Development of a Risk Management System for Consumables Used in Biopharmaceutical Manufacturing

by

David Linders
B.S. Bioengineering, University of Washington, 2009

Submitted to the MIT Sloan School of Management and the Mechanical Engineering Department in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration and
Master of Science in Mechanical Engineering

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Signature of Author _____
Mechanical Engineering, MIT Sloan School of Management
May 10, 2013

Certified by _____
Josef Oehmen, Thesis Supervisor
Research Scientist, MIT Sociotechnical Sciences Research Center

Certified by _____
Warren Seering, Thesis Reader
Weber/Shaughness Professor of Mechanical Engineering and Engineering Systems

Certified by _____
Roy Welsch, Thesis Supervisor
Eastman Kodak Leaders for Global Operations Professor of Management and Engineering Systems

Accepted by _____
David E. Hardt, Chairman, Committee on Graduate Students
Department of Mechanical Engineering

Accepted by _____
Maura Herson, Director of MBA Program
MIT Sloan School of Management

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Abstract

Injectable drugs, like those manufactured by the BioPharmOps group of Novartis Pharmaceuticals AG, must conform to strict guidelines for purity and potency. Recent non-conformances of critical supplied consumables have revealed potential business and patient safety risks for biotechnology manufacturers worldwide. As a result, Novartis has launched a program to enhance control systems over all consumables and their suppliers. Within this program, the author has developed a system to identify, analyze, and mitigate the various risks which may impact the business due to non-conformances in supplied consumables.

The first function of the system is the identification of key risks and their potential effects according to various failure modes that have been observed during the use of the consumables in production. This is accomplished with a standardized list of possible failure modes which can be applied to all consumables. The categorization allows the relative risk of each failure mode to be compared among consumables.

Secondly, the risk of contamination is evaluated using a Failure Modes and Effects Analysis (FMEA) framework. The three dimensions of the FMEA framework are the severity, likelihood, and detectability of a failure. The severity of each failure mode is assessed by analyzing the quantitative and qualitative impact that a failure might have on the purity and potency of the drug. This calculation is based on the properties of each consumable and its use in the production system. The likelihood of failure events is assessed through an analysis of the complexity of the consumable and its supply chain, and a review of the quality systems at the supplier. Detectability analysis considers the tests and inspections in place at various stages including consumable manufacturing, receiving inspection, and in-process tests during drug manufacturing which could detect a non-conformance. The total risk level is evaluated as the product of these three dimensions and a threshold is defined for requiring additional mitigations for these risks. This risk assessment method is implemented in an automated worksheet to ensure consistency among users and efficient analysis.

The third outcome of the system is the recommendation of mitigations to reduce total exposure to contamination risk. Mitigations may be internal (new tests and inspections) or implemented at the supplier (improved sampling rates, enhanced general quality systems, or new controls). The recommended mitigations provide guidance for the reduction of risks to an acceptable level, and when implemented, the impact and frequency of non-conformances will be diminished. Ultimately, this reduces Novartis' exposure to potential business loss and protects patients from injury caused by contamination.

Thesis Supervisor: Josef Oehmen
Title: Research Scientist, MIT Sociotechnical Sciences Research Center

Thesis Supervisor: Roy Welsch
Title: Eastman Kodak Leaders for Global Operations Professor of Management and Engineering Systems

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Glossary

These terms may not be explicitly defined in the text but are useful in the context of the research presented.

Definitions

Biopharmaceutical – A drug made using a biotechnology manufacturing process. In the context of this work, the drug is a monoclonal antibody protein made using mammalian cell culture.

Biotechnology – The use of biological systems to produce pharmaceuticals or other useful products.

Consumable – Disposable items that are consumed or used for a limited and pre-defined period of time (batch or campaign) in a production process or process environment that create or preserve the quality of the product (i.e. potency, purity, content of uniformity, microbiological purity, particles matter, identity).

Drug substance – Any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

Excipient – Substances other than the active pharmaceutical ingredient, which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Parenteral – A drug which enters the body through routes other than the mouth. This includes infusion, injection, or implantation. In the context of this work, parenteral drugs are injected.

Raw materials – A general term used to denote Starting Materials, reagents, and solvents intended for use in the production of intermediates and APIs. Also includes chromatography resins for filtering and any other powder or liquid used during the production process except for the maintenance of equipment.

Spare Parts – Spare parts are parts of equipment that are replaced during maintenance and repair. Spare Parts are intended to replace a corresponding item in order to restore the original function of the item.

Abbreviations

API	Active Pharmaceutical Ingredient
AQL	Acceptable Quality Limit
BPOG	BioPhorum Operations Group
BioPharmOps	Biopharmaceutical Operations

CoA	Certificate of Analysis
CoC	Certificate of Compliance/Conformance
DS	Drug Substance
DP	Drug Product
FMEA	Failure Mode and Effects Analysis
ICH	International Conference on Harmonisation
MCB	Master Cell Bank
QA	Quality Assurance
QC	Quality Control
RM	Raw Material
SOP	Standard Operating Procedure
UF/DF	Ultrafiltration/Diafiltration
WCB	Working Cell Bank

1 Introduction

1.1 Context and Thesis Summary

Biopharmaceuticals Context

Pharmaceutical drugs produced using biotechnology processes have been commercially available since the early 1980's when a form of insulin was first developed with recombinant DNA. Since then, the term "biopharmaceuticals" has been used to describe proteins (including antibodies), nucleic acids (DNA and RNA), or microorganisms which are produced using modified cell cultures. In general, cell cultures with special genetic attributes are grown in large batches, the active pharmaceutical ingredient (API) is extracted, the impurities are removed, excipients are added, and the formulated drug is distributed into doses for patients.

Company Context

The Novartis biopharmaceutical production facility in Huningue, France produces commercial and investigational monoclonal antibodies using mammalian cell cultures. The site has been producing the antihistamine Xolair® for the treatment of severe asthma since 2006 [1]. Simulect® is an immunosuppressive marketed for the prevention of organ rejection following kidney transplantation [2]. The site's most recent commercial release, Ilaris®, is indicated for the treatment of the rare diseases collectively known as cryopyrin associated periodic syndromes [1]. The site is the leading biopharmaceutical production center for Novartis and is also involved in several ongoing investigational programs.

Project Motivation

Recent deviations arising from non-conforming consumables (also known as disposables, examples shown in Figure 1), such as filters and temporary storage containers, have highlighted potential business and patient safety risks for biopharmaceutical manufacturers worldwide. Contaminants and functional failures in supplier consumables can lead to significant product loss, investigational costs, and even regulatory impact. As a result, Novartis has launched a program to enhance quality oversight of all consumables and their suppliers. To achieve a reduction in the frequency and impact of non-conformances, Novartis needs to understand the various risks, prioritize them for implementing mitigations, and dedicate resources to those actions which will have the greatest risk-mitigating effect.

Summary of Work

This thesis describes the conception and implementation of a risk management system which can be used to understand the various risks in supplied consumables and prioritize appropriate and effective mitigation activities. This was accomplished in three stages. First, a catalog of failure modes was categorized and defined enabling the effect of all potential failures to be directly compared. Second, a risk assessment method was developed which performs semi-automated calculations based on pre-defined risk factors to quantify the risk level for each failure mode of each consumable. Lastly, a method for identifying needs and prioritizing mitigation activities was developed to help Novartis allocate resources to those actions which have the biggest impact. This system has been implemented on a pilot group of consumables at the Huningue facility and improvements in supplier quality systems and internal controls are underway.

