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MASTER THESIS

DEVELOPMENT OF A QUALITY RISK MANAGEMENT METHOD FOR RISK ASSESSMENT IN CONTINUOUS MANUFACTURING PROCESS DESIGN

SUBMITTED BY:

DOMINIK NENDWICH, BSC

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AO.UNIV.PROF. DIPL.-ING. DR.NAT.TECHN. KAROLA VORAUER-UHL

INSTITUTE OF BIOPROCESS SCIENCE AND ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

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ABSTRACT

Production of biopharmaceuticals such as monoclonal antibodies continuously meet novel challenges in the shape of higher demand for flexibility and productivity all while consistently maintaining the highest level of product quality and efficacy. Established production typically relies on the well-known but rigid batch structure, which is notoriously cautious with rash adaption. Newer technologies like integrated continuous manufacturing are emerging but suffer from high research and development expenses due to their complexity.

Within this thesis, an ICH Q9 compliant qualitative risk assessment method was developed in order to support design decisions for the development of an integrated continuous manufacturing process. It is comprised of parts of various, well-established quality management tools and puts them in an innovative yet specific order, with each step still being flexible and adaptive to process available data. This approach enables risk detection and evaluation in early stages of process development, simultaneously identifying abstract considerations which are rarely included in traditional process development.

The method offers a sophisticated way to support process development by providing a profound basis for risk mitigation, consequently increasing process understanding even before prototype production which reduces overall development costs.

Die Produktion von Biopharmazeutika wie monoklonalen Antikörpern wird immer wieder vor neuen Herausforderungen wie die Erhöhung von Flexibilität und Produktivität bei gleichbleibend hoher Produktqualität und -wirksamkeit gestellt. Die etablierte Produktionsart ist die in der Regel weit verbreitete chargenmäßige Produktion, welche beim Thema Prozessanpassung notorisch zurückhaltend ist. Dennoch sind notwendige neue Technologien wie integrierte kontinuierliche Herstellungsprozesse auf dem Vormarsch, leiden aber aufgrund ihrer Komplexität aktuell unter hohen Forschungs- und Entwicklungskosten.

Im Rahmen dieser Arbeit wurde eine ICH Q9 konforme qualitative Risikobewertungsmethode entwickelt, um Designentscheidungen für die Entwicklung eines integrierten kontinuierlichen Herstellungsprozesses zu unterstützen. Sie setzt sich aus Teilen verschiedener bereits etablierter Qualitätsmanagement-Tools zusammen und bringt diese in eine innovative aber spezifische Reihenfolge, wobei jeder Schritt flexibel an die verfügbaren Prozessdaten anpassbar ist. Dieser Ansatz ermöglicht die Erkennung und Bewertung von Risiken in frühen Stadien der Prozessentwicklung. Es werden abstrakte Überlegungen sichtbar gemacht und einbezogen, was in der traditionellen Prozessentwicklung nicht der Fall ist.

Die Methode bietet eine ausgefeilte Möglichkeit zur Unterstützung der Prozessentwicklung, indem sie eine fundierte Grundlage für Risikominderung schafft und somit das Prozessverständnis noch vor der Prototypenfertigung verbessert, was schlussendlich die Gesamtentwicklungskosten senkt.

SUMMARY

Historically risk management is a rather young discipline when compared to general quality management, with authorities identifying its potential roughly sixty years after QM development. All biotechnological manufacturing processes (new and already established) now must undergo a risk-based assessment, often facilitated by various tools that ease risk determination, evaluation and mitigation based on available real-life process information and data to ultimately achieve regulatory compliance.

In this study, a method comprised of parts of different risk management tools has been created to facilitate risk-based decision-making during early stages of process development. Including risk-based decisions as early as possible achieves significant advantages like reduced R&D costs, improved process understanding, or incorporation of risk-related regulatory requirements. The latter having an impact on later stages of process development like qualification and verification.

Its ICH Q9 compliant core procedure is designed to be adaptable and not only supports processes in development but can also be used to assess risk of already established manufacturing processes.

The qualitative method has been tested in early developmental stages of an integrated continuous manufacturing process, yielding an overview of potential risks, usable as a sophisticated and cheap basis for mitigation strategies and process adaptions.

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1 INTRODUCTION

Amidst the last century's worst pandemic in the form of the SARS-CoV-2 virus, a global race to provide sufficient protection against the prevalent respiratory danger emerged, with pharmaceutical companies in the lead role as manufacturers of efficient vaccines against the virus [1]. On the global scale, with circa 7.8 billion people worldwide [2] and around 75 % being above 14 years old, a total of roughly 11.7 billion doses are required to fully vaccinate everyone considering typically two shots to reach immunity. This constitutes an immense task for the pharmaceutical field in the sense of flexibility, output demand, time, and product safety, all while maintaining their established product portfolio.

Research and Development (R&D) costs to bring a new drug to the market is estimated to be up to $2.8 billion [3] in 2016, and most likely even higher today due to the noticeable upward trend [4] which is priced into the finished product [5], therefore more expensive for the end user or the countries health care system. From a pharmaceutical plant perspective however, R&D is not the costliest part of drug production. In 2006, it constituted merely 12 % of overall expenses, whereas manufacturing equipment and tools make up around 8 % [6] in comparison. Although it might not seem much in relation, innovations and improvements in these sections do have potential to significantly reduce expenditures and therefore lower product price.

One of these innovations is continuous manufacturing which is already used in numerous industrial fields [7], yet still faces various challenges [8-9] prior to extensive adaption in the pharmaceutical sector. Possibilities for reduction of cost of goods per gram (COG/g) [10] have been shown, and further developments in this field will certainly increase transition to continuous processes.

This thesis was conducted to support development of an innovative integrated continuous manufacturing process: a fully automated end-to-end (E2E) process

combining up- and downstream into one device. This device is designed to serve as a flexible but blank canvas, which can be adapted to manufacture individual compounds using various microorganisms; whatever the customer desires. It is expected to significantly reduce operational (OPEX) and capital expenditures (CAPEX) for the pharmaceutical companies using this technology. Relief in the form of sophisticated automation of process control and therefore reducing manual intervention is expected to have positive impact on OPEX, whereas combining numerous assets used for batch production into one, consequently reducing the required spatial footprint tremendously, is expected to reduce CAPEX.

Process development was supported by the generation of a quality management (QM) method, which allows for substantiated risk-based decision making. It is comprised of different aspects from other, well-established quality management tools, combining them in a new and innovative way to combine risk assessment, control, and analysis into one procedure. A risk-based approach has been chosen because regulatory entities indicate in draft guidance that risk management will be needed for continuous manufacturing [11-14] as it is required and universally applied for any other manufacturing process in the pharmaceutical field [15-17], yet no official legally effective versions have been published. The method is adaptive to the type of data available and can be further evolved to meet the users demands.

Risk can be assessed in numerous different ways, mostly dependent on process type, data quality and level of detail. It can be assessed quantitatively and qualitatively, where neither has a distinct advantage over the other, it merely comes down to what the user wants to achieve: a quantitative assessment focusses on measurable and often pre-defined data, whereas a qualitative risk assessment is based more so on subjectivity and the knowledge of the assessor(s).

The developed method uses a qualitative approach in its core to effortlessly counterbalance inexperience, as process development is performed by a team that is mostly proficient with discontinuous processes. Trial application showed it was able

to support risk assessment satisfactorily by pointing out high-risk areas most probable of causing process termination or undesired product composition.

Finally, the thesis discusses future applications and possible adaptions of the method, and its possible role in industrial quality management.

1.1 STRUCTURE OF THE RISK ASSESSMENT METHOD

At its core, the method follows the traditional sequence described in ICH guideline Q9 (Figure 1): initial risk assessment subdivided into risk identification, analysis, and evaluation, followed by risk control subdivided into risk reduction and acceptance, concluded by risk review. An unacceptable conclusion during each step leads to a re-evaluation of the previous one until a whole cycle is completed and approved.

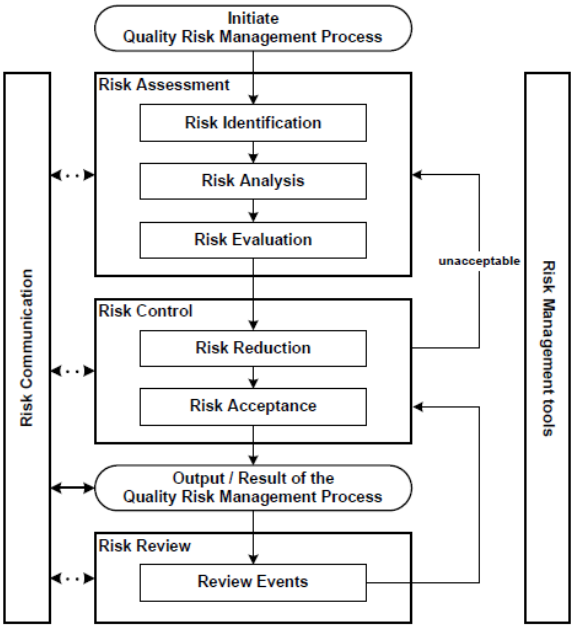

Figure 1: Overview of a typical quality risk management process as depicted in ICH Q9.

For risk identification, the method uses an established quality management tool: the Structured What-If technique (SWIFT) [18]. This flexible, high-level identification tool allows for generation of process related data in a brainstorming-like fashion by going through different hypothetical scenarios and determining their consequences. A fault-tree analysis-like (FTA) approach is used to bundle scenarios contributing to

a pre-defined undesired event, resulting in so-called nodes which all contributed to the undesired top-level event.

Risk analysis and evaluation are performed on each node by qualitative determination of four risk parameters which are rated using a pre-defined risk matrix and subsequently condensed into an overall risk score. This step is supported by a bowtie analysis-like graphical representation of each node, facilitating an overview of which scenarios it is comprised of, and how the process is already able to counteract them.

Findings were composed into an end report highlighting and describing nodes with the highest potential risk in detail. This report also contained recommendations to reduce risk of these nodes, serving as a basis for mitigation strategies which are agreed upon outside of this risk assessment process. The method can be performed again, after adaption of the process, for comparison to see if the chosen mitigation strategy was successful in reducing risk.

1.1.1 INNOVATION INCLUDED

A big advantage of the developed method is its flexibility and capability to condense down complex interactions, which are abundantly present in a pharmaceutical continuous manufacturing process. The method is designed to allow high-level risk identification but can also be used to narrow down onto a certain area of the process, identifying risks on a much more detailed level, without changes to the overall procedure.

Per definition, risk is a combination of the severity of a harm and its likeliness of occurrence, sometimes including detectability of a harm too. Additionally, the developed method extends this definition by introduction of another layer in the form of a new risk parameter termed “complexity”. It is a qualitative value of how much influence a certain event (or node) has on the overall process, and how complex consequences or their mitigation might be.

Traditionally, established risk management methods limit themselves to certain aspects of the whole sequence described in ICH Q9. It is up to the operator to choose which tool to use, depending on a few extrinsic factors like data quality or target object.

1.1.2 A TEAM EFFORT

The assessment method must be performed by a team to reduce single person bias while increasing the chance to cover more topics, as the core of data generation is a brainstorming activity. The most experienced person with the method serves as the facilitator, while other participants should be people with process knowledge and understanding.

Method testing has been performed by the author of this thesis as the facilitator, and several members of the development team, who design and work on the continuous manufacturing process. Specialists regarding the upstream as well as the first downstream subunit participated, supported by the project lead.

1.2 INTEGRATED E2E PROCESS CONCEPT

The continuous manufacturing process in development is designed to serve as an adaptive production device capable of hosting different microorganisms producing diverse products. The finished device will be able to flexibly change between production processes, individually tailored to customer needs and expectations.

The process is comprised of three main units: the cell culture unit which includes a perfusion reactor and a cell retention device, followed by the capture unit, which includes matrix exchange and product capture, and the polishing unit, which concentrates the product, removes unwanted viral particles, and is designed to yield the end-product formulation.

The first subunit is responsible for the upstream part of a biotechnological manufacturing process. It is based on a perfusion process reactor [19] wherein produced cells are continuously separated from process liquid via alternating flow filtration (ATF). Retained cells are subsequently recycled to the reactor to resume

biomass production. The upstream process is subdivided into three distinct phases: batch, ramp-up and perfusion. The first is a traditional cell growth process where a pre-defined amount of media is inoculated to reach a desired amount of biomass. It is followed by a time and substrate limited ramp-up phase aiming to accelerate cell growth into exponential regions, which is then maintained over 30 days in the perfusion phase. The last phase requires continuous addition of substrate material and constant process control. Part of the resulting product containing process liquid is continuously pumped into the second subunit where the components are separated from each other. Addition of new substrate into the reactor is in equal parts as the removed material to maintain a steady state. Product is then precipitated in the first part of the capture unit, and all unwanted process liquid components are successively removed by filtration using three hollow fiber modules. The product is then resolubilized via a change in pH and transported to the last subunit, where necessary polishing steps for a pharmaceutical component are performed: virus inactivation, product concentration and final removal of unwanted constituents.

Control of the process is achieved by a custom-made internal software, designed to control all areas of the process. It is capable of fully automated process monitoring by controlling every valve, pump, inlet, outlet, et cetera of the device.

1.3 REGULATORY CONSIDERATIONS

In February of 2019, the Food and Drug Administration (FDA), a subsidiary of the U.S. Department of Health and Human Services was the first regulatory entity to release a draft guidance on continuous manufacturing of small molecule, solid oral drug products that are regulated by the Center for Drug Evaluation and Research (CDER) called “Quality Considerations for Continuous Manufacturing”. Within this draft document, the FDA summarizes their current view on continuous manufacturing.

The guidance document covers many important topics for continuous pharmaceutical production processes to consider like batch definition, sampling,

quality control, and raw material control, especially focusing on aspects which differ from classic discontinuous production. As an example, batch definition is something completely different: in a classic production scenario, a defined and known quantity of (intermediate) product can be produced within one production run using a defined amount of raw materials, after which everything is cleaned, reset, and prepared for a new run. This produced quantity is considered a batch and given a unique identification number (lot number). When producing continuously, a batch must be defined accordingly to trace exactly when it was produced using which material. FDA recommends defining batches either by time frame or amount of material used.

In July of 2021, the European Medicines Agency (EMA) released their guidance draft version considering continuous manufacturing, covering many topics analogical to the FDA. Both regulatory entities highlight the importance of sophisticated process understanding and control to assure product quality and safety. Other entities like Japan's Pharmaceuticals and Medical Devices Agency (PMDA) did recognize the potential of continuous manufacturing but are yet to release a draft guideline, whereas further like China's National Medical Products Administration (NMPA) have not released any information on this topic to date.

1.3.1 Influence on the method

Not many aspects from the regulatory guidelines and outlooks could be considered for the development of the risk assessment method. The fact that it is a risk-based method is the extent of it, as all other aspects described in the guidelines require a much more developed state of the manufacturing process, as well as more sophisticated process data which both were not available at the time. However, future regulatory considerations are discussed in more detail in chapter 5.3.3.

2 OBJECTIVE

Development of new and innovative biopharmaceutical manufacturing processes is a huge financial and time-wise endeavor. Alleviations in any form are sought-after commodities enabling companies to pioneer into new fields, thus gaining a competitive edge. Earliest introduction of risk management is one of these advantageous alleviations as it, independent of progress, supports development by swiftly identifying suboptimal process areas without much expenditure. Adaptions to the process can be done quick, simple, and without any additional costs which is inherently a huge advantage compared to traditional process designs where flaws were often found after manufacture of an expensive prototype. Any adaption at this stage is much more costly and thus undesirable.

Aim of this thesis was to develop a quality management method that supports process development by means of risk assessment independent of design progression. Subsequently, the method was to be tested on a continuous manufacturing process still in development for its capability to support risk assessment and design adaption decision-making. The following objectives were to be attained:

- Development of a regulatory compliant risk assessment method to support early development of a continuous manufacturing process.
- Application of the risk assessment method and determination of potential risks for a continuous manufacturing process in early development.
- Proposition of risk mitigation strategies based on the obtained risk assessment.

3 METHODOLOGY

3.1 THE PROCEDURE

The methods procedure is related to the traditional sequence described in ICH Q9 and follows its logical progression to structurally analyse the target process. For each step, a different QM tool was carefully chosen to generate suitable data which can be progressively used to in the end achieve understanding of the process' risk situation. Figure 2 shows the direct comparison between procedures in ICH Q9 and this thesis.

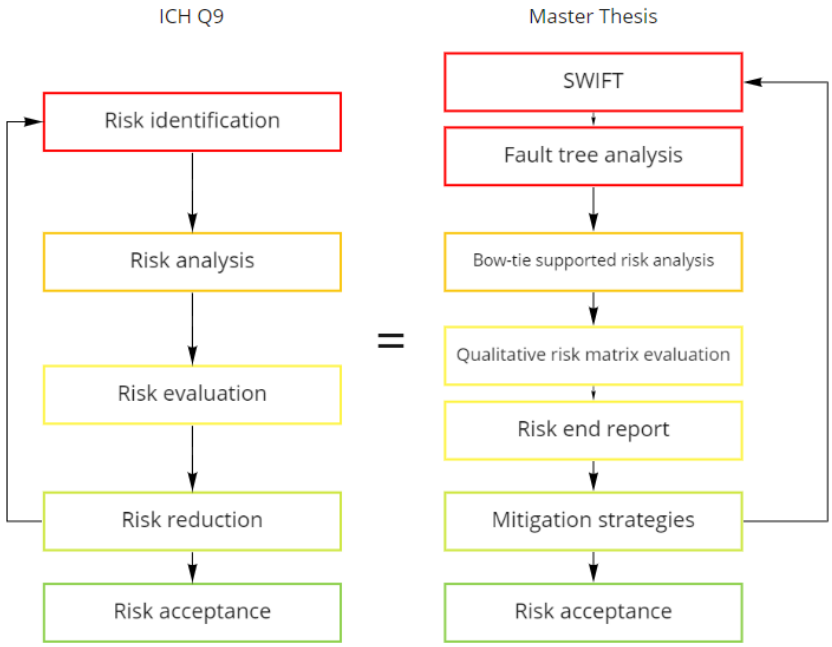

Figure 2: Sequence of the newly developed risk assessment method, in comparison to the established sequence described in ICH Q9. The overall procedure as depicted in Figure 1 was not altered but interpreted in an innovative, new way.

One person most familiar with the method is filling the role of assessment facilitator and leads the rest of the team through the process. He or she is responsible to ask questions during brainstorming activities, while also guiding the team without disrupting creative inputs, yet keeping the team on track as otherwise discussions tend to take up a lot of time. The team, consisting of process experts or experts of process subunits knowledgeable in the overall process or parts of it, is responsible to

answer questions as unbiased as possible. The final risk assigned to each node (see chapter 3.4) created during the methods process is agreed upon as a team. The author of this thesis took over the role of risk assessment facilitator for the method test run.

3.1.1 ESTABLISHING BOUNDARIES

Before this method can be performed, it is important to agree upon restrictive boundaries. The method cannot be performed in an everchanging setting but must be limited to a defined (intermediate) version of the process. This is done to prevent confusion during brainstorming, but also to ease risk estimation.

The following boundaries were agreed upon:

- The device is in a clean and sterile state at process start.
- The manufacturing process runs for 30 days straight.
- Cleaning takes place after whole process finish, and no parallel cleaning or sterilization of subunits occur when they finish.
- The polishing unit is omitted from the assessment. The observed process ends after the last capture unit step.
- Scenario influence is considered both on a single subunit as well as on an overall process basis.
- Reactor process control can automatically monitor upstream parameters and react accordingly to keep the process stable.
- Composition of the added media and inoculum is always considered correct (i.e.: material failures are impossible and omitted).

3.2 RISK ASSESSMENT MATRIX

One of the definitions of risk is that it is the probability of occurrence of harm combined with the severity of that harm [16]. Both values, severity and occurrence, need to be characterized in some way, either quantitatively using numbers or qualitatively using descriptions. To extent on that, more parameters can be considered to refine risk evaluation. For example, detectability as a value of how well

the harm can be discovered. In this thesis the parameter “complexity” is newly introduced, seen as a value of how much influence is exerted on the process and in what extent. In other words, the more areas of the process are influenced, and the more sophisticated countermeasures are necessary, the higher the complexity.

Each parameter must be subdivided into values of increasing magnitude. In the case of a quantitative risk assessment, these can be value ranges (often between 1 to 10), while for qualitative risk assessment a specification for each value is used; most commonly “low”, “medium”, and “high”. The degree of subdivision can be chosen individually but should be defined and agreed-upon by the team that facilitates the risk assessment. In this thesis, the contribution of four different parameters towards the overall risk were determined:

- Severity: A measure of how fatal the consequences of an event are, and how quick they arise. This parameter also includes consideration of the safety measures that are activated once an event occurred (= recovery safeguards).
- Detectability: A measure of how reliable (i.e.: automated) an event can be detected by the system control. This parameter also includes consideration of the safety measures that are active to prevent the event from initially happening (= prevention safeguards).
- Complexity: A measure of how many process subunits are influenced by the event, and from how many sources the event can arise.
- Occurrence: A measure of how often the event can occur.

Table 1 shows definitions of each parameter and its different magnitudes.

Table 1: Risk parameters and definitions of their subdivisions.

Parameter	Value		
	Low	**Medium**	**High**
Severity	Minor distress on the process, safeguards can recover from the issue automatically without much influence on the process. Process can continue	Medium distress on the process. Deviation procedures are necessary to keep process running. Aid from recovery safeguards is limited	High influence on the process. High chance for process termination or product quality impact when consequences arise. Safeguards are not sufficient or not existing
Detectability	The problem can be detected immediately, and safeguards can react to it. Very low chance for being undetected. Redundancies are established	The problem is not immediately identified but merely detected. The final root cause can be found after additional investigation. Safeguards are established, but might lack an automatic response	Problem is not detected or has a very low chance of being detected. Additional manual control is required, as the system does not detect the problem from deviating values alone
Complexity	Consequence can be narrowed down to one to two different process steps. Originates from one subunit only	Consequence can arise at a few parts of the process, and influence more than one of the two main subunits	Same consequence can arise at almost any stage of the process and influences many different aspects of it. (Does not necessary correlate with severity)
Occurrence	<10 %	10 - 50 %	>50 %

Severity and detectability were weighted more, as data and knowledge about safeguards supported a more sophisticated estimation of contribution towards the overall risk. Occurrence was rated the weakest, as it remained an assumption without data from repeated actual process runs. Each parameter was subdivided into “low”, “medium” and “high”, each one representing an increased magnitude compared to the previous one. The uneven weighting distribution can be seen in Figure 4 wherein the matrix is not symmetric, resulting in a more conservative risk estimation.

Safeguards were rated better if a high degree of automation was already achieved. Provided that an event could be prevented completely by automated detection and mitigation, the corresponding safeguard was rated satisfactory. Consequently, prevention or recovery actions that required manual input were rated lowest.

The four risk parameters are subsequently related using a matrix approach. However, in a 2D depiction, only two values can be related at once. A tiered approach was developed, which defines one value as constant while keeping two others variable, allowing for combination of three values. The resulting intermediate risk value is subsequently related to the last parameter in a second matrix, yielding the overall risk. The matrices in Figure 3 were pre-defined by the team, assigning each parameter combination to an overall risk value of either low, medium, or high magnitude.

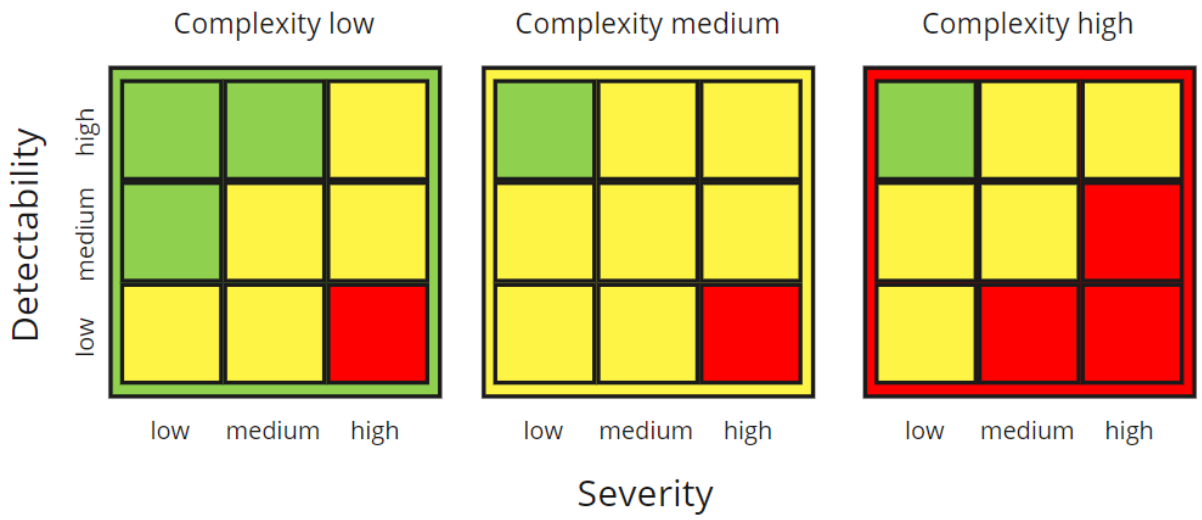

Figure 3: Combination of three risk parameters to yield an intermediate risk value. Its value is dependent on the color: green = low, yellow = medium and red = high. The fixed magnitude of complexity is indicated by the colored frame and varies with each matrix (left to right): low, medium, and high.

For example, the leftmost (green) tile in the first row of the center matrix corresponds to a high detectability, low severity, and medium complexity. The intermediate risk (low) is then related to the occurrence by another matrix depicted in Figure 4 using the same approach.

It is possible to omit the consideration of occurrence risk due to its minor significance in early stages of process development, however it was still considered during the performed test of the method.

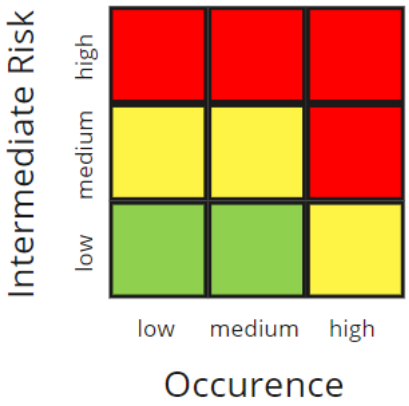

Figure 4: Final risk assessment matrix correlating all four risk parameters with each other. The overall risk is indicated by the colored tiles: green = low, yellow = medium, red = high.

