical or chemical forces are formed between nuclei. Granulation solution binds particles together forming aggregates (granules) with the short-range forces until the bonds are changed permanently with drying. Wetting and drying conditions affect the strength of the bonds between particles, and it can be affected by operating process parameters from the control panel. The droplet size of the liquid binder and temperature of the inlet air are examples of the affecting factors to the bonding of the particles in the granulation process. The filter bags prevent granules from escaping the granulator. Outlet air is filtered before it is

released into the atmosphere (Jacob, 2007; M. Jones, 1985; Parikh, 2005; S, S-R, H, & S, 2018).

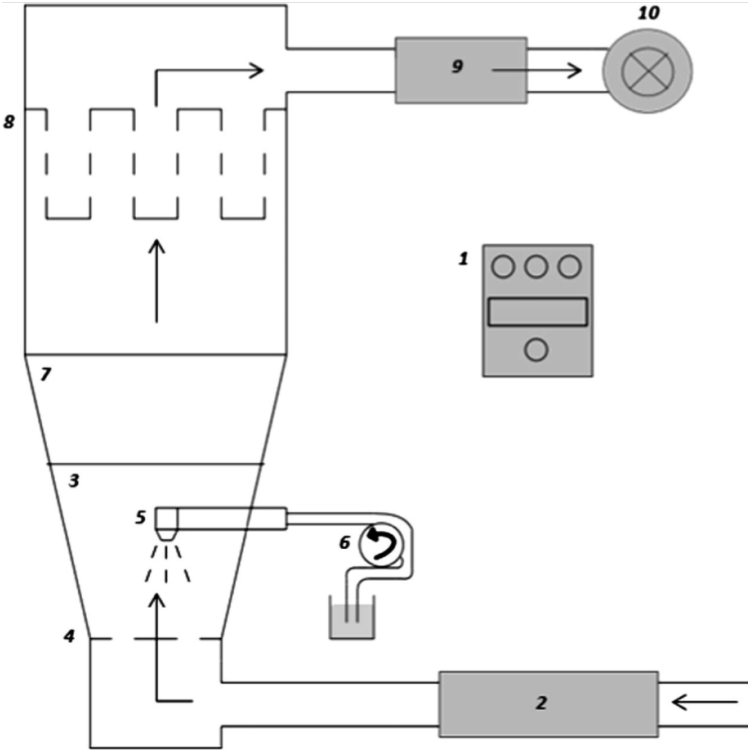

Figure 4. Schematic of a top-spray fluid bed granulator: (1) control panel, (2) air handling unit, (3) product container, (4) air distributor plate, (5) spraying nozzle of the granulation solution, (6) pump, (7) air expansion chamber, (8) filter bags, (9) air filter system, and (10) exhaust blower (Burggraeve, Monteyne, Vervaet, Remon, & De Beer, 2013).

Dry granulation

Dry granulation is another major granulation technique, which is less frequently used in pharmaceutical processing compared to wet granulation (Takeuchi, Yoshida, Ito, & Sunada, 2009). In the dry granulation method, liquid binder is not used which is the most significant difference for the formation mechanism of granules compared to the wet granulation. In dry granulation, granules are produced by compacting the powder mass, which is crushed and fractionated in ambient temperature without the binder. This enables the processing of heat and moisture sensitive products (Burggraeve, Monteyne, Vervaet, Remon, & De Beer, 2013; Hansuld & Briens, 2014).

Roll compaction

Roll compaction (RC) is the most commonly used dry granulation technique, which has growing importance in granulation processing. Powder is compacted to the flakes (ribbons, sheets or strips) when pressure is exerted in a roll gap, which is a space between the compaction rolls. Figure 5 shows that there are three different zones between the counter-rotating rolls. In the feed zone powder particles are rearranged and compacted. Then those particles are transported to the compaction zone through the gripping angle, where stress is applied and particles deform plastically or break (Kleinebudde, 2004; Takeuchi et al., 2009). The formed flakes are milled into granules, which can be transferred to the tableting process phase. One of the biggest advantages of this technique is reduction in powder segregation and increasing bulk density (Pishnamazi et al., 2019).

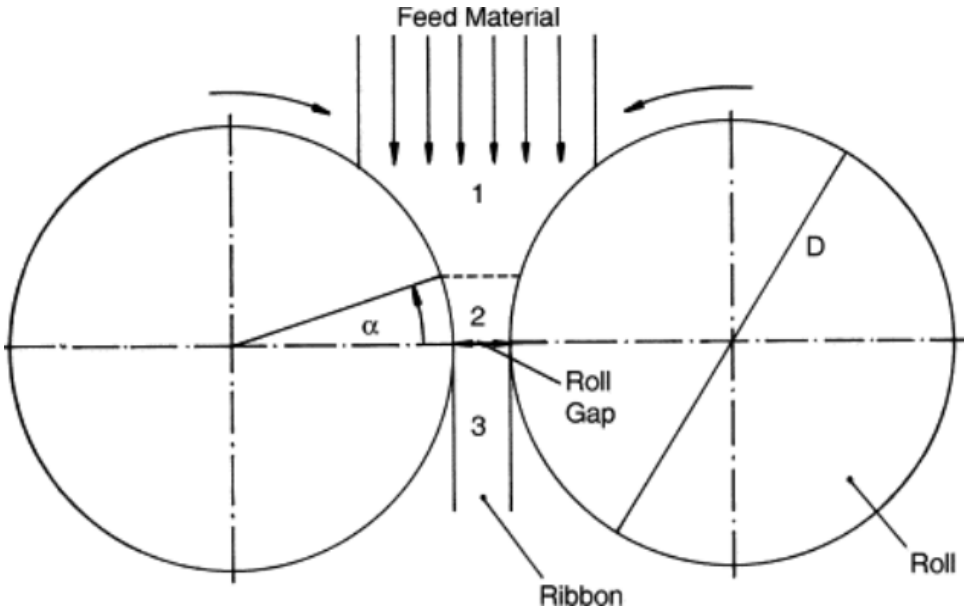

Figure 5. Roll compactor and different zones; 1. Feed zone, 2. Compaction zone, 3. Extrusion zone (Kleinebudde, 2004).

Cleaning processes

CIP cleaning process

Pharmaceutical manufacturing plant includes several different processes and unit processes that are also cleaned with various cleaning methods. Usable cleaning methods take into consideration size and material of the equipment and what kind of pharmaceutical product it has as a residue. The cleaning process may be executed as an automatic CIP (clean- in-place) process, where water and detergents are added straight into the equipment from the centralized cleaning distribution system. CIP processes are utilized for large equipment and assemblies, for example for granulators in the tablet department and for large production containers in the injection department (Ostrove, 2016). Usually several cleaning groups are included in the CIP processes of the same equipment. The cleaning group defines the used detergents and parameters of the CIP cleaning program for all produced products. Selection of the cleaning group depends on the properties of the API residue to be washed, because the CIP process can be executed in acidic and/or alkalic conditions in various parameters. If the API residue is likely to dissolve in alkalic conditions, a base-based cleaning group is used. In addition to alkalic conditions, higher temperatures are used if the API residue favors high temperatures for dissolving.

In the CIP cleaning process, washing and rinsing solutions are ordered from the centralized cleaning distribution system. The high shear wet granulator and the fluidized-bed granulator can be washed at the same time or both devices separately. The actual washing process proceeds in such a way that the process device indicates the need for washing, which creates a washing and rinsing line for washable equipment. The chemical station mixes rinse or wash solution according to the recipe in service and delivers it to the wash tank. The control system of the fluidized-bed granulator controls the pumps, valves and heat exchangers and monitors the execution of the steps of the requested recipe.

The washing process is divided into phases, which are typically pre-rinsing, washing, rinsing, draining, PW (purified water) rinsing, blowing and drying phases. In the pre-rinse phase, the main equipment is rinsed before the actual washing with the washing solution, in order to drain the largest residues left in the device after production. Generated wastewater of the pre-rinsing is always collected to the separate wastewater tank from tablet mass production. In the washing step, the surfaces in contact with the product are washed once or more with a detergent solution according to washing recipes. In the washing phase, the washing solution can be added as a flushing or it can be circulated in the system. The purpose of the washing step is to remove product residues. During the rinsing phase, the product contact surfaces

are rinsed once or more with water. The purpose of the rinsing step is to remove residues of detergent from the surfaces of equipment. During the drainage phase, the solution left in the pipelines is drained as wastewater by avoiding contamination of the solution to be pumped next. PW rinsing can be used as the last washing step to perform final rinsing on inner surfaces. These are the CIP cleaning phases, which are generating the process wastewater. After the last rinsing phase, pipes are blown with compressed air to help drainage and surfaces of the equipment are dried with air in order to decrease waiting time for the beginning of next product manufacturing. During the CIP cleaning process, the whole production room is cleaned by vacuuming, wiping and transferring garbage bags, containers and tools away (Central States Industrial, 2019; Ostrove, 2016).

CIP or manual cleaning processes are executed to the equipment and rooms only between the product changes, when the next manufactured product includes a different API than the previous product. In order to speed up production and reduce losses in production, the aim is to produce product campaigns with multi-batch series. In this case, the equipment is washed only once during the campaign after the last batch. So, this means that wastewater of one cleaning campaign includes accumulated API from several batches. In the case of bulk products, the duration of one campaign can be up to a week including several batches, in which case only one cleaning process is executed for all produced batches. Small products are only made batch by batch and maybe once or twice a year. During the product campaign, where only a batch is changed or the next product includes the same API as the previous product with higher concentration, a partial cleaning process is used. In the partial cleaning process which is executed within a product campaign, water is not used and the equipment is not disassembled. Because no water is used, outside surfaces of the equipment and the floor of the manufacturing room is vacuum cleaned during the partial cleaning process. After that, the other surfaces are cleaned with ethanol wipes and the garbage bags are changed to the new ones. Documents from the previous batch are also filed and removed from the room according to the data integrity policy. In the partial cleaning process of the tablet department, the sieve is also cleaned and after that the floor is cleaned again if necessary. The production schedule is planned to minimize total and maximize partial cleaning processes, because having longer production campaigns is a less time consuming, more cost efficient and sustainable way to produce pharmaceuticals with a high quality.

Tablet department

Washing area of weighing process

In the weighing process, dry raw materials are weighed and added to the containers in the weighing room. During the weighing process, the API dust is generated to the surfaces of the room. The room is cleaned with moist swabs by wiping dust away. When the weighed load is transferred to the mass manufacturing process, the emptied weighing container is transferred to the washing area. In the washing area, containers, swabs and tools used in the weighing room are cleaned. In addition, pallet hoods, which are made from textile and used by covering pallets as a secondary packaging material, are cleaned in the same room. Wastewater from cleaning processes of weighing tools and containers is not collected separately and all generated APIs are released to the wastewater treatment plant.

Cleaning processes of granulators

There are three different fluidized-bed granulators (Granulator 1, Granulator 2 and Granulator 3) and two different dry granulators (Compactor 1 and Compactor 2) in the mass manufacturing unit process. All the fluidized-bed granulators include a high-shear wet granulator unit, which is connected to the FBGs. Granulator 1 has the same cleaning programs as Granulator 2 because configuration of the devices is identical. The high shear wet granulator and the fluidized-bed granulator can be washed at the same time or both devices separately with all granulators.

Wet granulator 1 and Wet granulator 2 can be cleaned separately or together with the fluidized-bed granulators. If wet granulators are cleaned separately, wastewater are transported straight to the sewer from the wet granulators. If the wet and fluidized-bed granulators are cleaned together, the cleaning solution goes from the wet granulator through the fluidized-bed granulator into the sewer. Wet granulator 1 is connected to the fluidized-bed Granulator 1 and Wet granulator 2 is connected to the Granulator 2 fluidized-bed granulator. Wet granulator 1 has two cleaning programs, base and acid cleaning programs. The Wet granulator 2, only has a base cleaning program and a separate initial rinsing program. The separate pre-rinsing program is used as a pre-wash after the sealing surfaces of the granulator are cleaned manually. After that, the actual washing program recipe of Wet granulator 2 is started. Wastewater collection occurs similarly with both wet granulators, the wastewater from the first rinse is collected and the rest of the wastewater is led through an intermediate well to the wastewater treatment plant.

Granulators 1 and 2 have four different cleaning programs. The first and second cleaning programs of the Granulators 1 and 2 include acidic and alkalic detergents and the cleaning programs are processed at a maximum of x degrees. The third cleaning program is executed using a base detergent at a lower temperature with an extra circular washing phase. The last cleaning program of Granulators 1 and 2 include a base-based cleaning program for Product 2 mass production with an extra initial rinse. All the first phases of the granulator cleaning programs include wastewater collection.

Granulator 3 has three different cleaning programs: the first is for the fluidized-bed and wet granulators, where alkalic and acidic detergents are used. The second cleaning program is only for the fluidized-bed granulator, which also requires both alkali and acidic detergents. In the cleaning program of Granulator 3 is used only with the product including API4 as API. In that cleaning process, both the fluidized-bed and wet granulator units are cleaned. In the first and second cleaning programs of Granulator 3, the wastewater from the first phase is collected. In the API4 cleaning program, two first pre-rinsing phases are led to separate collection of wastewater.

Injection department

Injection department contains two different categories of products; ampoules and bottles. Ampoules are glass as a material and in the first they are washed, depolarized and sealed with a flame. Ampoules are manufactured in lines 5 and 6. Bottle product solutions are produced in lines 1 and 2. Production lines 1 and 5 have portable x-y L vessels that are cleaned with CIP processes. Production vessels that are difficult to clean are transferred to the washing area. Usually oil based products, for example API35 and API25 are cleaned in the washing area for this reason. Production lines 2 and 6 include larger x L containers, which are not transportable. Those are cleaned with CIP processes. Wastewaters are not collected separately in the injection department.

In the washing area of the injection department, small product contact parts from the filling line are cleaned. Those parts which included API residues are cleaned manually in baths and some parts are also cleaned in ultrasonic baths. There is also a dishwasher for format parts which are not in the product contact. Because parts of the devices are secondary contact parts or include small amounts of API residues, it can be assumed that the most API discharges are generated in automatic cleaning processes in the injection department.

There are large amounts of wastewater generated with no API discharges in the injection department. Steam is used in the sterilization process of ampoules and bottles, which generates a lot of wastewater. In addition to steam sterilization, the blue bath process is utilized in sterilization and in studying the quality of ampoules approximately x-y times a year. The load of ampoules is immersed in blue colored water, which is washed away. After the blue bath, each ampoule unit is inspected either mechanically or by a person for ampoule cracks. This process releases methylene blue into the wastewater, which is not collected separately.

Inhalation department

In the inhalation department, all vessels and tools which are in product contact are transported to the washing area. There are two rooms where the initial rinse of equipment and tools is done. There are nozzles on the ceiling, which are switched on for x seconds and sprayed water wets the dusty equipment and binds dust to the surface of the device by preventing the float of product dust in the air. In the same room, smaller tools are pre-washed manually. All of the generated wastewater from initial rinse rooms are collected separately. Because it can be visually observed that most API residues are removed from the equipment surfaces in the initial rinse room, it can be assumed that most inhalation API residues from the inhalation department are collected to separate wastewater tank.

After pre-rinsing, equipment and tools are transported to the washing area in racks intended for them. In the washing area, racks are installed to the pass-through dishwasher (Dishwasher 5), where almost all parts from the mass manufacture and filling lines are cleaned. In addition to the parts from the mass manufacture and filling lines, the cleaning utensils are also cleaned in Dishwasher 5. Pass-through washing machine is loaded from the dirty washing area space and cleaned parts are unloaded in the clean space.

The washing area also includes a smaller dishwasher (Dishwasher 6) and two ultrasonic baths. Some parts from the filling machines are cleaned in the Dishwasher 6. Certain tools are pre-washed in ultrasonic baths before starting the actual cleaning process. Dishwasher 7 is used to clean smaller no product contact parts from inhalation production. Strong acid and base detergents are not used in Dishwasher 7, which enables cleaning of materials with lower chemical durability.

Pharmaceutical wastewater

Active pharmaceutical ingredients are released to the wastewater in the pharmaceutical industry and in common use along the domestic wastewater stream (Gadipelly et al., 2014). Discharged pharmaceutical compounds are transferred through the pipelines to the wastewater treatment plant as active metabolites or in unmetabolized form. Because the common wastewater treatment processes are not able to remove pharmaceutical compounds, most of the discharged pharmaceutical compounds end up in the sea (Heberer, 2002; Mompelat, Le Bot, & Thomas, 2009). In the pharmaceutical industry, compounds are usually processed in a batch reactor, which releases accumulated compounds to the wastewater stream as pulses due to the washing processes. Generated wastewater includes a wide variety of pharmaceutical compounds (Gadipelly et al., 2014). In addition to the cleaning processes, active pharmaceutical ingredients might be released to the process wastewater in equipment failure situations, for example leakage of the pipe or tank.

According to the green chemistry principles, environmental risks should be minimized by managing pharmaceutical wastewater before the processes of the wastewater treatment plant. By using environmental risk assessment, it can be ensured that discharged API levels from the manufacturing plant are within limits. Environmental risk assessment is challenging to implement because pharmaceutical compounds are biologically active, which enables fatal consequences to living organisms. (Fatta-kassinos, Meric, & Nikolaou, 2011; Heberer, 2002; Huerta & Barcelo, 2012; Iliuta & Larachi, 2001)

Regulations of pharmaceutical wastewater

Industrial wastewater often differs significantly from domestic wastewater. These so-called industrial effluents can cause problems in sewers, wastewater treatment plants or can prevent utilization of sludge. To avoid environmental problems and to increase sustainability in manufacturing processes, several agreements are concluded with companies related to the production and treatment of generated wastewater. The activities of the pharmaceutical industry are regulated by, among other things, the laws and regulations regulated in the environmental permit. In addition to environmental permits, industrial wastewater agreements and other requirements affect pharmaceutical wastewater treatment (Laki ja Vesi, 2016; Orion Oyj, 2021a).

An Environmental Protection Act (527/2014) is part of a general law, which aim is to protect soil, water and the atmosphere. The main purposes of the environmental protection act are

to prevent pollution of the environment, reduce emissions and discharges of environmentally harmful substances and minimize risks of environmental damages. From the wastewater point of view, the aims of the environmental protection act are to reduce the amount and harmfulness of generated wastewater (Finlex, 2019). Environmental Protection Decree 713/2014 reguates for example application procedures and permit decisions. It is also nominating standards for the quality of the generated wastewater that is conveyed to sewers along with the Environmental Protection Act. Generated wastewaters are also taken into account in the environmental permit decisions (Finnish Water Utilities Association, 2018). Environment permit of Orion for example regulates that API residues from tablet production should be collected by vacuumed from devices before cleaning with water or collect wastewater from the first rinsing phases to the separate wastewater tank which is treated as a hazardous waste.