1.2 The Consumables Quality Problem

Quality defects in material provided from suppliers can have a significant impact on the quality of a biopharmaceutical drug if they are not detected before human use, leading to serious patient safety risk and potential business loss due to write-offs and investigational costs. Recent events in the biotechnology industry have caused many companies to invest extra effort and resources into ensuring the quality of the raw materials and single-use consumables from their suppliers. This section discusses various concerns with the quality of consumables and the need for a new method to assess and address the risk associated with them.

1.2.1 Sensitivity of Biopharmaceutical Manufacturing

Quality Requirements of Biotechnology Processes

Biopharmaceutical manufacturers are responsible for ensuring the safety and efficacy of the finished drug product. Much of the safety burden for the qualification of a new drug is borne during clinical development where the molecule's pharmacological and toxicological effects are evaluated in a series of prospective clinical studies. Once the molecule is approved for a particular indication, the safety and efficacy of the drug is primarily the responsibility of the production unit of the manufacturing facility and the drug must be formulated identically to the clinical batches. In the commercial phase, the quality of the drug product has two components, purity and potency. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), drug purity is defined as the absence of process impurities (proteins, DNA fragments, cell debris) and contaminants from chemical, particulate, or microbiological sources [3]. Potency is related to the concentration of the Active Pharmaceutical Ingredient (API) molecule which is correctly formed and

available for pharmacological action in the patient. In the case of proteins (including antibodies), this requires the molecule to be correctly synthesized and folded during cell culture, preserved in its conformation during all downstream steps, and not bound with other molecules which would reduce its availability in a patient.

The drug manufacturer is responsible for the purity and potency of the finished drug product, and is therefore responsible for monitoring and controlling the quality of materials received from suppliers. Translating the product quality criteria to the consumables, which are disposable components used for a single batch or campaign, we can say that consumables must be themselves free of contamination (chemical, particulate, and microbiological) and they must be free of defects which would disable their intended function in the process to remove or prevent potential contaminants.

Biotechnology processes and products are highly sensitive to deviations in the process conditions and contamination, making the quality requirements on consumables more critical than those used for small molecule pharmaceutical production (i.e. molecules synthesized from chemical reactions, not cellular production). During cell culture, the efficient growth of the cells is dependent on many tightly controlled parameters including nutrient concentrations, temperature, pH, and chemical and microbiological impurities. Chemical contaminations in the parts-per-billion (ppb) range have been observed stunting cell growth and suspending the production process. Microbiological contaminations, especially viral, have been reported infecting entire production systems and causing severe regulatory repercussions [4]. Even after the harvest of the API from cell culture, protein molecules have greater sensitivity to contaminations than small molecule drugs because their three dimensional conformation and binding sites may be altered by other molecules in the solution or on the surface of any material which it contacts.

Parenteral drugs are sensitive to contaminants

Parenteral drugs, which enter the body through a route other than the digestive system, often through injection or inhalation, are more sensitive to contaminants than oral drugs because of the bioavailability of contaminants when injected. Because the digestive system naturally breaks down impurities or passes them through without absorption, the bioavailability of impurities in a parenteral drug is higher than in an oral drug [5]. Accordingly, the purity requirements for parenteral drugs are stricter. The Product Quality Research Institute (PQRI), working in collaboration with the FDA, has performed significant research on the toxicity of impurities in inhaled drugs and has established a safety threshold for all potential impurities which can be applied to parenteral drugs. The Safety Concern Threshold, under which the toxicity and carcinogenicity of any contaminant is considered negligible, is 1.5 μg per day [6].

Regulatory pressure to improve supplier quality

In response to quality issues in final drug products which have been traced back to supplier non-conformances at an increasing rate, the FDA and other regulatory authorities have increased pressure on drug manufacturers to improve the controls on supplied materials. "The Gold Sheet", an annual publication by Elsevier Business Intelligence focused on pharmaceutical quality, reports that drug recalls and FDA warning letters have been increasing over the past decade, especially in the last five years [7]. This increase has been noticed by biopharmaceutical manufacturers and it has caused many to implement programs to increase their visibility and control of supplier quality.

1.2.2 Trends in Consumables

Increased dependence on consumables

The biopharmaceutical industry is becoming increasingly dependent on consumables leading to higher exposure to risk. Consumables are components purchased for the processing of a single batch or campaign (multiple batches of one product) and include bottles, bags, filters, tubing, connectors, sensor probes, dishes, syringes, and pipettes, as illustrated in Figure 1. Consumables have a significant impact on the quality of the drug product by removing substances from the process which should not be present in the drug product or preventing external substances (including from the consumable itself) from contaminating the drug. The industry has increasingly adopted consumables in their manufacturing systems because of their advantages in production efficiency. Since consumables are disposed of after each batch or campaign, there is a reduced risk for cross-contamination between products and only limited cleaning procedures are required on the consumables to prepare them for subsequent batches. Whereas the industry has traditionally used stainless steel vessels for containing all raw materials, intermediates, and product, some companies are now adopting fully disposable production systems. Additionally, the use of consumables offers greater flexibility for the volume of a batch and can reduce the capital cost of a new facility by reducing the number of permanent stainless steel vessels installed.

Because of the increased use of consumables, the consumables manufacturing business continues to grow both in volume and in complexity. Although the industry is dominated by relatively few suppliers, these are the result of many mergers and acquisitions over the past decade. This has led to a highly global supply chain and suppliers which maintain idiosyncratic quality systems among their various manufacturing facilities. In addition, new technologies are constantly being developed and marketed which will enable drug manufacturers to use consumables for new applications in the future. This growing volume and complexity adds significant risk to the supply chain as the suppliers rely on multiple manufacturing facilities for their products, source material from many more sub-suppliers, produce more

types of consumables on shared manufacturing lines, and spread the quality departments thin [8]. One supply chain manager at a large biotech company noted that the volume of one of their suppliers increased significantly over the last several years but the size of their quality department did not increase.

Figure 1. Examples of Consumables used in biopharmaceutical manufacturing. This collection includes several kinds of filters, storage bags, bottles, measuring dishes, connectors, and tubing.

Suppliers do not understand the risks

Few consumable suppliers provide materials exclusively for pharmaceutical companies and fewer still supply only for biotech applications leading to increased quality risk for the most sensitive applications. As discussed previously, biopharmaceutical manufacturers require a higher level of quality compliance, including lower contamination ratings, than their small molecule counterparts. However, there currently exists no set of specifications or guidelines for suppliers to meet biopharmaceutical needs and consequently biotech manufacturers are forced to accept the same products as small molecule manufacturers. Furthermore, many suppliers also provide material to other industrial applications such as food and beverage, chemical production, and cosmetics. While products provided to pharmaceutical manufacturers have stricter specifications, they are often produced on shared equipment and in shared facilities, leading to potential for cross-contamination or mix-up.