It is for the risk management team to decide which level of risk is acceptable beforehand, as this threshold is later required to differentiate the obtained method's results. In this thesis, risks with the same overall risk value were further differentiated by their severity parameter risk value, ranked from high severity to low severity. In other words, an overall medium risk with a high severity parameter risk value was considered of higher magnitude than an overall medium risk with a medium or low severity parameter risk value. The reason for this more delicate differentiation is discussed in chapter 5.1.3. During the method trial run, the team decided that high risk was unacceptable, whereas medium and low risks were not considered a threat.

3.3 Creating a database

No process can be evaluated just by looking at it. Data is required to perform a substantiated risk assessment. Depending on the quality and abundance of this data, fitting quality management tools can be chosen to evaluate risk. A SWIFT analysis [18] was chosen as the basis and risk identification (i.e.: data generation) tool of the whole method to support a wide range of pre-existing data situations.

SWIFT is a brainstorming activity where a facilitator asks the participating team of experts numerous “What if…?” questions regarding process related scenarios, trying to proactively predict their consequences and safety measures preventing them. A typical question followed the formula: “What if + guideword + deviation?”. Table 2 shows used guidewords and deviations. As an example, using the first guideword “Inoculum” and the first deviation “Too soon” results in the question: “What if the inoculum is added too soon to the process?”, which then requires the team to think about, and answer this specific scenario. Furthermore, the team envisions what consequences might arise from this deviation, and how the process is already able to prevent them. They not only need to think about how this scenario cannot occur in the first place, but also how the process control can react to it if it does. The team must eventually agree on each answer: different opinions are discussed, but a consensus must be found.

Table 2: Guidewords and deviations used in the SWIFT question process.

Guidewords			
Air/NO_2/O_2	Batch medium	Perfusion medium	Resolubilization buffer
Antifoam	Equipment	Precipitation buffer	Software
ATF	Hollow fiber module	Ramp-up medium	Tubular reactor
Base	Inoculum	Bioreactor	Wash buffer
Deviations			
Too soon	Too late	Too high	Too low
Missing	Twice / repeated	Out of sequence	

Because boundaries are agreed upon beforehand, the facilitator can guide the team away from estimating consequences or safeguards in case they take planned alterations into account. A safeguard that is not present in the version of the process that is assessed is considered non-existent, even if the implementation is already planned.

3.4 GROUPING OF DATA

The SWIFT process yields a fairly large amount of scenarios, their consequences, and safeguards. It is in the nature of the tool that redundancies or impossibilities occur (e.g.: the same consequence can have various origins) which must be resolved before further risk evaluation. It is up to the team if logically impossible scenarios, i.e.: unreasonable guideword and deviation combinations, are omitted from discussion or if they are discussed but omitted from further investigation. No informational gain can be expected from analysing these scenarios.

Data clarification is achieved by using another quality management tool: the fault tree analysis (FTA) [17]. This technique can identify and analyse factors that contribute towards an undesired event called the “top-event”. In other words, all scenarios are linkable towards one (or more) top events.

In a next step, the imminent causes for the top-event are added and linked to the top-event in a hierarchical order using AND, and OR logic gates. Each cause is then analysed in the same manner, until further division becomes cumbersome (i.e.: level of detail becomes too high). The finished result is a tree-like diagram, with the most basic causes on the ground level (from here on called “nodes”). Each scenario from the SWIFT can now be attributed to one of these ground-level nodes based on their individual threat and consequence for the process.

During application of the method, two top events were defined by the team; they were deliberately kept on a general level:

- Process termination: This top event describes any form of technical issue that leads to process disruption where continuation is not possible.
- Insufficient product composition: This top event includes any qualitative alteration of the end-product material composition, i.e.: any form of undesired impurity present in the liquid leaving the device.

3.5 SUPPORTED NODE ANALYSIS

Grouping of scenarios consequently allowed risk evaluation to become a manageable endeavor. Each node is analysed, the four risk parameters described in chapter 3.2 are determined, and subsequently combined into a single overall risk for each node. This step needs to be performed as a team effort, as each member needs to agree on the risk magnitude for every parameter and node. Discussions are welcome but should not take up exceeding time, so to remain productive.

To facilitate decision making for severity and detectability risk parameters, a graphical quality management tool was included into the process: the bow tie analysis [17]. This tool is traditionally used to depict pathways from causes of an event towards their consequences in a bow tie like fashion, with the target event as the central knot. In between threat and event there are prevention safeguards depicted: countermeasures which prevent the event from happening. Between the central event knot and the consequences are recovery safeguards: countermeasures that prevent the consequences from happening in case an event occurrence was not avertable.

The bow tie diagram was used so that the FTA node is placed as the central knot, with corresponding threats, prevention and recovery safeguards, and consequences from the initial SWIFT step included. The original bow tie diagram would show consequences on the rightmost side, whereas the adjusted version substitutes them for the hierarchical higher-level event from the FTA analysis (i.e.: one step closer to the top-level event) to form a bridge between the tools, creating a logical connection.

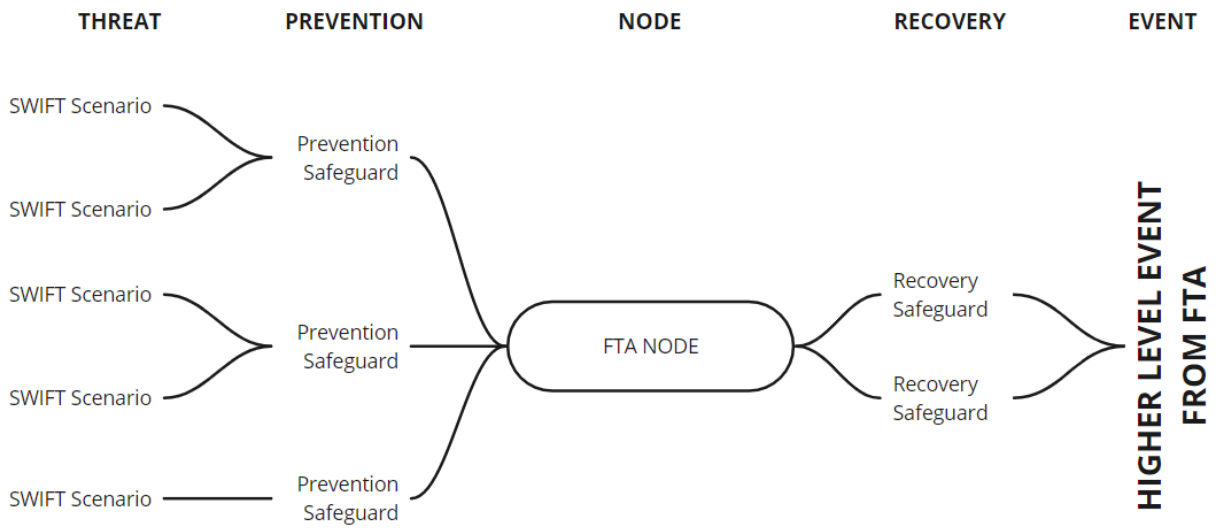

Figure 5: Template of a Bow tie diagram used in the risk assessment method. Threats from each node-related SWIFT scenario are on the leftmost side, followed by their corresponding prevention safeguards. The investigated FTA node is the central knot, followed by recovery safeguards which connect the node and its higher-level FTA event.

This visualization allows for a more sophisticated estimation of severity and detectability risk parameters, since they are directly related to safeguards as described in Table 1. The extent and quality of prevention and/or recovery safeguards can be seen much more clearly via this diagram. Each risk parameter is consecutively defined for each node and evaluated using the risk matrices in Figure 3 and Figure 4 to yield an overall risk value for each node.

3.6 AGGREGATION OF EVERYTHING – THE END REPORT

Preparation of all acquired data into a clear and presentable end report, serving as a basis for stakeholder decisions regarding sequential process adaptions and mitigations is recommended. The report's goal is to present and explain the applied method and its components on a broader level for people not included in the procedure to comprehensibly show how risk values and therefore the process hot spots were obtained.

Conduction of an end report is not necessarily part of the developed risk assessment method, as the facilitators can freely choose how to present their

acquired results. Typically, corporations have established policies or standards, muting considerations on how to present the risk assessment.

After the method test, an end report in the form of a typical corporate report was compiled, where each node is individually listed to keep track of all team decisions on individual risk parameters. Tool explanations, an executive summary and high-level risk mitigation strategy recommendations were included as well. As it is comprised of data described and discussed extensively throughout the thesis, it is of no added informational value and therefore excluded.

4 RESULTS

4.1 THE METHOD

Successful development of a novel risk assessment method was achieved, taking recommendations from drafted regulatory guidelines of established entities into consideration. The method is designed to be flexible and adaptive towards the target process and can adjust to various levels of process data details.

In a team, risk is determined qualitatively by combination of up to four different risk parameters, each evaluated for every identified group of threatening events (= node, see chapter 3.4). Due to the continuous integrated nature of the target manufacturing process, a novel risk parameter called complexity, as part of the four total parameters, was introduced to take complex interactions within the process into account.

4.2 RISK ASSESSMENT APPLICATION

Detailed results from the intermediate SWIFT and FTA analyses steps can be found in appendix chapters 7.2.1 and 7.2.2 respectively. The target process was compiled in numerous descriptive nodes, corresponding to various potential threats the process could face. Consequently, all nodes were assessed using the agreed-upon risk matrix. Detailed results can be found in appendix chapter 7.2.3. In total, four nodes were found to be of high risk to the target process:

- Handling mistakes that can lead to decreased cell growth
- Handling mistakes that can lead to contamination
- Pump malfunctions that can lead to capture unit process volume falling below working volume
- ATF system filter blocking due to decreased cell viability

The first two bullet points include manual tasks throughout the manufacturing process which lead to either decreased cell growth during the cell culture process and therefore reducing the overall product yield, or a device contamination via an undesired organism. The third bullet point describes the volume control for the capture unit, as it loses functionality in case the working volume is too low, resulting in process termination. The fourth bullet point describes an issue with the cell retention system. This subunit is responsible for separation of biomass and process liquid, wherein the latter continues forth into the subsequent unit while the former is brought back into the bioreactor. Filter blocking within this system poses a high risk, as process termination would be an inevitable consequence. This issue mainly arises from the fact that the process control unit of the ATF system does not communicate with the overall process control system but acts as a separate third-party device. The device does warn about impending pressure problems (indicating issues with the filter) but requires manual interference to counteract in time.

4.2.1 OMITTED SCENARIOS

During the SWIFT brainstorming, some guideword - deviation combinations led to impossible scenarios, or scenarios that could only be prevented by activities outside of the defined boundaries (i.e.: maintenance). These scenarios were omitted from further consideration, as risk evaluation would not be informative. They are still included in the raw SWIFT dataset found in appendix chapter 7.2.1, but were not considered for further analysis. Based on the exclusion mechanism when comparing SWIFT and node-corresponding scenarios, omitted ones can easily be determined.

4.3 MITIGATION PROPOSITIONS

Superficial mitigation strategy propositions for each of the four high-risk posing nodes were developed. They mainly revolve around automation of certain process aspects currently relying on operator or manual process control counteraction. The hereafter covered high risk nodes can be found in appendix chapter 7.2.3.

Addition of media, phase transition during biomass production, and activation of pumps are all parts of the process that should not remain manual tasks but be automated to reduce the currently high risk of decreased cell growth. Inoculum addition and preparation is another manual task where automation is proposed to decrease risk of contamination but also to streamline process initiation. This is achievable by addition of an automatic docking station which connects the inoculum flask to the process device via sterile connection. Alternatively, the inoculum can be grown in a specialized chamber integrated into the process device, combined with in-line measurement and control to automatically monitor all cell growth related parameters.

Good coordination between cell culture and capture unit pumps needs to be thoroughly established as their interplay not only determines downstream productivity, but more importantly prevents process failures related to working volume shortfalls. Regulated volume flow by diligent component control is of utmost importance, so each part needs to be connected to the control system which is currently not the case. Complete automation can only be achieved if every valve, pump, and switch is connected to the process controlling software.

Lastly, another important issue is that the ATF cell retention is not connected to the process control system. It does send individual alarms and allows for manual pump control, but a third-party control panel must be addressed by the operator. It is possible that the third-party device becomes hard to reach in the prototype design, which would then exacerbate manual interaction or even render it impossible in the worst case. Inclusion of cell retention control into the process controlling software not only eliminates the spatial requirement for manual interference, but also increases threat detectability and mitigation probability.

5 DISCUSSION

5.1 OBSERVATIONS DURING METHOD TESTING

5.1.1 TEAM PERFORMANCE

The team, set up as described in chapter 1.1.2, did an overall satisfying job. Remaining objective while steering participants through the whole method procedure was a strenuous facilitator responsibility, however previous experiences in general quality management and group moderation served as a huge advantage, since the team was not extensively familiar with quality management and its corresponding mindset. Discussions between team members were generally encouraged but stopped in case they got lost in detail which tend to happen due to the groups' unexperienced nature. Soon enough, new ideas and approaches were found due to the unconventional perspective provided by the method, which led the team to drift into discussions about potential adaptions for improvement of the manufacturing process. Partially tedious thwarting of these discussions were necessary to revert back on track; it is occasionally vital to suppress participant ego. Individual documentation of these potential adaptions was obviously permitted as it served the overall goal of process improvement.

Negative influence on the team morale was perceived in the form of unclear objectives. The method was developed simultaneously to its application, i.e.: every subsequent step of the procedure was not fully specified during execution of the current one. The overall objective of risk-assessment was clear throughout the process, but intermediate goals of every step were not. Because of this, every step after the initial SWIFT brainstorming was initially performed solely by the facilitator, followed by a team-wide review of the results and their successive corrections to reach broad consensus after each step.

The native SWIFT method suggests usage of a scribe who is responsible for documentation of results. Note: the scribe is responsible for documentation of

SWIFT-related data, not the previously mentioned process adaption ideas arising in between scenario discussions. For the trial run, the facilitator combined moderator and scribe roles which sometimes required slowing down of the procedure, subsequently influencing time management which resulted in more group sessions necessary than initially expected. Additionally, any form of flow disruption can impact brainstorming performance negatively, it is therefore strongly recommended to separate these roles to maintain high performance and output.

5.1.2 BIAS AND EXPERIENCE

An expected consequence arising from separation of facilitator and team input was over time emergence of effects such as subliminal bias. It was no longer a team effort to perform each data processing step, but a team effort to accept or reject proposals by the facilitator. This might have led to under- or over-estimation of risk, as the facilitator was not a process expert therefore requiring the team to review proposals as unbiased as possible. Literature recommends to not deviate from performing as a team, as individual evaluation unconsciously increases bias [20]. However, in a scientific work environment, employee responsibilities are often vaguer when compared to a highly structured industry setting. It is therefore more difficult to allocate specific personnel for the risk management process which led to the separated input approach.

During method application, team member roles were not individually defined but merely explained by the facilitator. Proper role descriptions would help participants to understand each function and their individual benefit to the process. However, it did not seem highly impactful to not have defined roles compared to relying solely on an extensive explanation of what was expected.

Experience with quality management and its mindset did prove to be advantageous since it reduced digressing discussions, maintained method progression, and supported general understanding of each steps' goal. It is highly recommended that at least the person fulfilling the facilitator role has a profound QM background whereas every additional experienced team member is of advantage.

The participating team consisted of scientists not overly familiar with quality management practices, required a more profound explanation of the method structure and its ultimate goal prior to application, i.e.: how does each step interlace with the next and how does it tie to the final risk assessment. The methods added value was not fully comprehensible for some participants throughout the trial run but understanding and acceptance increased with procedural progress.

5.1.3 Quality of results

Studies have shown that qualitative risk assessments can run into troubles regarding value of information for risk management decisions when compared to quantitative approaches [21]. However, quantitative risk assessment is not possible in early stages of process development due to process data scarcity, hence a qualitative approach was the only option.

The developed method was successful in highlighting areas in need of refinement to reduce the most prevalent risk sources. Partially handling issues, i.e.: events requiring manual interference by an operator were found to be of highest risk. Somewhat expected since the whole continuous manufacturing process goal is to have as little manual interaction, with the highest degree of automation, as possible. Automated safeguards were regarded as more safe than manual ones, so areas with a higher dependence on operator interaction were consequently considered of higher risk which influenced severity and detectability risk parameter evaluation. Nevertheless, the method was able to highlight variations between different handling issues (i.e.: nodes describing manual interactions but with miscellaneous consequences) and their associated risks. In case that the overall risk score was equal, differences in the severity risk parameter magnitude were examined, allowing for a more detailed distinction within the same overall risk category. This highlights the methods capability for nuanced differentiation of similar threats, despite a rather simple tiered overall risk score.

Ideally, pre-, and post-mitigation risk values are compared to have a juxtaposition illustrating the effectiveness of target system adaptions. Impact of adjustments are

obtained simply by application of a new risk assessment cycle, now examining the adjusted system. Problematic areas might become rectified by means of newly established sensors, process control systems, or other modifications most likely succeeding in reduction of the area's related risk probability or severity. Unfortunately, due to time and thesis boundary restrictions, proposed mitigations for the target process analysed within this thesis were not adopted. A new round to obtain data for comparison was not performed, which leaves the proposed mitigation strategies' success in an unknown state.

It is likely that the method yields numerous proposals for risk mitigation, which requires a decision on which to favor and implement. It is recommended to have a separated entity responsible for this decision, i.e.: no team member included in the risk assessment process should be part of the mitigation strategy decision. Overlap of these roles could lead to a bias issue: the decision might not be based on objective criteria but a subjective opinion of the individual. It is not expected to be a probable scenario though since operator and management roles are traditionally separated in the industries' hierarchical system.

5.2 INDIVIDUAL QM TOOL CONSIDERATIONS

5.2.1 DIFFERENCES TO THEIR NATIVE VERSIONS

As previously mentioned, the developed method uses only parts of each individual quality management tool from which it is comprised. The native version of each technique is described in ISO 31010:2019, whereas differences are discussed in this chapter.

The developed method does follow the procedure described by the original SWIFT technique authors [18], yet on a more sophisticated level when it comes to risk evaluation. Nonetheless, it follows, much as the original SWIFT technique itself does, the overall risk management process structure described in ICH Q9. During application of the developed method, the team refrained from using all the proposed

guidewords by the original authors. They were instead considered a category, supporting determination of the ultimately used guidewords and deviations listed in Table 2. Thesis boundaries as well as the state of the target process did not allow for inclusion of more guidewords during the test run as no data was available for e.g.: analytical or sampling errors. Once development of the target process reaches a sufficient level of detail, more guidewords can be included into the analysis, therefore increasing the methods assessment sophistication.

Differences to the native FTA analysis are considerably higher. It is originally intended to facilitate identification of risks correlated to a specific event, which can be achieved either quantitatively or qualitatively wherein the former requires a high availability of process related data and knowledge. Regardless of the type of approach, a tree diagram round a specific top-event is generated. The subsequent stepwise determination of imminent causes leading towards their underlying cause remained much like the native version but was used to achieve primary data grouping of SWIFT scenarios instead of direct risk determination. Each scenario could therefore be attributed to causing (either directly or indirectly) one of the two top-level events described in chapter 3.4.

Opposed to the main roles of SWIFT and FTA techniques, the bow tie analysis is used only as a supporting tool to depict prevention and recovery safeguard and consequence interactions for each node. Only minor alterations to the native form of this tool have been done before inclusion into the assessment method. Firstly, a determined node is located at the central knot, where the target event is in the native form. Secondly, various consequences emerging from the central event are natively depicted at the right hand of the knot, whereas in the altered version these consequences are represented by the next-higher level FTA cause of the node, i.e.: the node's hierarchical superordinated cause. This allowed for a logical representation of the connection between individual SWIFT scenario consequences, their safeguards, and their role in causing one of the two undesired top-level events from the FTA analysis.

5.2.2 USEABILITY

Retrospectively it can be said that the SWIFT tool fitted its purpose of data generation during early development very well. Posing proactive questions allowed for sophisticated data and knowledge generation even in this preliminary confined setting. These, for a scientific environment unconventionally structured questions have ungraspable merit because they governed the participating scientists to unconsciously adapt their process approach; in other words: they expanded their way of thinking about the process.

Using the FTA tool to bundle data together and achieve a more condensed form was difficult at first. The underlying logic required to craft the FTA diagram is abstract for an inexperienced team yet was eased by determination of the two top-level events. With more understanding of this step and its goal, diagram crafting became easier and more straightforward. In the end, this step turned out to be a much-needed data clearance and condensation process to purposefully support full-process risk determination. It should be noted, that due to the complexity as well as the informational degree of the target process, mostly OR gates were used in the FTA diagram. The author believes that occurrence of AND gates would increase when process knowledge increases, and more profound data is available to better detect relations between sub-systems of the overall process.

The bow tie analysis was well fitted for its purpose. The diagram gives a good representation of prevention and recovery safeguard states, which allowed for a sounder severity and detectability risk parameter estimation. It did not reveal any additional information regarding consequence interactions, as these were dependent on the grouping during the preceding FTA diagram creation.

5.2.3 TOOL SELECTION

In a vast sea of available quality management tools, development of a new one seems unnecessary at first. However, at closer inspection, one can see that every tool has its own merit and rather defined usage space. In the case of risk assessment

during early stages of process development, no existing tool would allow for well-founded risk assessment by its own.

SWIFT is a technique, serving as a risk identification tool much like FMEA or HAZOP [22]. However, decision on which one to use was driven by the data situation. Due to the early stage of process development where not (if any) process data is available, a tool like FMEA is not useful as it requires a certain level of information which SWIFT simply does not. Basic process understanding without much detail are sufficient to perform a SWIFT analysis, which is why it was chosen as the data generation step.

With many scenarios generated via SWIFT, analysis of each scenario was not a meaningful option. Ishikawa diagrams [17], event tree analysis (ETA) [17] or fault tree analysis (FTA) were considered as options for data condensation, with the latter being the ultimately chosen tool. ETA and FTA are similar, wherein they have similar basic structures, yet it seemed impossible to combine SWIFT-generated data to the ETA diagram tree form. The ETA procedure defines a top-level event and hierarchically adds options for either successful or failed controls, followed by more layers of subsequent control reactions. This approach was considered unfitting as process control cascades were not yet defined during process development and would also most likely be a combination of control measures instead of an escalating reaction due to the complexity of the process. ETA would therefore only be useful to further dissect each SWIFT scenario instead of bundling them together. The FTA procedure with its cause-based approach to analyse top-level events not only allowed for a theoretical setting, but also accomplished the desired bundling of SWIFT data into the naturally obtained “nodes”: causes where further distinction would not be productive anymore.

Usage of the bow tie analysis was decided upon quickly as its native purpose seemed very fitting for the developed method. Understanding nodes and their corresponding safeguards is facilitated by using this graphical method, since otherwise information had to be tediously extracted from each SWIFT scenario of

which the FTA node is comprised. Alternatively, a hazard and critical control points analysis (HACCP) [17] was considered for safeguard analysis but was deemed too sophisticated as it does require a high quality of input data (including knowledge about risks) which would be a paradox.

Conclusion via conduction of an end report is not necessarily part of the developed risk assessment method, as the facilitators can freely choose how to present their acquired results.

5.3 FUTURE OUTLOOK

5.3.1 RECOMMENDATIONS

The scientific sector is not used to approach issues in a structured, highly defined way, which is why quality management methods might experience unexpected challenges during application. Two main recommendations were deduced from the method's trial run which should be factored in if future application is intended.

- The participating team must be informed about the procedure structure prior to implementation. The merit of each step, its structural role and goal must be explained: insecurities and lack of understanding about the procedure need to be addressed as early as possible.
- Each participating team member must reserve time specifically for the procedure to eliminate distractions, increase quality of discussion and consequently consensus.

5.3.2 STATE OF THE INDUSTRY

Regulatory authorities do not dictate how a company must perform risk assessments but give guidelines on what must be assessed which is then interpreted individually by each company desiring to market its products. It is difficult to compare assessment strategies within the industry, as each company most likely has their own approach and philosophy regarding risk management. Many products and processes were already established before the introduction of risk management in 2004 by the

FDA [15], yet these still need to be retrospectively assessed and if necessary, adapted. In this case, the developed method would need adaption to support this abundant data situation.

Risk management today is a routinely performed part of quality management, and a staple for newly developed processes. A company can decide on either proactively assess risk during development, or reactively assess it once the process has been established. Either approach is approved by regulatory authorities if performed accordingly. The developed method can be advantageous here, as it can be used for both approaches with little adaption necessary.

Even though every company has their own approach and philosophy to quality risk management, introduction of this newly developed method and exchange of the old, rigid ones can help streamline and uniform risk assessments, satisfying regulatory authorities while giving a competitive edge.

5.3.3 Regulatory considerations

With rising popularity of continuous manufacturing, the currently dire regulatory situation will surely change in the foreseeable future. FDA and EMA, as the two main regulatory authorities, already drafted guidelines [11, 14] so it becomes more and more clear which aspects of a continuous manufacturing process requires special focus. It is expected that usage of the method will shift towards smaller, more defined areas of the target processes, assessing more detailed aspects of the process to reliably fulfil regulatory requirements.

For example, residence time distribution (RTD) of ingredients within the process is an important parameter to understand and track. The method can be used to assess which areas of the process poses the highest risk of RTD deviations.

5.3.4 Adaptability

In its current form, the method is purposefully designed for a rather specific scenario: to support early process development. Nevertheless, since the core idea is based on the general risk management procedure (see chapter 3.1), its area of

application is manifold. Depending on the available data situation, the overall method, or subsections of it, can be sharpened and adapted towards present circumstances. It is possible to focus the method only on certain areas of the target process to assess risk for this specific area. Questions posed during the SWIFT step would then be more focused on the designated section dealing with more in-depth scenarios.

It is also possible, even recommended if the data situation allows for it, to divide the risk assessment matrix into more subdivisions. For example: by introducing two more defined classifications (e.g.: “very low” and “very high”) a finer risk assessment can be achieved. In any case, risk assessment is never a rigid process that is set in stone but needs to be adapted to the present situation.

It is important to note that if the risk of two processes are to be compared, the same method should be used. It is also recommended that the same team members partake in both assessments to reduce individual bias to a minimum.

5.3.5 A STEPSTONE FOR QUALIFICATION

Processes for pharmaceutical production need to undergo certain steps, including qualification and validation, before they can be used in routine production. The former is a procedure in which the devices’ functions are verified, examining if everything works as described and intended. Validation on the other hand focusses on the process itself, i.e.: if the process can produce the described product in a safe and reliable fashion.