Risk assessment of pharmaceutical wastewater

Risk assessment of the pharmaceutical wastewater is used when the toxicity of the generated wastewater is unsure. Figure 6 shows that the risk assessment can be done by calculating a risk quotient, and the persistence and accumulation of the compound. Comparing the amount of discharge generated by the manufacturing plant to the discharge caused by users is not actual environmental risk assessment method but with that method it is possible to solve the importance of the discharges of manufacturing plant (Hernando, Mezcua, Fernández-Alba, & Barceló, 2006).

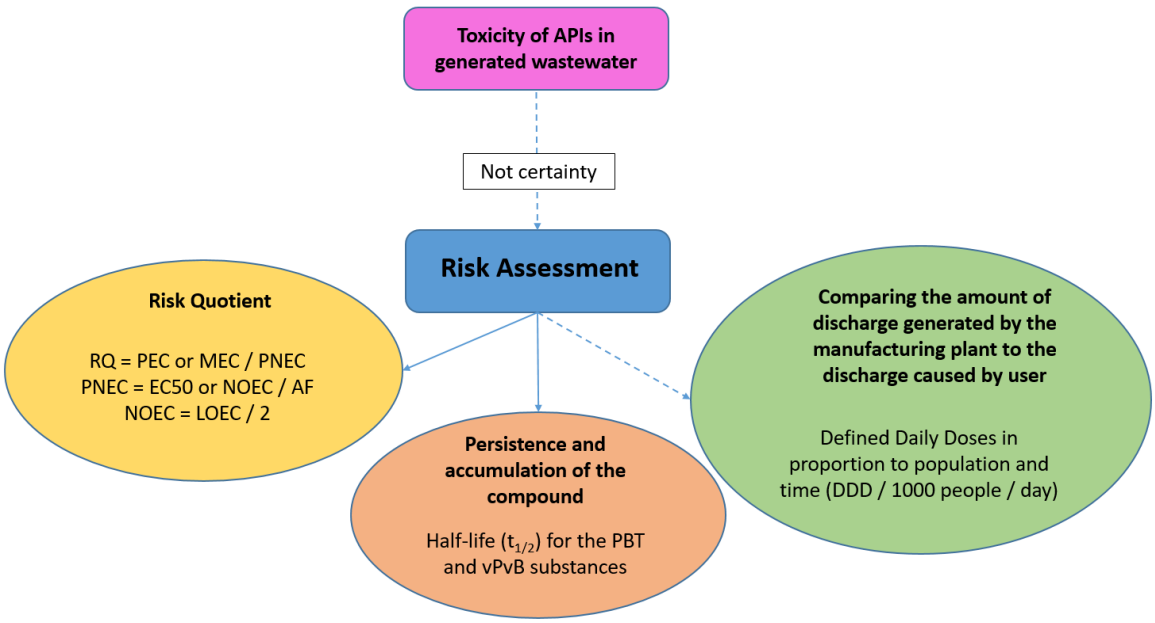

Figure 6. Different methods for API Risk Assessment calculations.

Risk Quotient

The environmental risk of an individual API can be assessed by calculating the Risk Quotient (RQ). Equation 1 shows the risk quotient is based on the ratio between PEC or MEC and PNEC values. PEC value is estimated environmental concentration of a substance and MEC value is measured environmental concentration of the substance. PNEC value is assessed as harmless environmental concentration for the substance (Hernando et al., 2006).

Equation 1. Formula for the RQ calculation.
RQ = PEC or MEC / PNEC

RQ value can be calculated for acute and chronic impact areas in the environment by using daily API discharge masses. The reason why daily API discharging masses are used is that the API discharges from the manufacturing plant are not constant because those are strongly connected to production campaigns. Based on the cleaning campaigns, API discharges are usually presented as daily pulsed discharges with kg/d unit. The calculations of a maximum daily discharge have taken into account the API pulse discharge between minimum and maximum losses in addition to wastewater segregation efficiency. The amount of production campaigns indicates the frequency of daily discharges.

As table 1 shows, when the calculated RQ value is over 1, environmental risk characterization or management of the pharmaceutical is required by avoiding harmful effects to the living organisms. Factors affecting the high RQ value are related to ecotoxicity, persistence, transport and fate of substances, environmental presence as well as disposal management and prescription use (Barrie, Rhiannon, Alfred, TongLouis, & Tremblay, 2016). For example, the RQ value of analgesic or anti-inflammatories (e.g. ibuprofen) is high in the surface waters, because their occupancy is rather high (Hernando et al., 2006).

Table 1. Risk Quotient values and explanations for environmental risk assessments (Wennmalma & Gunnarssonb, 2009). Colors are indicating the risk levels of RQ.

Number of Risk Quotient	**Explanation**
≤ 0,1	Negligible environmental risk of the substance.
0,1 < RQ < 1	Low environmental risk of the substance.
1 ≤ RQ ≤ 10	Medium environmental risk of the substance.
RQ > 10	High environmental risk of the substance.

Predicted Environmental Concentration

Predicted Environmental Concentration (PEC) refers to the calculated amount of the API in the environment. The PEC value is based on the modelling, which is derived from known environmental persistence, transportation and bioremediation of the substance by utilizing third-party data, for example EMEA or FDA. Persistence of the API is described as its ability to be degraded spontaneously in the environment or in the wastewater treatment plant. A term transportation is used when the pharmaceutical substance can penetrate biological membranes and accumulate inside flora and fauna. The bioremediation describes the property of the API when all ecotoxic effects are eliminated by the metabolism of living organisms. Measured Environmental Concentrations (MEC) values are obtained by qualification of pharmaceutical substances in the environment. MEC and PEC values can be compared with each other by ensuring the accuracy of used PEC models (Barrie et al., 2016).

In the PEC calculations, the characteristics and location of the receiving sea area affect the dilution factor of the calculations. The assessment should be made on a case-by-case basis and based on that, dilution factors of the oceans can be divided into two days (acute) or 10 days (chronic) mixing zones. The environmental location and characteristics strongly influence the used dilution factor. If the characteristics of the water area are not available, the default dilution factors of PSCI can be used for rivers, lakes and sea water (PSCI, 2020).

Predicted No-Effect Concentration

Predicted No-Effect Concentration (PNEC) is the concentration of the pharmaceutical substance, which does not affect the ecosystem toxically. The PNEC value is usually derived by using ecotoxicity data. An Assessment Factor (AF) is usually used to describe uncertainty of the toxicity of organism in the calculations of the PNEC value. Therefore, the more ecotoxicity is studied, the lower is the AF value. Equation 2 shows that the PNEC value can be calculated by dividing the toxicity test result (usually marked with EC50 - Effect Concentration of 50% or NOEC - No-Observed Effect Concentration) with the assessment factor (Barrie et al., 2016). According to the “Pharmacology beyond the patient – The environmental risks of human drugs” study, the default PNEC value for APIs is 0,1 µg/L if the substance does not belong to antibiotics, hormones or their water-octanol partition coefficient ($LogP_{ow}$ or LogD when $pH < pK_a$) is below 3 (Gunnarsson et al., 2019). The default value can be used if API fulfils previous requirements and there are no study based PNEC values available.

Equation 2. Formula for the PNEC calculation (Hernando, Mezcua, Fernández-Alba, & Barceló, 2006):
PNEC = EC50 or NOEC / AF

Persistence and bioaccumulation

The environmental hazards of a substance can also be assessed by its physicochemical properties. These properties determine mobility, persistence and bioaccumulation of the substance. Pharmaceutical substance properties are strongly connected to the properties of the environment, like the salinity of the sea water. However, the estimate of the mobility, persistence and bioaccumulation is not describing numerical risks but it can be categorized as a PBT (Persistent, Bioaccumulative and Toxic) or vPvB (very persistent and very Bioaccumulative) (Qingwei, Xiao, Gang, Jun, & Bin, 2016).

The identification of PBT or vPvB substances is regulated by the European Union law, the REACH Regulation (253/2011). In the table 2 persistence, bioaccumulation and toxicity half-life ($t_{1/2}$) are defined for the PBT and vPvB substances. The term half-life describes the time it takes for a substance to be 50% degraded. In some cases, very persistent substances have a higher half-life time than persistent substances. The bioconcentration factor (BCF) is also higher when substances are classified to the vPvB class instead of PBT class. Toxicity has a limit only for PBT substances, which is defined as a NOEC or EC10 value (European Union, R., 2011).

Table 2. Persistence, bioaccumulation and toxicity indicators according to REACH (253/2011) regulation (European Union, 2011).

	Water systems		**Sediments**		**Ground**	**BCF**	**NOEC or EC10**
	Fresh water	**Marine**	**Fresh water**	**Marine**	**Soil**		
PBT substance	> 40 d	> 60 d	> 120 d	> 180 d	> 120 d	> 2000 l/kg	< 0,01 mg
vPvB substance	> 60 d	> 60 d	> 180 d	> 180 d	> 180 d	5000 l/kg	-

Consumed based risk assessment

The last option to assess the risk of released APIs from the manufacturing plant is to compare the amount of discharge discharged by the manufacturing plant to the discharge caused by users. This is not an actual environmental risk assessment method, because the purpose of the consumed based risk assessment is to determine the order of magnitude of API discharges between manufacturing plant and consumers. By comparing discharges from the manufacturing plant to the discharges of consumers, the significance of discharges of manufacturing can be noticed. Fimea publishes annual pharmaceutics consumption by using ATC (Anatomical Therapeutic Chemical) classification. The use of the pharmaceutical products are divided into 14 different ATC categories, where consumption is presented as defined daily doses in proportion to population and time (DDD / 1000 people / day) (Fimea, 2020a; Fimea, 2020b). The DDD is the assumed average dose per day for adults (WHO, 2018). Calculated value indicates, in parts per thousand, the proportion of the population who have used the drug as a daily dose. Consumption data of Fimea is based on the sale of pharmaceutical wholesalers to pharmacies and hospitals (Fimea, 2020; Fimea, 2020). Consumed based risk assessment can be used for annual risk assessment of generated wastewater by determining whether the plant is a significant point source.

Active Pharmaceutical Ingredients in environment

Active Pharmaceutical Ingredients (APIs) are organic molecules which are synthesised and modified to pharmaceutical products (European commission, 2006). Organic molecules include carbon and usually hydrogen, oxygen or nitrogen. There can be other elements or functionality groups in the organic molecule structure. Organic molecules can be degraded to carbon dioxide and water due to the oxidation reaction. As a result of oxidation, the other gases such as oxygen and nitrogen can be formed as by-products. However, elements alone are not necessarily harmful but their overall structure and pharmacological activity can be harmful for the environment.

Pharmaceuticals work as an interaction with the binding site of a receptor and formatting a drug-receptor complex, thus promoting the desired pharmacological activity. The receptors to which drugs often bind to produce a drug effect are chiral. Thus, receptors can only bind molecules of a certain shape, but their mirror images do not bind to the receptors properly. The chirality of pharmaceuticals is important from the wastewater point of view because one of the enantiomers may be pharmacologically active and the other enantiomer may also be toxic. That is a reason why discharges of APIs are a cause concern, because their

pharmacological activity may affect negative impacts to the environment. For example antibiotics work on the cell wall of bacteria and do not affect the human body, because cell walls are not available (Gonzalez-Pleiter et al., 2013). If they end up in the environment, there is a risk that antibiotics can affect other living organisms. This study focuses on the effect of two different organic molecules as pharmaceutical products and indications, on structure, and on environmental effects.

Darolutamide

Darolutamide ($C_{19}H_{19}ClN_6O_2$) is approved for treatment of men with non-metastatic castration-resistant prostate cancer (nmCRPC), who are at high risk of developing metastatic disease (Orion Corporation, 2020; PubChem, 2012). Darolutamide is a newcomer in the pharmaceutical industry, because the structure was developed in 2008 and the darolutamide product received a marketing authorization in 2020. The compound is only researched from a patient-orientated point of view in the three phases ARAMIS study (Orion Corporation, 2020). Figure 7 shows that the molecule structure of darolutamide includes cyclic structures of which only one is fully delocalized benzene ring. In addition to the cyclic structure and carbon elements, the structure of darolutamide also includes nitrogen, oxygen and chlorine.

Even though the darolutamide product, Nubeqa, has only been manufactured for a short period of time, its effects on the environment are well studied by Bayer. According to the Assessment report of European Medicines Agency (EMA), darolutamide is stereoisomere due to the presence of two chiral centres ((S, S)- and (S, R)-darolutamide). Both configurations are used in the synthesis as a 1:1 mixture. Darolutamide is not a PBT substance in the environment, because half-live studies of the persistence, bioaccumulation and toxicity do not fulfill the requirements of the PBT substance. Darolutamide is insoluble in water and in the pH range from 1 to 6,5, but in neutral conditions its water solubility is 12,9 mg/L (European Medicines Agency, 2020). As the number of marketing authorizations for darolutamide products increase and production expands, it is essential to understand the quantity and sources of darolutamide discharges in order to make the most accurate risk assessment of their effects on the environment.

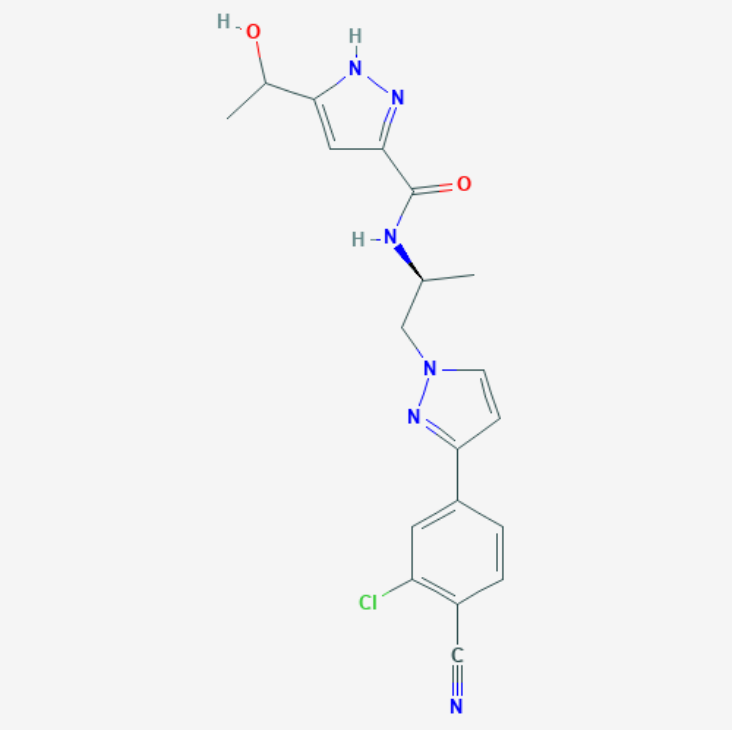

Figure 7. Chemical structure of Darolutamide (PubChem, 2012).

Quetiapine

Quetiapine ($C_{21}H_{25}N_3O_2S$) is an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder, which is derived from piperazine derivatives that affect several neurotransmitters in the central nervous system (PubChem, 2005). Figure 8 shows that quetiapine has a tricyclic molecular structure, which includes three interconnected rings of atoms. Molecule structure also includes carbon, sulfur, nitrogen, oxygen and hydrogen as elements. Risk Quotient value for environmental risk assessment has been calculated for quetiapine by AstraZeneca. Quetiapine is water soluble and it is not biodegradable in the wastewater treatment process (anaerobic degradation after 57 days was 0%). However it is extensively degrading in aquatic environments and that is the reason why quetiapine has no persistent properties in the environment. Also $LogP_{ow}$ value is low in the ambient pH of aquatic environments, which means that the risk for bioaccumulation of quetiapine is also low. The PEC value for quetiapine is 1,2 µg/L and the PNEC value is 10 µg/L. By calculating the ratio of PEC and PNEC values, the RQ is 0,12. The value means that quetiapine has a low environmental risk. However, that number defines only the risk quotient of quetiapine for the usage in Sweden, because the PEC value takes into consideration the total maximum daily discharge. Therefore, the value of RQ is not very comparable in the risk assessment of manufacturing plant discharges (AstraZeneca, 2021).

The study of “Experimental and in silico assessment of fate and effects of the antipsychotic drug quetiapine and its bio- and phototransformation products in aquatic environments” indicates that quetiapine and its phototransformation products are not readily biodegradable in aquatic environments. The main biotransformation product of the quetiapine is carboxylic acid derivative, which is also formed by human metabolism. The results of the study observed that transformation products of quetiapine have a greater impact on the environment than quetiapine. UV treatment for degradation of quetiapine was also tested in the study. Based on the results, UV treatment in the degradation of quetiapine compounds is not sufficient, because after the treatment, phototransformation products are present and the biodegradation of them is slower compared to the biodegradation of quetiapine itself. Because the parent compounds may form many potentially and even more dangerous decomposition products as degradation products, the transformation products and metabolites of the API are required to take into consideration in the environment risk assessment process and at the design stage of wastewater treatment methods. (Herrmann, Menz, Gassmann, Olsson, & Kümmerer, 2016)

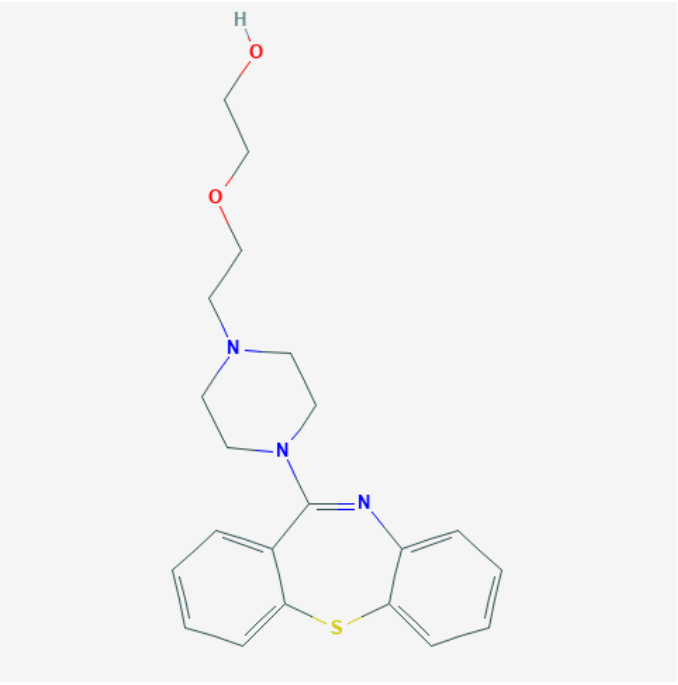

Figure 8. Chemical structure of quetiapine (PubChem, 2005).