In addition, since the consumable manufacturers are not drug manufacturers, their knowledge of biotech processes and the associated risks is limited. This affects the way that suppliers inform the drug

manufacturers of changes in their process. By contract, the supplier is required to notify their customers when they make a process, supplier, or material change which may affect the quality of their product. However, without insight into the changes in the consumable which may affect the quality of the drug, many changes go unreported. When they are reported, the impact of the change is often understated.

Increased quality issues from consumables suppliers

Together, the increased reliance on consumables, greater regulatory quality pressure, supply chain complexity and growth, sensitive processes, and unique quality needs has led to an increase in supplier quality issues in the past several years. At the BioPhorum Operations Group (BPOG) Supplier Quality and Continuity Assurance (SQCA) working group meeting in September 2012, most companies noted an increase in supplier quality problems over the last several years and attributed these to increased cost pressure and lack of quality department oversight. Many of these drug manufacturers, consequently, have intensified their audit programs, are standardizing their previously custom consumables, and are working more closely with their suppliers to ensure high quality. At the Novartis Huningue facility, the number of complaints issued to suppliers regarding quality issues in consumables has grown significantly since 2004, as can be seen in the graph below.

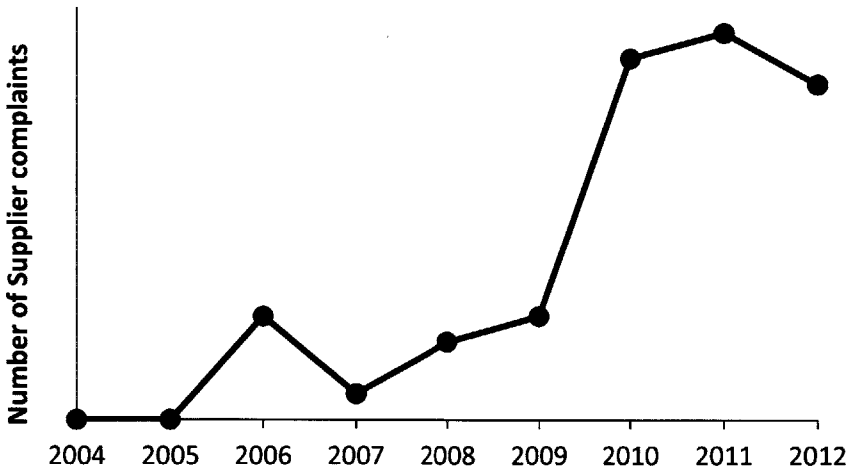

Figure 2. Increasing consumable supplier complaints at Novartis BioPharmOps, Huningue.

1.2.3 The Need for Improved Quality Oversight

Quality impacts from consumable non-conformances

Non-conformances in supplied consumables can impact product quality in various ways. If the consumable is contaminated with chemical, particulate, or microbiological substances, these contaminants will migrate into the product stream and if not sufficiently cleared by the process, they will be present in

the final drug product. These contaminations can occur through many routes including raw materials from sub-suppliers, mis-handling during the production process, process deviations, cross-contamination, insufficient cleaning, insufficient sterilization, and improper transport or storage. The consumables can also affect product quality if they fail to perform their intended function as specified. For example, if a product filter's pore size is not well controlled, it can fail to remove certain particles from the product stream, leading to a particulate or microbiological contamination of the drug. A weak seam in a storage container can allow product to leak out or allow environmental contaminants into the product. In addition, the potency of the drug can be affected by the adsorption of the protein to foreign compounds in the product stream or by improper filtering of impurities out of the product. In short, there are many potential defects in each consumable and many potential impacts to the product. Considering that there are hundreds to thousands of unique consumable articles used at any biopharmaceutical production facility, the quality control task is complex.

Business Impact from non-conformances

All of the effects from these complex interactions between potential non-conformances and impacts to the product quality also have business impact to varying degrees. The primary goal of all drug manufacturers' quality systems is to ensure patient safety through product quality but the business impact of non-conformances can vary significantly depending on when and where the non-conforming consumable is used. At one end of the spectrum are non-conformances which are so minor as to cause no patient harm; on the other end are those which could cause significant patient harm leading to enormous business loss due to regulatory penalties, law suits, and brand equity damage. In the first case, it can be assumed that every consumable includes some negligible contaminant which is undetected by the supplier and drug manufacturer and has no patient impact. If, however, the contaminant is discovered during or after it is used in production, an internal deviation investigation is launched to determine the potential patient safety impact. Regardless of the outcome, the investigation itself may take several months and may interrupt production, costing hundreds of thousands of dollars. If the deviation is found to be hazardous, the production batch or even the whole campaign may be destroyed. This may cost the company tens of millions of dollars. In the case that the drug has already been distributed to the market for patient use, a recall would be issued, having direct logistical cost and reputation damage. In the case where the deviation is not detected before human use and causes harm, the company faces all previously mentioned costs as well as legal and regulatory ramifications. This can cost hundreds of millions of dollars. Genzyme Corp., for example, was forced to surrender $175 million in profits in 2009 after a consent decree issued by the FDA cited drugs contaminated with metal, fiber, rubber, and glass particles [4].

The graphic below illustrates the costs from various scenarios associated with non-conforming consumables and demonstrates two considerations. First, if the deviation is not significant, that is, the effect to the patient would be negligible even if used in production, then all costs are avoided if the deviation is not detected. If the deviation is detected, the company is obligated to carry out an investigation and justify the acceptance of the deviation. This can be expensive not only in devoting the direct resources to the investigation but also in potential production delays. The implication of this consideration is that drug manufacturers need to be selective in the non-conformances they attempt to detect so that they do not expend resources on potential deviations which have no practical impact to patients. The second consideration is that if a non-conformance is significant, the earlier the non-conformance is detected, the less expensive it will be. This is illustrated in the progression of costs in the right hand side of the tree diagram below. In this diagram, the intensity of the color box in the bottom row indicates the magnitude of the cost in the worst-case scenario.