The developed risk assessment method can be used to support qualification of the target process. Based on the many unconventional questions posed during the initial data generation step, points to consider during qualification can be derived. A part of qualification is testing operational functions of the device, e.g.: how the device processes a specific incoming signal. Using information generated during methods procedure, compilation of an overview of device functions can be facilitated. More areas of the process can therefore be tested during qualification, increasing its sophistication and reliability and consequently the process’ success.

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7 APPENDIX

7.1 ABBREVIATIONS

CAPEX	Capital expenditures
CDER	Center for Drug Evaluation and Research
COG/g	Cost of Goods per gram
E2E	End-to-End
EMA	European Medicines Agency
ETA	Event Tree Analysis
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
FTA	Fault Tree Analysis
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
OPEX	Operational expenditures
PMDA	Pharmaceuticals and Medical Devices Agency
QM	Quality management
R&D	Research & Development
RTD	Residence Time Distribution
SWIFT	Structured What-If Technique

7.2 RAW DATA

7.2.1 SWIFT DATABASE

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
1	Inoculum	Too soon	Inoculum added too soon	Added while the sterility recipe is running. Environmental conditions are "good" enough for cells to grow. Maybe pH not in range. Cell growth influenced -> different behavior	Deliberate decision by operator to add inoculum. Time windows for batch and fed-batch process are programmed at beginning. If Inoculum is added too late, these time windows are exceeded. -> Process control needs to warn operator
2	Inoculum	Too late	Inoculum added too late	No influence if a few hours later If days, the media might be altered which leads to different growth behavior in the reactor Whole process is on hold until batch culture is finished	Deliberate decision by operator to add inoculum. Time windows for batch and perfusion process are programmed at beginning. If Inoculum is added too late, these time windows are exceeded.
3	Inoculum	Too high	Too high volume of inoculum added	Maximum working volume is reached. Process strategies are based on the volume of inoculum Not inside operating space Influence on downstream: flowrates are different purification efficiency lower	Feedback loop-controlled level device of reactor -> addition of inoculum is stopped Flowrate sensor and levels in place to react -> Process control warning
4	Inoculum	Too high	Too many cells with inoculum added	Process time shortened. Not enough media to go with feed control strategy, and cells might be damaged/not viable damaged cells might agglomerate and block filter and alter process performance (titer might not be reached)	Feed control strategy enabled. (Can react to different process parameters) Might alter flow rates which leads to lower purification efficiencies Online monitoring of cell retention possible -> filter exchange (possible since parallel units)

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
5	Inoculum	Twice / repeated	What happens if you add inoculum twice	same as too high	Not possible - there is no inoculum backup
6	Inoculum	Missing	What happens if you forget to add inoculum	Nothing - process still in waiting mode	Process controls
7	Inoculum	Out of sequence	What happens if you add the inoculum at the wrong process step (can only be too soon)	same as too soon	Process values are illogical. Alarm of reactor that working volume is not reached
8	Inoculum	Too low	Too low volume of inoculum added	Process strategies are based on the volume of inoculum Not inside operating space Influence on downstream: flowrates are different purification efficiency lower	Feedback loop-controlled level device of reactor Flowrate sensor and levels in place to react
9	Inoculum	Too little	Too few cells with inoculum added	Process time lengthened. No further influences on cell viability	
10	Batch media	Too soon	What if the batch media is added too soon?	Reactor is still hot from sterility process. Glucose will be degraded (caramelized). Nutrients are lower as expected	Addition of batch media is a manual process. Temperature of the reactor must be checked by the operator
11	Perfusion media	Too soon	Perfusion media is added too soon to the process (Ramp-Up process not finished)	perfusion media cannot be used for growth effect of ramp-up phase, process parameters might be influenced (lower titer, process time) Earlier depletion of media during perfusion phase if not enough media is present	automated reactor control is responsible for correct time-point of perfusion addition start addition needs to be triggered manually for it to happen Volume exceeding a certain volume will trigger an alarm

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
12	Perfusion media	Too late	Perfusion media is added too late to the process	process parameters outside of desired range. Not enough media to go with feed control strategy, and cells might be damaged/not viable damaged cells might agglomerate and block filter and alter process performance (titer might not be reached)	automated reactor control is responsible for correct time-point of perfusion start addition needs to be triggered manually for it to happen pump rate of perfusion media will send an alarm -> 100% pump efficiency as it tries to balance missing scale input
13	Perfusion media	Too little	Too little perfusion media is periodically added	Feed control strategies will lower process parameters. Lower flow rate and yield	pump calibration and process control redundancies in the system: pump AND flow sensor as a parameter pair to see if one is not working correctly
14	Perfusion media	Too little	Not enough Perfusion media is added in total	Target titer not reached, lowered cell growth. nutrient depletion might lead to lower cell viability depending on end point of cell culture process	Media preparation is done according to SOP. Calculation of max. media requirement is part of batch record. If still wrong, and media is depleted, process control will send out a warning because of lower volume (low media volume and low reactor volume)
15	Batch media	Too little	Not enough batch media is added	Not enough nutrients for the inoculated cells. Titer influenced.	Alarm from process control. Operator checks weight too. Reactor knows when no media is in
16	Perfusion media	Too high	Too much perfusion media is periodically added	Bleed rate increased Influence on downstream: flowrates are different polishing efficiency lower	Bleed is increased by the system to maintain constant harvest rate Does the concentration decrease?
17	Perfusion media	Out of sequence	Perfusion Media is still added once the cell culture process is finished	Level increase of the reactor volume If operator doesn't check, overflow can occur	Alarm for reactor Harvest + bleed pump are already shut down Operator needs to check the system

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
18	Batch media	Too high	Too much batch media is added	Process time lengthened. No further influences on cell viability	Operator needs to check media. Level shows if too much media is inside the reactor
19	Perfusion media	Missing	perfusion media is not added at all	Process cannot proceed. Parameters are wrong. No more cell growth due to nutrient depletion. process stops	Process control sees due to parameters being off that something is wrong. Operator sees that media is not added. Media level is not changing
20	Batch media	Twice / repeated	Batch media is added twice	Exceeds working volume, reactor overflows	Level control, visually identified due to overflow
21	Perfusion media	Out of sequence	What if the perfusion media is added before ramp-up phase	perfusion cannot increase titer/concentration, so values from batch culture are taken and kept in steady state (-> results in undesired low yield)	Start of perfusion media addition is manually controlled Two media inlets (if available) allow for fast switching of media types
22	Ramp-up media	Too soon	What if the Ramp-Up media is added during the batch process	process parameters outside of desired range. Cells in too much nutrients -> growth is altered	automated reactor control is responsible for correct time-point of ramp up start addition needs to be triggered manually for it to happen Level alarm of reactor -> operator can open harvest/bleed pump, and lead unwanted volume to the exit valve there
23	Ramp-up media	Too late	What if the Ramp-Up media is added too late?	process parameters outside of desired range. Not enough media to go with feed control strategy, and cells might be damaged/not viable damaged cells might agglomerate and block filter and alter process performance (titer might not be reached)	automated reactor control is responsible for correct time-point of ramp up-batch addition start; Operator can start process manually if he sees alarm pump rate of ramp up media pump will send an alarm -> it is near 100% as it tries to balance missing scale input

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
24	Ramp-up media	Too little	What if too little Ramp-Up media is periodically added?	Feed control strategies will lower process parameters. Lower flow rate and yield	pump calibration and process control redundancies in the system: pump AND flow sensor as a parameter pair to see if one is not working correctly
25	Ramp-up media	Too little	What if too little Ramp-Up media is added in total?	process parameters might be influenced (lower titer, process time) Earlier depletion of media during perfusion phase if not enough media is present Volume in reactor decreases (harvest pump active)	Level alarm of the reactor harvest pump transports early feed to exit (drain), not to capture unit
26	Ramp-up media	Too high	What if too much Ramp-Up media is periodically added?	Reactor volume exceeds as only harvest pump is active (fixed value)	pump calibration and process control
27	Ramp-up media	Too high	What if too much Ramp-Up media is added in total?	Reactor volume exceeds as only harvest pump is active (fixed value)	Switch to perfusion is done manually, even if some ramp-up media is left
28	Ramp-up media	Missing	What if no ramp-up media is added at all?	If completely forgotten and perfusion process has been initiated: perfusion media cannot increase growth but only maintain current one - titer will be too low If next step is not initiated and system expects ramp-up phase to occur: cell death due to nutrient depletion	automated reactor control is responsible for correct time-point of ramp up start, but operator for actual addition start Operator has to check correct tubing before initiating ramp-up phase -> alarm is sent out if no media addition occurs

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
29	Air/O2/NO2	Too soon	What if any of the gaseous inlets is opened too soon	O2: increase dissolved oxygen rate -> can get toxic for cells NO2: kills the cells -> process termination	valves are controlled by the system opening of NO2 valve is a manual decision, but when process started valve can't be opened
30	Air/O2/NO2	Too late	What if any of the gaseous inlets is opened too late	Batch process parameters will not comply, batch process will not work and cells die after a certain time due to lack of oxygen If recognized in time, consequences are minimal	Process control sees due to parameters being off that something is wrong. Operator sees it too at flow meters of inlets
31	Air/O2/NO2	Too low	Not enough gaseous material is added to the process	Oxygen limitation Lower buffer capability, pH out of range. Lower cell growth, higher process time	Feedback loop can react to altered process parameters and adapt Operator can control flow meters on inlets
32	Air/O2/NO2	Too high	Too much gaseous material is added to the process	PA/O2: increase dissolved oxygen rate -> can get toxic for cells Higher shear stress from increased bubble amount/size -> cell damage	Feedback loop reacts to process parameters and adapt valves of inlets
33	Air/O2/NO2	Missing	Addition of gaseous material stops during the process	Process cannot proceed. Parameters are wrong. No more cell growth due to nutrient depletion. process stops	Feedback loop system shows parameters out of range during batch process -> alarm. No problem if found prior to inoculation.
34	Air/O2/NO2	Missing	No gaseous material is added at the beginning of the process	Process is not capable of running No calibration possible	Parameters show that somethings off. Operator checks opened valves prior to process start. Flow meters show if nothing is added even with opened valves
35	Air/O2/NO2	Out of sequence	What if the gaseous materials are added when the actual perfusion process has finished? (too soon/late is already covered)	Idle state = closed	Idle state = closed

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
36	ATF	Damaged	ATF pump stopped working	alternating flow for ATF doesn't work anymore; lower harvest flow rate; faster membrane fouling	Alarm from system due to increasing working volume pressure sensor and flow meter on the ATF pump device -> sends alarm to QUBICON Regular pump maintenance
37	ATF	Damaged	ATF vacuum pump stopped working	No cell retention - vacuum pressure if harvest pump still running; no harvest flow; working volume will increase	Alarm from system due to increasing working volume pressure sensor and flow meter on the ATF pump device -> sends alarm to QUBICON Regular pump maintenance
38	ATF	Damaged	What if the ATF membrane gets blocked	TMP increase, cell damage, shear stress	Switching to alternate filter can reduce influence of damaged cells (filter blocking) Calibration of pressure sensor. Sensor + control system can adapt pump rate and therefore pressure
39	ATF	Too high	ATF air pressure is too high	Device pressure reducer (air inlet is at max) does not work properly, so set pressure is exceeded. Overpressure between ATF and harvest pump -> combination part between those 2 pumps might be damaged or even burst. Also, possible damages the membrane	ATF system sets pressure point low automatically (fixed value, regardless of inlet pressure). This is not controllable. Membrane pressure is seen in process control -> alarm sent
40	ATF	Too little	ATF pressure is too little	Overtime event in control algorithm from ATF device; Pump cycle never finishes in primary method Fiber system might not fill the whole fiber, and fouling might occur faster -> under pressure in ATF system as harvest pump stays constant. If not enough material can be transported, reactor volume starts to exceed	Control algorithm initiates cycle switch. increases pump rate and therefore pump rate to get out of overtime events Node from ATF device to QUIBCON is not available Operator must manually change pump rates in QUBICON, how much change necessary is taken from manual and experience

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
41	ATF	Too soon	ATF pump started too soon	Pump is already active during batch process (too soon has no influence). (Also, during sterility process) alternating flow for ATF doesn't work anymore -> increased membrane fouling	Pump started manually at the beginning of the process
42	ATF	Too soon	ATF vacuum pump started too soon	Pump is already active during batch process (too soon has no influence). (Also, during sterility process) alternating flow for ATF doesn't work anymore -> increased membrane fouling	Pump started manually at the beginning of the process
43	ATF	Too late	ATF pump started too late	ATP pump is started during batch process to prime membrane for process liquid and is also required to reach equilibrium (e.g.: temperature) -> starting too late influences process parameters; ATF might not be ready for ramp-up which leads to cells running into nutrition limitations -> assuming sterility is reached, starting later has no effect alternating flow for ATF doesn't work anymore -> increased membrane fouling	Pump started manually Operator knows when to start ATF pump. ATF can only be turned on manually

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
44	ATF	Too late	ATF vacuum pump started too late	ATP pump is started during batch process to prime membrane for process liquid and is also required to reach equilibrium (e.g.: temperature) -> starting too late influences process parameters; ATF might not be ready for ramp-up which leads to cells running into nutrition limitations -> assuming sterility is reached, starting later has no effect alternating flow for ATF doesn't work anymore -> membrane fouling	Pump started manually Operator knows when to start ATF pump. ATF can only be turned on manually
45	ATF	Missing	ATF pump is missing	No cell retention - no perfusion process	Manual ATF system check required before overall process is started
46	ATF	Too little	ATF pump is not pumping enough material	Overtime event in control algorithm from ATF device; Pump cycle never finishes in primary method Fiber system might not fill the whole fiber, and fouling might occur faster	Control algorithm initiates cycle switch. increases pump rate and therefore pump rate to get out of overtime events Node from ATF device to QUIBCON is not available Operator must manually change pump rates in QUBICON, how much change necessary is taken from manual and experience
47	ATF	Too high	ATF pump is pumping too much material	Overpressure between ATF and harvest pump -> combination part between those 2 pumps might be damaged or even burst. Also, possible damages the membrane	Membrane pressure is seen in process control -> alarm sent

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
48	ATF	Too little	ATF vacuum pump does not reach vacuum	ATF might not be ready for ramp-up which leads to cell running into nutrition limitations might influence sterility process (bad mixing) alternating flow for ATF doesn't work anymore -> membrane fouling	Pump started manually; value is fixed by the system -> alarm if not reached but only on ATF device. Operator needs to control before process start
49	ATF	Too high	ATF vacuum pump exceeds vacuum limit	Overtime event in ATF control cycle, membrane damage, ATF damage?	
50	Bioreactor	Damaged	If reactor control doesn't work anymore	Process is not capable of running, parameters out of range, cell death, process termination	Maintenance
51	Equipment	Too soon	Pump (harvest) starts too soon	Batch process still running, mass balance no longer maintained, volume not constant, lower limit of level reached	initiation of harvest pump is done at ramp-up phase, controlled by the system reactor and harvest vessel scales indirectly show the pump rate
52	Equipment	too soon	Bleed pump starts too soon	volume not constant, lower-level limit reached, cells are lost as well (via bleed)	system sends an alarm if level gets too low bleed pump has to be turned off manually by operator
53	Equipment	Too late	Pump (harvest) starts too late	System switched to ramp-up phase; ramp-up media gets added. Reactor volume increase until working volume is exceeded	alarm from system that reactor level is high
54	Equipment	Too late	bleed pump starts too late	Too high cell densities are reached, leads to reduction in growth, reduced efficiency in nutrition uptake; increase in absolute amount of dead cells (viability decrease) -> loss of steady state -> process termination	System switches bleed pump on at switch from ramp-up to steady-state phase Online sensor measures cell densities -> Operator has to check sensor viability is measured off line

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
55	Equipment	Too little	Harvest pump flow rate too little	Reactor volume increase until working volume is exceeded (media addition is higher than harvest pump subtraction)	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system
56	Equipment	Too little	Bleed pump flow rate too little	Too high cell densities are reached, leads to reduction in growth, reduced efficiency in nutrition uptake; increase in absolute amount of dead cells (viability decrease) -> loss of steady state -> process termination	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system
57	Equipment	Too high	Harvest pump flow rate too high	Mass balance no longer maintained, volume not constant (gets lower), lower limit of level reached ramp-up phase is still possible to be operated	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system
58	Equipment	Too high	Bleed pump flow rate too high	Working volume in reactor decreases steadily; total cell amount decreases too -> loss of steady state -> process termination	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system
59	Equipment	Damaged	Harvest pump stopped working	Reactor volume increase until working volume is exceeded	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system
60	Equipment	Damaged	Bleed pump stopped working	volume not constant, lower-level limit reached	reactor and harvest vessel scales indirectly show the pump rate level measurement sends alarm via the process control system

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
61	Base	Too soon	Base is added too soon to the process	sterility run works even at addition of pH, no further influence as pH levels are controlled before batch process start amount needed for pH adaption is rather low, so base pump rates are low	Reactor feedback loop reacts to pH deviation and corrects pH back into the desired range (by addition of CO2). stops base addition system sends an alarm
62	Base	Too late	Base is added too late to the process	pH deviation depending on time, the effect can be low (fast detection and reaction) or high (late detection)	Reactor feedback loop reacts to pH deviation and corrects pH back into the desired range. increases base addition
63	Base	Too little	Base is not added in the desired amount	pH will be too low constantly, cell growth influenced -> cell death -> process termination after certain time	Reactor feedback loop reacts to pH deviation and corrects valve setting. if pH is still too low: alarm. operator has to manually interfere
64	Base	Too high	Pump doses too much, setpoint not reached	pH will be too high constantly, cell growth influenced -> cell death -> process termination after certain time	Reactor feedback loop reacts to pH deviation and corrects valve setting. If pH is still too high: alarm. Operator has to manually interfere
65	Base	Missing	Base control/bottle/line is missing	pH deviation	base addition system check established prior to start (operator has to check)
66	Antifoam	Too soon	antifoam pump starts too soon	idle state = closed. Only if foam probe detects foam, it adds antifoam oxygen transfer is decreased, and oxygen transfer mechanisms (stirrer, process air) needs to cope with that up to a point where oxygen can't be transferred anymore, and cells die	Pulse & Pause control is responsible for antifoam addition. Fully automated by reactor control
67	Antifoam	Too late	antifoam pump starts too late	Foam problem, blocking of offgas filter	Reactor feedback loop reacts and corrects pump setting. Short term addition of higher antifoam amount possible

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
68	Antifoam	Too little	Pump doses too little, setpoint not reached	Foam problem, blocking of offgas filter	Reactor feedback loop reacts and corrects pump setting.
69	Antifoam	Too high	Pump doses too much, setpoint not reached	Alteration in oxygen transfer, control out of range	Reactor feedback loop reacts and corrects pump setting.
70	Antifoam	Missing	Antifoam control/bottle/line is missing	Foam problem, blocking of offgas filter	antifoam addition system check established prior to start (operator has to check)
71	Bioreactor	Too little	What if the mantle (heating unit) heats too litte	The necessary process temperature cannot be reached sterility might not be reached due to too low temperatures	Reactor feedback loop reacts to temperature deviations and adjusts Temperature setpoint for sterility is within the reactor control system
72	Bioreactor	Too high	What if the mantle (heating unit) heats too much	Cooling capability might be exceeded so process temp exceeds limit and damages cells	Reactor feedback loop reacts to temperature deviations and tries to adjust by cooling via mantle
73	Bioreactor	Damaged	What if the reactor mantle (heating unit) does not work at all	Temperature of the process cannot be controlled at all. Process won't be able to run.	Maintenance
74	Bioreactor	Too soon	What if the reactor mantle (heating unit) starts heating too soon	Heating unit is required from the beginning, there is no too soon	Higher cooling effort necessary. Reactor controls stop heating and tries to get temperature back into operational space
75	Bioreactor	Too late	What if the reactor mantle (heating unit) starts heating too late	Temperature of the process will be out of desired temperature range. Cell growth due to lower temperatures decreased and process time increased. Oxygen transfer is higher and stirrer therefore lower?	Reactor feedback loop immediately turns on mantle to reach desired temperature range. If temperature is out of the limits an alarm is sent

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
76	Bioreactor	Too late	The reactor stirrer starts too late	desired aeration and homogenization (substrate distribution) is not achieved. Cell growth is influenced; flow rates not achieved	Reactor feedback loop shows unfavorable process parameters (oxygen saturation) and increases stirrer speed to catch up aeration
77	Bioreactor	Too soon	The reactor stirrer starts too soon	Can't start to soon. Immediately turned on at system start	
78	Bioreactor	Too little	The reactor stirrer doesn't stir enough	desired aeration and homogenization (substrate distribution) is not achieved. Cell growth is influenced; flow rates not achieved	Reactor feedback loop shows unfavorable process parameters (oxygen saturation) and increases stirrer speed
79	Bioreactor	Too high	The reactor stirrer stirs too much	shear stress damages the cells	Reactor feedback loop shows unfavorable process parameters (oxygen saturation) and decreases stirrer speed if no upper limit of stirrer speed is given, speed can increase to lethal values
80	Bioreactor	Damaged	The reactor stirrer does not work or is missing	Process not capable of running.	Operator checks stirrer presence and function before process start
81	ATF	Missing	What if the ATF membrane is missing	Batch process can theoretically run, but pressure values are completely off. Ramp-up can't work because there is no outlet towards the harvest pump if no membrane is there	The membrane is not a fixed part of the ATF column. Wrong connection is possible Operator must check correct setup of ATF and membrane
82	ATF	Damaged	What if the ATF membrane is damaged	Retention does not work effectively, and cells can get into the subsequent process parts, which disrupts the process	Membrane pressure is outside of expected limits, indicating membrane problems.
83	Software	Damaged	What if the QUBICON software does not work correctly	Process cannot proceed. Immediate loss of control as QUBICON controls technical and process parameters	

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
84	Equipment	Damaged	What if the power outlet of the machine does not work	Process can never start, or gets interrupted during	
85	Equipment	Damaged	What if the scale for the media bottle does not work correctly	The amount of substrate added to the process cannot be monitored correctly - the feed control does not work	Reactor feedback loop depends on scale feedback to correctly add the right amount of substrate, but can alter other process parameters to adapt to the actual substrate addition rate
86	Equipment	Damaged	What if the scale for the bleed bottle does not work correctly	Process control sends wrong information to the bleed pump and too much/not enough material is transported which alters feeding strategy and also whole growth process	Reactor feedback loop depends on scale feedback to correctly pump the right amount of bleed.
87	Equipment	Damaged	What if the scale for the permeate bottle does not work correctly	Process control sends wrong information to the permeate pump and too much/not enough material is transported which alters feeding strategy and also whole growth process	Reactor feedback loop depends on scale feedback to correctly pump the right amount of harvest
88	Equipment	Missing	What if the air inlet filter at the reactor is missing/damaged	unfiltered process air/CO2/O2 gets into the system and sterility can't be reached. Process can't start	Operator needs to check filter. It is part of routine start of reactor
89	Equipment	Missing	What if the air inlet filter at the ATF is missing/damaged	unfiltered process air gets to the diaphragm of the ATF system, possible contaminating the diaphragm room. No product contacting parts	Operator needs to check filter. It is part of routine start of reactor
90	Equipment	Missing	What if the vacuum pump filter at the ATF is missing/damaged	vacuum pump is only sucking air from the system. If no filter is there, air must travel against designed direction to cause problems (filter sits at the OUTLET). Highly unlikely	Operator needs to check filter. It is part of routine start of reactor

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
91	Equipment	Missing	What if the air filters for membrane sterility at ATF is missing/damaged	During sterility run this outlet is used for steam flow (pressure equilibrium), so a one-way outlet. After the sterilization process it is clamped off -> no influence during sterilization run	Operator needs to check filter. It is part of routine start of reactor Operator has to clamp off this exit after sterilization (but not too soon, because cooling after hot sterilization can lead to under pressure)
92	Equipment	Missing	What if the clamp on the ATF membrane or diaphragm housing air filters are missing	if clamping off is forgotten, then an additional outlet has been created. system is open and permeate can flow out	Operator has to clamp off these exits after sterilization (but not too soon, because cooling after hot sterilization can lead to under pressure)
93	Equipment	Missing	What if the air filters for sterility of the diaphragm housing of the ATF is missing/damaged	During sterility run this outlet is used for steam flow (pressure equilibrium), so a one-way outlet. After the sterilization process it is clamped off -> no influence during sterilization run	Operator needs to check filter. It is part of routine start of reactor
94	Equipment	Missing	What if the offgas filter on the reactor is missing/damaged	Offgas is usually a one-way outlet of reactor air, but filter is there in case air is sucked into the system (sterility barrier) if it is missing, and air gets sucked in, contamination might occur	Operator needs to check filter. It is part of routine start of reactor
95	Precipitation Buffer	Too soon	What if the precipitation buffer is added too soon	Buffer is not mixed with cell culture unit product, but solely added to the tubular reactor.	Pump is added to control system. Connected to the harvest pump. Flow meter in the cell culture inlet that sends signal to activate precipitation buffer pump. Flow meter in front of pump to measure correct pump function

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
96	Precipitation Buffer	Too late	What if the precipitation buffer is added too late	Product precipitation is not achieved as desired. Gets filtered out at hollow fiber module	Pump is added to control system. Connected to the harvest pump. Flow meter in the cell culture inlet that sends signal to activate precipitation buffer pump. Flow meter in front of pump to measure correct pump function
97	Precipitation Buffer	Too little	Not enough precipitation buffer is periodically added	Product precipitation is not achieved as desired. Gets filtered out at hollow fiber module	Pump is added to control system. Connected to the harvest pump. Flow meter in the cell culture inlet that sends signal to activate precipitation buffer pump. Flow meter in front of pump to measure correct pump function
98	Precipitation Buffer	Too high	What if too much buffer is periodically added	Buffer can run out. No influence on the process parameters otherwise	Operator dependent. Has to check Buffer bag regularly to see if enough is still there
99	Precipitation Buffer	Missing	No precipitation buffer is added at all	Product is not precipitated and removed in hollow fiber module. Process termination	Flow sensor at buffer addition is sending alarm because no value is measured
100	Tubular Reactor	Damaged	What if the static mixer within the tubular reactor is damaged?	Not proper mixing, and precipitation doesn't work properly	Drop in the flow rate is measured.
101	Hollow fiber module	Too soon	What if the feed pump of the hollow fiber module activates too soon?	Module is a loop. Water would just be pumped in circle	Activation of pump from vessel 1 to vessel 2 (tubular reactor now) only at certain concentration levels within the circle