Technical possibilities for pharmaceutical wastewater treatment

In the pharmaceutical industry, wastewater with a high concentration of APIs is generated abundantly every year. Currently, the first rinsing water is collected to the separate tank from sources where manual removal of the API residuals is not possible. Those sources are for example granulators. Inhalation department also has a wastewater collection from rinsing rooms where most of the API residues from the inhalation mass manufacturing process and filling lines are generated. Wastewater collection with a high amount of APIs has been seen as an obligatory option for minimizing API discharges of the wastewater treatment plant. However, API discharges could be treated at-source by having an API degradation process instead of the storing and transporting separate collected wastewater to a third-party waste management company.

Currently, wastewaters are externally treated by evaporating the water and burning the residue, which releases CO_2 emissions and generates additional costs for the company. Treatment and transportation of separately collected wastewater releases CO_2 emissions approximately 8% of all waste in the manufacturing plant. Absolute net CO_2 emissions from wastewater treatment are the second most significant source of CO_2 emissions from all generated waste in manufacturing plant. By treating API process wastewater streams with at-source techniques, the company saves on transportation costs and over time, it could be more economically viable. In addition, CO_2 emissions can be reduced if wastewater treatment is changed to more emission-free technology and if there is no need for the transportation of the wastewater. If the wastewater is treated internally, it is also easier to influence the energy source needed for the process, for example by utilizing solar energy. At-source segregation and treatment of wastewater supports Orion's future emission targets, because Orion aims to significantly reduce greenhouse gas emissions in the near future (Orion Oyj, 2021).

It requires a lot of study of different kinds of wastewater treatment methods before the at-source segregation and treatment of the process wastewater can be executed by the company. In addition to the environmental requirements, the treatment process needs to be economically viable. Process, infrastructure investments and operational cost should be at a level that at-source processing is economically profitable. Before the investments can be calculated and even estimated, different kinds of pre-treatment methods need to be studied to understand their functionality and suitability to meet the needs of the processes. In this section, three different wastewater treatment technologies for controlling discharges from

pharmaceuticals manufacturing are presented. Materials are based on the Pharmaceutical Supply Chain Initiative (PSCI) webinar.

Vacuum evaporation

Vacuum evaporation is a wastewater treatment method based on the wastewater evaporation under vacuum conditions. In the treatment process, concentrated API wastewater and clean distillate are produced. This method seems to be promising because the treatment process is not selective for different APIs. Separation of the APIs and water is based on the fact that water evaporates and APIs are not volatile. Other advantages of this method are that the vacuum enables low operational temperature and because of that the consumption of energy is low. In addition to the low energy consumption, this technology includes a heat recovery system. In the vacuum evaporation method, API removal rate is very high, even a few percentage higher than the API removal rate of the competitive ozone test. A few percentage lower removal rate can increase the RQ too high for separated water. However, the capacity of the vacuum evaporation might be a limiting factor because maximum capacity for high API removal rate is a few cubic meters per day. Also a waste segregation system is needed in this method (Pharmaceutical supply chain initiative, (PSCI), 2020).

Advanced oxidation process

Advanced oxidation process (A.O.P.) can be used as a pre-treatment method with pharmaceutical wastewater processing. Figure 9 shows that the method is based on the function of a catalyst which are converting initiators into OH· radicals. Ultraviolet radiation, ultrasonic, semiconductor or metal can be the catalyst for this reaction. The initiator can be hydrogen peroxide, ozone or water. The formed radicals oxidize the API of the wastewater and degrade APIs to the harmless form. This technology has a high effectivity with organic pollutants due to the reactive OH· radicals. That enables a high API removal rate. The treatment unit is also built as a flexible and it is scalable from 1 m^3/d to 100 m^3/h. However, the chemistry behind the APIs is quite complex and pH of the wastewater affect the formation of OH· radical. This technology requires physico-chemical pre-treatment before A.O.P. can be processed (Pharmaceutical supply chain initiative, (PSCI), 2020).

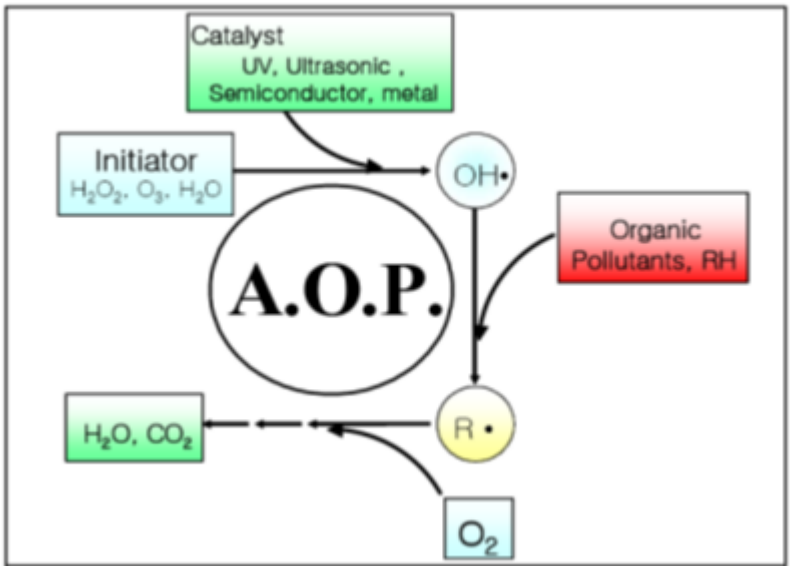

Figure 9. Oxidation pathway of the ozone pre-treatment technology (Pharmaceutical supply chain initiative, (PSCI), 2020).

Electrochemical oxidation

Electrochemical oxidation (EOx) technology is a branch of A.O.P. and a very potential option for pharmaceutical wastewater processing. Figure 10 shows that electrochemical cells include cathode, anode and external source of electricity. Principle of this technology is that electricity is applied to the system which generates hydroxyl radicals (OH·) and other mixed oxidants at anode. Due to the oxidation, APIs are degraded to trace by-product gases N_2, H_2, O_2 and CO_2. EOx is effective treatment technology because in reduction with several APIs is >99% after the treatment process. It works for a wide range of APIs, like antibiotics, anti-parasitics, anti-fungal, anti-depressants, opioids, steroids, oncology, hormones, cardiovascular drugs. The other advantages of this technology is that the process does not require hazardous chemicals and no liquid or solid waste generated during the process (Pharmaceutical supply chain initiative, (PSCI), 2020).

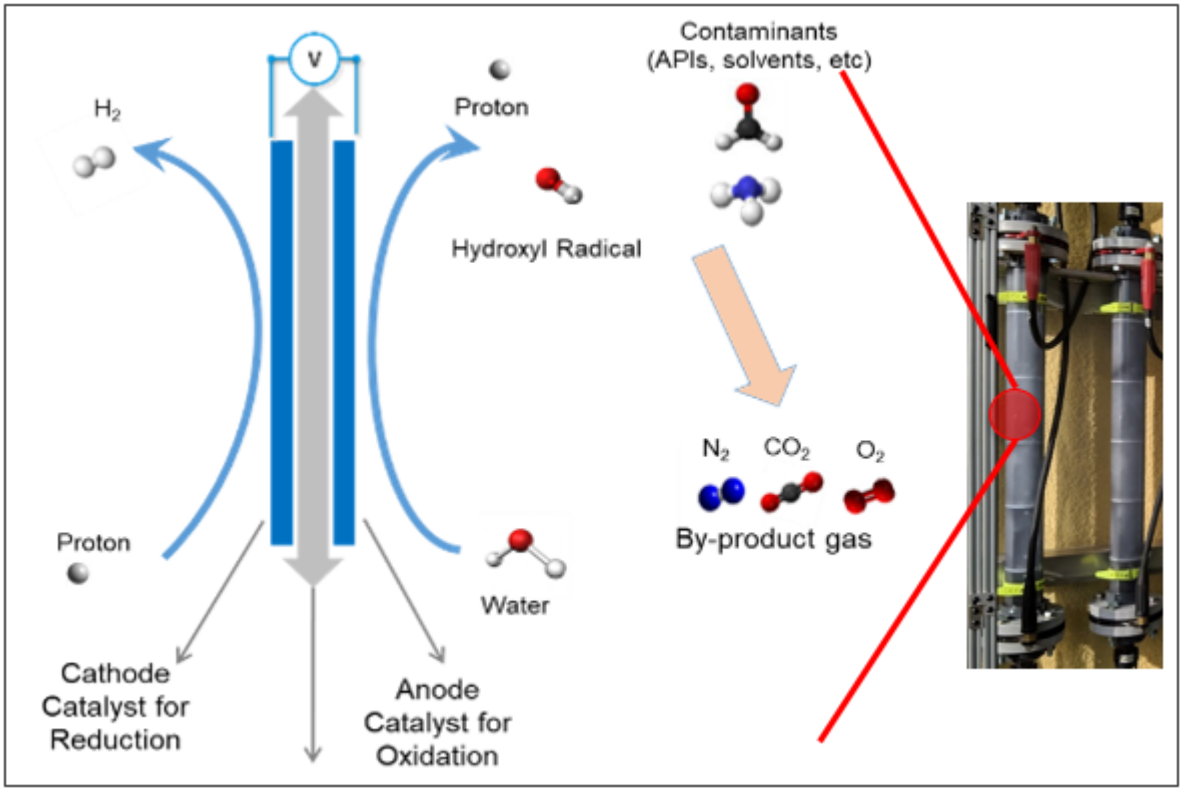

Figure 10. Working principle of the electrochemical oxidation technology (Pharmaceutical supply chain initiative, (PSCI), 2020).

Materials and methods

Data collection

Process of analyzing different data for pharmaceutical wastewater is a rather challenging project, because the facility includes multiple departments, different products and a large number of different APIs within the manufactured products. Process wastewater is produced during cleaning processes, where APIs losses are released as an effluent. The APIs that are released with the non-collected wastewater are discharged to the wastewater treatment plant through the process wastewater. By researching data related to the API losses and discharges, it is required to understand the number of manufactured products and batches and the cleaning processes of the spaces and equipment after manufacturing. This requires a deep understanding of the operation of the entire plant and knowledge where all the cleaning processes are undertaken. It is also important to understand that APIs classification is different depending on their toxicity to the environment.

Process wastewater inventory is based on pharmaceutical production in 2020. That was a typical manufacturing year, even though the Covid-19 pandemic complicated several things. Data searching started by listing all manufactured products of all departments. After product listing, data of the manufactured batches is collected from SAP software. The number of produced batches, the amount of raw materials, API concentration of the produced mass, used devices and all inflows and outflows of the product are collected from the PI-sheets of certain products. After collecting all required information about the products, the amount of the accumulated API is calculated. After determining the amount of accumulated API, the mass of the lost API can be assumed to be the same. Figures 11-15 show the material flow diagram for the manufacturing processes and wastewater generations with collected data.

By having a knowledge of the accumulated product mass, it is possible to calculate the total residue of APIs in the devices and spaces. It is regulated in the environmental permit that most of the accumulated mass needs to be collected before cleaning devices with water. For example, the wastewater collection is included in the first cleaning phase of the granulators according to the environmental permit. By minimizing API discharges to the wastewater, the whole device is not fully cleaned between every batch of the tablet products. Manufactured products with the same API are not cleaned with water between different batches, because devices are cleaned at the end of the campaigns. Between the batch changes in the same campaign, the room and some parts are cleaned by vacuuming. When the production of the

next product with a different API is started, the device and room are cleaned with water and needed detergents. Calculating the amount of the generated wastewater requires an understanding of what cleaning methods are used between batches. In addition to calculations, the study of API4 discharges of the Granulator 3 is implemented by sampling wastewater from an intermediate well.

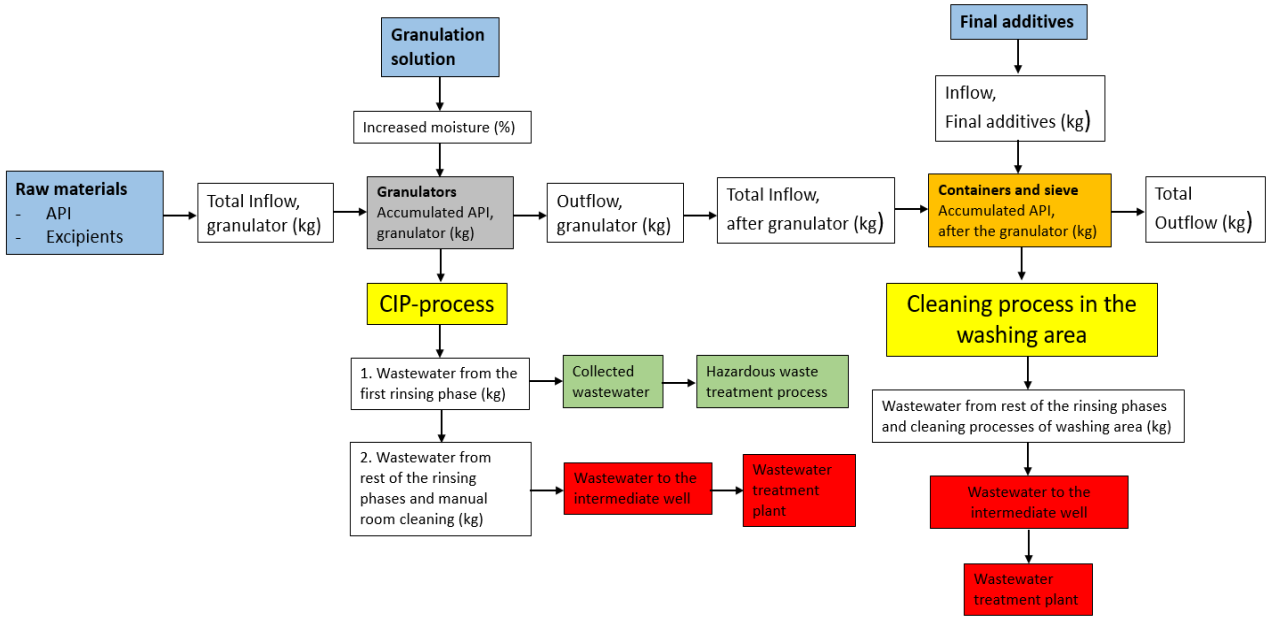

Figure 11. Material flow diagram from the mass manufacturing process of granulators and wastewater generation in the tablet department.

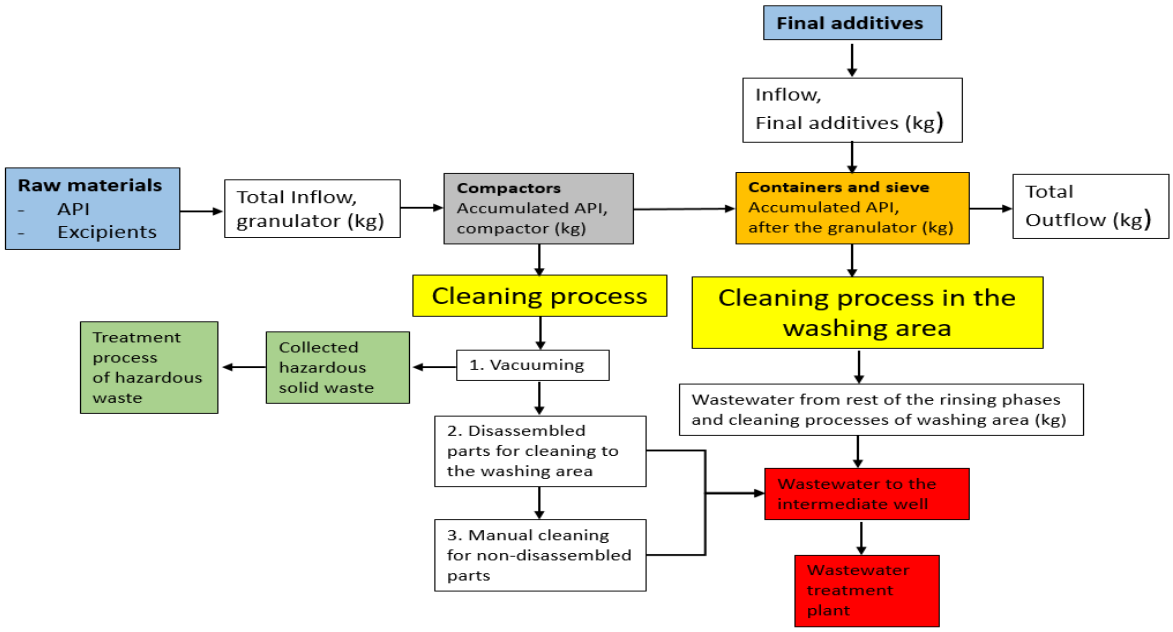

Figure 12. Material flow diagram from the mass manufacturing process of compactors and wastewater generation in the tablet department.

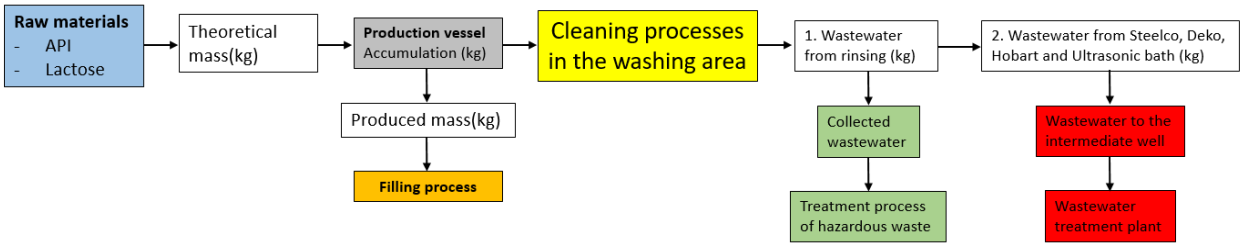

Figure 13. Material flow diagram from the manufacturing process and wastewater generation in the inhalation department.

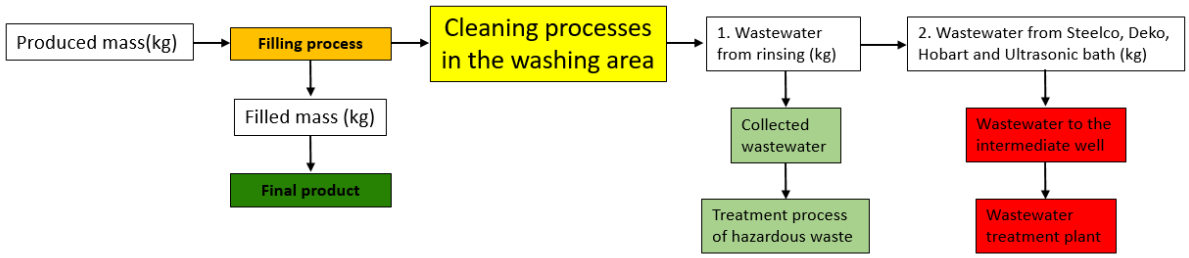

Figure 14. Material flow diagram from the filling process and wastewater generation in the inhalation department.