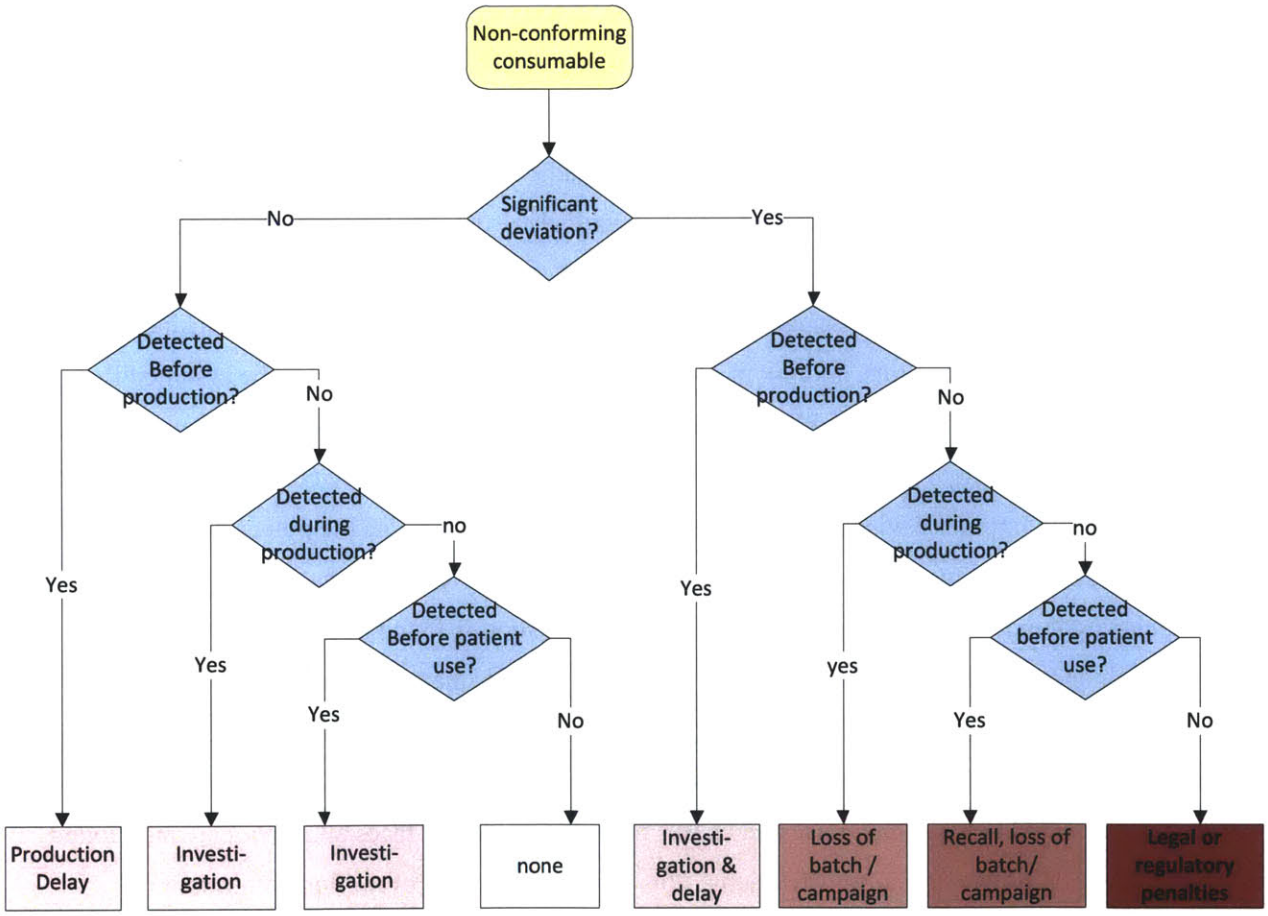

Figure 3. Quality and business impact from non-conforming consumables.

Need for standard consumable controls

Because the business impact is lowest when significant non-conformances are detected before production, appropriate quality controls on consumables should be implemented before production use whenever possible. These controls may be upstream at the supplier or internally at the receipt of the consumable. As discussed previously, the controls should be appropriately selective such that insignificant deviations do not cause a unnecessary investigation or production delay but they should be sensitive enough such that deviations with potential patient safety impact are interrupted as early as possible.

Historically, pharmaceutical companies have implemented thorough quality controls on all raw materials used in the production process but the control of consumables is inconsistent and not always adequately justified. Various pharmacopeia from international regulatory bodies have defined standard test procedures for the majority of raw materials used in pharmaceutical production. In contrast, the vast majority of consumables are accepted based on the Certificate of Analysis (CoA) from the supplier. Because of the breadth of variety and uniqueness of consumable form factors, there are very few standard tests which are recommended or required by regulatory agencies. Consumable manufacturers often perform tests which are idiosyncratic to their own products and difficult to compare across companies. Subsequently, few consumables currently receive the rigorous testing protocols which are applied to raw materials.

Need for a strategy for improving controls

Although it can be shown that enhanced controls on consumables can reduce the patient safety and business risks associated with potential non-conformances, Novartis needs a strategy for implementing those controls which will have the biggest risk-reducing impact. Whereas some companies have responded to recent quality issues by defining every product contact consumable as critical, Novartis believes that if everything is critical, nothing is critical. Stated another way, the best way to implement enhanced controls is to prioritize the areas with high risk and allocate the limited resources to the articles which can have the biggest impact.

There are several challenges associated with this goal. First, the Huningue manufacturing site alone uses several hundred different consumable articles with many different forms and functions and degrees of contact with the drug. The same test methods cannot be applied to each article even within the same family, nor may it be necessary to do so based on the supplier's controls and the criticality of the article. In addition, all of the potential failure modes of each consumable are not well understood and their potential impact on product quality has not been fully analyzed. Therefore, there is currently no method for prioritizing high-risk items. Lastly, few consumables have internally-defined specifications by which Novartis can objectively evaluate the quality of the consumable. As stated previously, most consumables

are accepted on CoA alone but even these documents are not standardized across the industry or even within a supplier.

In summary, Novartis' ultimate goal is to reduce the frequency and impact of non-conformances on their drug product. To accomplish this requires a method to understand, analyze, and prioritize quality enhancement actions to mitigate the various risks posed by the growing consumables supplier quality problems.

1.3 Research Questions

The remainder of this thesis will address the following three research questions.

Failure Modes

How should Novartis categorize and generalize failure modes to apply to all consumables and to allow comparison among them? A set of standardized failure modes will allow the relative comparison of consumables and a greater understanding of the potential effects of those failures on the product.

Risk Assessment

How should Novartis assess the various risks from all consumables in a consistent and logical method in order to understand the current risk landscape? A standardized method for evaluating the non-conformance risk will allow Novartis to monitor their exposure to risk, prioritize their response, and allocate the appropriate resources for mitigation.

Risk Mitigation

How should Novartis use the risk assessment method to prioritize mitigation activities so it can focus its resources on implementing the highest impact opportunities? And what mitigations will have the biggest impact? A risk mitigation strategy will help Novartis focus on the most impactful mitigation activities, and thereby reducing the frequency and impact of non-conformances.

1.4 Research Methods

This work employed an Action Research method as described by Westbrook (1995) wherein the implementation was built on iterative cycles of collecting data, developing theories, testing those theories, and implementing into applications [9]. The method is useful for theory building in which understanding can be formed through interacting with the specialists involved in multiple areas of work. It is employed here in an effort to develop a solution and understand its effects in practical deployment. This co-development allows a continuous refinement of the proposed solution.

1.4.1 Process for Categorizing Failure Modes

Data collection

In order to categorize and standardize the failure modes in a useful way, a catalog of observed and anticipated failure modes was first collected through interviews with process and quality experts, historical data of reported deviations and non-conformances, and interaction with other biopharmaceutical companies. All of these failure modes, their causes, and the magnitude of their effect on product quality were recorded. In addition, the consumables used at the Huningue production facility were cataloged and their use, form factor, and other relevant properties were recorded.

Theory development

A fault tree analysis was conducted to categorize a set of failure modes that was mutually exclusive and cumulatively exhaustive. The branches were based on categories of contamination from quality standards and the types of failures observed historically in each of the consumable families.

Theory testing

These standard failure mode categories were then tested by cross-referencing the families with all failure modes previously cataloged to ensure that the system included all potential failures. In addition, the definitions were tested and iteratively refined with production and quality experts and managers from Novartis as well as from other biotech companies within the BioPhorum Operations Group. As new failure modes were found, the definitions were tested to determine applicability and iteratively refined.