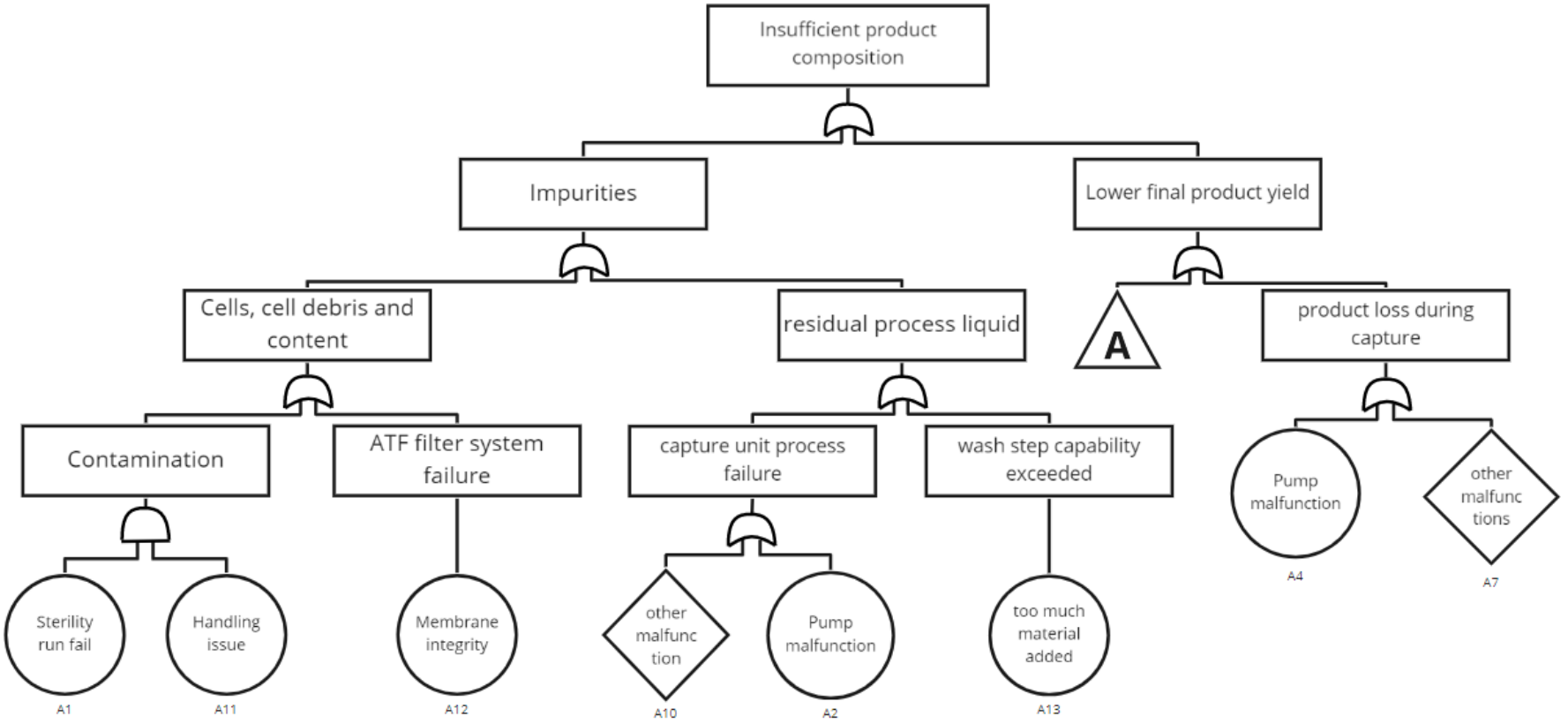
No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
102	Hollow fiber module	Too late	What if the feed pump of the hollow fiber module activates too late?	Pressure is too low to push broth through the fiber module. Culture broth is going to hollow fiber module from the wrong side, since vessel-to-vessel pump is not active yet	Pressure sensor in the hollow fiber loop indicates deactivated pump
103	Hollow fiber module	Too low	What if the pump rate of the feed pump of the hollow fiber module is too low?	Lower circulation rate, concentration decrease -> pump dependent on conc. Deactivates Membrane fouling -> system switches to other filter (tandem mode) -> more filters required	TMP increases faster than expected
104	Hollow fiber module	Too high	What if the pump rate of the feed pump of the hollow fiber module is too high?	precipitate can be destroyed because of increased shear rate -> lower yield (similar to precipitate buffer too low)	
105	Hollow fiber module	Damaged	What if the feed pump of the hollow fiber module is not working?	Pressure is too low to push broth through the fiber module. Culture broth is going to hollow fiber module from the wrong side, since vessel-to-vessel pump is not active yet	Pressure sensor in the hollow fiber loop indicates deactivated pump
106	Hollow fiber module	Too soon	What if the permeate pump of the hollow fiber module starts too soon?	Small under pressure on the permeate side of the membrane develops	Flow meter after the pump will show a value indicating pump start Pressure sensor shows unexpected value
107	Hollow fiber module	Too late	What if the permeate pump of the hollow fiber module starts too late?	Overpressure from the system will push liquid through the membrane -> permeate happens, but maybe too low flow rate	Pressure increase before the membrane and no flow rate at flow meter after permeate pump

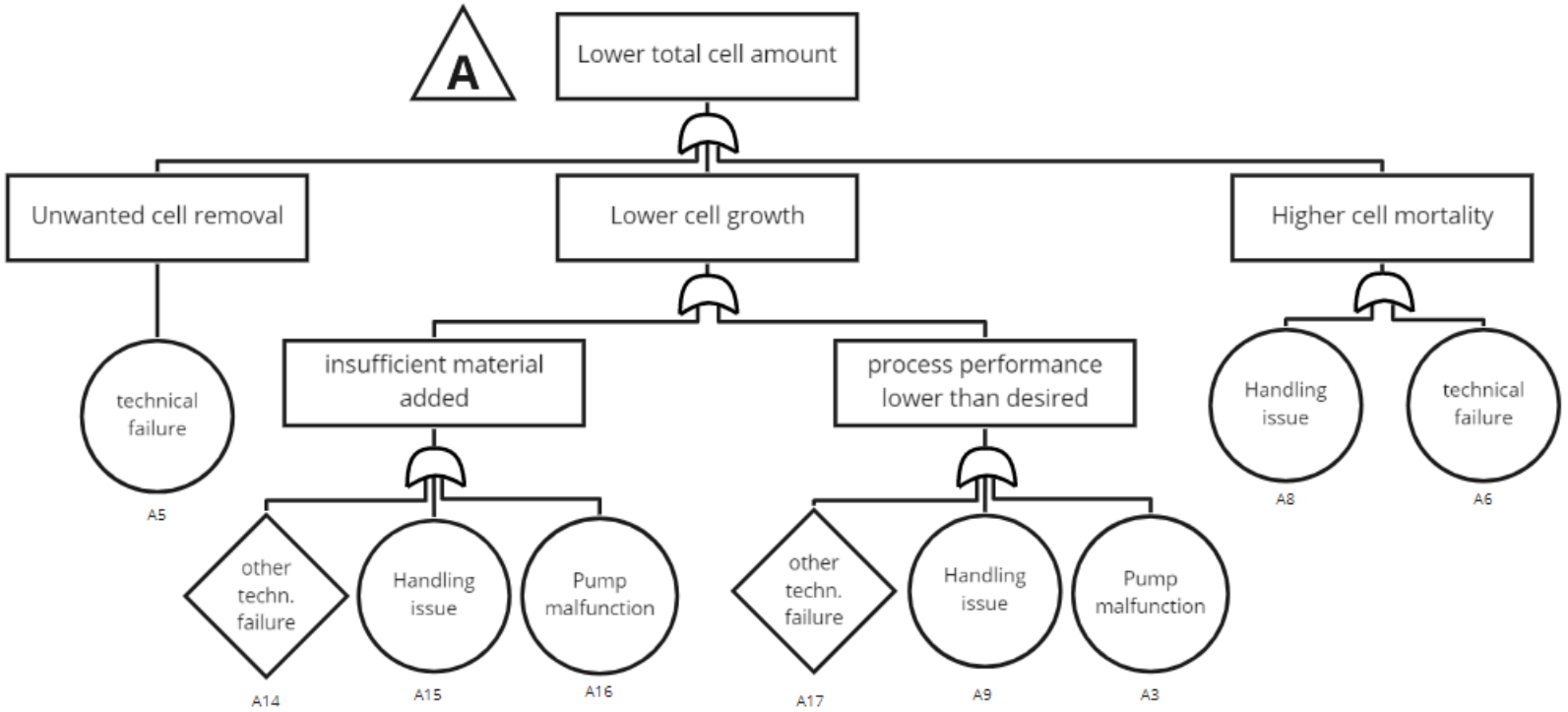
No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
108	Hollow fiber module	Too low	What if the pump rate of the permeate pump of the hollow fiber module is too low?	Overpressure from the system will push liquid through the membrane -> permeate happens, but maybe too low flow rate	Pressure increase before the membrane and no flow rate at flow meter after permeate pump
109	Hollow fiber module	Too high	What if the pump rate of the permeate pump of the hollow fiber module is too high?	Under pressure on retentate side of the membrane and increase membrane fouling	Increase in TMP measured; membrane exchange to reduce fouling flow meter at permeate pump shows high value
110	Hollow fiber module	Out of sequence	What if the hollow fiber module permeate pump is working out of sequence (activates during batch process)	Nothing - the pump is pumping either air or water (whatever the default substance is within the capture unit) see too soon	
111	Hollow fiber module	Out of sequence	What if the feed pump of the hollow fiber module is activated after its process has been completed (no more material)	Module is a loop. Residual liquid is pumped in circle	
112	Wash buffer	Too soon	The wash buffer is added too soon (during precipitation step)	Depends on the default state: If permeate side is closed: pressure in the system increases If permeate side is open: buffer leaves the system, and it is wasted	If pressure is getting too high, control system can shut down the pump Removal of too much buffer is only an economical risk
113	Wash buffer	Too late	The wash buffer is added too late at the start of the process	product concentration increases, which can't be reduced since wash buffer addition rate is fixed	Opening of drain valve to remove exceeding process liquid (product loss)

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
114	Wash buffer	Out of sequence	Wash buffer stops being added during steady state	product concentration increases, which can't be reduced since wash buffer addition rate is fixed	Opening of drain valve to remove exceeding process liquid (product loss)
115	Wash buffer	Too high	Too much wash buffer is periodically added	product concentration decreases, bleed rate from fiber module can be increased but that adds stress to the membranes. Cleaning of membranes might come sooner (switching to tandem filter)	Wash buffer pump gets its value from the harvest pump rate. If harvest increases, so does washing buffer pump. Operator cannot tinker with the value Flow meter controls the actual pumped amount and can adapt the pump rate
116	Wash buffer	Too low	Not enough wash buffer is added	product concentration increases, which can't be reduced since wash buffer addition rate is fixed	Wash buffer pump gets its value from the harvest pump rate. If harvest increases, so does washing buffer pump. Operator cannot tinker with the value Flow meter controls the actual pumped amount and can adapt the pump rate
117	Wash buffer	Missing	What if no wash buffer is added to the process	product concentration increases, which can't be reduced since wash buffer addition rate is fixed	Operator has to check washing buffer bottle before process start
118	pH adjustment buffer	Too soon	The pH adjustment buffer is added too soon	Buffer is wasted	buffer addition starts when bleeding at 2nd TFF starts process controlled
119	pH adjustment buffer	Too late	The pH adjustment buffer is added too late	product is not resolubilized completely	buffer addition starts when bleeding at 2nd TFF starts process controlled flow meter and pH meter sees if no buffer is added
120	pH adjustment buffer	Too low	Not enough pH adjustment buffer is added to the process	product is not resolubilized completely	buffer addition starts when bleeding at 2nd TFF starts process controlled flow meter and pH meter sees if no buffer is added

No.	Subcategory	Deviation	What If...? Scenario	Consequences	Safeguard
121	pH adjustment buffer	Too high	Too much pH adjustment buffer is periodically added to the process	concentration of the product decreases, due to dilution by too much buffer	buffer addition starts when bleeding at 2nd TFF starts process controlled flow meter and pH meter sees if too much buffer is added
122	pH adjustment buffer	Missing	No pH adjustment buffer is added to the process	protein doesn't resolubilize, and is lost	pH meter in design, but not realized yet. -> checks correct pH after buffer addition if no pH meter, no way to check if protein is actually resolubilized
123	pH adjustment buffer	Out of sequence	What if the pH adjustment buffer is added when cell culture process is still running	You waste buffer.	process control starts addition of buffer when bleeding at 2nd TFF starts End2End connector allows for automatic diversion of process liquid between capture unit and polishing unit
124	Hollow fiber module	Damaged	What if the hollow fiber module membrane is damaged?	product titer decreases due to precipitated product reaching permeate stream and goes to waste	control via transmembrane pressure
125	Hollow fiber module	Damaged	What if the hollow fiber module is already damaged when building it into the system (after membrane exchange e.g.)	product titer decreases due to precipitated product reaching permeate stream and goes to waste	Manufacturer of the module has to ensure that the integrity is available

7.2.2 FTA TREES




A
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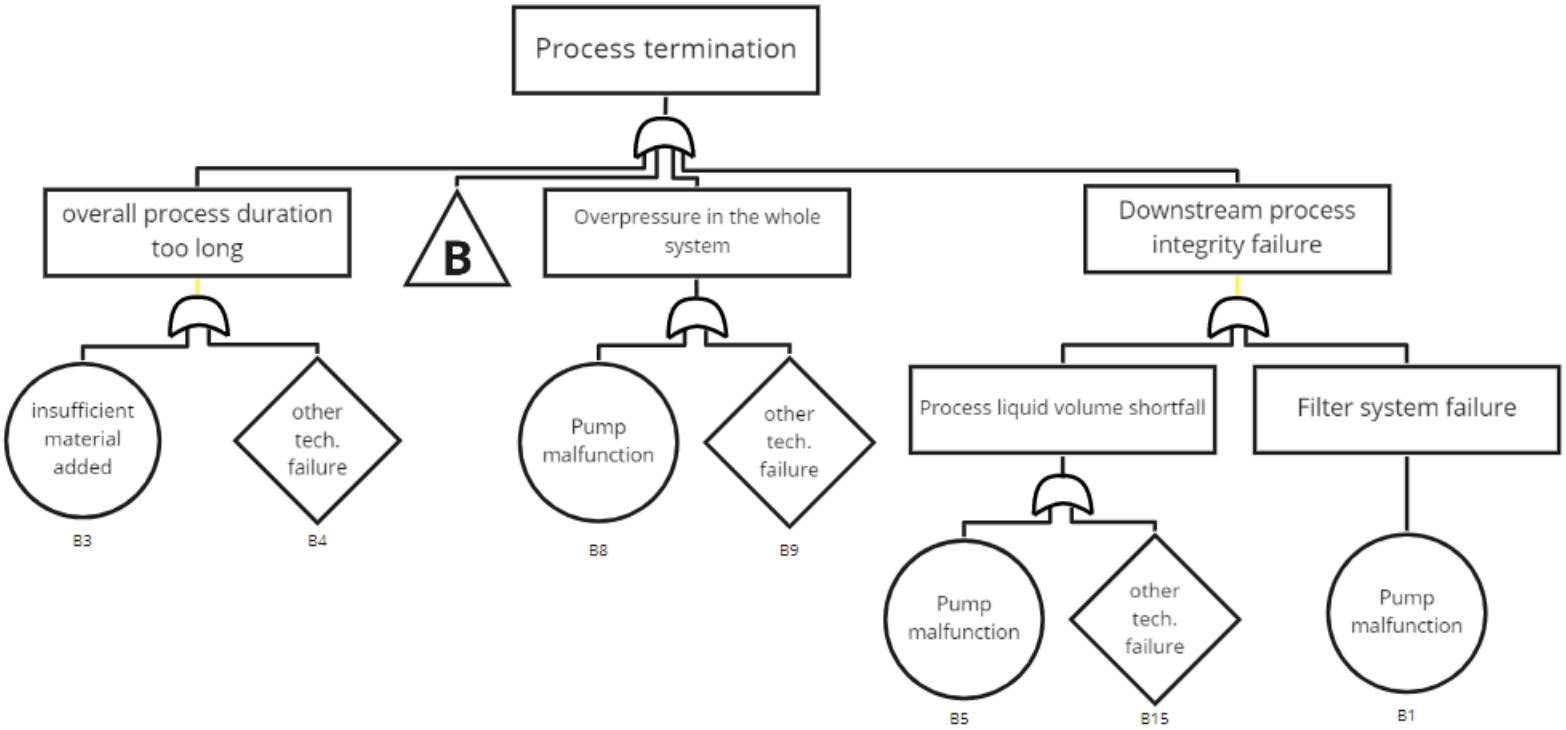
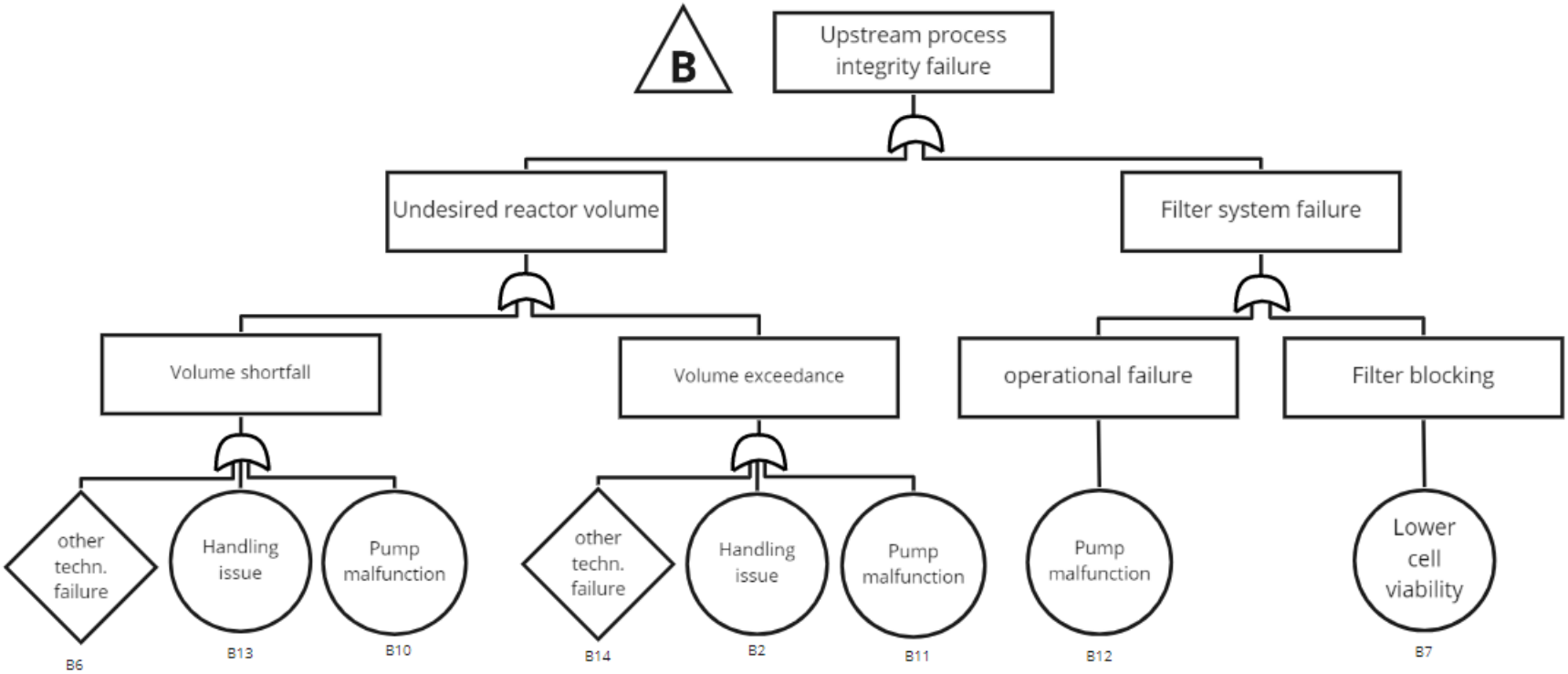
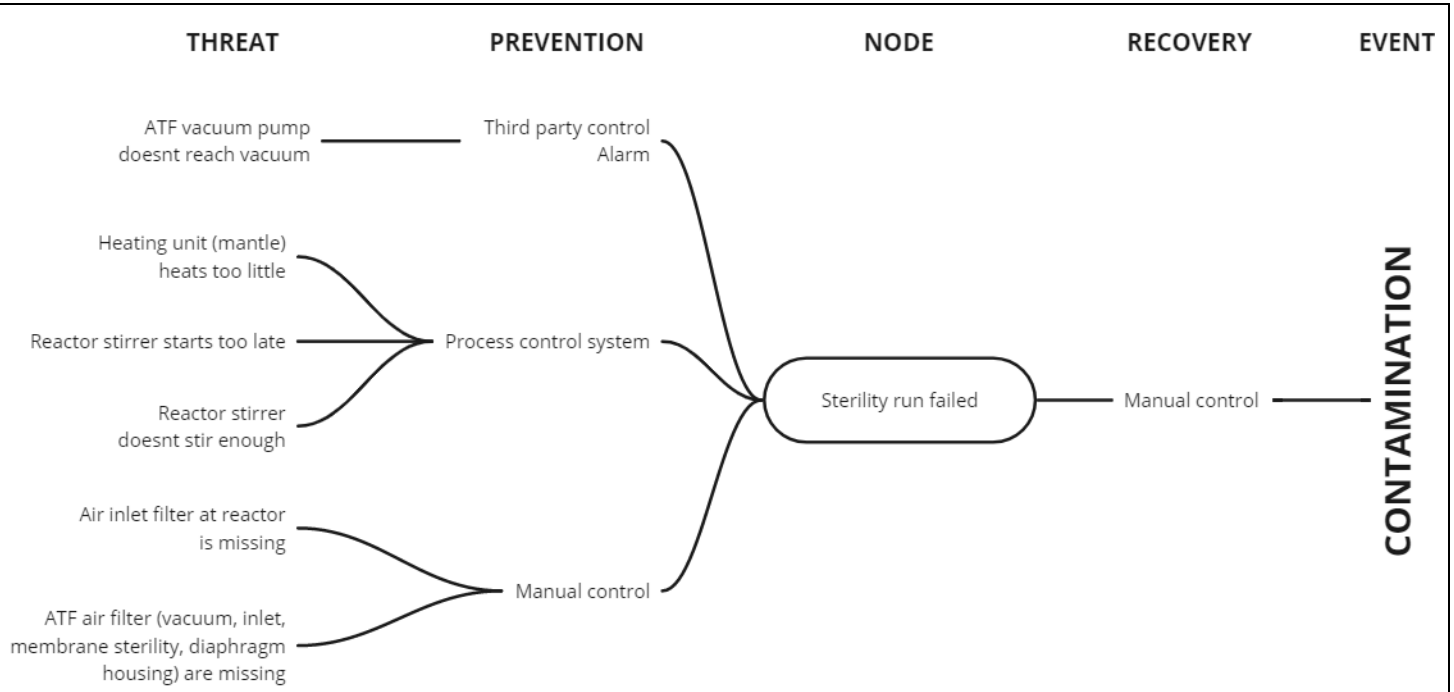
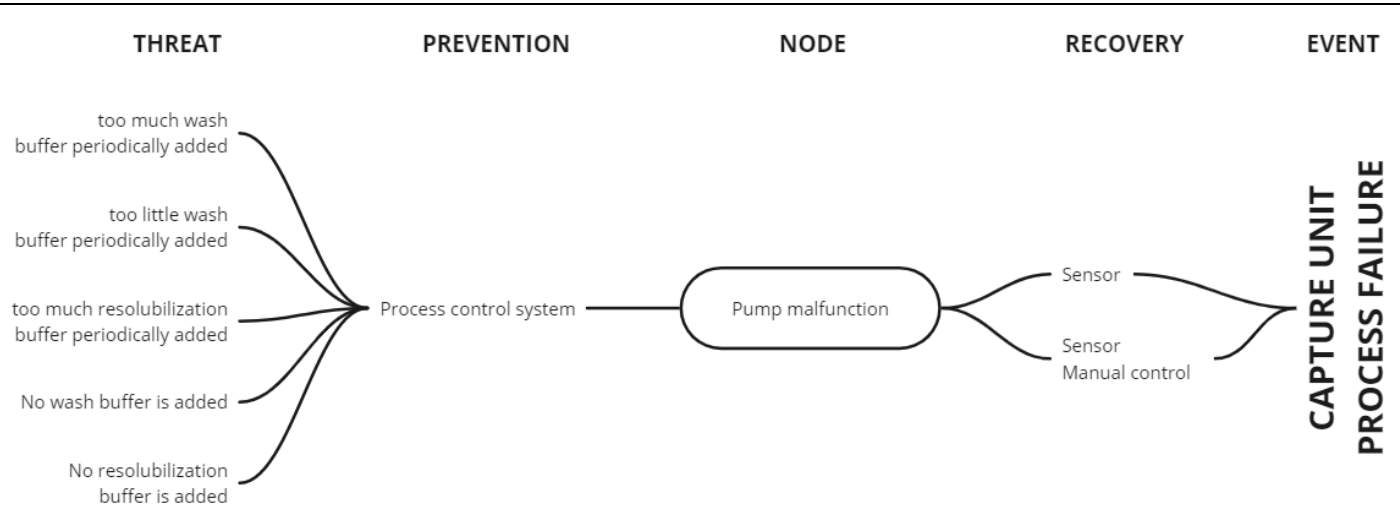
Unwanted cell removal
Lower cell growth
Higher cell mortality
technical failure
A5
insufficient material added
process performance lower than desired
Handling issue
technical failure
A8
A6
other techn. failure
Handling issue
Pump malfunction
A14
A15
A16
other techn. failure
Handling issue
Pump malfunction
A17
A9
A3