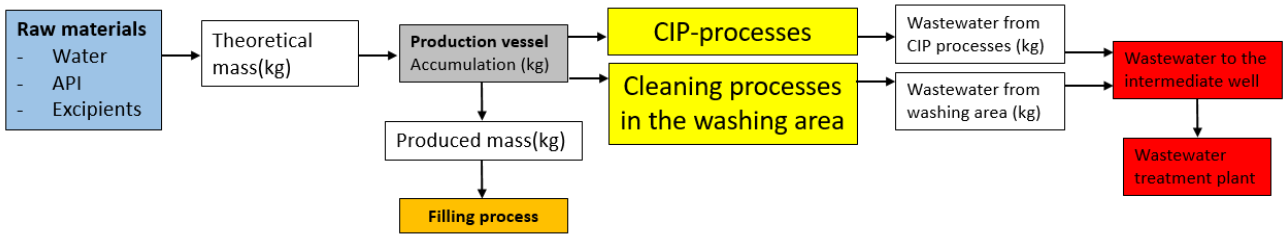

Figure 15. Material flow diagram from the manufacturing process and wastewater generation in the injection department.

Quantity of discharged pharmaceuticals on the process wastewater

Calculations of discharged APIs are based on mass flows of the unit processes. Processes are not in steady-state, because devices have product residues after production of batches. According to equation 3, accumulation ($m_{accumulated}$) of the APIs to the equipment are calculated by subtracting the outflows from the inflows. Accumulated mass includes excipients in addition to API. Because only discharged APIs to the wastewater have been taken into consideration in the inventory calculations, content of API in residues is calculated. Equation 4 shows calculation of API content in the accumulated mass.

Equation 3. Calculation of the accumulated mass.

$m_{accumulated} = m_{in} - m_{out}$

Equation 4. Calculation of the API content of the accumulated tablet mass.

$API(\%) = m_{API} / m_{in} * m_{accumulated}$

Tablet department

In the tablet department, API discharges are calculated in the mass manufacturing unit process. Tables 4-6 show that batches with certain API belong to cleaning campaigns. The cleaning campaigns include different amounts of batches which are also marked to the table. After producing batches under one cleaning campaign, devices are cleaned and accumulated APIs end up in the wastewater. Figure 16 shows that calculations are divided into two parts: API discharges in the granulator and after granulator.

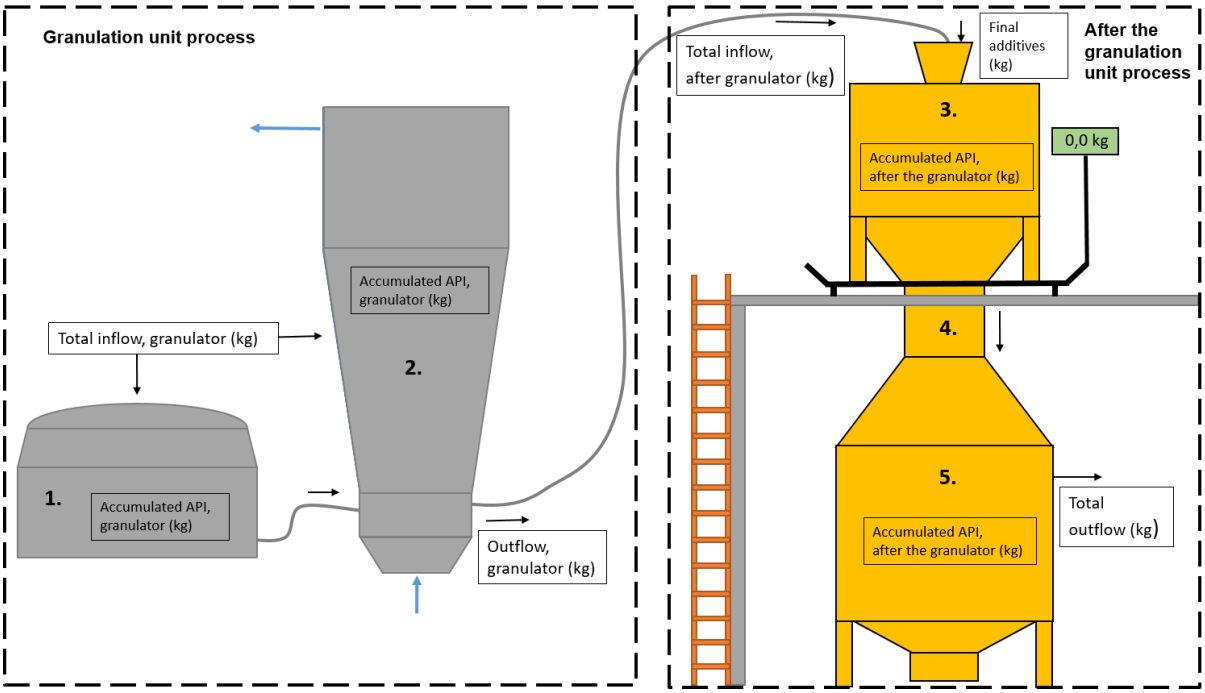

Figure 16. Schematic figure of mass manufacturing process of tablet department. Granulation unit process includes 1. high shear wet granulation and 2. fluidized-bed granulator. After the granulation unit process includes 3. intermediate container, 4. sieve and 5. final container. Black arrows describe mass flows of raw material, granules and excipients. Blue arrows describe mass flows of added air and produced flue gases.

Total inflow of the granulator has been calculated by summarizing masses of the raw materials, which consist of API or several APIs and excipients. Also, the content of the

moisture is taken into account in the calculations. At the beginning, the initial moisture content of raw material is quite low because they are in a solid powder form. After loading raw material into the granulator, the binder solution is sprayed into the raw material particles by increasing the moisture of the mass. Before unloading the granulator, granules are dried to the final moisture. The unloaded granules are sucked though the hose to the intermediate container and the container is weighed, where comes Outflow, granulator (kg) value. After weighing the granules, those are sieved with final additives to the final container. API residuals in the sieve and intermediate container are calculated to the Accumulated API, after the granulator (kg) part. The intermediate container is washed every cleaning campaign, not between batches. The final container is weighed and transferred to the tableting unit process. API residues of the sieving unit process and intermediate container are calculated by subtracting the final mass of granules from the mass of the granules and final additives. That is named as an annual API, after granulator (kg). Total API residues in the whole mass manufacturing unit process is calculated by summing API discharges from the granulator and after granulator unit processes. Equations 5-9 are included in the calculations of the tables 3-5.

Equation 5. Calculation for total inflow in the granulator.
Total inflow, granulator (kg) = API (kg) + Excipients (kg) + (Increased moisture (%) * (API (kg) + Excipients (kg)))

Equation 6. Calculation for the accumulated mass of API inside the granulator.
Accumulated API, granulator (kg) = (Total inflow, granulator (kg) - Outflow, granulator (kg)) * API (%)

Equation 7. Calculation for inflow to the containers and sieve.
Total inflow, after granulator (kg) = Outflow, granulator (kg) + Final additives (kg)

Equation 8. Calculation for the accumulated mass of API inside containers and sieve.
Accumulated API, after the granulator (kg) = (Total inflow, after granulator (kg) - Total outflow (kg)) * API (%)

Equation 9. Calculation for lost API in the mass manufacturing process.
Total API mass to wastewater in mass manufacturing unit process (kg) = Accumulated API, granulator (kg) + Accumulated API, after the granulator (kg)

In calculation of PEC values, estimated daily API discharge value is used. Equation 10 shows that estimated daily API discharges include only the amount of discharged API, not the amount of collected APIs. Collected wastewater indicates the mass of the wastewater which has been collected to the separate wastewater collection tank. The rest of the wastewater is non-collected wastewater, which is led through the intermediate well to the wastewater treatment plant. Because the “Total API mass to wastewater in mass manufacturing process (kg)” mass value includes all lost APIs from the mass manufacture unit process, it is required to define a factor for the amount of “API collection to separate tank (kg)”. This factor is defined in this study based on the wastewater sampling results of Granulator 3. In cases where treatment of collected wastewater is done internally, the effectiveness of the treatment process is deducted from the amount of the API collection to a separate tank.

Equation 10. Formula for estimated daily API discharge calculations.
Estimated daily API discharge (kg/d) = Total API mass to wastewater in mass manufacturing unit process (kg) – API collection to separate tank (kg)

Table 3 shows that eleven different products with different APIs are produced with the Granulator 1 fluidized-bed granulator. API3, API13, API15, API16 and API17 are first mixed and/or wetted in Wet granulator 1 high shear wet granulator and transported to the Granulator 1 fluidized-bed granulator where drying takes place. With those products, the amount of the wastewater includes wastewater from both granulators. API19, API21, API5, API6, API18 and API12 are granulated only in the fluidized bed granulator. The cleaning campaigns might include several different contents of API but the content of API has been taken into account in the calculations. Negative numbers indicate that accumulation of the previous batch has shifted with the mass of the new batch. Calculations are based on the equations 3-9.

Table 3. Discharged APIs of the Granulator 1 and Wet granulator 1.

Table 3.

Table 4 shows that the Granulator 2 is used for production of seven different products. There are listed x pieces of different APIs, but API7, API10 and API3 belong to the Product 3. Product 3 is also wet granulated in the Wet granulator 2 before it is dried in Granulator 2. In the production of Product 3, API3 is added after granulation. This explains the zero discharges of API3 in the granulator. Negative numbers are indicating that residues of the previous batch have moved with the next batch. Calculations are based on the equations 3-9.

Table 4. Discharged APIs of the Granulator 2 and Wet granulator 2.

Table 4.

The Granulator 3 is a combination granulator of high shear wet granulator and fluidized-bed granulator. Table 5 shows that x different products are produced with that equipment. API4, API20 (x campaigns, y batches) and API15 are first mixed and/or wetted in a high shear wet granulator and then the mass is dried in a fluidized-bed unit. With those products, both the high shear wet granulator and the fluidized-bed granulator unit are cleaned. API9, API2, API8, API20 (x campaigns, y batches), API16 and API14 are granulated only in fluidized-bed granulator. API20 is listed twice on the table, because it is included in two different products whose manufacturing and cleaning processes differ from each other.

According to table 5, there are listed different APIs and their cleaning campaigns. The amount of the produced batches of separate cleaning campaigns are also marked to the table. Also in this granulator, API discharges are calculated in two phases: API residues in granulator and after granulator. Accumulated APIs in the granulator means the mass of API left on the surface of the Granulator 3. After granulation part includes tools and phases when granules are transported out of the granulator. Masses of the accumulated APIs are calculated by using equation 3-9.

Table 5. Discharged APIs of the Granulator 3.

Table 5.

Inhalation department

In the inhalation production process, no liquid is used. In the manufacture, the dry powders are mixed together, as a result of which API residues appear as dust on the surface of the equipment. According to the cleaning processes of the inhalation department, all tools and vessels are transported to the washing area where pre-rinsing wastewater is collected to the separate wastewater tank. So, it can be visually observed that most API residues end up in the separate wastewater tank. In the equations 11-14, mass flows of the API discharges are calculated based on the masses of the raw materials and produced mass in the production process. After production of the inhalation mass, inhalator devices are filled with the produced mass in the filling lines. The residues of the APIs in the filling lines have also been taken into consideration in the calculations. In the inhalation department, all the parts of the devices are cleaned between every batch, which means that the cleaning campaigns are not used in this department.

Equation 11. Calculations of the theoretical mass of the inhalation department.
Theoretical mass (kg) = API inflows (kg) + Lactose (kg)

Equation 12. Calculations of the accumulated mass of the inhalation department.
Accumulation (kg) = Theoretical mass (kg) - Produced mass (kg)

Equation 13. Calculation of the API content of the inhalation department.
API (%) = API inflow (kg) / Theoretical mass (kg) *100%

Equation 14. Calculation of lost API mass in the inhalation department.
API to wastewater (g) = (API (%) / 100 * Accumulation (kg)) * 1000

The washing area of the inhalation department includes pre-rinsing rooms where all devices, vessels and tools are rinsed before cleaning processes. All the wastewater which is generated during the pre-rinsing process is collected separately. Wastewater from the cleaning processes is led to through the intermediate well to the wastewater treatment plant. Amount of the lost API to the non-collectable wastewater is dependent on the result of the pre-rinsing process. To ensure minimal API discharges from the inhalation washing area, devices, tools and vessels from the production line and the filling line are studied by taking photos before and after the pre-rinsing process. Figures 17 and 18 show some parts from the production and the filling lines before the pre-rinsing process. It can be noticed that there is white product dust on the surfaces.

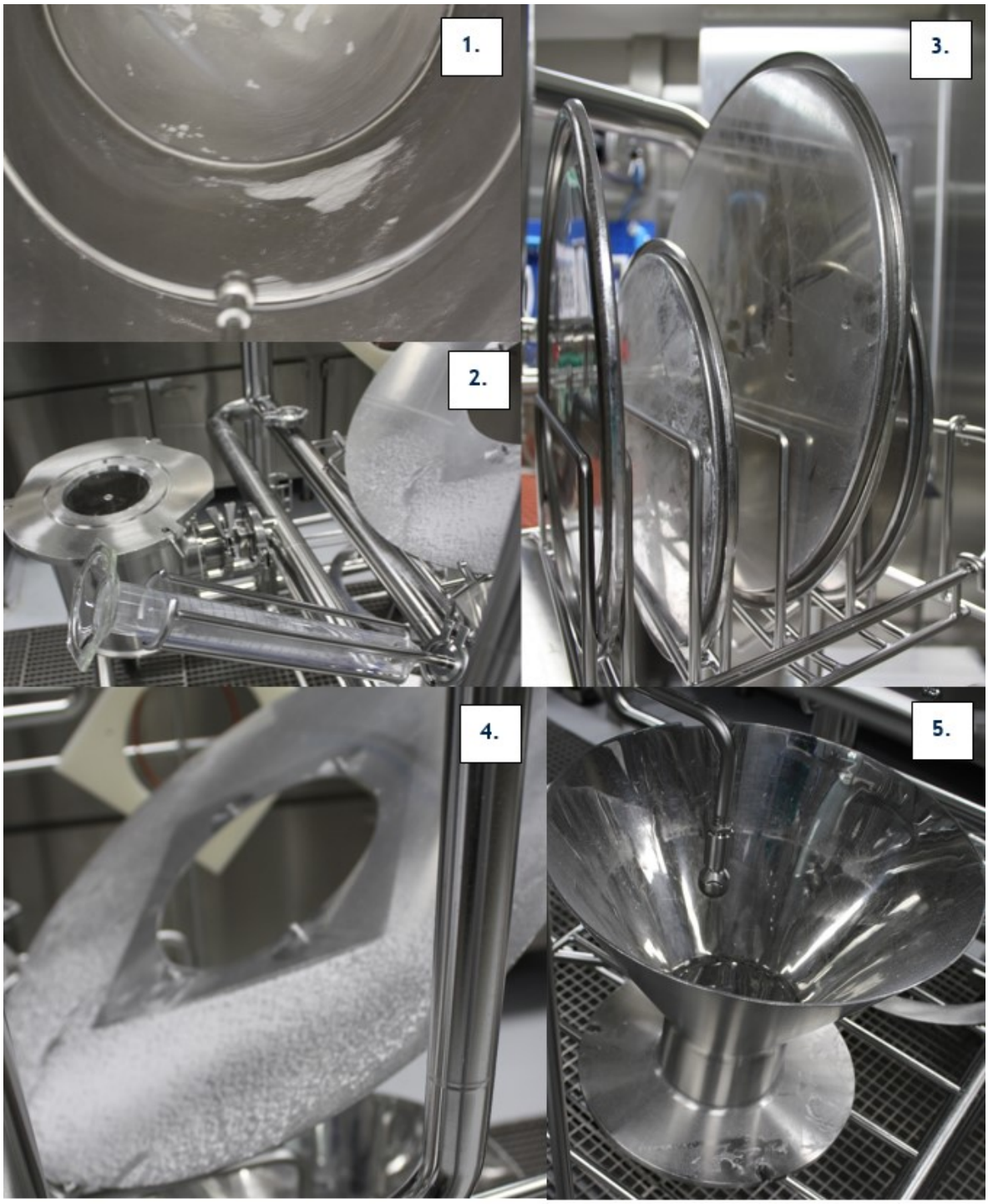

Figure 17. Tools and vessels from the production lines before the pre-rinsing process. The production line includes e.g. 1. Vessel, 2. Measurement glass and milling head, 3. Lids of the vessels, 4. Mass container lid and 5. Sieve feed hopper.

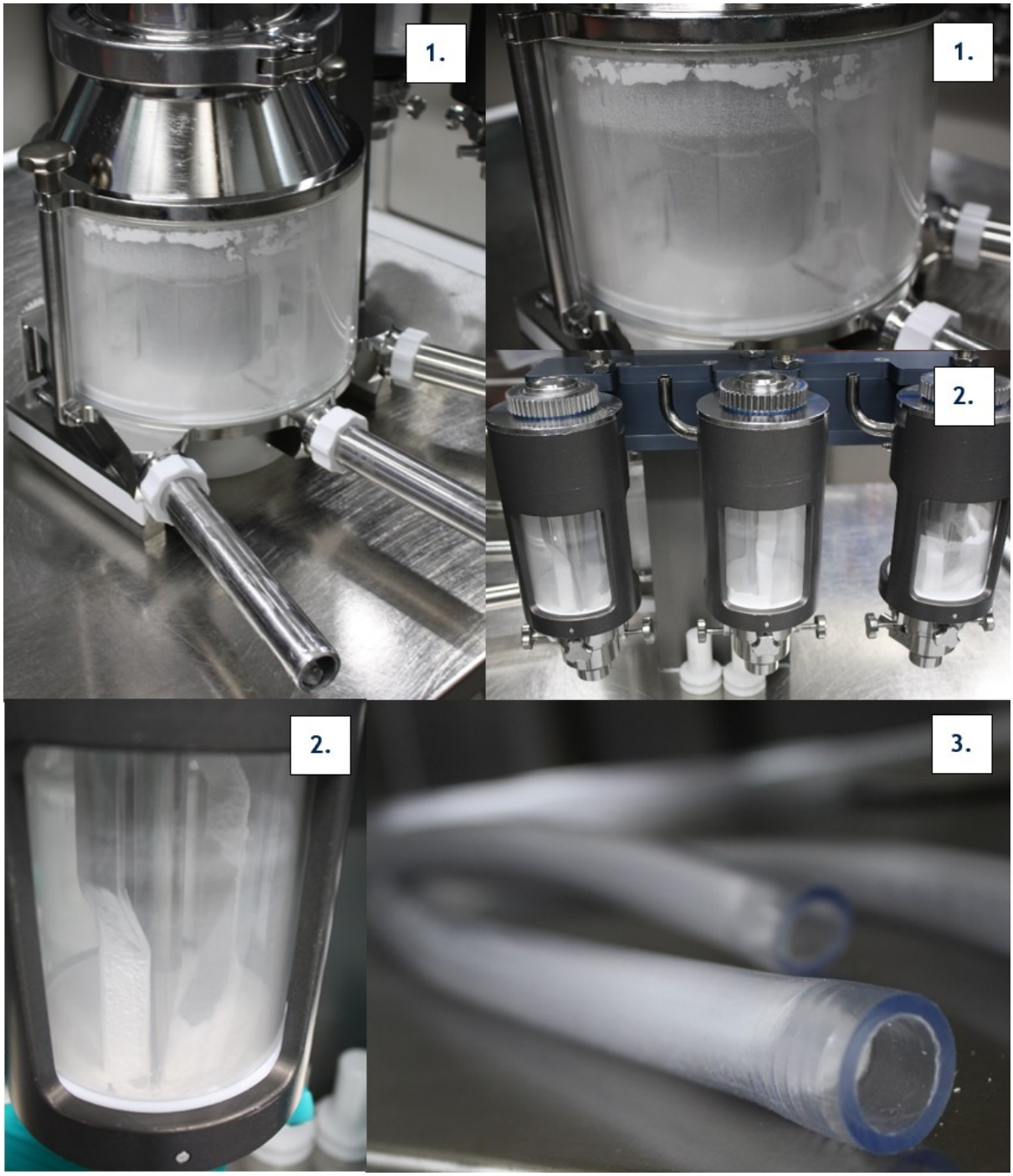

Figure 18. Equipment from the filling line before the pre-rinsing process. The filling line includes e.g. 1. Filling unit, 2. Dispensers and 3. Dust extraction hoses.