Application

These standard failure mode definitions then became the basis of analysis for the risk assessment method. A set of definitions and examples from the site's history help to communicate the failure modes and their risks to managers.

1.4.2 Processes for the Development of Risk Assessment Method

Data collection

In order to develop a risk assessment method that would enable a standardized evaluation of the relative risk of the various failure modes for each consumable, a preliminary risk assessment method was first chosen. Several methodologies were researched and compared and the best fitting method was chosen for this application. As the risk model was developed, various data from the consumables was required and was subsequently obtained. For every consumable used on site, the usage and type were recorded and a preliminary criticality assessment was performed to select the 48 most critical consumables for

subsequent analysis. For each of these, additional information was collected including detailed usage conditions from process experts, material properties and supplier processes from datasheets and supplier interviews, supplier quality systems and history from audit reports and quality questionnaires, supplier tests and inspections from Certificates of Analysis, and internal tests and inspection from process experts.

Theory development

The risk model was built on an FMEA method with customizations to allow standardized risk calculation and evaluation. The following list describes the main steps which were employed in the development of the risk assessment system but it should be understood that each step was iterative and the various levels of the system were continually refined and may still undergo continuous improvement.

1. **Developed the risk calculation model.** That is, the mathematical relationships that will be used to calculate the overall risk profile of each consumable.
2. **Defined the variables that affect risk.** For each risk dimension (Severity, Likelihood, and Detectability), those variables in each consumable which explain the risk (for example, "material" or "usage conditions") were defined.
3. **Identified alternatives within each variable.** For each variable, all possible alternatives were identified to include each consumable type (for example, the variable "material" may contain alternatives "fiber", "polymer", "metal", and "glass").
4. **Assigned numeric factor to each alternative.** For each alternative, a numeric factor was assigned to provide relative impact to the risk calculation for that dimension.
5. **Defined decision thresholds.** In this implementation, decision rules were defined for the Risk Priority Number in order to trigger mitigation actions in appropriate scenarios.

Theory testing

Based on several well-known consumables and their most significant areas of risk, the risk models were tested and the factors were reworked to achieve the expected risk outcomes. As the tool was developed, those consumables which were used to test the model were expanded. Two standards were used for evaluating the tool, expert experience and historical failure events. Since the risk assessment is a cross-functional tool, each risk dimension was evaluated by the specialists in that field. For severity analysis, the production experts and analysis in deviation reports provided the most relevant feedback. For likelihood analysis, the quality assurance department and historical complaints were most relevant. Lastly, for detectability analysis, the quality control department was most familiar with test methods and therefore most qualified to test the correctness of the analysis tool.

Application

As the method was being developed and its accuracy and relevance being refined, it was implemented into a tool and an accompanying procedure which could be deployed at the site and used by various functions for a standardized risk assessment. The tool was implemented as an Excel worksheet with automated calculations based on pre-defined variables and factors that enables full documentation and justification of risk acceptance and mitigations. The assessment was first performed on a pilot group of 48 critical consumables.

1.4.3 Process for the Development of Mitigation Decision-Making Alternatives

Data collection

In order to develop a set of possible mitigations for the outstanding risks calculated using the risk assessment tool, test methods used by several internal and external groups were researched. These included tests performed by suppliers, internal Quality Control, validation specialists, root cause analysis from recent failures, other biopharmaceutical companies, external laboratory service vendors, and pharmacopeias. The risk assessment performed on the pilot group of consumables formed the needs basis for mitigation development.

Theory development

With the list of potential mitigations, the applicability of each to the specific risks generated by the assessment was evaluated on a case-by-case basis. Since each consumable family has peculiar form factors and materials, the test methods and other controls which can be applied to each is unique. On the other hand, some mitigation activities can be generally applied to multiple consumables to decrease the overall risk. This menu of mitigations was collected and each option was evaluated for the types of risk which it could mitigate.

Theory testing

To evaluate the suitability of the various mitigation options collected, proof of concept tests were conducted and external vendors were consulted. The internal tests demonstrated sufficient sensitivity of mass spectroscopy as a possible test method for detecting chemical contaminants. Other recommended mitigations were confirmed through informal interviews with external laboratory services and consumable suppliers.

Application

In addition to the practical laboratory development of a mass spectroscopy test method, the mitigation decision-making method was also applied to the list of critical consumables in an effort to mitigate as

much of the outstanding risk as possible. These mitigation plans were captured in an electronic dashboard which allows managers to monitor the current risk profile, prioritize the implementation of mitigation activities, and chart progress over time.

1.5 Thesis Chapter Summary

Review of Risk Management Approaches

This chapter explores the various approaches to supply chain risk management found in academic literature and in industrial guidance documents. It also presents an overview of various risk management tools which have been used and from which the tool presented in this thesis was chosen. Lastly, this chapter includes a short review of the strategy that other biopharmaceutical companies are pursuing in an effort to maintain oversight of supplier quality.

Failure Modes Categorization

This chapter briefly describes the process and results of the categorization of failure modes which feeds into the consumables risk assessment.

Development of Risk Assessment Method

This chapter similarly describes the process and results of the risk assessment method and tool which were developed to help Novartis understand and prioritize the consumable-related risks. In it, the mathematical models are explained in detail and an analysis of the robustness and validity of the tool are also presented.

Mitigation Decision-Making

This chapter details the mitigation activities which have been researched and developed in an effort to address the various risks observed in the assessment. In addition, a process is presented for establishing appropriate specifications to control internal and suppliers' tests and inspections. Lastly, this section explores the business processes which are involved in the system that enable informed decision making for devoting resources to consumables quality control.

Conclusions

The final chapter discusses the merits the system as it is currently conceived for consumables and explores additional applications for this risk assessment and mitigation decision-making approach. In addition, future work for the present application is recommended and a strategy for implementing the system more broadly is presented.

2 Review of Risk Management Approaches

2.1 Supply Chain Risk Management Strategies

A standard risk management framework

The International Standard Organization provides useful guidance for risk management (ISO 31000) including a working definition of risk and a broadly applicable framework for managing it. In this work, risk is defined as the effect of uncertainty on objectives. Both the uncertainty and the objectives are peculiar to the context, implying that the risk management system should be tailored to a specific application in every case. In addition, the guidance asserts that risk management is part of decision-making, that is, it provides information to help managers make appropriate decisions between alternative actions. It should also be systematic and structured such that the strategy can be implemented into a standard system providing efficient and consistent results. Transparency of the system can allow for continuous improvement to ensure the approach matures and adapts with improved information.

The risk management process is depicted in Figure 4 includes the following five main components:

- Communication and consultation takes place throughout the process and involves information sharing with the various internal and external stakeholders.
- Establishing the context requires the organization to set the objectives and boundaries of the risk management system with a reasonably implementable scope.
- The risk assessment process is comprised of three steps, identification, analysis, and evaluation. In this process, all of the various risks should be identified, their magnitudes estimated and compared, and ultimately prioritized for action.
- Risk treatment involves the selection of certain mitigation actions which are designed to reduce the likelihood or consequences of specific risks and are implemented according to their residual risk priority. Risk treatment also includes the acceptance of risks which have low likelihood and/or consequences.
- Monitoring and review can be periodic or triggered by certain events, but should involve an assessment of the risk management system, identification of emerging risks, re-evaluation of the current assessments, and monitoring of the outputs of the system.