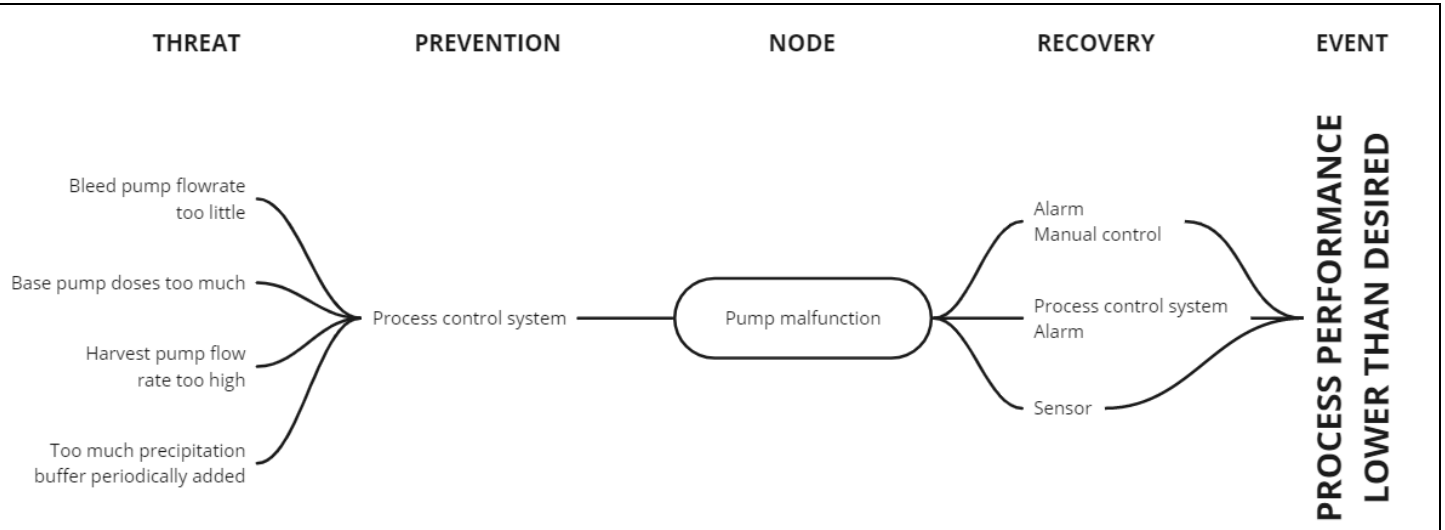

Process termination
overall process duration too long
B
Overpressure in the whole system
Downstream process integrity failure
insufficient material added
other tech. failure
Pump malfunction
other tech. failure
Process liquid volume shortfall
Filter system failure
Pump malfunction
other tech. failure
Pump malfunction
B3
B4
B8
B9
B5
B15
B1

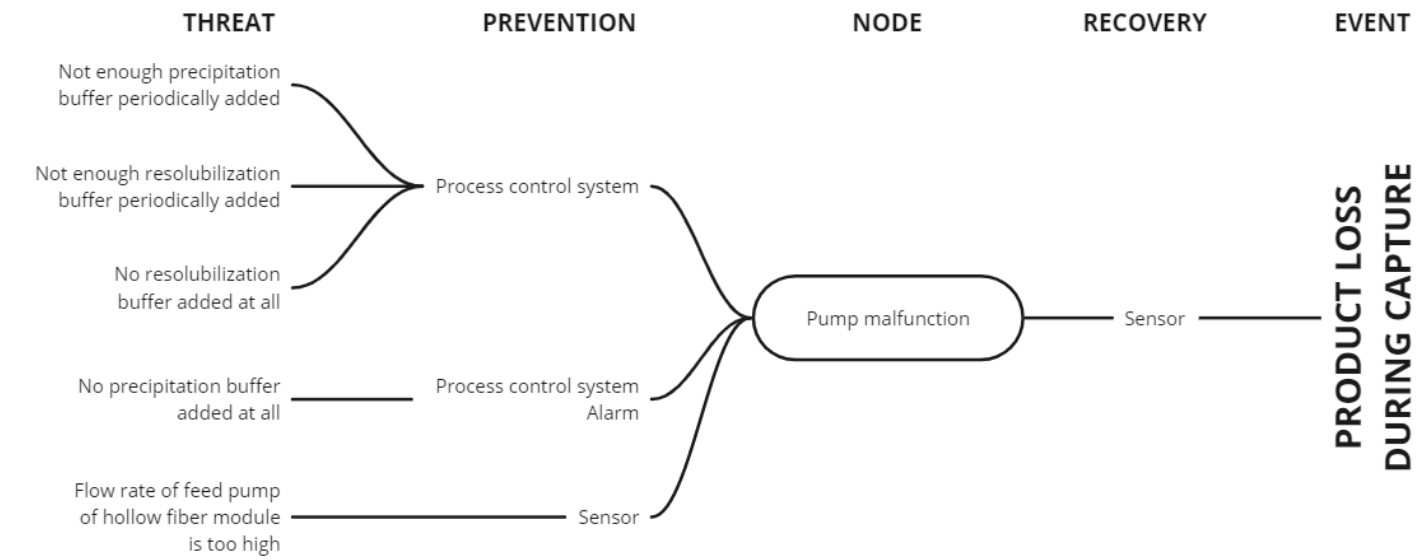

B
Upstream process integrity failure
Undesired reactor volume
Filter system failure
Volume shortfall
Volume exceedance
operational failure
Filter blocking
other techn. failure
Handling issue
Pump malfunction
other techn. failure
Handling issue
Pump malfunction
Pump malfunction
Lower cell viability
B6
B13
B10
B14
B2
B11
B12
B7

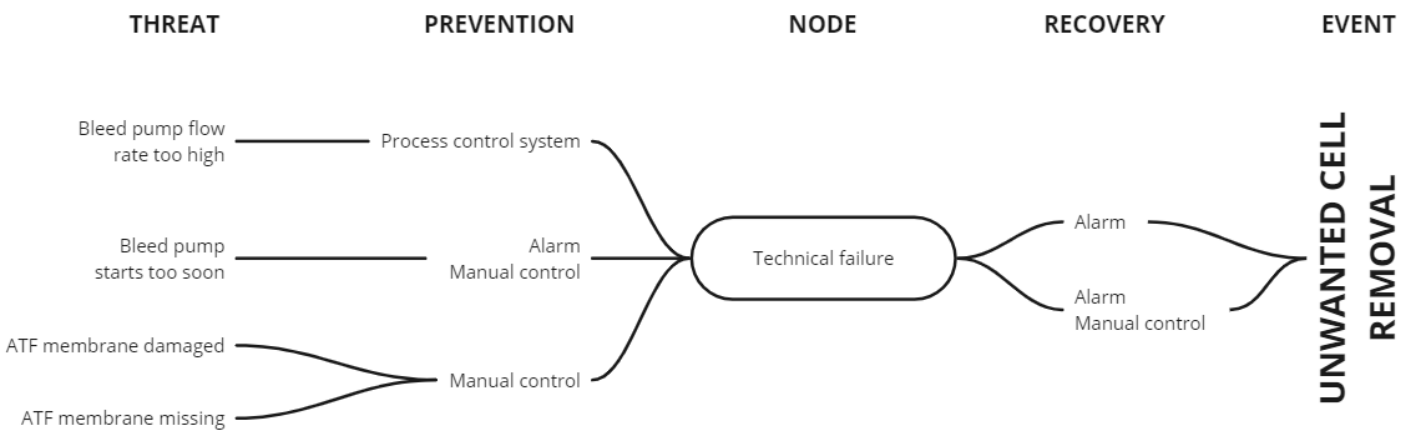
7.2.3 INDIVIDUAL NODE ANALYSIS

Node: A1		
Description: Threats that can lead to a failure in the sterility process and therefore lead to contamination. This node is the partner node to A11 which describes handling mistakes leading to contamination. Both need to appear in combination as a failed sterility run can still be mitigated by an operator decision to not start the production.		
Corresponding SWIFT lines: 49,72,77,79,89,90,91,92,94		
Risk parameter	Rating	Justification
Severity	High	A failed sterility run will undoubtedly lead to a failed process as the product is not useable after contamination occurs. Missing ATF filters do not have recovery safeguards while also being dependent on manual control.
Detectability	Medium	Operator caused threats are during process preparation, so should be easily detectable before process start. Threats caused by technical problems during the sterility run are controlled by automated responses (mantle/stirrer issues) which is good.
Complexity	Low	The node is straightforward. Either contamination arises or not. Either sterility was achieved or not.
Occurrence	Low	A failed sterility run should not occur often, as most operator caused threats are mistakes during process preparation (not during manufacturing).
Overall Risk	Low	

Node: A2		
Description: The final product is expected to come in a certain matrix. This node describes pump malfunctions that can alter the matrix constituents and amounts.		
Corresponding SWIFT lines: 116,117,118,122,123		
Risk parameter	Rating	Justification
Severity	Medium	It is not yet defined how the matrix should be composed. Rated as medium, since there is no strategy established if pumps do malfunction (problem can only be detected, but not mitigated).
Detectability	High	Fully automated process control in place that controls all capture unit pumps. In case a pump does not function accordingly, the system automatically adjusts values.
Complexity	Low	The whole capture unit is dependent on the harvest flow rate, which is a fixed value. However, the problem is contained within this subunit and not many points of origin exist.
Occurrence	High	As long as no matrix description is established, fluctuations in the process can rather frequently lead to different matrix constituents.
Overall Risk	Medium	

Node: A3		
Description: This node includes all pump malfunctions that reduce process performance and therefore lower cell growth. Node does not include pumps that do not add enough material, which is included in node A16.		
Corresponding SWIFT lines: 57,58,65,99		
Risk parameter	Rating	Justification
Severity	Medium	Bleed and harvest pumps are automatically controlled, only activation is manual. However, value adaption during recovery is manual. Adding too much precipitation buffer can alter resolubilization efficiency, extent is dependent from other factors as well.
Detectability	Medium	Adding the value for the harvest pump is manual, and the system cannot control it. The other parts are automated and controlled easily.
Complexity	Medium	Even though only two pumps are part of it, they influence both process subunits substantially.
Occurrence	Medium	Pump flow rates can fluctuate rather common, especially at low values. Therefore, risk for occurrence is set to medium.
Overall Risk	Medium	

Node: A4		
Description: This node describes pump malfunctions that can lead to product loss during the capture process		
Corresponding SWIFT lines: 98,100,105,121,123		
Risk parameter	Rating	Justification
Severity	High	Loss of product is something that is never wanted, and the chance of recovery when pumps malfunction is basically nonexistent. The feed pump of the hollow fiber module does not have any recovery safeguards and is only detected by a sensor.
Detectability	High	All pumps that are included in this node are system controlled.
Complexity	Low	Once product is gone, its gone. Only sensors show that the pump flow rates are off.
Occurrence	Low	Even though some kind of product loss is expected (no perfect system exists), additional loss is not commonly expected.
Overall Risk	Medium	

Node: A5		
Description: This node describes the unintentional removal of cells from the process. As there are no diversion processes defined yet, this node is limited to bleed pump malfunctions, or a damaged/missing ATF membrane. Without the membrane, the cells can reach parts of the process where they can no longer be used for production.		
Corresponding SWIFT lines: 53,59,82,83		
Risk parameter	Rating	Justification
Severity	Medium	With cells lost, it is considered indirect product loss. Therefore, the severity is set to medium.
Detectability	Medium	Bleed pump rate is automatically adapted by the system, but the initial start is only shown by the system yet performed by the operator.
Complexity	Low	Currently only bleed pump and a defect ATF membrane can lead to cell removal. Not a complex situation.
Occurrence	Low	Start of the bleed pump is indicated by an automated alarm, which tells the operator to start the pump. Risk of occurrence of an alarm malfunction is considered low, same as the ATF membrane issues as they need to be checked numerous times during system setup.
Overall Risk	Medium	

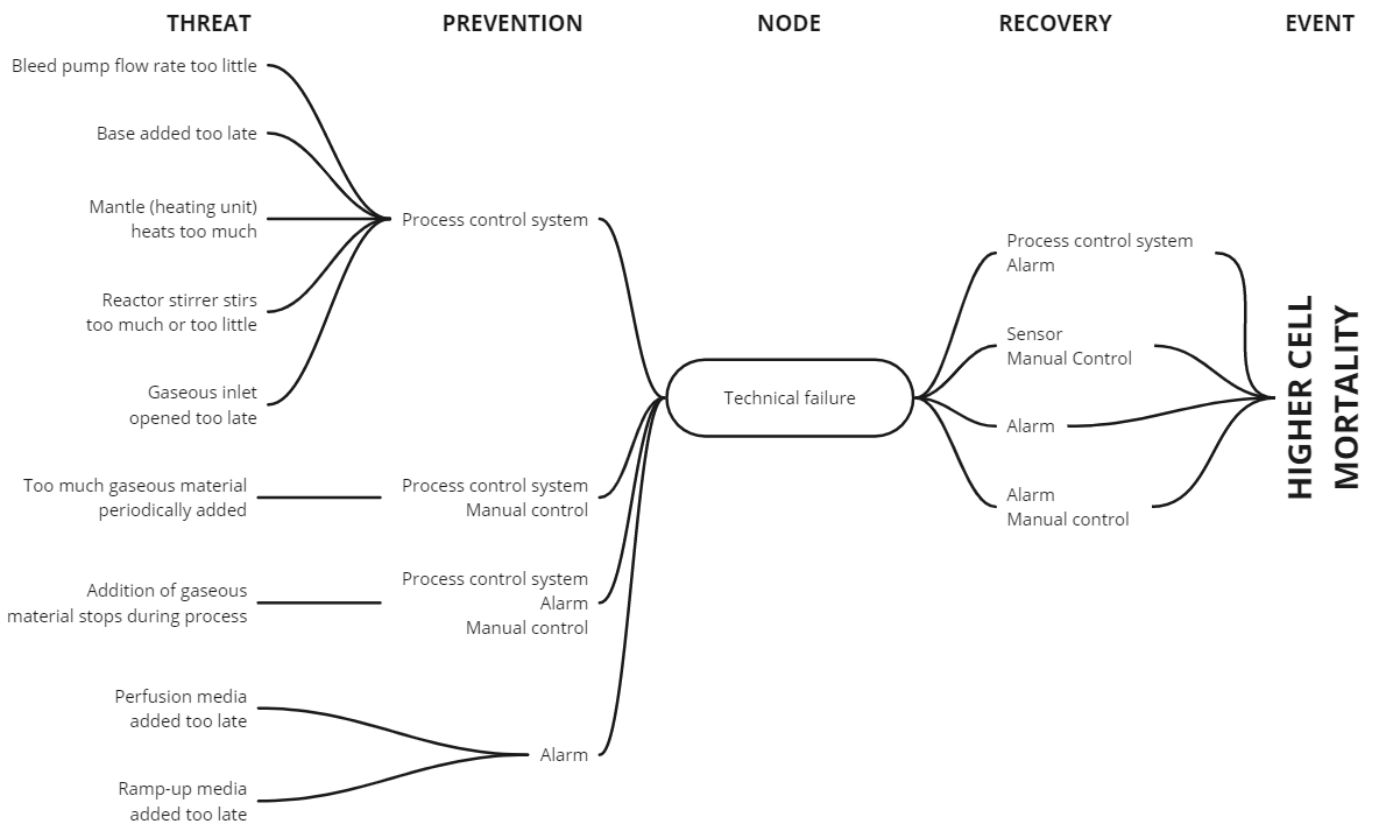
Node: A6

Description:

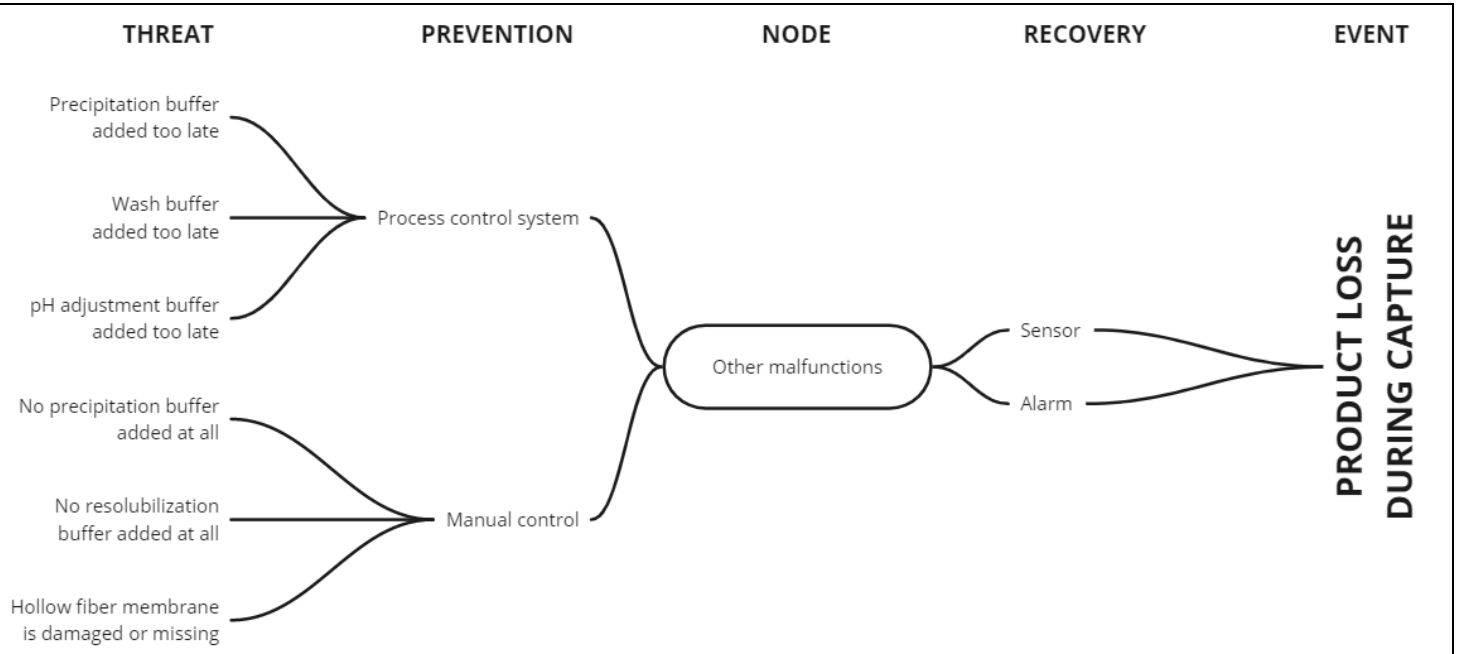
This node describes technical defects that increase cell mortality, leading to lower final product yield due to less cells available for production.

In the case of media addition, only the system alarm at the time of phase change is included while the operator error is included in node A8.

Corresponding SWIFT lines:
20,29,31,33,34,57,63,73,79, 80



Risk parameter	Rating	Justification
Severity	Medium	Higher cell mortality is considered indirect product loss. Therefore, the severity is set to medium.
Detectability	High	Almost all scenarios have automated prevention established, only phase change is not fully automated. However, this node only contains the alarm that the system issues to remind when cell culture phases must start
Complexity	Medium	Many sources, but all revolve around the cell culture unit.
Occurrence	Medium	Cell death will most certainly occur regularly in varying extent.
Overall Risk	Medium	

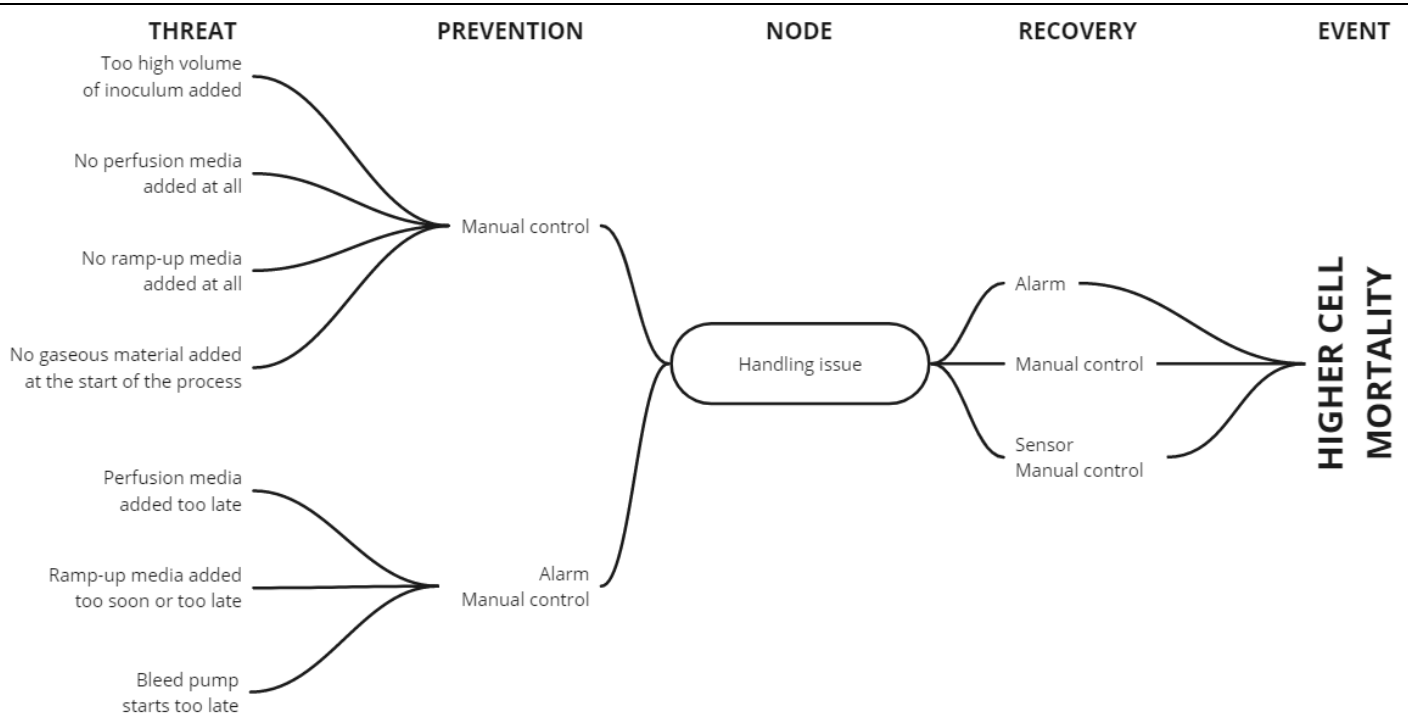
Node: A7		
Description: This node describes defects that cause product loss during the capture process. It mainly includes bad timing during buffer addition because the whole capture unit should work in unison. In case a buffer is added too late, or not at all, product can be easily lost.		
Corresponding SWIFT lines: 97,100,114,120,123,125		
Risk parameter	Rating	Justification
Severity	High	Loss of product is something that is never wanted. Almost all problems can only be seen via parameters being off. Only the damaged hollow fiber membrane threat causes an alarm due to unexpected transmembrane pressure. The no buffer addition scenarios describe the operator forgetting to connect the buffer bottle to the system. Node A4 describes the same scenario but with a pump malfunction as the root cause.
Detectability	Medium	The addition of buffers is connected to the harvest pump. Depending on the activation and rate of the harvest pump, either capture unit pump adapts accordingly. The operator is responsible to check if buffer bottles are connected to the system which poses a weak point as the system cannot check that by itself.
Complexity	Low	Each buffer addition system (precipitation, wash, resolubilization) is designed in the same way, only values differ.
Occurrence	Medium	Due to no experiences or justifiable estimations, occurrence is valued more conservatively as medium.
Overall Risk	Medium	

Node: A8

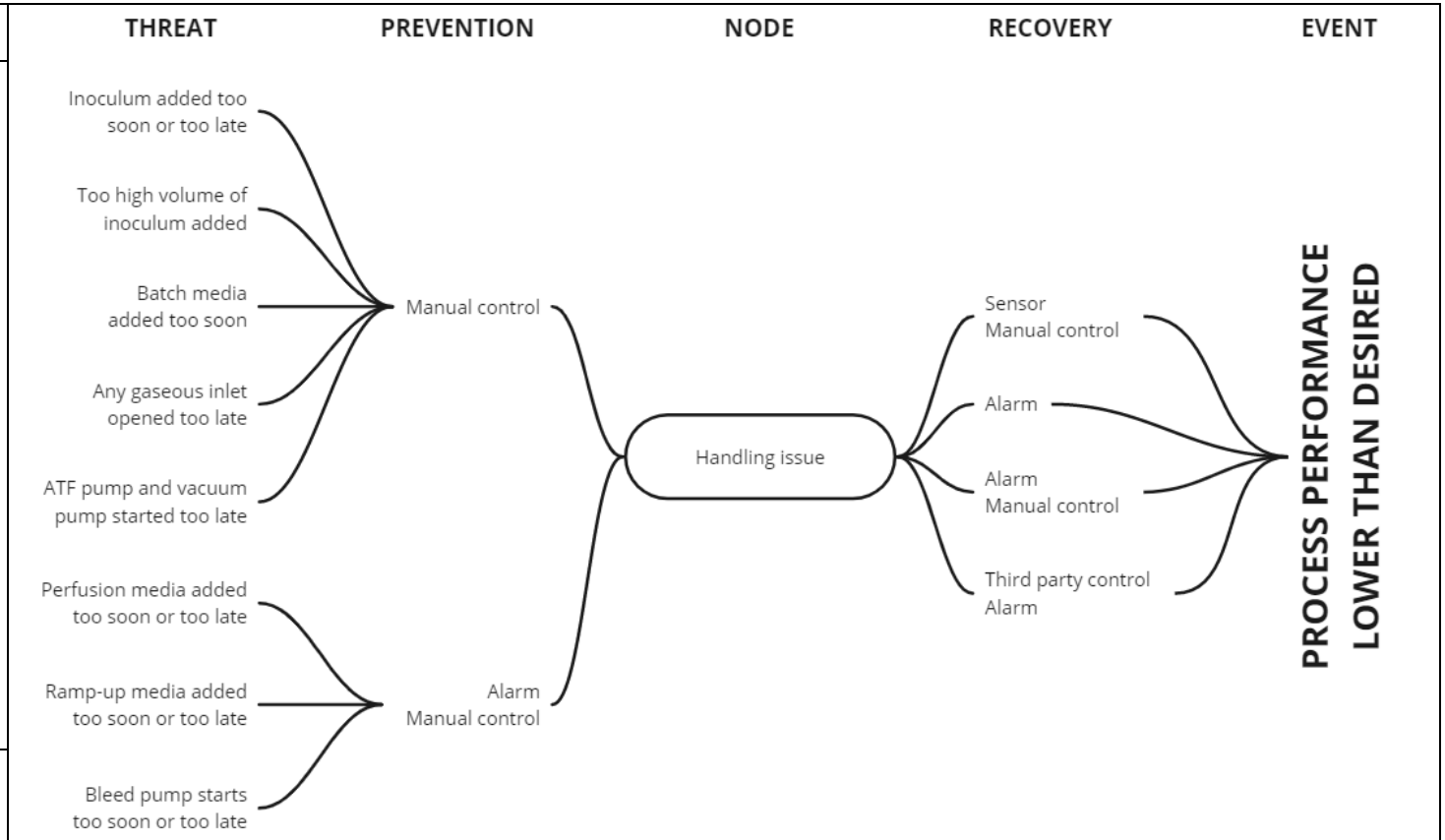
Description:

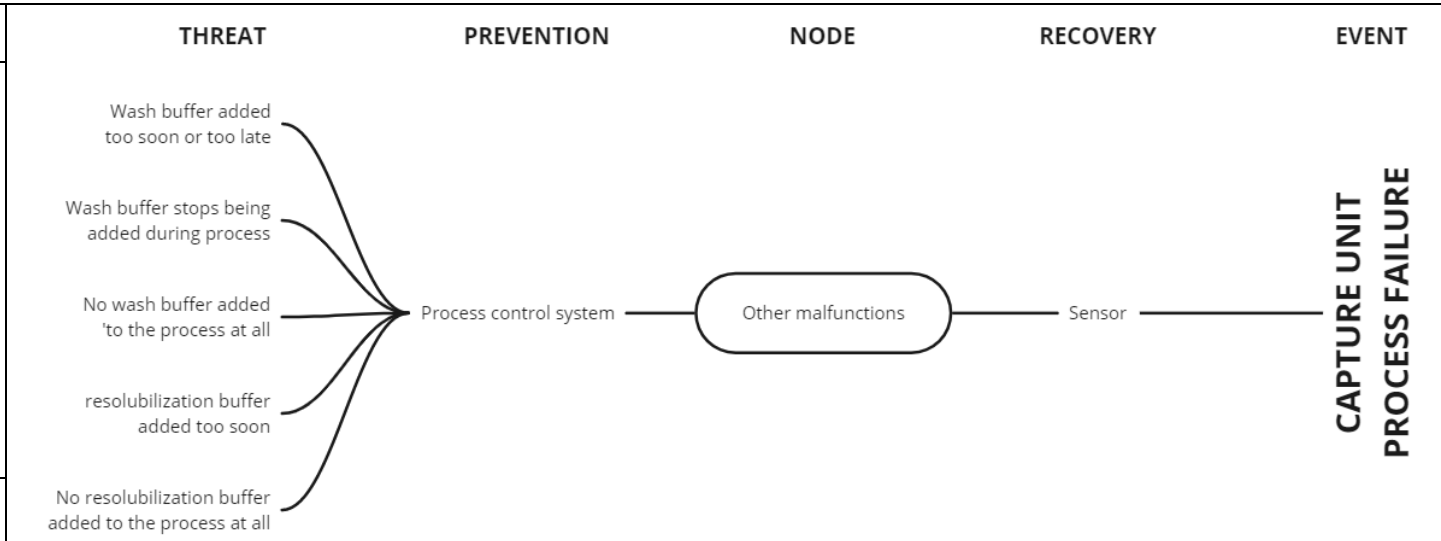
This node describes handling mistakes that increase cell mortality, leading to lower final product yield due to less cells available for production.
In the case of media addition, only the operator part is included in this node. The case where the system does not trigger an alarm when the phase switch has to occur is included in node A6.