Injection department

In the injection products APIs are dissolved, because products are in liquid forms. After the manufacturing process, the surfaces of the emptied production container drain almost clean and potential residues are in small amounts at the bottom of the containers. In addition, several injection products include very small content of dissolved API and no dust is generated during the production, it can be assumed that API discharges from the injection department are minor. Size of the batches are also smaller compared to the batch sizes of the tablet department. In the injection department devices are cleaned between every batch, which means that all API residues of the batches go straight to the wastewater. Mass of the discharged APIs is calculated in equations 15-18.

Equation 15. Calculation of theoretical mass in the injection department.
Theoretical mass (kg) = API inflow (kg) + Additives inflow (kg)

Equation 16. Calculation of accumulated mass in the injection department.
Accumulation (kg) = Theoretical mass (kg) - Produced mass (kg)

Equation 17. Calculation of API content in the injection department.
API (%) = API inflow (kg) / Theoretical mass (kg) *100%

Equation 18. Calculation of discharged API mass in the injection department.
API to wastewater (g) = (API (%) / 100 * Accumulation (kg)) * 1000

Sampling of wastewater

Wastewater sampling and a working instruction of the sampling were also done in this study. Sampling procedure is possible to do by using a discrete sampling method or composite sampling method. The discrete sample is taken at a precise location in a certain time. It describes the level of the API concentration at a specific time. Discrete samples are not dependent on the volumetric flow of wastewater because the API concentration characterizes a general API concentration level and not discharged masses of APIs. An advantage of discrete sampling is that the sampling time can be planned according to the cleaning processes in the production. As the sampling time follows the production schedule, API concentration peaks can be detected. This sampling method enables identification of sources of potential API discharges, but it is quite time sensitive. By taking samples before and after the cleaning process, it can be determined whether rinsing of equipment and separate collection of wastewater are sufficient.

In the composite sampling two or more samples or subsamples are collected either discretely or continuously mixed together in appropriate known proportions. Volumetric flow of wastewater is required for composite sampling, because masses of APIs are calculated. The results of composite sampling give an average of the API level in the longer term, which enables estimation of wastewater quality and average of the discharged APIs. Composite sampling analyzes the quality of generated wastewater for example per day, but its disadvantage is that possible API concentration peaks might not be noticed.

Figure 19 shows the differences between discrete or composite sampling methods. Red curve corresponds to the API concentration level of the discrete sampling and black stars describe discrete sampling points. Yellow line corresponds to the API concentration level in the composite sampling, which is an average from the red curve. Blue columns in the chart are mass flow of the generated wastewater to the intermediate well. Mass flow of wastewater is based on the CIP and manual cleaning processes of the manufacturing plant. Data of the chart is not based on the measurements.

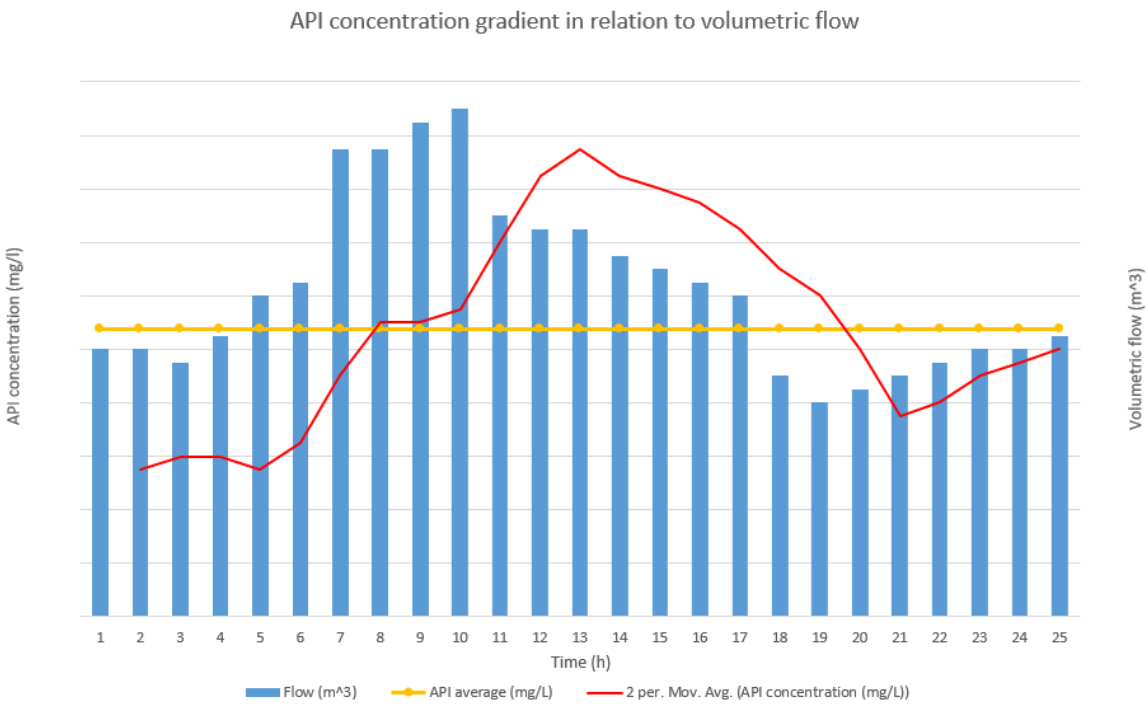

Figure 19. Comparison graph of discrete and composite sampling method. Black stars are discrete samples and the yellow line describes composite sampling during 24 hours.

At the beginning of the sampling, the working instruction was written. The working instruction includes information about the sampling place, dimensions of the sewage well, sampler, safety, sampling schedule, step-by-step procedure and measurement report template. After the working instruction had been approved, the sampling was planned according to the manufacturing schedule. The aim was to take a wastewater sample before the cleaning process in the tablet department starts. The sample was a so-called blank sample of wastewater. When the automation report registered the cleaning process of the desired equipment to be performed, a certain time was consumed to ensure that the effluent fraction was transported from the equipment through the pipeline to the well before the sampling was started. The sample was placed in a sample bottle and warning signs were added according to the CLP regulations. The sample was analyzed in an external laboratory.

The first sample after the cleaning process was planned to be taken after API4 mass production. API4 is manufactured by using the Granulator 3. The cleaning process for API4 mass includes two rinsing phases with water. Both phases are collected separately to the wastewater tank, which is processed at Fortum. The rest of the generated wastewater from the cleaning process phases are transferred to the municipal sewerage network through the intermediate well. The intermediate well includes all process waterwater. Process wastewater and sanitary wastewater are collected together after this well. Intermediate well is located at Orion and samples are taken from there.

Dimensions of the intermediate well

The intermediate well includes two separate manhole covers on the ground. In figure 20, the left side of the intermediate well includes process wastewater input. Volume of the wastewater in the intermediate well is approximately x m^3. The length of the well is x m, width x m and height x m, where the maximum surface level of wastewater is x m. In the middle of the well, there is a x m high wall which includes five pieces of x cm holes placed x cm from the bottom and x cm from the surface. Holes enable flow of the wastewater from the left side to the right side. On the right side of the well, process wastewater continues to another well where the process wastewater and sanitary wastewater are combined.

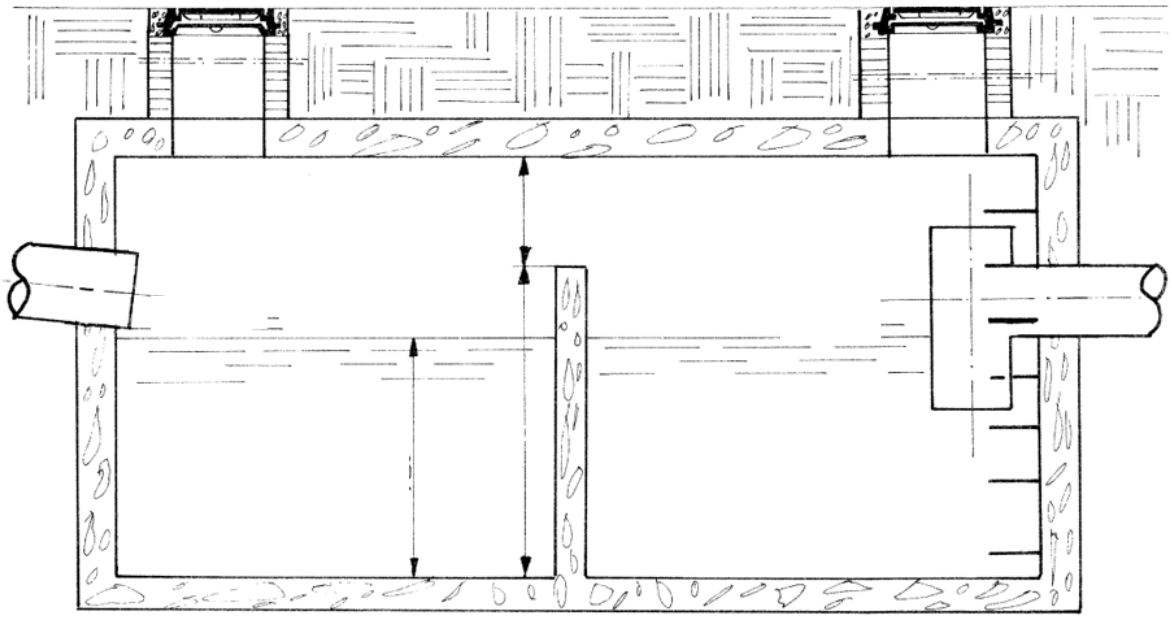

Figure 20. Cross-section of intermediate well for process wastewater.

Sampling from intermediate well

Safety is one of the main issues when starting a sampling procedure. Process wastewater includes very acidic and alkaline detergents from cleaning processes of the manufacturing processes. Wastewater may also contain several potent drugs in different concentrations. During sampling, it is important to ensure that the effluent is not in contact with the skin and eyes. Due to the hazard of the effluent, the protective gear was worn during the sampling. The protective gear includes a reflective overall, which prevents harmful droplets from entering the skin. The protective overall has a reflective surface, which improves visibility for other road users, for example for the heavy traffic. The protective gear also includes goggles or a visor. A visor may be better because it prevents all splashes from entering the face

area. A visor helmet may also be worn during sampling if a separate visor is not available. Nitrile protective gloves should be worn during the sampling, preferably two on top of each other due to the risk of tearing. In image 21, a respirator mask was used only for preventing the spread of Covid-19 infection. In addition to the safety gear, the sampling area must be separated and marked with safety cones and the main gate is informed about the work.

Figure 21. Sampling from the intermediate well. 1. Taking the process wastewater sample from the intermediate well and 2. Bottling the sample.

In the sampling situation, the person from facility maintenance (FM) was asked to open the cover of the manhole. The cover should be open only when the sample is lifted from the well

to the ground. Before and after that it should be closed to avoid accidents like someone falling into the well. When a sampler is put down to the well, the depth of the sampling container is verified from the measurement scale of the telescope stick. When a sample is lifted up from the well, the cover is closed and the sample is bottled at least 3 meters from the well for safety reasons. Before the sample bottling, the sampling time is marked down in the measurement report. At the beginning of bottling, the sample bottle is rinsed once with the sample. Rinsing solution is poured into the waste bottle. After rinsing, the sample volume was measured with a plastic measuring glass and poured into the bottle. The sample bottle was marked with the name of the sample, sampling date and warning signs before the sample was placed into it. After bottling, the sample bottle was closed tightly and splashes outside were removed. The cap was sealed with parafilm and the bottles were placed in double plastic bags before they were sent to an external laboratory.

Two samples were taken in the sampling. The first sample was a blank sample which was taken before the cleaning process of the granulator started. The second sample was taken after x hours from the granulator cleaning process. The first sample was planned to be taken approximately x-y hours after the cleaning process, but the cleaning process was finished on Friday at 9 pm and it was not possible to take the sample that late because people from FM were not available. The staff in the pharmaceutical manufacturing process work in three shifts, from 7 am to 3 pm, from 3 pm to 11 pm and from 11 pm to 7 am. Saturday is not a workday and the work week starts the Sunday night shift. Even though x hours had elapsed since the cleaning process, it is likely that the wastewater from the granulator was still in the intermediate well because no CIP washes were performed on Sunday evening. Generated wastewater is transferred through a sewage pumping station and pipelines before it reaches the intermediate well of process wastewater. The capacity of the pumping station is estimated to be approximately x cubic meters.

Sampling after changes of the cleaning process

After the first sampling from the intermediate well, the API4 was observed to remain in the process wastewater. Because all API4 placed in the intermediate well is discharged to the wastewater treatment plant, the cleaning program of Granulator 3 is changed. In the original cleaning program where the first samples were taken, x kg of wastewater is collected to the separate wastewater tank and x kg of non-collected wastewater is led to the intermediate well. In the changed cleaning program, 40% more wastewater was collected. The rest of the

x kg of the wastewater from the changed cleaning program of Granulator 3 was led to the intermediate well.

Like in the first sampling, two samples were also taken in this sampling. The first sample was a blank sample, which had been taken before the start point of the cleaning process of Granulator 3. The second sample was taken x hours after the end point of the changed cleaning program of Granulator 3. In the wastewater sampling of the original cleaning program, the waiting time between the end point of the cleaning program and the sampling after cleaning was x hours. In the optimal situation, the waiting time should be the same as in the previous sampling, but then the sample of the after changed cleaning program should have been taken on Sunday evening and it is not possible because people from the FM are not available. The x hours should be sufficient time from wastewater to attain the intermediate well, because wastewater is piped from the granulator to the production water pumping station where pumps are pumping approximately x cubic meter per hour of wastewater through the pipelines to the intermediate well. If x kg of wastewater is led to the intermediate well, it can be assumed that at least the first phases after wastewater collection are led to the intermediate well. After waiting time, the second sample was taken and samples were sent to the external laboratory to get an analysis of the quality of wastewater samples.

Sampling in the washing area

The purpose of the washing area sampling was to determine generated API residues from the small tools (buckets, spoons etc.). The sampling was done in the washing area of the weighing process. Because tools might contain dusty potent APIs, protection against potential exposure is certainly important. Because the washing area is classified to the cleanliness class E, gauze overall, cap and shoe covers are required. In addition to the general protective gears of the hygienic requirements of the department, a waterproof apron, sleeve protectors and motorized fresh air hood were used to prevent exposure of the API dust and solution. Also, double nitrile protective gloves were worn during the sampling.

The cleaning process of small tools includes rinsing in the sink, manually dishwashing in the sink with neutral detergent and cleaning in the Dishwasher 1, which uses purified water in the last rinsing phase. After the pre-rinsing and manual dishwashing, most of the API residues are removed. Thus, it can be assumed that all API residues from the tools go through the sink straight to the intermediate well without separate wastewater collection.

Because the amount of API residues in the tools was unknown, it was determined by taking samples from the rinsing water.

Figure 22 shows the uncleaned tools of API39. The tools were rinsed with warm water by brushing the tools with a dish brush. Rinsing water was collected to the bucket during rinsing. The aim of the rinsing was to use as little as possible water, because a large amount of water dilutes the concentration of the API. Figure 23 shows the results of pre-rinsing. The total volume of rinsing water was measured, sample bottles were rinsed with sample and measured samples were poured into the bottles. The sample bottle was marked and packed in the same way like previous samples before sending it to the external laboratory.

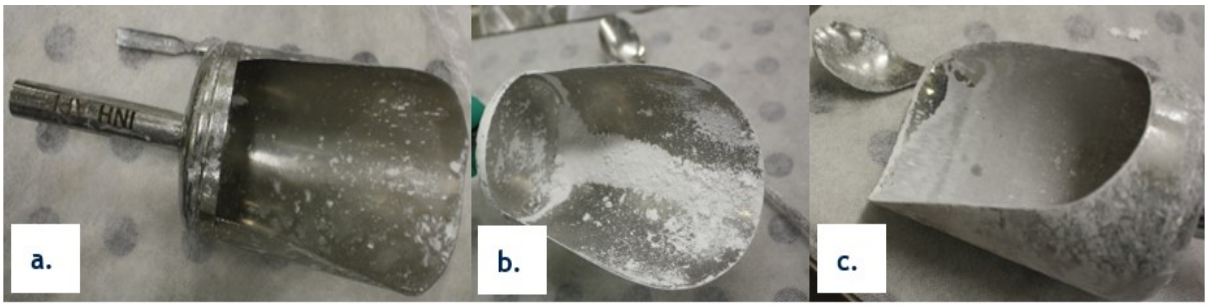

Figure 22. Unwashed API39 tools in the washing area.