Lastly, the risk management system should be recordable. That is, the system should provide a mechanism for the decisions made to be traced to the risk evaluation outputs and justified based on rationale. [10]

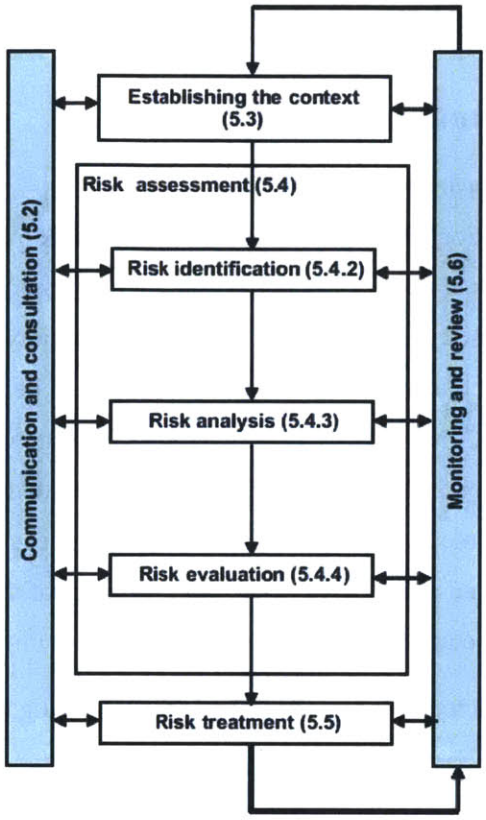

Figure 4. Risk Management process from ISO 31000 [10].

Supply chain risk management

Much work has been devoted to risk assessment in the area of supply chain management particularly studying the risk of supply disruptions. One such example comes from Ericsson, a mobile phone manufacturer who suffered $200 million in lost sales due to a disruption in their supply chain from a small fire at a sub-supplier of a critical component. In response to the disaster, Ericsson implemented an exemplary risk management system throughout their business. In addition to permeating a risk-aware culture and instituting a risk management organization within the business areas, a system of tools were developed to help managers make informed decisions about their various areas of risk. The tools assumed that risk could be estimated as the product of business impact and probability of supply chain disruptions and mitigations were established to reduce either the impact or probability. The semi-quantitative information was converted to a "Business Interruption Value", an estimate of the business loss in the event of a certain disruption, and displayed in a dashboard for management decision-making. [11]

Kleindorfer and Saad and Norman and Jansson both describe a simple optimization model in which the cost of implementing mitigation actions should be balanced with the potential costs of supply chain disruption. The cost of applied risk mitigations can be assumed to increase monotonically with the degree

of protection afforded by the actions. Similarly, the expected value of the loss incurred from business interruption due to supply chain disruption can be assumed to decrease monotonically with the degree of protection in place. Therefore, the sum of these two costs has a minimum value which should be sought in the decision-making of risk mitigation implementation [12, 11]. It should be noted that the expected value of the business loss is the product of the probability and magnitude of loss; a low expected loss can be calculated even if an event is catastrophic, given sufficiently low probability.

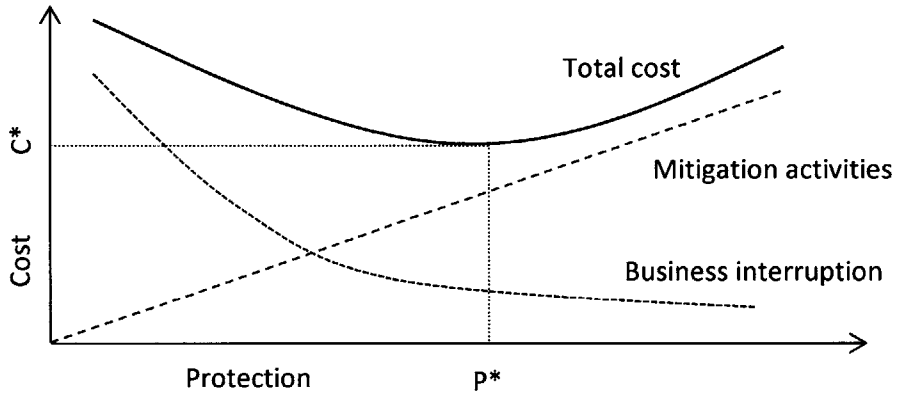

Figure 5. Minimizing combined business interruption and mitigation costs. Adapted from Kleindorfer and Saad [12].

Kleindorfer and Saad also provide ten principles from their work in supply chain disruption risk management. Of these, three are particularly relevant to the present application. They state that prevention is better than a cure and similarly crisis management is not enough to prevent negative events. Both of these principles imply that proactive risk management provide better protection for a business than reacting after a significant event and attempting to find a singular solution to the particular failure. Crisis management removes resources, especially people, from their normal operating activities to devote them to a unique problem-solving mode which may have been prevented with careful planning and preventative risk mitigation. Their third relevant point is that extreme leanness increases a manufacturer's vulnerability to supply chain uncertainties. The implication in this principle is that certain risks require tradeoffs from operating efficiency, speed, and carrying costs in order to maintain supply chain integrity. These tradeoffs should be recognized and carefully balanced. [12]

Risk management for pharmaceutical manufacturers

Pharmaceutical manufacturers worldwide face unique supply chain challenges due to the strict specifications and limited supplier options. In addition, they experience increasing problems due to the globalization of the supply chain. Marucheck, *et al* notes that cost pressures are driving the trend of supply chains to increasingly source materials from emerging economies where costs are lower. These sub-supplier choices are not always visible to the pharmaceutical manufacturer but can have severe

consequences to the quality of their product. According to Marucheck, *et al*, the lengthening supply chains and diversification of operations locations increases the risk of contamination or even substitution, and the risk management systems required by the FDA may not be adequate for detecting these errors, especially when they are unintentional and in low concentrations. Recent examples related to this increasing globalization include counterfeit Viagra, contamination from wood pallets in Tylenol, and raw ingredient substitution in Heparin, which have all led to enormous business loss due to legal activity and voluntary recalls. Maruckeck, *et al* states "the high costs associated with supply disruption, product liability and potential recall might indicate that some low-cost suppliers are really high-cost suppliers when the expected costs of safety risk are considered." [13]

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has adapted the guidelines in ISO 31000 for pharmaceutical-specific use. The Quality Risk Management Q9 guidelines set forth two principles of risk management:

- "The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk." [14]

In the context of risk management for consumables used in pharmaceutical production, the risk management system should be tailored to consider patient safety as the primary objective. In addition, since the level of patient risk is demonstrably high, the system should be highly formalized and the rationales for each decision appropriately documented.

Although the ICH process is diagrammed differently, as seen below, its basic components essentially follow those set forth by ISO 31000. This system does, however, clarify the risk control cycle in which the assessment is re-performed once mitigating risk reduction activities are implemented. If the re-assessment and re-evaluation then demonstrates that the total risk level is acceptable, then the rationale may be recorded and the acceptance recorded and communicated. This process also describes a periodic risk review in which the risk acceptance and reduction decisions are regularly reviewed by appropriate and knowledgeable stakeholders.