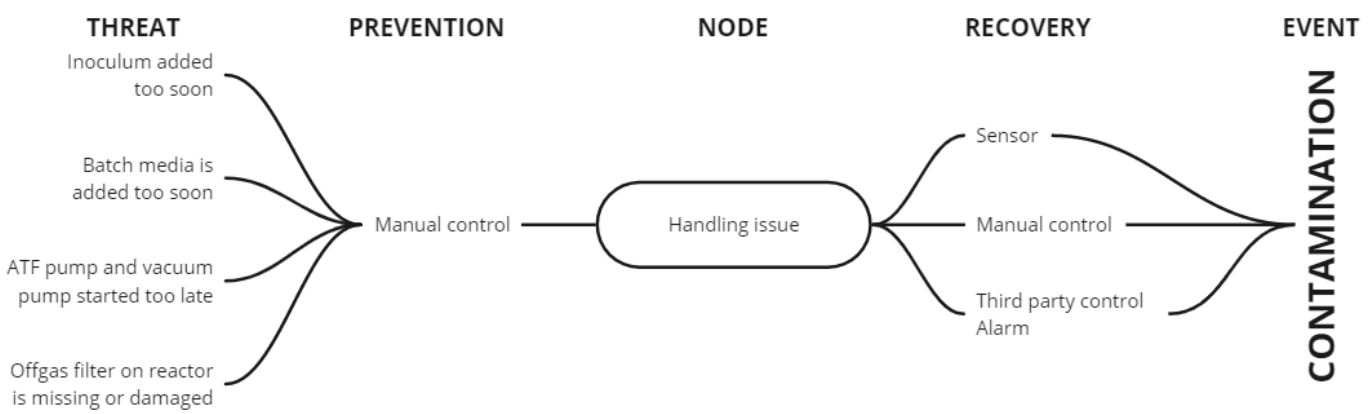
Corresponding SWIFT lines:
4,13,20,23,24,29,35,55

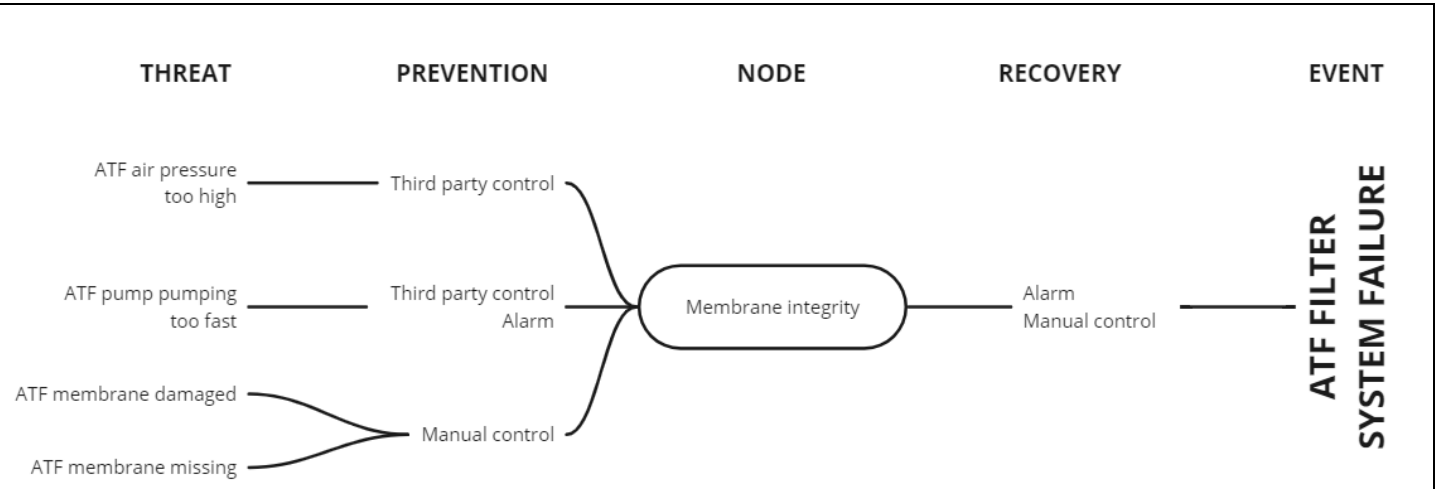


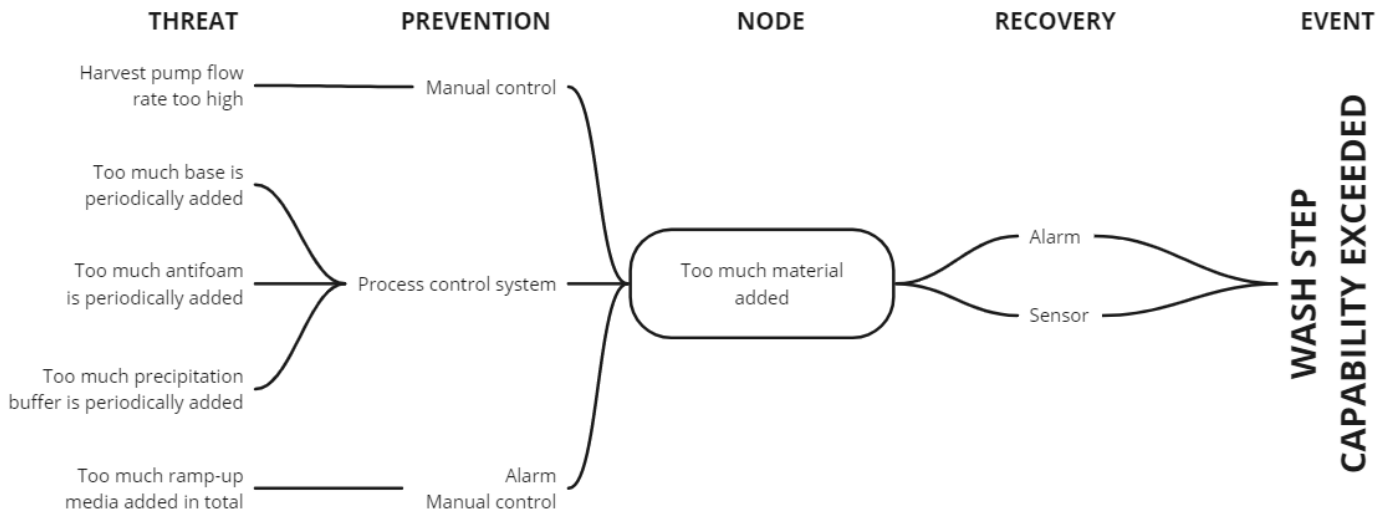
Risk parameter	Rating	Justification
Severity	Medium	Higher cell mortality is considered indirect product loss. Therefore, the severity is set to medium.
Detectability	Low	Handling issues are dependent on the operator itself, there is no automated process that relieves the operator from their responsibilities. Media bottle connection, as well as the correct addition time point are processes including manual steps.
Complexity	Low	The node revolves around the correct switch between cell culture phases, or simple material addition.
Occurrence	Medium	Due to many manual tasks included in this node, the occurrence is set to at least medium as human error are to be expected if the process is not described accordingly. Currently there are no SOPs in place.
Overall Risk	Medium	

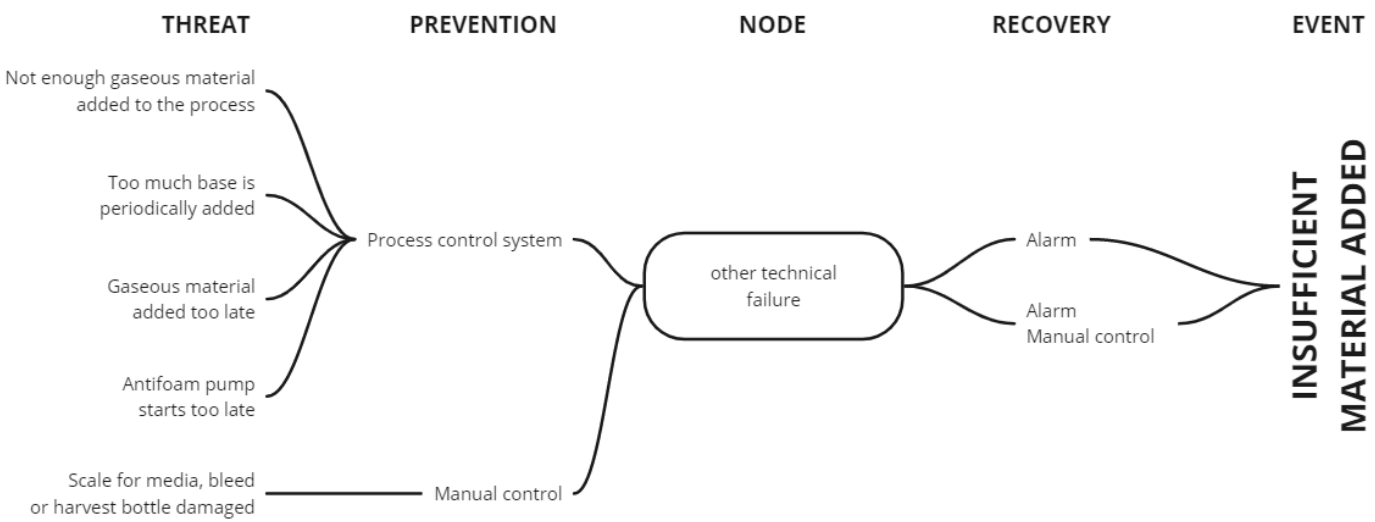
Node: A9		
Description: This node describes handing mistakes that can lead to lower cell growth which in turn lowers the overall product yield. It is similar to the A8 node as in that similar scenarios are included; however, the impact or timeframe of each scenario are considered not as severe as in A8 (e.g.: media addition too late, but not by much so the consequences are minor).		
Corresponding SWIFT lines: 2,3,4,11,12,13,23,24,35,44,45,53,55		
Risk parameter	Rating	Justification
Severity	High	Reduced process performance is severe due to resulting lower cell growth and therefore product yield. The existing recovery safeguards are not sufficient to compensate for the handling errors.
Detectability	Low	As media and inoculum addition is mostly manual, no automated safeguards are in place. If operational mistakes were made, the system would not detect them in most cases.
Complexity	Low	Like node A8, this one revolves around media-, material addition and cell culture phase switches.
Occurrence	Medium	Due to many manual tasks included in this node, the occurrence is set to at least medium as human errors are to be expected if the process is not described accordingly. Currently there are no SOPs in place.
Overall Risk	High	

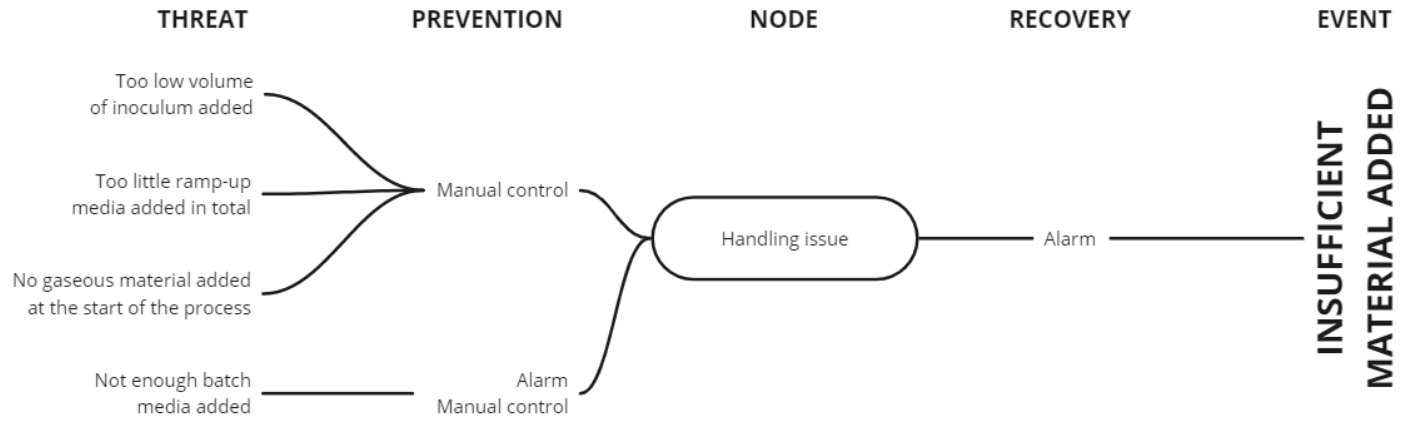
Node: A10		
Description: This node describes malfunctions that cause the capture unit process to fail. Failure of this process results in residual process liquid in the final product.		
Corresponding SWIFT lines: 113,114,115,118,119,123		
Risk parameter	Rating	Justification
Severity	High	As the final product composition is not yet defined, extent or identity of undesired components are hard to evaluate. However, independent from the type of impurity, extra components in the final product are undesirable. In case something goes wrong, off values can be seen but no recovery strategies are developed yet.
Detectability	High	All threats are controlled by the automated system, so malfunctions should be detected easily.
Complexity	Low	The problem is confined to the washing as well as the pH adjustment (resolubilization) step.
Occurrence	Low	Due to the automated nature of the threats, the risk of occurrence is expected to be low.
Overall Risk	Medium	

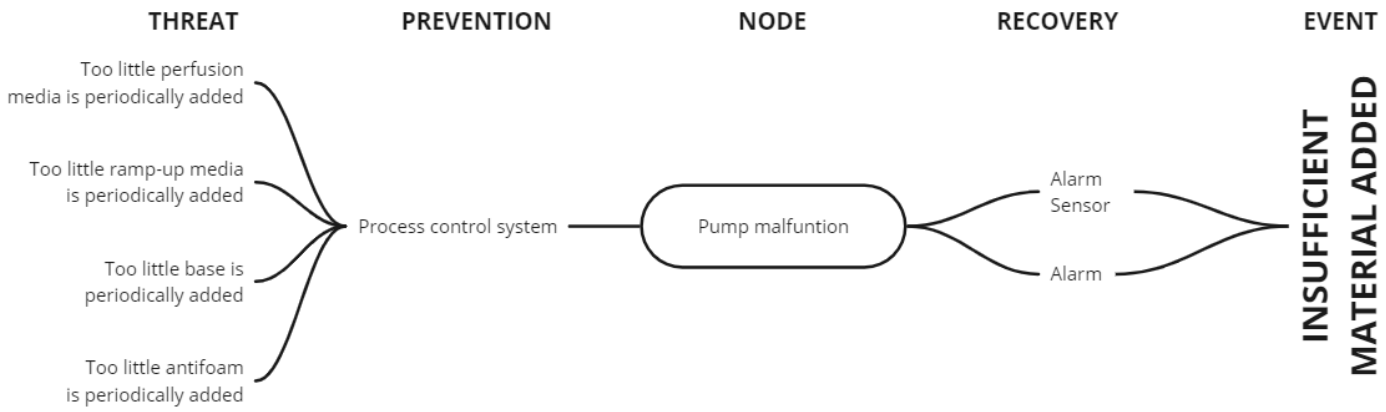
Node: A11		
Description: This node includes handling mistakes that can lead to contamination. It is the partner node to A1 since the combination of handling issues (after the sterility run) and a failed sterile run lead to contamination. The material addition threats only cause problems if the addition is done before the sterility run is finished.		
Corresponding SWIFT lines: 2,11,44,45,95		
Risk parameter	Rating	Justification
Severity	High	Contamination will cause the process to stop. There is no recovery once it occurs.
Detectability	Low	All threats are dependent on the operator's performance. Especially during addition for the batch phase, no automated controls are established.
Complexity	Low	Only few handling issues can cause the undesired contamination, and two of three are during batch process preparation.
Occurrence	Low	Only a few steps have to be performed. The chance of operator failure is expected, but still rather low.
Overall Risk	High	

Node: A12		
Description: This node includes scenarios where the membrane of the ATF system is damaged, or its filtration capability is lost. As a result, cells and or cell debris can enter process steps that they should not yet reach, but do not enter the final product due to numerous subsequent filtration steps.		
Corresponding SWIFT lines: 40,48,82,83		
Risk parameter	Rating	Justification
Severity	Medium	Even though cells or cell debris might get into other process steps, the capture unit is comprised of many filter steps which would filter these impurities out. It is still not desired, yet the final product should be rather safe.
Detectability	Medium	The ATF system is not connected to the process control system, meaning it must be checked by the operator, however it can detect problems and send alarms.
Complexity	High	A disrupted ATF system influences all subsequent units as well.
Occurrence	Low	The threats are not expected to occur often, even though some are operator dependent.
Overall Risk	Medium	

Node: A13		
Description: This node describes the scenario where addition of too much material can lead to exceedance of the wash step in the capture unit subunit. Even if the bleed rate is adapted to adjust to the exceedingly added materials, the composition of the matrix is altered which might not be possible to reduce by washing.		
Corresponding SWIFT lines: 28,58,65,70,99		
Risk parameter	Rating	Justification
Severity	Medium	As the final composition of the product is not yet defined, and the total amount that could end up in the final product is expected to be low at max., severity is rated at medium even if the recovery safeguards are mostly alarm based and not automated.
Detectability	High	Most threats are controlled automatically. Total amount of ramp-up added is managed by the system and exceeding this can only happen by a not well-timed switch to perfusion phase which is manually controlled (the system gives the timepoint).
Complexity	Low	It is a simple node. If too much material is added, and the wash step can't filter everything out, something ends up in the final product.
Occurrence	Low	The system is designed to exchange much material during the wash step. Exceedance of this capability is not expected to be happening often.
Overall Risk	Low	

Node: A14		
Description: This node includes technical malfunction, excluding pump rate defects (node A16) or handling issues (node A15), which lead to insufficient amounts of material (e.g.: substrate) added to the process. Due to lower amount of material, final yield is lower as well.		
Corresponding SWIFT lines: 31,32,65,68,86,87,88		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the extent of material missing, the effect is either more severe or not. On average, it is expected to not undergo lower limits of addition and therefore stay within the expected yield ranges.
Detectability	High	Most threats are automatically managed, and the scales are maintained regularly. The problem is considered well detectable.
Complexity	Medium	Since the harvest pump flow rate is fixed, insufficient material addition (e.g.: substrate) will cause problems for the capture unit.
Occurrence	Low	Fluctuations in addition are to be expected but that they are far outside the desired value is rather rare.
Overall Risk	Medium	

Node: A15		
Description: This node describes handling issues that lead to insufficient material being added to the process, resulting in lowered cell growth.		
Corresponding SWIFT lines: 9,16,26,35		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the scale of material missing, the effect is either more severe or not. On average, it is expected to not undergo lower limits of addition and therefore stay within the expected yield ranges.
Detectability	Low	All threats are dependent on manual interactions, there is no automated detection except for batch media addition where the reactor scale sends an alarm.
Complexity	Low	The principle is simple. Do not add enough material, and product yield will be lower.
Occurrence	Low	Fluctuations in addition are expected but having them well outside of the desired amount is rather rare.
Overall Risk	Medium	

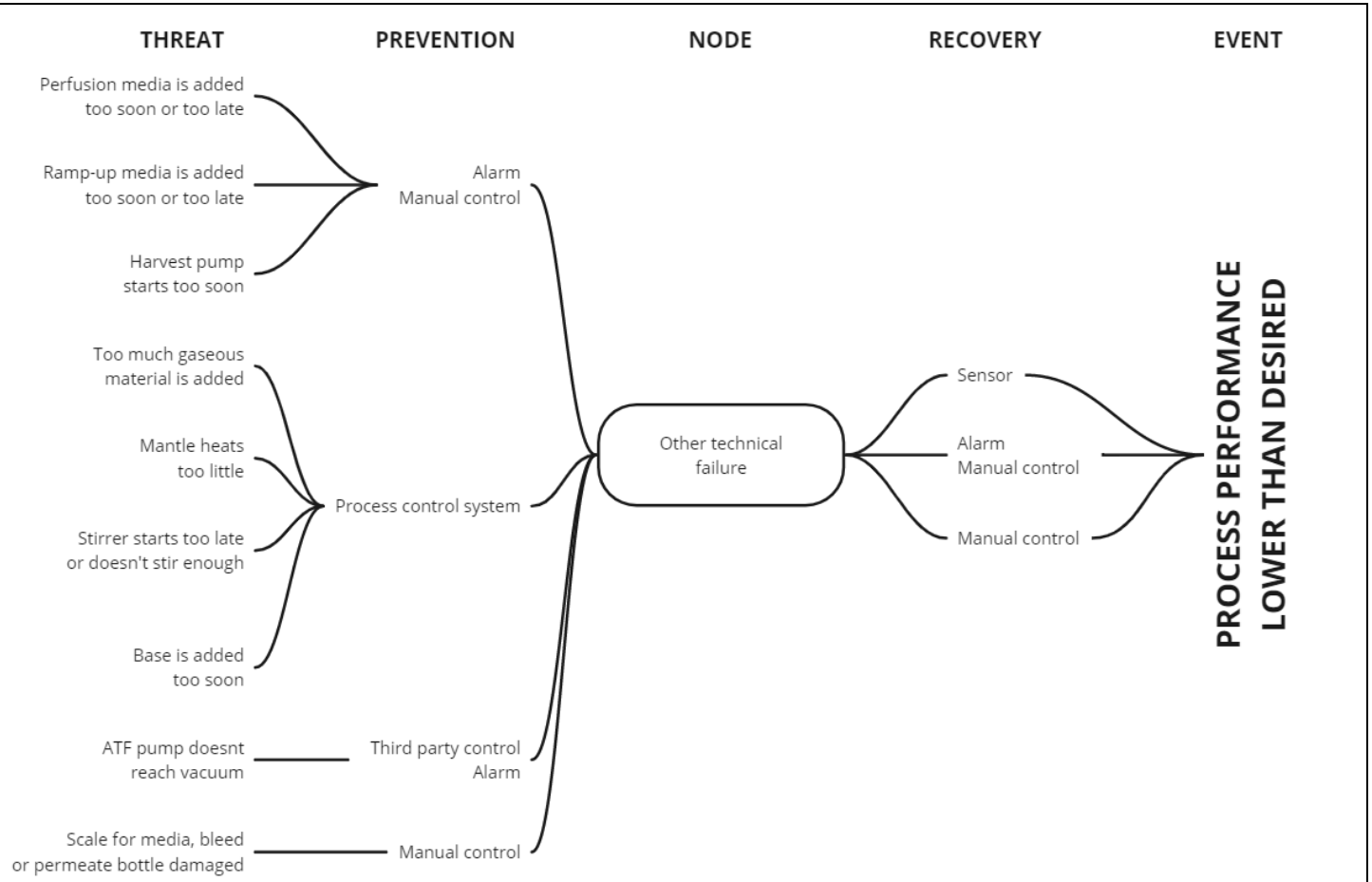
Node: A16		
Description: The node describes situations, where pumps did not add enough material which in the end resulted in lower cell growth during the cell culture process.		
Corresponding SWIFT lines: 14,25,64,69		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the scale of material missing, the effect is either more severe or not. On average, it is expected to not undergo lower limits of addition and therefore stay within the expected yield ranges.
Detectability	High	All pumps are automatically controlled, and flow sensors are used for real-time monitoring. The system can detect if too low volumes are pumped.
Complexity	Low	The node is straightforward. In case not enough material is added, product yield will be lower.
Occurrence	Low	Fluctuations in addition are expected but having them well outside of the desired amount is rather rare.
Overall Risk	Low	

Node: A17

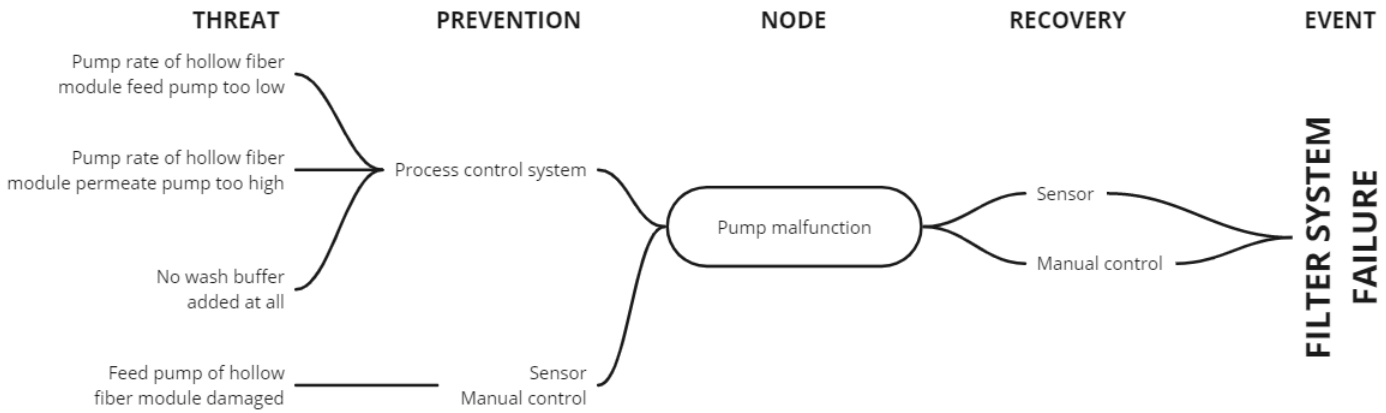
Description:

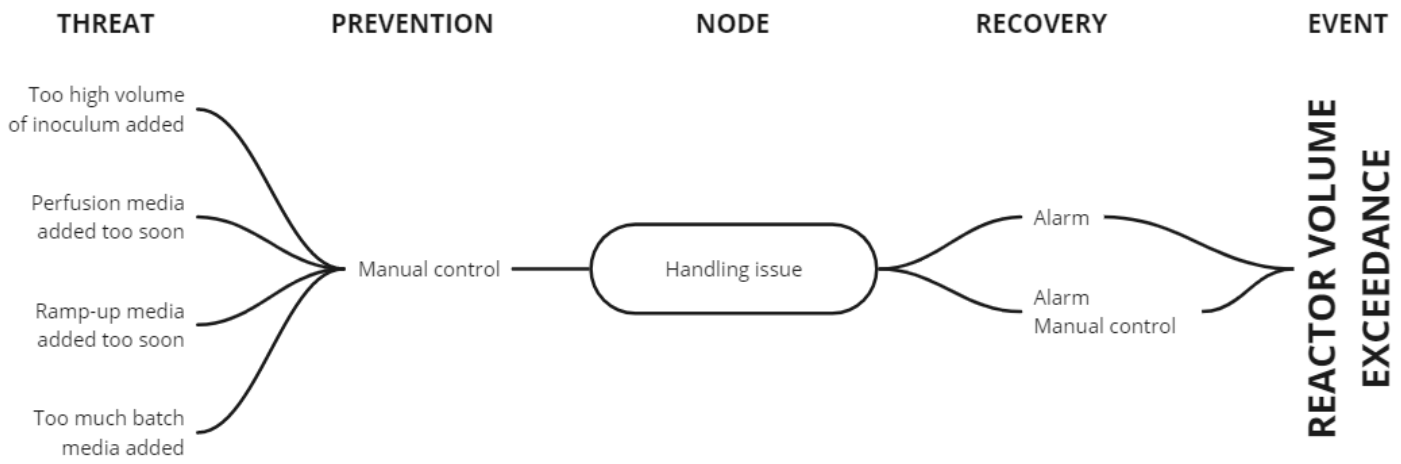
This node includes all technical failures that can lead to reduced process performance but excludes pump malfunctions (node A3) or handling issues (node A9).