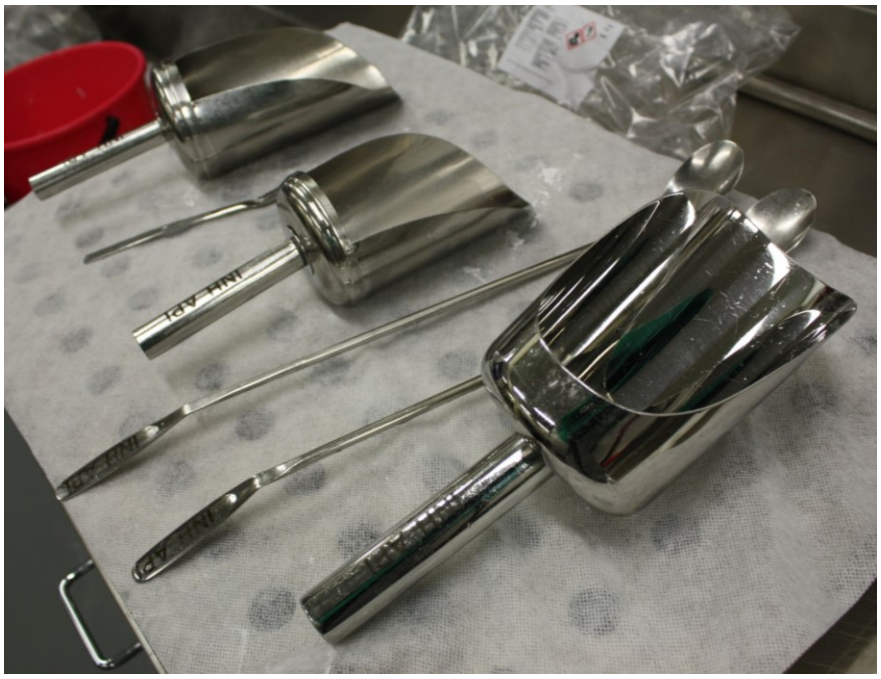

Figure 23. Rinsed API39 tools in the washing area before cleaning those in the Dishwasher 1.

Results and discussion

Tablet department

In the tablet department, the cleaning actions occur in many different places. Generally, the type of cleaning objects defines the cleaning location. Table 6 shows locations, cleaning objects and equipment used for cleaning in all unit processes of the tablet department. Wastewater (WW) collection of the cleaning processes is also marked to the table.

Table 6. Wastewater generation locations in the tablet department.

Room	What is cleaned?	Equipment	WW collection	More information
Cleaning processes of granulators				
1+2	High shear and fluidized bed granulators	Granulator 1 + Wet granulator 1	Partly	CIP: WW from rinsing is collected
3+4	High shear and fluidized bed granulators	Granulator 2 + Wet granulator 2	Partly	CIP: WW from rinsing is collected
5	High shear and fluidized bed granulators	Granulator 3	Partly	CIP: WW from rinsing is collected
6+7	Roll compactor	Compactor 1	No	Most API is vacuumed before rinsing, manual cleaning
8+9	Roll compactor	Compactor 2	No	Most API is vacuumed before rinsing, manual cleaning
Washing area of weighing process				
10	Containers of raw materials Other: Swabs and pallet hoods	Container washers 1+2 Smaller tools: Dish washer 1 Textiles and hoses from vacuum cleaner: Washing machines 1+2	No	API discharges from tools is estimated
Washing areas of mass manufacture				
11	Portable parts from granulation process	Rinsing area, dish washer 2 and washing machine 3	Rinsing area: no Dish washer 2: no Washing machine 3: yes	Rinsing area: API residues from disassembled parts of mass manufacture, leftovers from coating solutions
12	Containers from granulation process	Container washer 3	No	Dust from granules, small API discharges. This room will be removed when room 2052 is ready.
Washing areas of tableting process				
13	Portable parts and tools form tableting process	Dish washers 3+4	No	Most dust is removed by vacuuming.
14	Die table from tableting process	Manual cleaning 1	No	Most dust is removed by vacuuming.
15	Small parts from tabletting process	Ultrasonic bath 1	No	Small amount of API (dust from tabletting)
16	Punches and their cover	Ultrasonic bath 2	No	Small amount of API (dust from tabletting)
Washing area of coating process				
17	Barrels from coating process	Container washer 4	No	No API discharges, only coating solution. This room will be removed when room 2052 is ready.
18+19	Coating Machines	Coating 1+2	No	CIP

Washing area of weighing unit process

All the weighing tools and raw material containers of different departments are cleaned in the weighing washing area. Wastewater is not collected from that area. The weighing tools of inhalation products are rinsed before cleaning in the Dishwasher 1. Other weighing tools are disposable. The API loss of weighing tools is studied for API39 spoons and scoops. According to the results, x g of API39 is released to the non-collected wastewater from one pair of spoon and scoop. It is assumed that all the spoons and scoops release the same amount of API to non-collected wastewater. Amount of the discharged API in weighing tools

is calculated by taking into consideration the amount of the used tools of spoons and scoops per year.

In addition to the weighing tools, emptied containers for weighed raw materials are cleaned in this washing area. Containers are cleaned in Container dishwashers 1 and 2. This study does not contain data from API residues from containers. Cleaning utensils, like swabs, used for weighing rooms cleaning are also cleaned in this room in Washing machines 1 and 2. Those include only a small amount of API as a dust. Pallet hoods used as a secondary packaging material are cleaned in the same washing machines as swabs, but those do not include API residues.

CIP and washing area in mass manufacture unit process

High shear and fluidized-bed granulators include CIP cleaning programs, where wastewater from the first rinsing phases are collected to the separate wastewater collection tank. Compactors are vacuumed before manual cleaning with water. Because of the wastewater collection and vacuuming, most API losses from granulators and compactors are disposed of as pharmaceutical waste to the third-party waste management company. Only the leftover API residues after the rinsing and vacuuming are discharged to the wastewater treatment plant. Table 7 shows calculated API losses for all high shear and fluidized-bed granulators and also for compactors and direct mixers. API losses are the amount of manufactured mass, which does not end up in the product. Calculated API losses describe the total amount of lost API in devices, from which some part is vacuumed and collected to the wastewater collection tank and rest of the API residues is discharged through the intermediated well to the wastewater treatment plant. The rest of the API residues are called as estimated daily API discharges, which is calculated for all APIs by utilizing results from the wastewater sampling of Granulator 3. In the sampling of wastewater, the split factor between collected and non-collected wastewater was defined for wastewater collection of the cleaning process of API4 mass at Granulator 3. The split factor of Granulator 3 was used as a default value for all granulators and the cleaning programs, which enabled possibilities to calculate estimated daily API discharges for all APIs. The PEC values are possible to calculate by using estimated daily API discharge masses.

Table 7. Lost and discharged APIs in the mass manufacturing unit process. *=no data.

Table 7.

Granulator 1 and Wet granulator 1

Table 7 shows that most loss of APIs comes from the high shear and fluidized-bed granulators. In Granulator 1 fluidized-bed granulator is granulating API3, API5, API6, API12, API13, API15, API16, API17, API18, API19 and API21. In the mass production of API3, API13, API15, API16 and API17, the high shear granulator 1 is also used. In Product 2 production API13 is only dry mixed in the high shear granulator without adding a granulation solution.

API losses of mass manufacturing processes are divided into two units. The first unit of the mass manufacture process includes mass production in granulators. Granulators are cleaned at the end of every cleaning campaign in connection with product changes. API losses for different products are calculated for separate cleaning campaigns and those include different amounts of produced batches. Highest API losses in total for Granulator 1 are for API3, API13, API15, API16 and API17. The highest estimated daily discharge was for API13 and API15. The reason for higher API losses is affiliated to the amount of produced batches and the process of mass manufacture. All of those APIs are granulated in both granulators which affects the amount of API losses.

API loss after the granulation comes from containers and sieve, to which granules are transported out from the granulators. API losses are also calculated for them. For API13 and API5 mass of the after granulation unit process is negative. For API5 the slightly negative value is only -x kg/y which can be caused by the inaccuracy of the weighing scale. For API13, the annual mass of after granulation is -x kg/y. The mass difference of lost API13 per batch varies from -x kg to y kg. Because the mass for many batches is slightly negative, therefore the total mass of that unit process is highly negative. During the research phase the manufacturing process of Product 2 was observed in order to locate the cause for mass loss. The main reason for negative numbers is changes in mass humidity during the process, because it is the biggest variable and the same phenomena is not faced with inhalation and injection products, where products are totally dry or in liquid form.

Granulator 2 and Wet granulator 2

Table 7 shows that Granulator 2 fluidized-bed granulator is used to granulate API6, API7, API10, API14, API16, API18, API19 and API20. Granulator 2 and Wet granulator 2 are mainly used with the mass production of Product 3. Product 3 includes x different APIs: API10, API7 and API3. API3 is not granulated because it is added to the intermediate container with granules which contain API10 and API7. High shear granulator is used in mass production of API7, API10 and API16. After that the wett mass is dried in the Granulator 2 fluidized-bed granulator. API7, API10, API16 and API19 have the highest total API losses in the mass manufacturing process. API19 is the only API from those which does not include a high shear granulation process. API19, API7, API14 and API18 also have a negative mass value for the after granulation part, which is caused by the changes of the mass moisture.

Granulator 3

Granulator 3 includes high shear and fluidized-bed granulator units. Table 7 shows, API2, API4, API8, API9, API14, API15, API16 and API20 are granulated with excipients in that granulator. API4, API20 and API15 are granulated in both granulation units. Rest of the APIs which are granulated in Granulator 3 utilizing only the fluidized-bed granulator unit. The biggest API losses in the Granulator 3 are with API4, API9 and API15. API14, API16 and API20 also have some API losses per year, but those losses are clearly smaller compared to the annual API losses of API4, API9 and API15. API4 losses might increase in the future if the amount of the increased batches increase the amount of the cleaning campaigns.

Sampling of wastewater

The API discharges from the Granulator 3 were studied with wastewater sampling from the intermediate well. Table 8 shows the results of samplings, where the Zero sample 1 was taken before the cleaning process of Granulator 3 and After cleaning sample 1 was taken after the original cleaning process of Granulator 3. In the cleaning process, the first rinsing phases of high shear granulator and fluidized-bed granulators were collected to the separate wastewater tank. The zero sample 1 and After cleaning 1 are taken with the current cleaning program where x kg of the wastewater is collected and x kg of the wastewater are led to the intermediate well. Before the cleaning process, x batches of API4 mass were manufactured. API4 concentration of the zero sample was x µg/L. After the cleaning process, the concentration of the API4 was x µg/L. This means that the difference of API4 concentration is x µg/L. Because the data of the mass flow of the wastewater to the intermediate well is not available, the mass of discharged API4 is calculated by using the volume of the intermediate

well. According to the calculations, x g of API4 is discharged with that cleaning program. This amount corresponds to the mass of API4 in x tablets. Based on the sample results and maximum daily API loss which is x kg/campaign without collection, only x% of API4 is discharged.

Table 8 also shows the API4 concentration difference in the changed cleaning program. In the changed cleaning program, x kg of wastewater is collected instead of x kg. The remaining x kg of wastewater is led to the intermediate well where the sampling takes place. Before the cleaning process, x batches of API4 mass were manufactured. The API4 difference between zero sample 2 and After cleaning 2 is x µg/L. Based on the concentration difference and the volume of the intermediate well, at least x g of API4 is discharged in the changed cleaning program during the cleaning campaign. Thus, prolonging the collection rinse increased API4 discharges by x g per cleaning campaign. It was not an expected result, because the increased wastewater collection should reduce API discharges. The reason for the unexpected result was probably that the waiting time was x hours longer in the first sampling (Zero sample 1 and After cleaning 1), when the wastewater from the cleaning of Granulator 3 might already pass the intermediate well. Another reason for lower discharges in the first samples might be that effluent had been in the well over the weekend without flow and at the time of sampling the well effluent may not have been so well mixed. The possible lack of mixing may affect how a representative sample was taken.

Table 8. The amount of the discharged API4 and risk quotient after the cleaning processes of Granulator 3. The worst case is not the real situation, it only demonstrates the need for wastewater collection. *= not analyzed, the discharge mass for the worst case is based on the maximum loss of API4 in a campaign. Question mark is an unknown variable.

Table 8.

With risk assessment, it is possible to calculate the maximum limit for daily discharging of API4. A chronic PNEC value is x µg/L and an acute PNEC value x µg/L for API4. If the loss of API4 is calculated as a daily loss, the discharge per day is x-y kg/d for API4 without wastewater collection. In the worst case without wastewater collection, x kg/d of API4 would lead to the wastewater treatment plant. Currently, the wastewater collection is used and based on the Zero sample 1 and After cleaning 1 results, estimated daily API4 discharge in the campaign of the original cleaning process is x kg/d. With that estimated daily API4 discharge value, the chronic PEC value is x µg/L and the acute PEC value is x µg/L. According to these values, the acute risk quotient value for the original cleaning process of API4 mass is x and the chronic RQ is x. In the second sampling, the estimated daily API4

discharge value is x kg/d, and then the chronic PEC value is x µg/L and the acute PEC value is x µg/L. RQs for the API4 discharges of the changed cleaning program are ≤ 0,1. Those mean that there is negligible environmental risk of the API4 with both cleaning processes, when x-y kg of wastewater is collected. So, the wastewater collection of the original cleaning program is sufficient. If wastewater collection would not exist, the acute RQ for API4 would be x and the chronic RQ x in the worst case. In that case, RQ values indicate that there is a high environmental risk of the substance. This explains the imperative need of the wastewater collection.

According to the lost mass calculations, total API4 maximum loss for one cleaning campaign is x kg, from which only x g is discharged in the original cleaning program. Limit for daily discharge of API4 is x kg. This is defined by calculating the mass of the discharged API4 when RQ < 1. When the maximum API4 discharge limit for one cleaning campaign has been taken into consideration, approximately x% of lost API4 is allowed to discharge. Based on that value, the original cleaning program for API4 collection is sufficient because only x% was discharged. Because API4 has become a very important API for the future, the amount of lost API will slightly increase. However, the loss of API4 does not increase linearly with the number of batches produced, because the number of cleaning campaigns does not increase in proportion to the number of batches. The length of the campaign is an important factor in the formation of API discharges, because increasing the number of batches within a series reduces the number of washes and thus API discharges. Based on the unexpected sampling results, it would be usable to do a third sampling after x hours of the end point of the original cleaning program of Granulator 3.

Washing area of the mass manufacture process

After the granulation process, some portable parts from granulators are also transported to the mass manufacture washing area. The room includes a rinsing area, Washing machine 3 and Dishwasher 2. Figure 24 shows the rinsing area, where all parts of the granulators, vessels and vacuum cleaner hoses are rinsed before the cleaning in the machines. Figure 25 shows the API residues on the vacuum cleaner hose surface before rinsing. The generated wastewater in the rinsing unit process is not collected. Also, the leftovers of granulation solutions are released in the rinsing area. Granulation solutions do not include APIs, but usually they include ethanol or gelatin in addition to the water.

Figure 24. The rinsing area in the washing area of the mass manufacture process. Vessel of the granulation solution appears on the right side of the figure.

Figure 25. Vacuum cleaner hose before rinsing.

In the Washing machine 3, filter bags from granulators are cleaned. As the figure 26 shows, filter bags from the granulator include abundantly mass from the granulation process. Before transportation of filter bags to the washing area, they are required to be shaken and wetted inside the granulator. Then the rinsed filter bags are ready to be washed in the Washing machine 3. Hoses from vacuums are also cleaned in that washing machine after pre-rinsing. Rinsing water from vacuum hoses is not collected. Washing machine 3 has a manual wastewater collection button which can be switched on for all washes by operator so API residues from filter bags are collected and treated. Rest of the fluidized-bed granulator is cleaned with a CIP cleaning process.

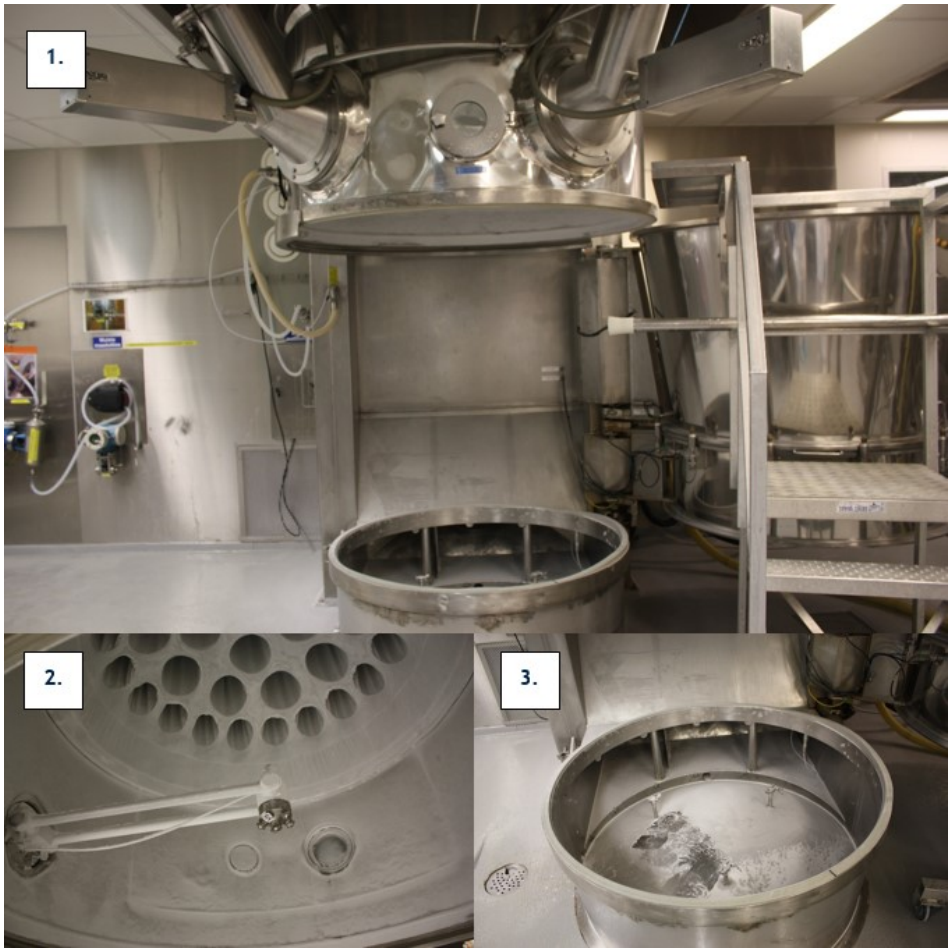

Figure 26. The lower part of the fluidized-bed granulator after the Product 2 mass manufacture process. 1. Opened fluidized-bed granulator, 2. Filter bags of granulator and spraying nozzle and 3. The bottom of the granulator.

Compactors are disassembled and the parts are transported to the washing area of the mass manufacture. Non-disassembled parts of the compactors are vacuumed and cleaned manually. Discharges of the direct mixing process include API as dust, which is released from the Container dishwasher 3. According to the results of table 7, losses of APIs in compactors are approximately x kg/y API7 and x kg/y of API17, from where most losses are vacuumed and disposed as a hazardous waste. From the containers of direct mixing x kg/y of API1 and x kg/y of API11 are discharged.

Because API discharges are pulse-like, the risks to the environment should be calculated according to the maximum possible discharges during one campaign. Table 9 shows estimated daily discharges, RQ acute and chronic values and API maximum daily limits of APIs of tablet department. Range for estimated daily discharges are calculated by listing minimum and maximum API losses in the cleaning campaigns for each API and taking account the percentage of non-collected wastewater. The API content of non-collected

wastewater is x%, which is based on the sampling results. RQs is calculated as a proportion of PEC and PNEC. For the APIs of unknown PNEC value, the default PNEC value for APIs is 0,1 µg/L is used.