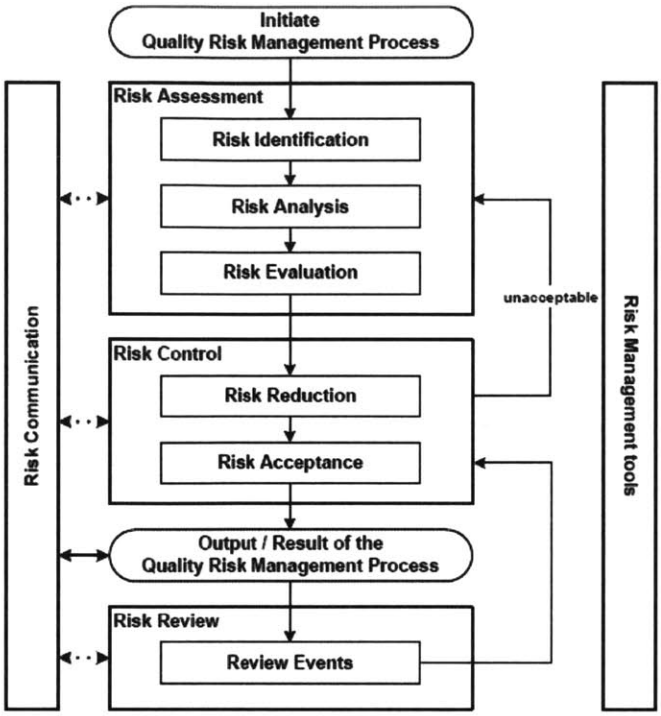

Figure 6. Risk Management Process from ICH Q9 [14].

As an example of a risk management strategy relevant to pharmaceutical manufacture, the Parenteral Drug Association (PDA) has published an approach to performing a risk assessment on raw materials in order to determine audit frequency [15]. The recommended assessment includes four risk dimensions, Compliance, Availability, Complexity, and History each of which is graded with a semi-quantitative score. The product of these four risk dimensions constitutes the Risk Priority Number (RPN), styled after the Failure Modes and Effects Analysis (FMEA) method. Materials with scores above a certain pre-defined RPN threshold are required to have audits in the forthcoming year and those with scores below the threshold are exempt for the year. Since this score changes depending on the recentness and outcome of the last audit, the strategy is cyclical and self-adjusting. The system provides identification of the various risks, a method for assessing these risks and evaluating them using pre-defined calculations, and requires certain mitigation actions based on pre-defined thresholds.

Summary

The literature cited in this section teaches that the risk management system should be well-structured and methodical, with input from several collaborating functionalities. It must pre-define methods for evaluating risk and levels of risk acceptability. Mitigation implementation should be based on risk acceptability and the business implications of mitigation in an effort to reduce overall cost. Lastly, the risk management system should mandate reviews according to periodic schedule or pre-defined risk events.

2.2 Review of Risk Management Tools

Many tools have been developed to put risk management theory into practice. This section introduces a selection of risk analysis tools and discusses their merits in the context of consumables quality. The International Electrotechnical Commission (IEC), in conjunction with ISO, have published a useful overview of many of these tools in IEC/ISO 31010 from which the brief summary below is drawn [16].

Structured brainstorming

Prompted with pre-defined questions or guidance, a group of experienced individuals collect a broad set of potential risks and may rank order them. This technique is useful for gathering input from many diverse perspectives and for populating a starting list of failure modes during the identification phase, but it is not useful for quantifying risks or for providing rigorous justification or decision-making rationale. According to Charoo and Ali, brainstorming is the most commonly used risk identification technique for risk analysis in pharmaceutical development. They acknowledge, however, that it is uniquely susceptible to missing ideas depending on the composition of the analysis team. [17]

Hazard Operability Analysis

Hazard Operability Analysis (often called HAZOP) is a form of brainstorming for risk identification but uses a guideword structure to help identify potential deviations from the intended design or operation. In the pharmaceutical industry, this method is most commonly used for process safety where the relative magnitude of risk estimation is not as critical as determining a list of critical points for which extra precautions must be given [14]. Like other brainstorming methods, HAZOP requires a deep understanding of the process in question to identify all potential risks and is unable to independently quantify those risks.

Hazard Analysis and Critical Control Points

Hazard Analysis and Critical Control Points (HACCP) is a preventative tool in which critical control parameters in an operating system are identified and limits for normal operating conditions are defined. It uses a technical and scientific approach to calculating the magnitude of deviations at a highly specific level for localized conditions. This approach is most useful in production systems where the process parameters and requirements are sufficiently understood to enable specification setting. The output of this system is a set of critical control points with bounds on operating parameters to ensure the quality of the final product. The overall risk is not itself quantified, however, making it difficult to monitor progress and implement scaled mitigations to reduce risk. Among other examples, HACCP has been used in food and drinking water systems to establish control points to reduce exposure to hazards instead of relying on end-product tests for quality [18].

Fault Tree Analysis

Using logic structures, fault tree analysis begins with an effect (often an event) and explores all possible and necessary events which lead to that failure. This tool is useful for understanding the relationships between failure modes and providing a logical and rigorous method to identifying root causes. It is also capable of quantifying the analysis and estimating uncertainty within the analysis but requires a very deep understanding of the process and factors which affect risk. It must be paired with another technique to generate the starting list of potential failure events and estimate their consequence. In addition, this method is generally limited to the Bernoulli assumption that each element has two mutually exclusive states – there are no intermediate effects [19]. This makes it unsuitable for the quantification of contamination events which have inherently continuous consequences.

Event Tree Analysis

Event tree analysis is essentially an inverted fault tree wherein the consequences are inductively reasoned from potential upstream failure modes. This method is most useful for estimating probabilities of certain consequences from specific failure modes and for exploring all possible consequences in the risk set. It must be paired with another technique to generate the starting list of potential failure modes from which the consequences are generated. The probabilistic and quantitative nature of event tree analysis makes the method useful in low probability, high consequence applications such as nuclear operations and it is now being applied to patient safety within healthcare organizations [20]. Like fault tree analysis, however, it suffers from the binary states assumption.

Risk ranking and filtering

The Risk Ranking and Filtering method is useful for prioritizing actions to various risks when there are no other quantification methods available. The relevant risk factors are weighted according to consequence and identified risks are evaluated by each factor and an overall score is given which enables the relative ranking of the risks. Filters, or cutoff thresholds, are then applied to determine those risks which require mitigating action. This method is often used when various factors both quantitative and qualitative need to be compared and ranked to provide a single output such as determining which sites to audit [14].

Failure Mode and Effects Analysis

Failure Modes and Effects Analysis (FMEA) is a widely used tool for evaluating the effects of failure modes on a process. The International Electrotechnical Commission provides the standard guidance document for performing FMEA [21]. FMEA may be performed at many levels with varying degrees of detail and quantification included in the analysis from whole system down to component analysis. In general, a list of failure modes is generated using one of the other tools mentioned above and is input into

the FMEA framework. Then the analysis is performed on three risk dimensions, severity, likelihood, and detectability. Each of these risk dimensions is traditionally evaluated semi-quantitatively for each failure mode on a scale from 1 to 10 and the total risk, called the Risk Priority Number (RPN) is the product of the three risk dimensions. This enables the prioritization of the various failure modes and actions to be prescribed based on the rank. FMEA relies on deep process understanding and is particularly useful for breaking down complex systems into manageable pieces and monitoring risks for making informed management decisions.