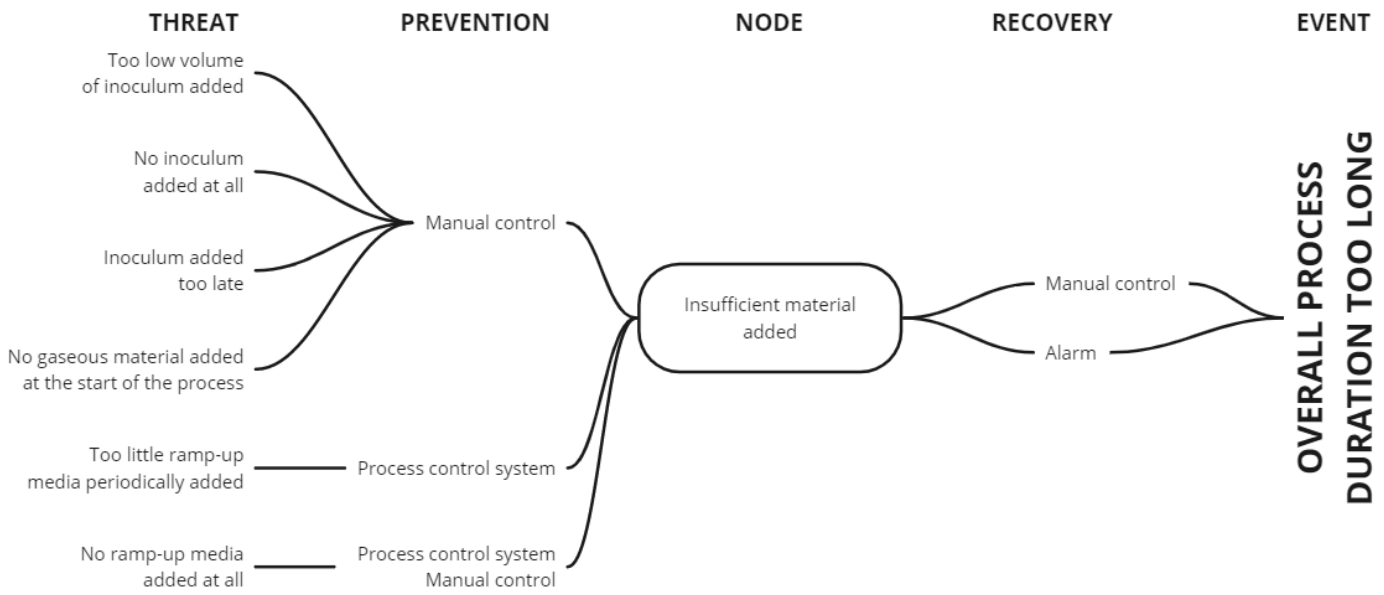
Corresponding SWIFT lines:
12,13,23,24,33,49,52,62,72,77,79,86,87,88



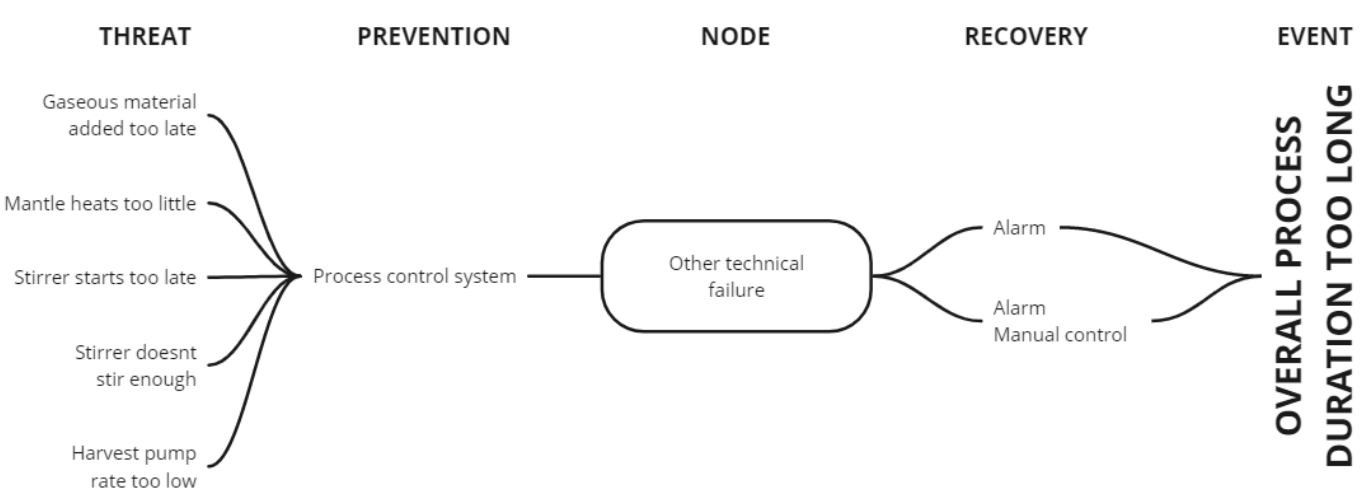
Risk parameter	Rating	Justification
Severity	High	Lowered process performance subsequently results in lower product yield, which is undesirable.
Detectability	Medium	Most of the threats are either automated, or at least automatically sending an alarm, and scales are maintained regularly.
Complexity	Medium	The problem revolves around the cell culture unit however, it can come from various sources and is therefore hard to pinpoint where the root cause of problems actually arise.
Occurrence	Medium	Due to many different threats, something is bound to be out of expectance. Therefore, the risk of occurrence is set to medium.
Overall Risk	Medium	

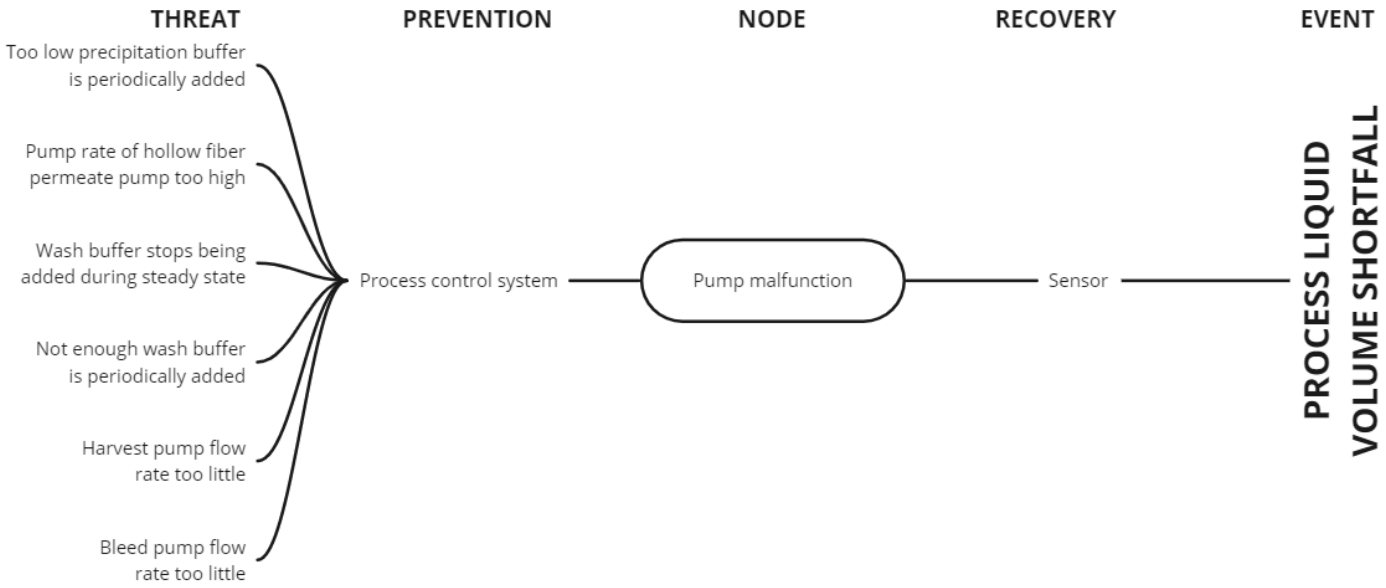
Node: B1		
Description: This node describes pump malfunctions in the capture unit, which lead to a failure of this subunit. For example: process liquid that gets pumped in the wrong direction or drying of the system due to lack of buffer addition. Does only include scenarios that result in technical shut down, not reduced product yield.		
Corresponding SWIFT lines: 104,106,110,118		
Risk parameter	Rating	Justification
Severity	High	In case the downstream unit has to shut down, the whole process is terminated. However, it is dependent on how bad the pumps malfunction.
Detectability	High	Pump regulation is automated, in case one is damaged, sensors detect something is off. Maintenance also helps preventing failures.
Complexity	Medium	Even though only a handful of pumps can cause this specific problem, the way it does is not that simple. Most faulty pump rates lead to different symptoms like liquid being pumped in the wrong direction or causing pressure problems.
Occurrence	Low	It is not common for a maintained pump to malfunction. Also, only two pumps can drive this problem. Therefore, a low risk of occurring.
Overall Risk	Medium	

Node: B2		
Description: This node describes mishandling by the operator which leads to excessive reactor volume in the cell culture unit. Material used for process control like base or antifoam are not included as their added amounts are very low and therefore considered negligible in comparison.		
Corresponding SWIFT lines: 4,12,19,23		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is exceedingly added, severity might differ. The system does alarm once too much volume is added, so the working volume is not exceeded. However, this requires manual interference (by increasing the bleed rate). In case of batch or inoculum addition, small excursions are not detected.
Detectability	Medium	There is no automated safeguard which stops the volume from exceeding, however sufficient monitoring tools are established to quickly detect the problem.
Complexity	Low	Add too much material and exceed the reactor volume. The whole node is based on simple logic.
Occurrence	Low	Small excursions can occur frequently, but to actually exceed the working volume and causing a problem for the system is considered rare.
Overall Risk	Medium	

Node: B3	
Description: This node describes threats, where delays result in an undesirable long process time. Either caused by omitted process steps, or wrongly performed steps that elongate process time beyond acceptable ranges. Other technical issues are described in node B4.	
Corresponding SWIFT lines: 3,7,9,25,29,35	

Risk parameter	Rating	Justification
Severity	Low	The actual delay is hard to predict as it depends on the amount of material missing. In the current development stage, time delay is not considered a critical issue.
Detectability	Low	Most of the threats are manually caused. There is no automation for inoculum addition. Only the ramp-up addition is somewhat automated, yet the initial addition is still dependent on the operator.
Complexity	Low	Simple node. If less material is added, process duration increases.
Occurrence	Medium	Due to most threats being manually performed, the risk for occurrence is medium as long as process descriptions or GMP-based safeguards (4-eye principle etc.) are established.
Overall Risk	Medium	

Node: B4		
Description: This node describes technical failures leading to increased process duration. Any threats that describe insufficient material addition is included in node B3.		
Corresponding SWIFT lines: 31,56,72,77,79,104		
Risk parameter	Rating	Justification
Severity	Low	It is not yet defined how long a process should take. Therefore, a delay cannot be evaluated sophistically. Furthermore, the actual delay is hard to predict as it depends on the type and extent of the technical malfunction. In the current development stage, time delay is not considered a critical issue.
Detectability	High	All threats are controlled by the system and easily detectable.
Complexity	Low	Even though various technical issues can arise from different sources, the underlying principle remains simple as only the process time is considered in this node.
Occurrence	Low	Due to the automated nature of the threats, risk of occurrence is considered low.
Overall Risk	Low	

Node: B5		
Description: This node describes pump malfunctions resulting in lower process liquid within the capture unit. Similar to reactor volume shortfall (node B10). Not enough liquid within the system would cause the capture unit to fail as pressure within the system will be messed up. The resolubilization buffer addition is not included, as it is located at the end of the process and missing it would not cause the process to terminate.		
Corresponding SWIFT lines: 56,57,98,110,115,117		
Risk parameter	Rating	Justification
Severity	Medium	Overall, the system should be able to handle lower amounts of process liquid within the capture unit. However, currently the whole subunit is adjusted to the harvest pump rate. In case some pumps do malfunction, the system cannot adjust and therefore causes problems. The severity however depends on the amount pumped.
Detectability	High	All threats are controlled by the system and easily detectable.
Complexity	Medium	Even though the node seems simple, the interactions between the pumps is rather complex. They should react to each other in order to adjust to different values apart from the harvest rate. The harvest rate itself can influence the whole volume shortfall as well if pumps can not react to altered harvest or bleed rates.
Occurrence	High	Even though the pumps are automated, risk for occurrence is considered high due to the sheer number of pumps involved.
Overall Risk	High	

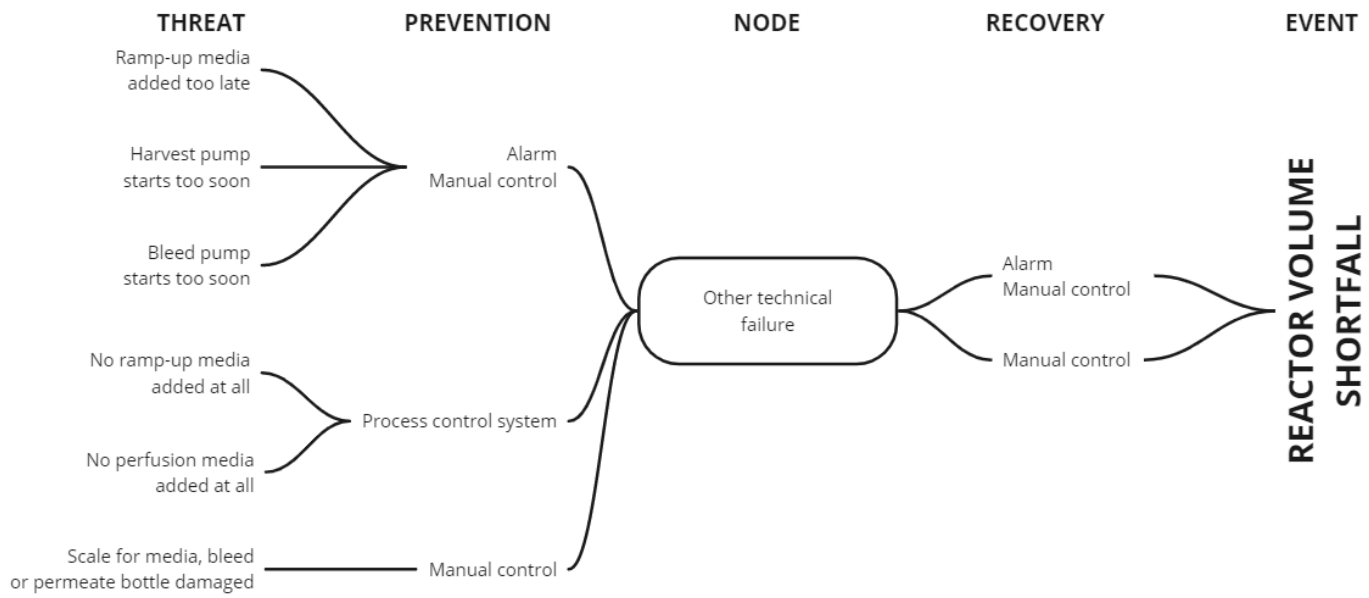
Node: B6

Description:

This node describes technical threats that cause the cell culture reactor to have low volume. Falling below the working volume terminates the cell culture process and therefore the production.

It does not include handling issues (node B13) or pump malfunctions (node B10).

Corresponding SWIFT lines:
24,29,52,53,86,87,88



Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is missing, severity might differ. The system does alarm once too low volume is reached, so the system does not fall under the working volume. However, this requires manual interference (manual start of media addition or pump adjustment).
Detectability	Medium	Roughly half of the threats are at least semi-automated, but the manual portion is still prevalent. The bottle scales are maintained, so manual interference is not necessary often.
Complexity	Low	Either delayed media addition, or premature pump activation can lead to the simple outcome.
Occurrence	Low	Most of the threats are at least semi-automated, and scale defects are rare if maintenance is kept up to date. Therefore, risk of occurrence is low.
Overall Risk	Medium	

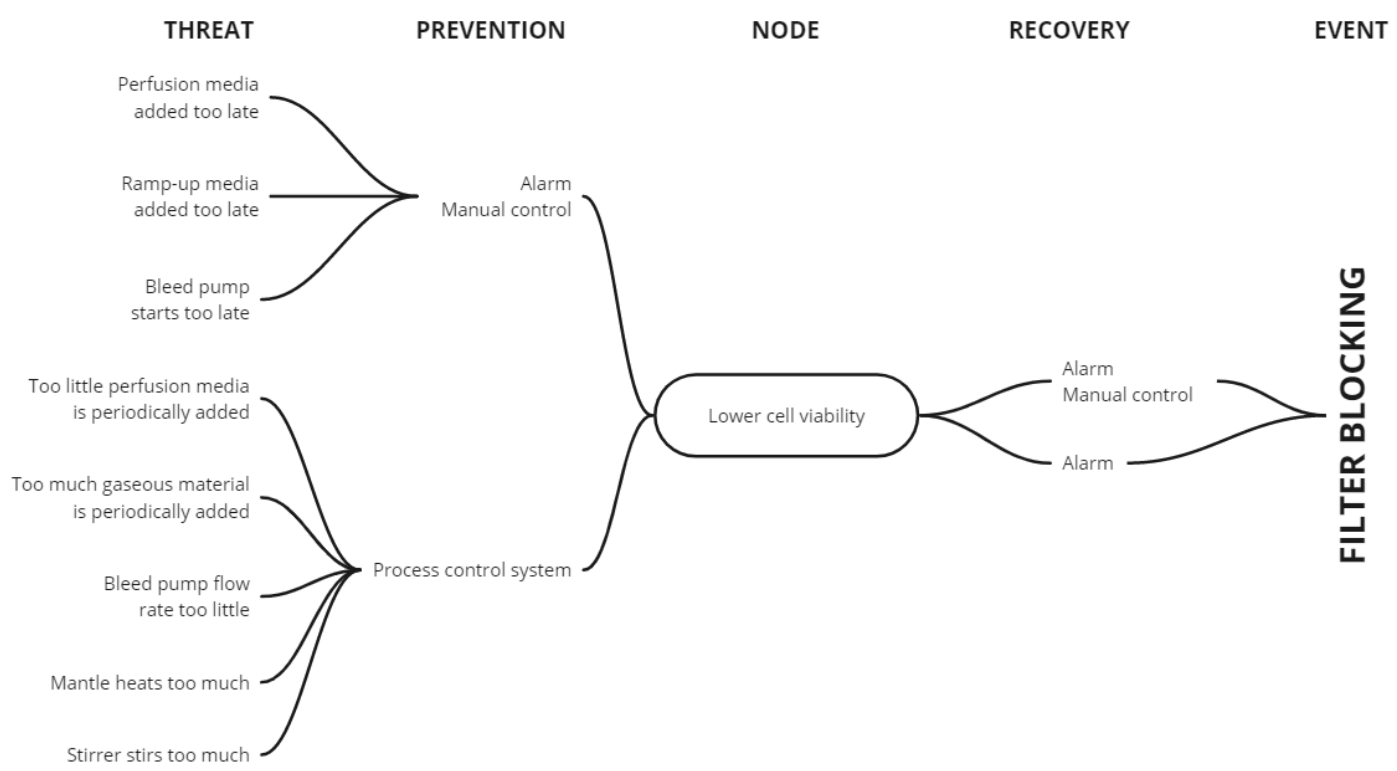
Node: B7

Description:

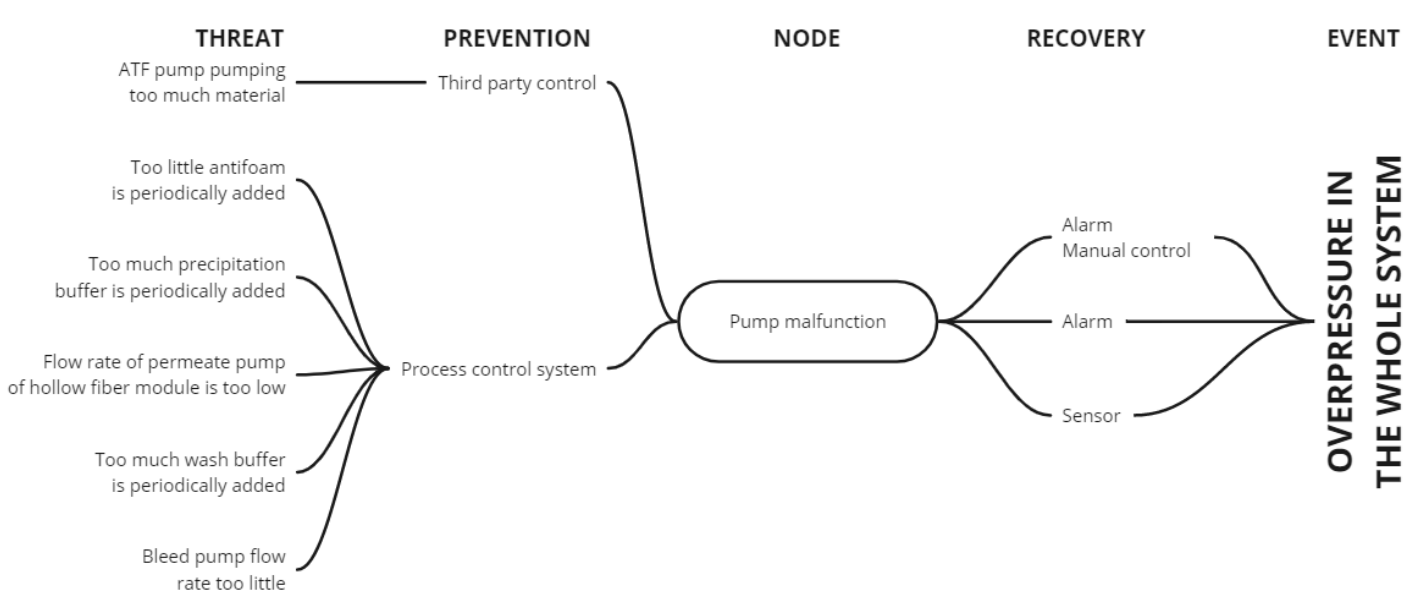
This node describes threats that lead to reduced cell viability, meaning increased dead cells in the system. These cells and cell debris can subsequently lead to filter blocking of the ATF subunit.