According to the Average of RQ acute values API19 might have a medium environmental risk in acute areas. It is necessary to collect more data and study the ecotoxicity of API19. API19 is manufactured in Granulator 1 and Granulator 2. High shear wet granulators are not used in the mass manufacturing of products including API19. Annual production of API19 has x cleaning campaigns. That means that API is discharged approximately once in x months. The cleaning group of API19 belongs to group x, where the granulator is cleaned with base detergents at x degrees. In addition to the ecotoxicity studies, it would be necessary to take a closer look for API19 mass calculations. API9, API12 and API15 have low environmental risks in the acute and chronic areas. API10 and API14 also have low environmental risks in the acute area. In addition to API9, API12 and API15, low environmental risks in the chronic area might also occur with API3, API13 and API17. Rest of the APIs in the tablet department have negligible environmental risk in acute and chronic areas.

Table 9. Estimated daily discharges, RQ acute and chronic values and API maximum daily limits of APIs of tablet department.

API	Amount of cleaning campaign	Total lost (kg/y)	Range of estimated daily discharges (kg/d)	Average of estimated daily discharge (kg/d)	Max daily discharce limit (kg/d)	Range of RQ chronic (µg/L)	Range of RQ acute (µg/L)	Average of RQ chronic (µg/L)	Average of RQ acute (µg/L)
API1	x	x	x	x	x	x	x	x	x
API2	x	x	x	x	x	x	x	x	x
API3	x	x	x	x	x	x	x	x	x
API4	x	x	x	x	x	x	x	x	x
API5	x	x	x	x	x	x	x	x	x
API6	x	x	x	x	x	x	x	x	x
API7	x	x	x	x	x	x	x	x	x
API8	x	x	x	x	x	x	x	x	x
API9	x	x	x	x	x	x	x	x	x
API10	x	x	x	x	x	x	x	x	x
API11	x	x	x	x	x	x	x	x	x
API12	x	x	x	x	x	x	x	x	x
API13	x	x	x	x	x	x	x	x	x
API14	x	x	x	x	x	x	x	x	x
API15	x	x	x	x	x	x	x	x	x
API16	x	x	x	x	x	x	x	x	x
API17	x	x	x	x	x	x	x	x	x
API18	x	x	x	x	x	x	x	x	x
API19	x	x	x	x	x	x	x	x	x
API20	x	x	x	x	x	x	x	x	x
API21	x	x	x	x	x	x	x	x	x

Because either acute or chronic PNEC value is available only for half of the tablet APIs, the rest of the RQs are calculated by using 0,1 µg/l as a default PNEC value. The default PNEC value may be misleading for some APIs. However, another problem is that different references offer different PNEC values for the same API and it is very difficult to find out which of the results is the most reliable. Some studies are providing computer modelled PNEC values, but those are not reliable because there is no experimental ecotoxicity data available. In addition, the properties of APIs affect the PNEC values. If the API is lipophilic and $LogK_{ow}>3$, the default PNEC value is not appropriate for risk assessment calculations. Also in cases of hormones and antibiotics, default PNEC is not reliable. In these calculations, it is expected that all API discharges end up in the environment without biodegradation or binding to the sludge. Figure 27 shows the RQs of different tablet APIs in acute and chronic areas. APIs which RQ use default PNEC values as acute area are marked with orange colour and chronic RQ calculations with default PNEC values are marked with black colour.

Figure 27.

Figure 27. Risk quotient chart for APIs of the tablet department. Default PNEC values for acute RQs are marked with orange colour and for chronic RQs with black colour.

Inhalation department

In the inhalation department all parts from production and filling lines are cleaned in the washing area. Table 10 shows that all the parts from production and filling lines are rinsed in separate rooms where all generated wastewater is collected to the separate tank. After pre-rinsing tools are mainly cleaned in the washing area of the inhalation department. Generated wastewater from that room is led through the intermediate well to the wastewater treatment plant. After rinsing, some parts having poor chemical resistance are cleaned in Dishwasher 7. The washing area of the inhalation department does not include wastewater collection. Inhalation weighing tools are cleaned in the same washing area where weighing tools from the tablet and injection department are cleaned. Tools are rinsed and then washed in Dishwasher 1. Rinsing wastewater form inhalation weighing tools are not collected.

Table 10. Locations for the inhalation cleaning actions.

Room	What is cleaned?	Equipment	WW collection	More information
Washing area of weighing process				
10	Inhalation weighing tools	Dish washer 1	No	API residues are rinsed before cleaning.
Inhalation washing area				
20+21	All parts form production and filling lines	Spraying nozzles	Yes	Only rinsing
22	Parts form production and filling lines	Dish washer 5, Dish washer 6, Ultrasonic baths 3+4	No	Cleaning of rinsed parts from production and filling lines, which have a good chemical resistant. Difficult-to-clean parts are also washed in an ultrasonic baths.
23	Parts form filling line and non-product contact parts	Dish washer 7	No	Cleaning of rinsed parts from production and filling lines, which have a poor chemical resistant.

In the inhalation department, cleaning campaigns are not used because all production and filling lines are cleaned between every batch. Because of that, the amount of batches indicates also the amount of cleaning processes. In the inhalation department, API losses are calculated for 7 different APIs. Table 11 shows the total amount of lost APIs in the inhalation department. Amounts of the lost APIs are in grams per year. Figure 28 shows that the reason for highest API loss for API39 is that its production volume is annually highest. Amount of the produced API41 batches is second highest, but the API41 loss is rather small because its concentration in the product is small. Table 11 also includes the number of the annual produced batches and the amount of the lost API in one batch for all APIs. Maximum daily discharge limits calculated for inhalation APIs with default PNEC value. Whether to collect the wastewater or not can be determined by comparing the lost API per batch masses to maximum daily discharge limits. Because of that, it can be noticed that API loss

per batch is higher for API38, API39 and API40 than the daily maximum limit. Without wastewater collection, those APIs would be a risk to the environment. Based on that, it can be proved that wastewater collection is required in the inhalation department.

Table 11 also includes inhalation API losses in the weighing washing area. API losses in the weighing washing area were studied with API39. The result of the study was that x g of API39 is lost per spoon and scoop. The API loss is assumed to be the same with all other APIs in the weighing washing area. Masses of lost APIs in the washing area are calculated by multiplying the amount of the washed spoons and scoops with x g which comes from the one pair of those. Masses of lost APIs from the weighing area are discharged, because there is no wastewater collection. If the annual masses of lost APIs from the weighing area are compared to the max daily discharge values, all of the API discharges from the weighing area are below the discharge limits. Discharge limits are set for a one day and masses of lost APIs from the weighing area are for the whole year. So daily API discharges from the weighing area are very minor and there is negligible environmental risk from those. Based on that, wastewater collection is not needed for weighing tools.

Table 11. Summary of annual lost APIs in the inhalation department.

API	Masses of lost APIs in production (g/y)	Masses of lost APIs in filling lines (g/y)	Masses of lost APIs from weighing tools (g/y)	Total API lost (g/y)	Produced batches in 2020	Lost API per batch (g/batch)	Max daily discharce limit (kg/d)
API38	x	x	x	x	x	x	x
API39	x	x	x	x	x	x	x
API40	x	x	x	x	x	x	x
API41	x	x	x	x	x	x	x
API42	x	x	x	x	x	x	x
API43	x	x	x	x	x	x	x
API44	x	x	x	x	x	x	x

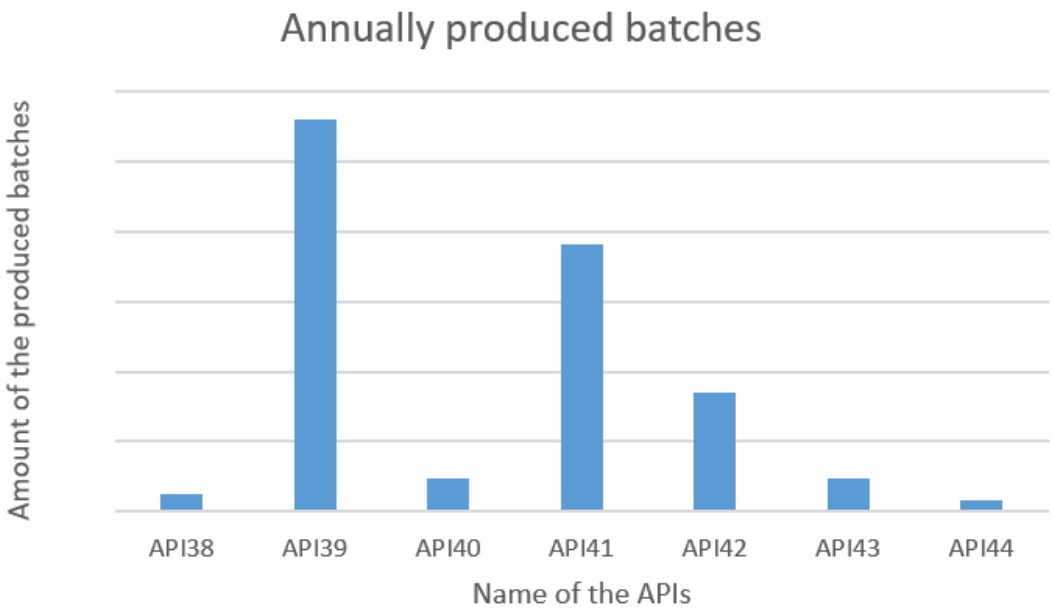

Figure 28. Amount of the produced batches for different inhalation APIs in 2020. APIs from the combination products have been calculated separately.

In the inhalation department, all used tools and vessels are transported to the washing area. At the beginning of the cleaning process, tools and vessels from the production and filling lines are rinsed in the pre-rinsing room. To ensure that most APIs from the inhalation department are led to the separate wastewater tanks as an effluent, pictures were taken of the production and filling lines parts before and after pre-rinsing. Figures 29 and 30 show results of pre-rinsing. Those figures are taken after pre-rinsing and before cleaning in Dishwasher 5. Figure 29 shows that production tools include some small API residues on the surfaces after pre-rinsing. At least the figure 29 part 5. shows that the lids of vessels include some API residues on the surfaces.

Figure 29. Equipment of the production line after pre-rinsing. 1. Mass container lid, 2. Sieve, 3. Measurement glass, 4. Vessel and 5. Lids of the vessels.

Figure 30 shows that glass parts from the dispenser and filling unit seem to be clean after pre-rinsing. Wheel parts, feed screw and mixer include white product residues. In figure 30 part 4, the feed screws are only parts which are cleaned in an ultrasonic bath after pre-rinsing. Even though some parts still include residues from products, it can be assumed that a negligible amount of API residues are led to the intermediate well from the inhalation washing area. That is a reason why RQ values are not calculated for the inhalation department.

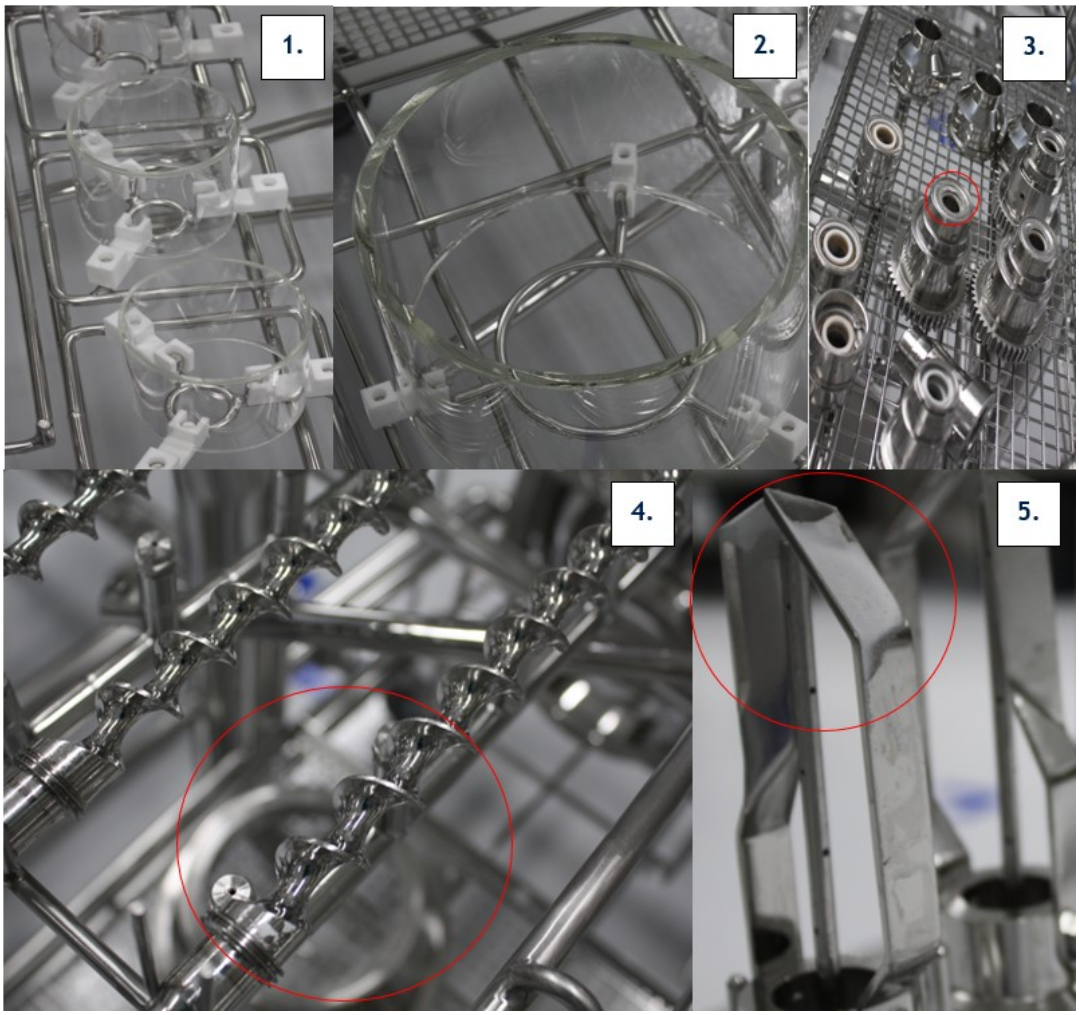

Figure 30. Equipment of the filling line after pre-rinsing. 1. Glass parts from the dispensers 2.Glass parts from filling unit, 3. Wheel part. 4. Feed screw and 5. Mixer.

Injection department

In the injection department, API wastewaters are mainly generated in the CIP cleaning processes of the production vessels. Table 12 shows that the production vessels are mainly cleaned with CIP processes but with some difficult-to-clean products, for example products with API34 and API35, vessels are first transported to the washing area for pre-rinsing. In addition to the pre-rinsing of vessels, some small tools are cleaned in the washing area of the injection department. Wastewater without APIs is also generated in sterilization processes and quality tests. In the sterilization process ampoules, bottles or other equipment are heated with steam. Tests of the material quality are performed about x times per year with a blue bath. In the injection department, wastewater is not collected.

Table 12. Wastewater generation sources and the cleaning objects.

Room	What is cleaned?	Equipment	WW collecting	More information
Injection manufacturing area				
24+25	Manufacturing line 1	CIP	No	Portable vessel. Products with API34 is rinsed in washing area.
26+27	Manufacturing line 2	CIP	No	Non-portable vessel
28+29	Manufacturing line 5	CIP	No	Portable vessel. Products with API35 is rinsed in washing area.
30+31	Manufacturing line 6	CIP	No	Non-portable vessel
Injection washing area				
32	Small tools and non-product contact parts	Dish washer 8, Ultrasonic bath 5 and manual cleaning	No	Small API discharges
33	Rinsing of production vessels	Manual rinsing	No	Pre-rinsing of difficult-to-clean vessels
34	No cleaning processes, only sterilization	Sterilization machine	No	Blue bath with methylene blue, no API discharges

In the injection department, all APIs are in liquid form during the manufacturing. In the injection department, cleaning campaigns are not used because all production lines are cleaned between every batch. Because of that, the amount of batches indicates also the amount of cleaning processes. Table 13 shows that the amount of the API lost is highest for API22. If the amount of the produced batches is compared between different APIs, products with API22 are produced over x times less than products with API27 and still the API22 discharges are x times higher than API27 discharges. The reason for different API discharges is that the API22 concentration is approximately x% in the product and the concentration of API27 is varying between x-y%. Based on that, products with high API concentration should be paid more attention from wastewater point of view. The second highest API losses are for API23 and API37. But for those APIs, the annual API lost is below x kg. API37 belongs to vitamins, and risk assessments are not calculated for the vitamins. API losses per batch are highest for API22, API23, API31, API35 and API37. The higher API losses for those APIs are the result of the higher API concentration in the product.

Table 13 includes the estimated average daily discharges for APIs. Estimated average daily discharge is an average of minimum and maximum API discharges from manufactured batches. If estimated average daily discharges are compared to the maximum discharge limits, API22, API23, API26, API29, API31, API35 and API36 might have risk to the environment. However, the risk quotients have many uncertainties because all the RQ values for injection APIs are calculated by using the default PNEC value. The value is not usable for all APIs, because they might be a lipophilic and default PNEC value is usable only for APIs with $LogK_{ow}$ below 3. So, API22, API23, API26, API29, API31, API35 and API36 require more study about the ecotoxicity before it is possible to categorize it to any group of environmental risks. Before changes to the injection wastewater collection it is required to study more the APIs with possibility of environmental risk, because default PNEC value is used for all injection APIs and it is not suitable for all of them. After further risk assessment, that it is necessary to consider if some wastewater needs to be collected from the injection department. First-hand solution for minimizing API discharges is to collect manually rinsing water from the production of APIs with possible environmental risks. When more accurate risk assessment is done, further long-term solutions can be selected.

Table 13. Summary of the discharged APIs and risk quotients in the injection department. *=not calculated, belongs to vitamins.

API	Amount of cleaning campaign	Total loss (kg/y)	Estimated minimum daily discharge (kg/d)	Estimated maximum daily discharge (kg/d)	Estimated average daily discharge (kg/d)	Range of RQ chronic (µg/L)	Range of RQ acute (µg/L)	Average RQ chronic (µg/L)	Average RQ acute (µg/L)
API22	x	x	x	x	x	x	x	x	x
API23	x	x	x	x	x	x	x	x	x
API24	x	x	x	x	x	x	x	x	x
API25	x	x	x	x	x	x	x	x	x
API26	x	x	x	x	x	x	x	x	x
API27	x	x	x	x	x	x	x	x	x
API28	x	x	x	x	x	x	x	x	x
API29	x	x	x	x	x	x	x	x	x
API30	x	x	x	x	x	x	x	x	x
API31	x	x	x	x	x	x	x	x	x
API32	x	x	x	x	x	x	x	x	x
API33	x	x	x	x	x	x	x	x	x
API34	x	x	x	x	x	x	x	x	x
API35	x	x	x	x	x	x	x	x	x
API36	x	x	x	x	x	x	x	x	x
API37	x	x	x	x	x	x	x	x	x

Figure 31.

Figure 31. Risk quotient for discharges of injection APIs.

Suggestions for wastewater management and inventory system

Wastewater management

Figure 32 shows the comparison of annual API losses in different departments. It is easy to see that API losses of the tablet department are by far the highest. However, most of the lost API in tablet and inhalation departments are collected. API losses from injection are not collected. Even though the large amount of API losses are collected from the tablet department, figure 32 still indicates that the largest discharges come from there.

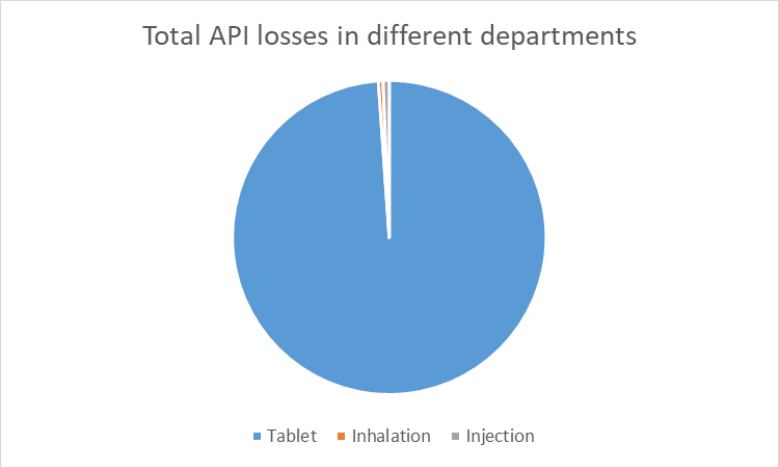

Figure 32. Comparison of annual API losses in different departments.

Dishwasher 9 room includes pre-rinsing areas for small tools and containers and the pass-through dishwasher, where after the granulation parts, e.g. containers, will be washed in the future. Currently, there is no wastewater collection in Dishwasher 9. By minimizing API discharges, it is necessary to plan the collection of the generated wastewater from this room according to calculated discharges. API losses from sieves and containers are approximately x kg/cleaning campaign. For several APIs of the tablet department the maximum daily discharge limit is x kg. By minimizing environmental risks of APIs, API residues should be vacuumed before washing or wastewater collection should be included to the Dishwasher 9 room. By planning cleaning actions in the Dishwasher 9 room, wastewater collection should be included in the pre-rinsing area for containers and vessels. If the wastewater will be collected from that drain, leftovers from the granulation and coating solutions can be disposed of in the same area. This also lowers risk of sewers blockage, if the leftovers are collected to the separate tank. Total API discharges from the weighing tools are approximately x g/y from inhalation APIs. All the annual API discharges are below the daily maximum API discharge limits, which means that wastewater collection of weighing tools is not required.

Inventory system

After calculating total losses of API for all departments, data is required to be in the form which is easy to utilize in other manufacturing plants. In this study, separate excel files have been done for each department. In the tablet department Granulator 1, Wet granulator 1, Granulator 2, Wet granulator 2 and Granulator 3 have their own Excel data sheets. Table 14 shows how the lost API is calculated. All data is collected from SAP software. By calculating "Total API lost to wastewater in mass manufacture process (kg)" value, it is required to calculate first API losses in the granulator and after the granulator unit processes according to the mass flows. When annual API losses for the tablet department are calculated, it is required to understand frequency of cleaning campaigns which defines type of the cleaning and the used cleaning program which defines amount of the generated wastewater and its collection. After calculations, discrete wastewater sampling is required for all granulators that it is possible to define the split factors for wastewater collection. After that PEC values can be calculated based on the estimation of daily discharges. With PEC and the PNEC values, RQ can be defined for all APIs. The used excel form is easily utilized also in other manufacturing plants, but raw material data of product is required to search manually from PI-sheets of SAP application.

Table 14. Required data from SAP PI-sheets to calculate the mass of lost APIs of mass manufacture unit process of the tablet department.

GRANULATOR	AFTER GRANULATION (sieve, containers)
Increased humidity, granulator (%)	-
Inflow API, granulator (kg)	Only for Product 3
Inflow additives, granulator (kg)	Inflow additives, after granulator (kg)
Total inflow, granulator (kg)	Total inflow, after granulator (kg)
Outflow, granulator (kg)	Total granules outflow (kg)
Accumulation, granulator (kg)	Accumulation, after granulator (kg)
API (%)	API (%)
API lost, granulator (kg)	API lost, after granulation (kg)
Total API lost to wastewater in mass manufacture process (kg)	
Cleaning type	-
Cleaning group	-
Collected wastewater	-
Non-collected wastewater	-
Annual API, granulator (kg)	Annual API, after granulator (kg)
Annual collected ww	
Annual non-collected ww	

For the inhalation department, mass manufacture and filling lines have their own data sheets. Table 15 shows the principle for mass calculation is quite similar for manufacturing and filling lines, differences are that mass manufacture line includes masses of raw materials and filling lines include produced mass as a residue instead of raw material masses. In the inhalation mass calculations, humidity of the manufactured mass is not included because liquid is not used in the manufacturing process.

In the injection department, the principle of lost API calculations follows the same forms that calculations in the inhalation mass manufacture process. At the beginning, the masses of the raw materials are calculated for total inflow value, and after the manufacturing process, accumulation is calculated by subtracted mass of the outflow from inflow value. Humidity of the product does not need to be taken into consideration, because the whole product is in the liquid form.

Table 15. Required data from SAP PI-sheets to calculate the mass of lost APIs of the inhalation department.

Mass manufacture	Filling line
Mass of lactose (kg)	Produced mass (kg)
Mass of API1 (kg)	
Total inflow/ theorethical mass (kg)	Used/filled mass (kg)
Total outflow/ real mass (kg)	Filling weigh (g)
Accumulation (kg)	Accumulation (kg)
API1 (%)	API1 (%)
API1 in loss (g)	API1 in loss (g)

After calculating the total losses, the results are presented in one table. According to the Table 1 results from Appendix 2, further risk assessment for the APIs in tablet and injection department is possible to calculate based on the data layout of the figure 33. RQ values for inhalation APIs are not needed, because almost all APIs are collected. When the maximum daily loss of APIs is defined, the PNEC and PEC values are required to find for each API. The PNEC and PEC values are defined for acute and chronic cases by writing estimated maximum daily discharge to the figure 33 Excel. According to the RQ values, maximum daily API discharge can be calculated. Figure 33 shows a possible tool where the name of the API is selected from the drop-down menu and the tool calculates the RQ values for different objects according to the API discharges in the manufactured process. With this tool, it is easy to see if there is environmental risk from the API discharges.

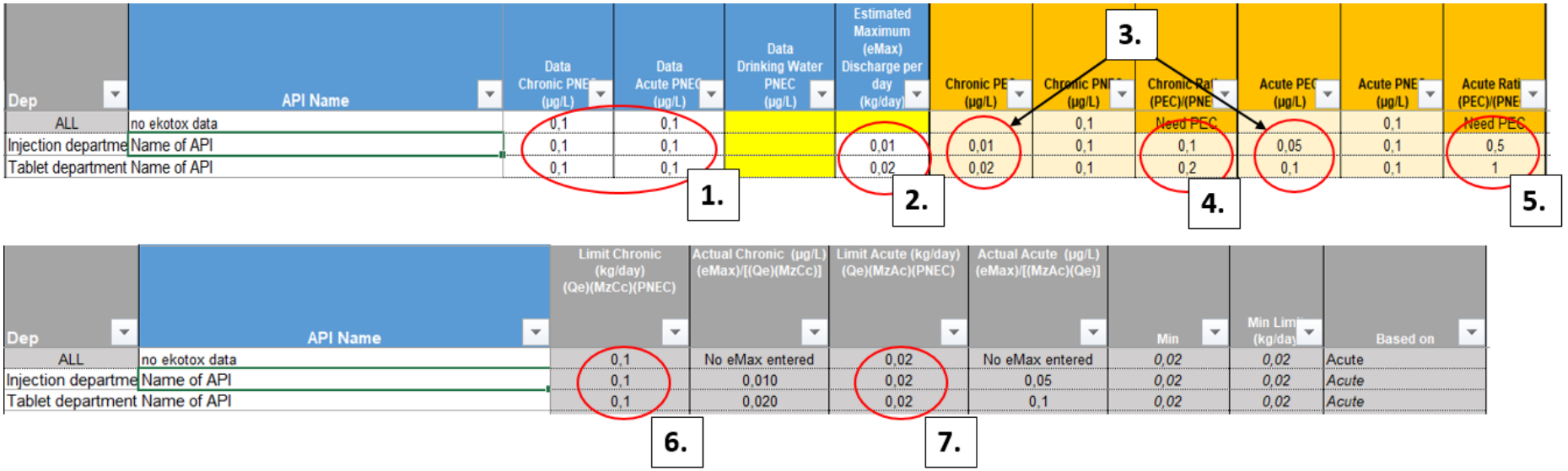

Figure 33. PSCI environmental risk assessment calculator based on the mass calculation of estimated daily discharge of APIs. 1. Insert PNEC values for acute and chronic areas, 2. Insert estimated max daily discharge of API, 3. Calculator calculates PEC values for acute and chronic areas based on the estimated max daily discharge, 4. Calculator calculates RQ for chronic area, 5. Calculator calculates RQ for acute area, 6. Calculator calculates maximum daily discharge limit for chronic area and 7. Calculator calculates maximum daily discharge limit for acute area.

Conclusions and implications

The amount and sources of the lost APIs

In the tablet department, the highest API losses are located in the mass-manufacturing process. If the wastewater collection split factor from the API4 sampling results is used in the discharge calculations, API losses from Granulator 1 and Wet granulator 1 are approximately x kg/campaign, where approximately x kg is discharged. API losses for the Granulator 2 and Wet granulator 2 are a x kg/cleaning campaign, where only x kg is discharged. For the Granulator 3, x kg of APIs is lost during one campaign, from which x kg is discharged. With that collection factor, it seems that rinsing of granulators is sufficient. API discharges from the containers and sieves are approximately x kg/cleaning campaign and APIs from that part of the process should be minimized by vacuuming API residues or collecting generated wastewater.

Because the API discharges are released pulse-like to the environment in accordance with production campaigns, the risk quotient value uses estimated daily discharges of APIs in the PEC calculations. Risk assessment was done for tablet APIs, based on the estimated daily discharges and the default or studied PNEC values. RQ values showed that API9, API12 and API15 might have a low risk to the environment in acute and chronic areas. However, the real environmental risk of API9 and API15 is smaller by the fact that these calculations do not take into account biodegradation during the wastewater treatment process. API19 might have medium environmental risk in acute area. Because the RQ calculations of some APIs use the default PNEC value, there are some uncertainties in the calculations. Searching for the PNEC values is difficult, because the PNEC values from computer modelling have no experimental data and several studies are also providing different PNEC values. In addition, the default PNEC value is not suitable for all APIs because it can not be used for lipophilic substances, antibiotics or hormones. Risk quotients for default values provide important information about the most problematic APIs, but the ecotoxicity and PNEC values require more studies before the risk values are fully reliable.

For the Granulator 3, sampling results showed that the original cleaning program discharges x g of API4 to the intermediate well. That is approximately x% of the maximum loss of API4 in one cleaning campaign. After the changes of the cleaning program, the amount of the discharged API was x g, which is x% of the maximum loss of API4 in one cleaning campaign. After changing the cleaning program, it was assumed that the API4 discharges

would decrease. Because the waiting time between the endpoint of the cleaning program and sampling was x hours shorter, the result of discharged API4 was unexpectedly higher despite the extra wastewater collection. Even though the discharge result was expected, it was proved that the sample can be taken after x hours of the endpoint of the cleaning program in the future. According to the RQ values, API4 maximum daily discharge limit is x kg. Currently for these losses of API4, x% of the API4 is allowed to discharge. So, based on that, this sampling method should be repeated for the original cleaning program with x hours waiting time for ensuring that the API discharge is still in the limits. Because this sampling method was done only for the Granulator 3, the same sampling procedure should be done for the most difficult-to-wash APIs, for example API19, for Granulator 1 and Granulator 2 by ensuring the wastewater collection split. Based on the mass calculations, sampling results and RQ values, it can be deduced that the original wastewater collection of the CIP cleaning processes of API4 mass is sufficient for these API losses. After further sampling it can be even considered, if it is possible to optimize the wastewater collection system. Optimization is important from the three point of views: pharmacovigilance, environmental and economy. The amount of the collected rinsing water should minimize the cost of the wastewater treatment and the environmental impacts without compromising the cleaning results.

In the inhalation department, it can be assumed by visual observation that almost all the API losses are collected to the separate wastewater tank. So, there is negligible risk to the environment from the API discharges of the production and filling lines. If total API losses without wastewater collection is compared with maximum daily discharge limits, it can be seen that the wastewater collection for inhalation department is important and a significant factor in minimizing environmental risks. In the current situation for the cleaning of inhalation production and filling lines is sufficient and no changes are needed. According to the API losses in the weighing washing area, API39 has the highest annual discharges, x g. By comparing annual discharge to the maximum daily API discharge limit, the annual discharge of inhalation APIs is smaller. Based on that, inhalation API discharges have a negligible risk to the environment and separate wastewater collection for weighing tools is not required.

In the injection department all the lost APIs are led to the intermediate well. Because APIs are dissolved to the injection products, losses of the API are annually rather small. The most problematic APIs are those whose concentration in the product exceeds x%. According to the risk quotient, the discharges of API22, API31 and API35 might have a risk to the environment. However, the risk quotient is calculated with default PNEC values, which may not be suitable for calculating the RQ value of those APIs. At least a few APIs are lipophilic and the $LogP_{ow}$ is above 3. Therefore, the ecotoxicity and the PNEC values for those APIs

should be studied and new RQ values calculated for API22, API31 and API35. Before the calculation of new RQ values, pre-rinsing water from the cleaning processes of products with API22, API31 and API35 can be manually collected. Also, the environmental risk from methylene blue should be taken into account in the environmental risk assessment. When more accurate RQ values are available, it can be considered if some long-term changes for the wastewater collection are needed.

Sampling

In this study, the discrete sampling method was used. With discrete samples it is easy to compare API levels before and after the cleaning process by taking samples from the intermediate well where process wastewater streams are led. By analyzing simple samples, the amount of API discharge is easy to calculate from the change of the concentration. With this method it is possible to study the split factor between collected and non-collected wastewater, which can be included in the estimated daily discharge calculations. But this sampling method also has its disadvantages. Because the schedule of the production is very hectic, timing of the sampling lives all the time. The problem is that production is three-shift work and usually people who are taking samples from the intermediate well are working only during the day. If the time between the end point of the cleaning process and sampling of the after cleaning should be constant, it is too difficult to obtain a sampling procedure every time in the same way. It is also a challenge to schedule sampling, because wastewater is led through the long pipelines and production wastewater pumping station to the intermediate well. It is difficult to know when the wastewater is in the intermediate well, because the flow meter is not available and there are several other cleaning actions running at the same time in the manufacturing plant. Even though the timing of the sampling is challenging, this study proves that x hours is a sufficient time to obtain wastewater to the intermediate well.

The optimal situation could be that the online probe is measuring data from the wastewater and based on the data, the probe sends an automatic message for valves by controlling wastewater collection, but that is far away from the current off-line method situation. By obtaining better data from the quality of wastewater, the sample should be taken from the wastewater of each granulators. Sampling can be done for the most difficult-to-wash APIs. By this way, it is possible to define split factors of wastewater collection for all granulators and find API discharge sources if some rinsing phase of the cleaning program is not sufficient. After the risk assessment of all APIs, quality of wastewater requires monitoring by ensuring the function of the wastewater system. For long-term monitoring of wastewater,

composite sampling from the intermediate well is a better option because then multiple cleaning processes may be included in the sampling instead of one cleaning process. It will better describe the wastewater quality for the manufacturing plant.

Wastewater management and suggestions for the future

The next step is to find reliable PNEC values for tablet and injection APIs in the production. After having those values, a more accurate RQ value is possible to calculate for all APIs. When RQ values are calculated for the APIs of the tablet department, discrete samples from the intermediate well should be taken for the most difficult-to-wash APIs with x hours waiting time. Then the study based daily discharge limits are possible to calculate for APIs with the wastewater collection split factor of granulators. After these phases, it can be ensured that the collection of wastewater is at a sufficient level in the cleaning of granulators. In the injection department, the need of the wastewater collection can be solved when RQ values are calculated with new PNEC values. If environmental risks are observed, then the collection of pre-rinsing phases should be included in the cleaning processes.

After the study of the API discharge limits, the quality of the generated wastewater is known. If the company is interested in the at-site pretreatment process of the API wastewaters, the cleaning techniques require a lot of studying because APIs can decompose during the process into even the most harmful compounds. The reaction routes of all APIs in the wastewater is important to understand. After studying the reaction routes of APIs, it is inevitable that all wastewater treatment technologies are not suitable for all APIs, for example UV treatment for quetiapine is not sufficient. It is an optimal situation that the company could treat concentrated API wastewater at-source and reduce CO_2 emissions, but that project requires great desire for investment from the company. However, it might become more economically viable to treat a sufficiently large amount of wastewater at-source treatment than transporting wastewater to the third-party company for treatment.

Even though the pharmaceutical industry is seen as a polluter of the environment, it is good to remember that only 2% of European API discharges comes from the pharmaceutical manufacturing processes. The potential point sources are good to be highly regulated but if the protection of the environment is the most important thing, maybe it could be better to think how to deal with the rest of 98% API discharges.

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Appendix

Appendix 1. Calculations of the API discharges from the coating process.

After the coating process of the Product 1 tablet, a sample was taken from the pre-rinsing water in the coating drum. x liters of pre-rinsing water was left inside the equipment and it was mixed. After mixing, x L sample was taken and analyzed in the external laboratory. Concentration of API7 was x mg/L, which means that x L pre-rinsing water includes y mg of API7. One tablet includes x mg of API7.

According to the sample results, API discharges are corresponding to the concentration of x-y tablets. Based on the results, there is no need to collect wastewater from the coating process.

Appendix 2. Total API losses from the tablet and injection departments.

Table 1. Total losses, discharges and discharge limits for tablet and injection APIs.

API	Number of cleaning campaigns	Total loss (kg/y)	Estimated average daily discharge (kg/d)	Max daily discharce limit (kg/d)
Tablet department				
x	x	x	x	x
Injection department				
x	x	x	x	x