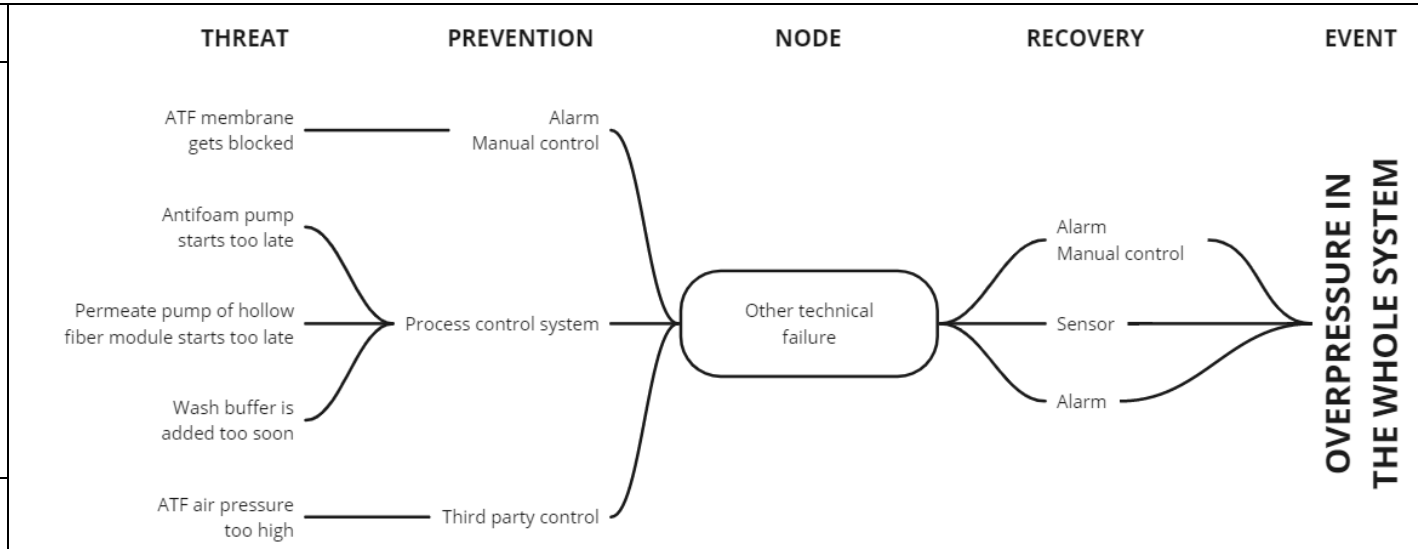
In case the blocking is not detected, and membrane rupture occurs, the issue becomes much bigger and process termination is pretty likely.

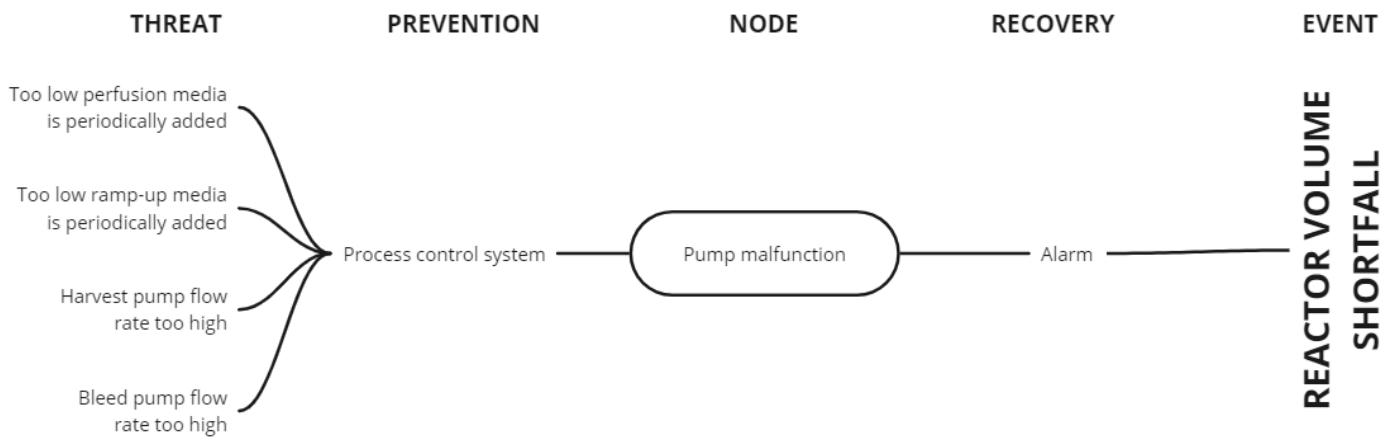
Corresponding SWIFT lines:
13,14,24,33,55,57,73,80

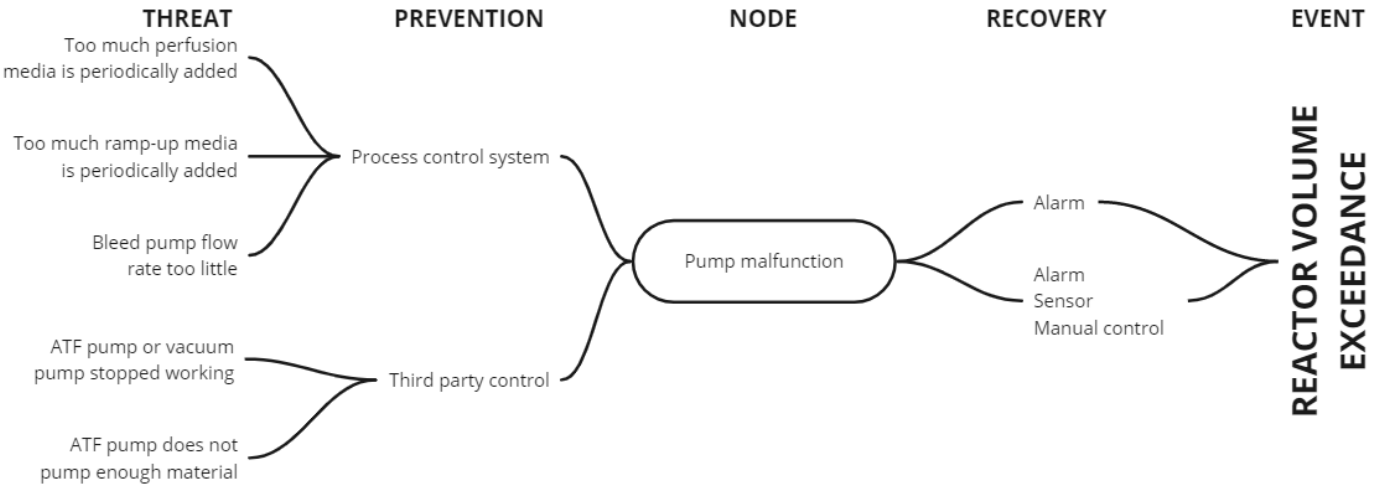


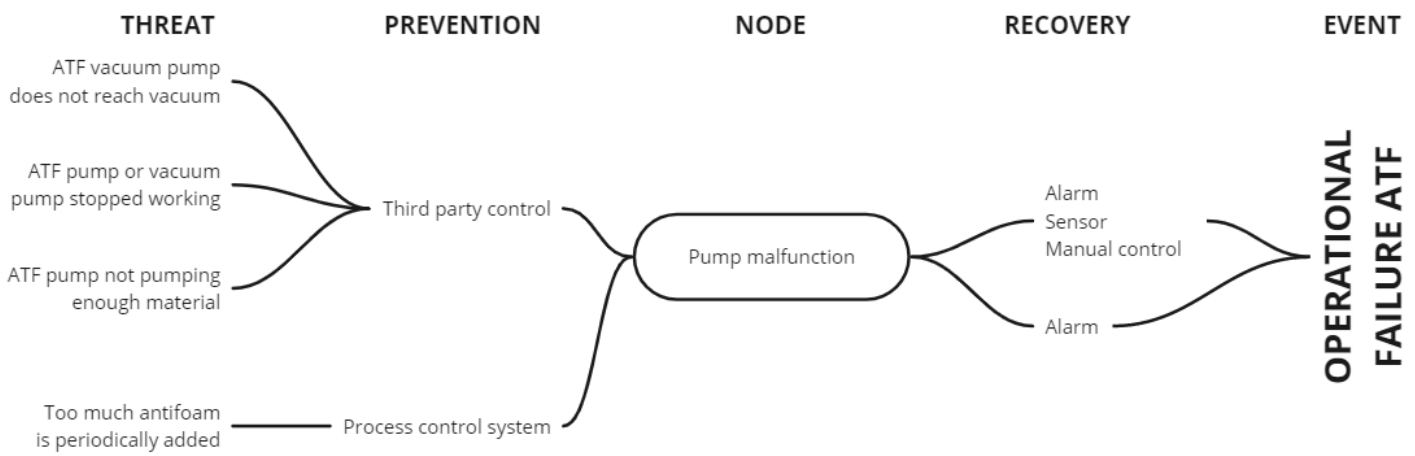
Risk parameter	Rating	Justification
Severity	Medium	In case the filter is blocked, it can be exchanged. However, this interrupts product flow to the capture unit and subsequently causes problems there. Furthermore, most threats do send an alarm which can then be interpreted as an indicator for lower viability as it is currently not directly measured.
Detectability	High	Good detectability, as most threats are automated. Those that are not, send an alarm at least.
Complexity	Medium	Even though many threats can cause the problem, it all boils down to a single component in the whole process. The consequence can therefore always be pinpointed to the ATF membrane. However, in case it is not maintained in time, and membrane rupture occurs, the issue becomes much more severe and complex as the capture unit is influenced.
Occurrence	High	It is expected that the filter will block after a certain time of running the production process. The threats will reduce the time until this is happening, therefore the risk of occurrence is set to high.
Overall Risk	High	

Node: B8		
Description: This node describes pump malfunctions, that lead to increased pressure within the system. Pressure issues might alter the liquid flow or put strains on tubing or filters. Other technical defects leading to the same issues are described in node B9.		
Corresponding SWIFT lines: 48,57,69,99,109,116		
Risk parameter	Rating	Justification
Severity	Medium	Overpressure poses a problem for the system by influencing pumps and the hollow fiber capsule within the capture unit. Overpressure results in a premature switch of the hollow fiber due to increased feed pressure, which messes with the overall system control.
Detectability	High	A high degree of automation is present for this node. The ATF pump is controlled by the ATF system, and it sends out an alarm in case something goes wrong. Furthermore, pressure sensors are established in the capture unit, allowing for early detection.
Complexity	Medium	Different subunits can be impacted by overpressure in the system.
Occurrence	Medium	Some sort of pressure fluctuation is to be expected, however as limits are not yet set, occurrence of overpressure is hard to predict. Therefore, it is set to medium.
Overall Risk	Medium	

Node: B9		
Description: This node describes technical malfunctions, that lead to increased pressure within the system. Pressure issues might alter the liquid flow or put strains on tubing or filters. Pump malfunctions leading to the same issues are described in node B8.		
Corresponding SWIFT lines: 39,40,68,108,113		
Risk parameter	Rating	Justification
Severity	Medium	Overpressure poses a problem for the system by influencing pumps and the hollow fiber capsule within the capture unit. Overpressure results in a premature switch of the hollow fiber due to increased feed pressure, which messes with the overall system control.
Detectability	High	Threats for this node can be reliably detected, even if not all are fully automated. Issues revolving around the ATF are seen on the ATF console, but not connected to the overall process control system. Pressure sensors within the capture unit are established as well.
Complexity	Medium	Due to the unknown impact of overpressure, complexity is hard to predict. To be on the safer side, the risk of complexity is considered medium.
Occurrence	Medium	Some sort of pressure fluctuation is to be expected, however as limits are not yet set, occurrence of overpressure is hard to predict. Therefore, it is set to medium.
Overall Risk	Medium	

Node: B10		
Description: This node describes pump malfunctions that cause the cell culture reactor to have low volume. Falling below the working volume terminates the cell culture process and therefore the production. It does not include handling issues (node B13) or other technical failures (node B6).		
Corresponding SWIFT lines: 14,25,58,59		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is missing, severity might differ. The system does alarm once too low volume is reached, so the system does not fall under the working volume. However, this requires manual interference (manual start of media addition or pump adjustment).
Detectability	High	All pumps are controlled by the system. Threats can be detected easily, by means of flow sensors.
Complexity	Low	Either not enough material is added, or too much is drained from the reactor. Either way the risk of complexity for this node is low.
Occurrence	Low	Fluctuations are expected, but not on a scale where the working volume is regularly fallen below. Therefore, risk of occurrence is still set to low.
Overall Risk	Low	

Node: B11		
Description: This node describes pump malfunctions that cause the cell culture reactor to have high volume. Exceeding the working volume terminates the cell culture process and therefore the production. It does not include handling issues (node B2) or other technical failures (node B14).		
Corresponding SWIFT lines: 17,27,37,38,47,57		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is exceedingly added, severity might differ. The system does alarm once too much volume is added, so the working volume is not exceeded. However, this requires manual interference (stopping of media addition).
Detectability	High	Most of the threats for this node can be reliably detected, even if not all are fully automated. Issues revolving around the ATF are seen on the ATF console, but not connected to the overall process control system.
Complexity	Low	Add too much material and exceed the reactor volume. The whole node is based on simple logic.
Occurrence	Low	Small excursions can occur frequently, but to actually exceed the working volume and causing a problem for the system is considered rare.
Overall Risk	Low	

Node: B12		
Description: This node describes pump malfunctions that lead to failure of the cell culture ATF filter system. It basically describes possible failures of the two ATF pumps (feed and vacuum) leading to the system not being able to function anymore. Extensive Antifoam addition is included in this node, as it can lead to system failure due to blocking of the filter membrane.		
Corresponding SWIFT lines: 37,38,47,49,70		
Risk parameter	Rating	Justification
Severity	Medium	If the filter unit does not work anymore, the whole cell culture unit process and subsequently the overall process must be terminated. However, it does operate in tandem mode, meaning that there are two ATF modules which operate alternatively, and the process termination can be circumvented by using the second unit.
Detectability	Medium	Threat detection is dependent on the ATF control system, which does send alarms, but these need to be act upon by the operator. It is not connected to the main process control system therefore the risk is set to medium.
Complexity	Low	The principle is rather simple. Everything is revolving around the ATF subunits and its pumps. Threats are easily pinpointed.
Occurrence	Low	Most of the threats are prevented by a good maintenance schedule. Sudden failures are expected to be rare and therefore risk is considered low.
Overall Risk	Medium	

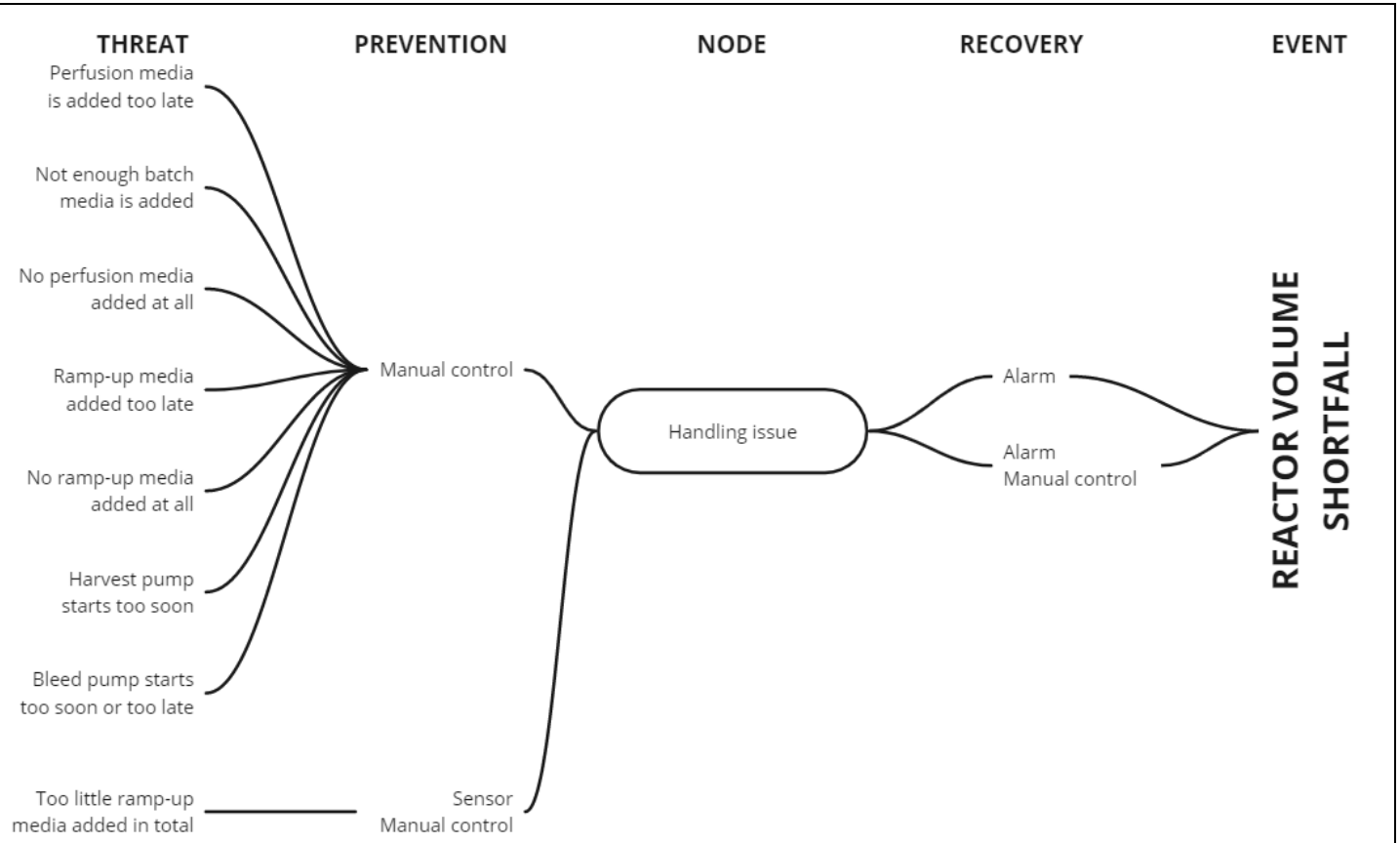
Node: B13

Description:

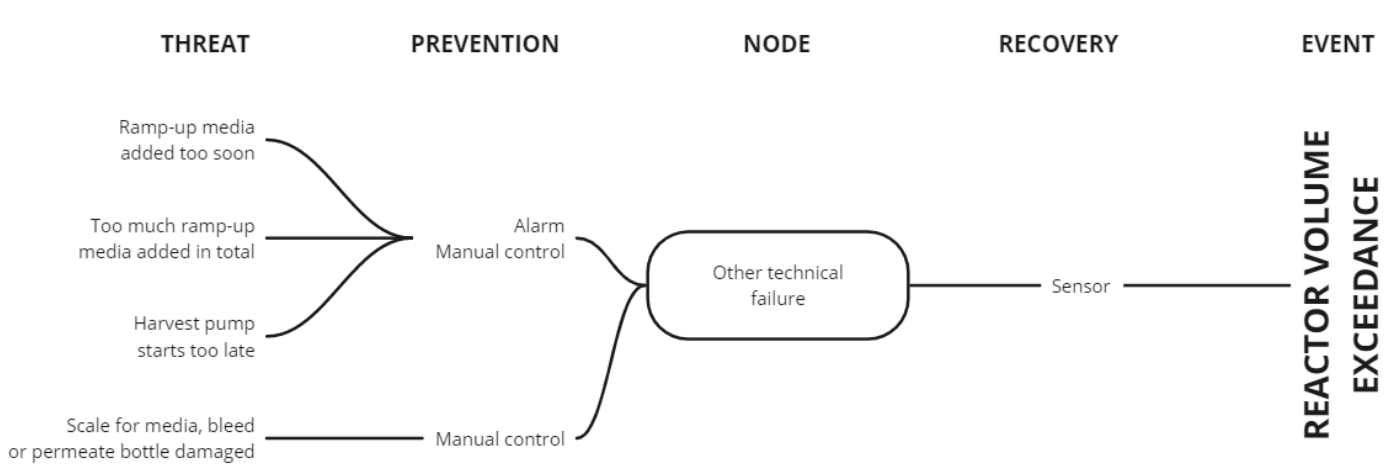
This node describes handling issues that cause the cell culture reactor to have low volume. Falling below the working volume terminates the cell culture process and therefore the production.

It does not include pump malfunctions (node B10) or other technical failures (node B6).

Corresponding SWIFT lines:
13,16,20,24,26,29,52,53,55



Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is missing, severity might differ. The system does alarm once too low volume is reached, so the system does not fall under the working volume. However, this requires manual interference (manual start of media addition or pump adjustment).
Detectability	Medium	The system does send alarms but requires operator interference.
Complexity	Low	The issue revolves around the addition of the cell culture media and the correct timepoint of addition. It is rather simple.
Occurrence	Low	Fluctuations are expected, but not on a scale where the working volume is regularly fallen below. Therefore, risk of occurrence is still set to low.
Overall Risk	Medium	

Node: B14		
Description: This node describes other technical failures that cause the cell culture reactor to have high volume. Exceeding the working volume terminates the cell culture process and therefore the production. It does not include handling issues (node B2) or pump malfunctions (node B11).		
Corresponding SWIFT lines: 23,28,54,86,87,88		
Risk parameter	Rating	Justification
Severity	Medium	Depending on the amount of volume that is exceedingly added, severity might differ. The system does alarm once too much volume is added, so the working volume is not exceeded. However, this requires manual interference (stopping of media addition).
Detectability	Medium	Scale issues are covered by maintenance, but an immediate defect would not be detected by the operator. The system cannot react automatically to the pump timepoint failures but do detect and alarm it.
Complexity	Low	Add too much material and exceed the reactor volume. The whole node is based on simple logic.
Occurrence	Low	Small excursions can occur frequently, but to actually exceed the working volume and causing a problem for the system is considered rare. Furthermore, the threats in this node occur rather rare by nature.
Overall Risk	Medium	

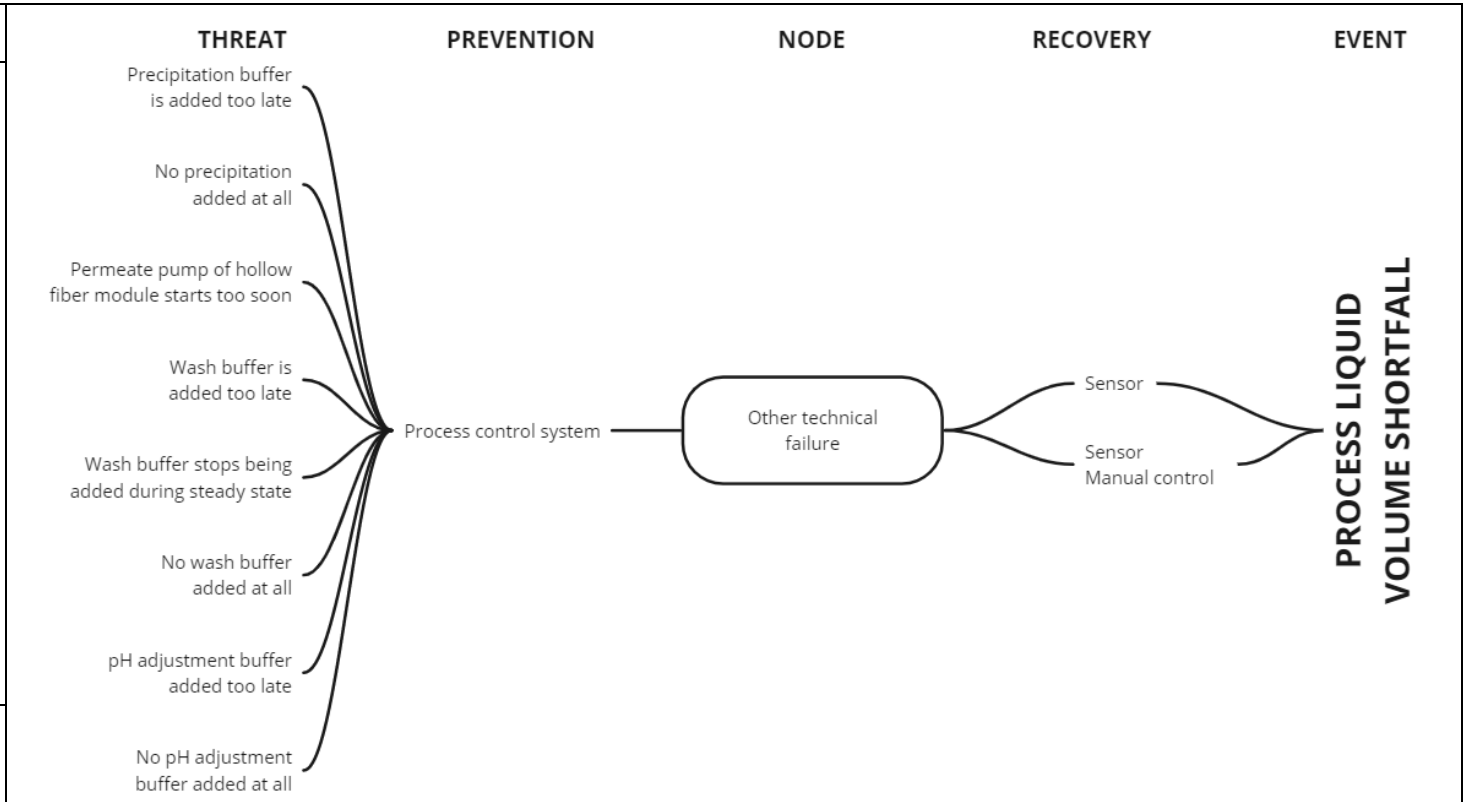
Node: B15

Description:

This node describes other technical failures resulting in lower process liquid within the capture unit. Similar to reactor volume shortfall (node B10).
Not enough liquid within the system would cause the capture unit to fail as pressure within the system will be messed up.

Pump malfunctions leading to the same event are described in node B5.

Corresponding SWIFT lines:
97,100,107,114,115,118,120,123



Risk parameter	Rating	Justification
Severity	Medium	Overall, the system should be able to handle lower amounts of process liquid within the capture unit. However, currently the whole subunit is adjusted to the harvest pump rate. In case some pumps do malfunction, the system cannot adjust and therefore causes problems. The severity however depends on the amount pumped.
Detectability	High	All threats are controlled by the system and easily detectable. In case no buffer is added at all, operator interference is necessary for recovery.
Complexity	Medium	Even though the node seems simple, the interactions between the pumps is rather complex. They should react to each other in order to adjust to different values apart from the harvest rate. They currently do not, so it is still considered low.
Occurrence	Low	Due to the automated nature of the threats, risk of occurrence is considered low.
Overall Risk	Medium	