The IEC provides additional examples of practical ways to evaluate each of the risk dimensions. In general, instead of calculating a quantifiable magnitude of severity, probability of failure, or probability of detection, a lookup table is developed where each relative severity, likelihood, or detectability level is given a pre-defined non-dimensional score. Similarly, the total risk (RPN) may be compared to pre-defined thresholds in which particular actions are required. ISO 31010 recommends three bands:

a) "an upper band where the level of risk is regarded as intolerable ... and risk treatment is essential whatever its cost;
b) a middle band (or 'grey' area) where costs and benefits are taken into account and opportunities balanced against potential consequences;
c) a lower band where the level of risk is regarded as negligible, or so small that no risk treatment measures are needed." [16]

The IEC also points out that RPN values can be misleading if not fully understood because the scales of the various risk dimensions are neither equivalent nor linear. In addition, the calculations for performing a full FMEA for a very complex system may be burdensome due to the quantity of detailed information required to make a full assessment.

While FMEA is typically performed using a full ordinal scale for each risk dimension (e.g. 1, 2, 3, ... 10), including a recommended framework specific to biopharmaceutical process risk assessment [22], some practitioners at Novartis have adopted a more discrete scale in order to arithmetically separate the decision thresholds in the RPN and to clarify the analysis. A 1-5-9 scale is instead used, where "1" is low, "5" is medium, and "9" is high impact, in each of the dimensions. Since the analysis inevitably requires input from many functions in multiple departments, it has been found that communicating "high, medium, or low" risk leads to faster consensus-making. In addition, the RPN values more efficiently discriminate high risk areas due to the non-linearity of the product of the three dimensions. This can be seen in the figure below which illustrates the relative frequency of RPN scores which are generated using two different scoring systems (1 through 10 versus 1-5-9). With 1-5-9 scoring, the thresholds can be less

ambiguous and easier to rationalize because there are larger gaps between neighboring RPN values. The rationale behind threshold scenarios will be discussed later.

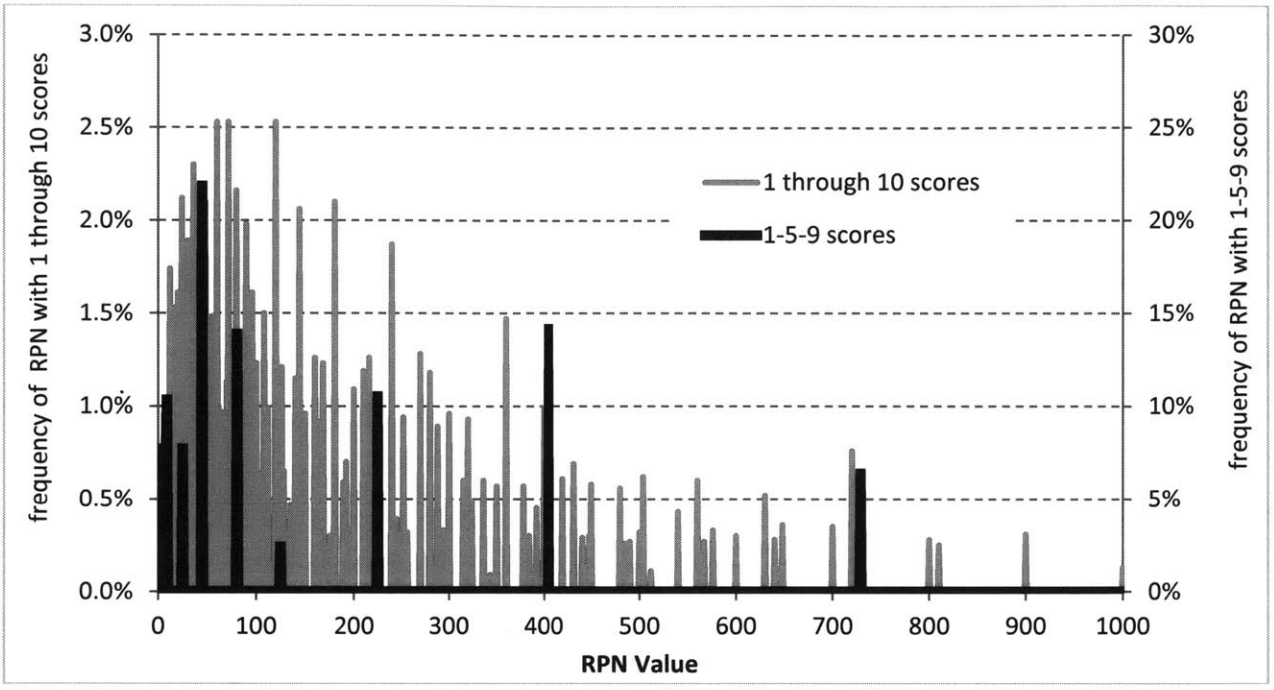

Figure 7. Comparison of RPN output using 1 through 10 scoring vs. 1-5-9 scoring. These data were generated using a simulation of 10,000 runs with individual scores for Severity, Likelihood, and Detectability randomly generated on a uniform distribution of scores. The RPN is calculated as the product of the three random risk dimensions.

Summary

This section explores several risk assessment methodologies which are commonly used for various applications. For the present work, brainstorming and fault tree analysis are most useful for failure mode categorization and the FMEA method with 1-5-9 scoring is most useful for the risk assessment calculations.

2.3 Current Biopharmaceutical Supplier Quality Approaches

Biopharmaceutical Manufacturers' Objectives

Discussions with other leading biopharmaceutical manufacturers have elucidated many key objectives including the following short list.

- High product quality – Purity and potency of the final drug product
- High process reliability – Reliable delivery of the drug product without shortages
- Excellent reputation – Maintenance of a strong public appearance and confidence among clinicians and investors

- Regulatory compliance – Compliance with regulatory agencies in order to maintain both reputation and process reliability
- Low cost – Preservation of low manufacturing costs including sourcing, quality control, production, and distribution.

It can be seen that these objectives are often interdependent, and the quality of purchased materials including consumables is a key variable affecting all of them. Non-conformances in consumables can have an impact on product quality, can lead to supply chain disruptions, can lead to quality and regulatory issues which are damaging to the company's reputation, and can be very costly as previously shown.

Current approaches in the biopharmaceutical industry

Because of these potential impacts on high-level business objectives, biopharmaceutical companies are devoting extraordinary resources to ensuring the quality of consumables and their suppliers. During the BioPhorum Operations Group (BPOG) Supplier Quality and Continuity Assurance (SQCA) working group consortium in September, several large biopharmaceutical manufacturers shared their strategies for ensuring consumable quality. Most of these companies employ a multi-prong approach including several functions within their organization such as Quality Assurance, Quality Control, Purchasing, Development, and Production. A summary of these approaches for risk mitigation is listed below.

- Receiving inspections and testing are limited. In general, consumables are accepted on the supplier's Certificate of Analysis. However, external spectroscopy identification testing is performed on drug substance containers.
- The general approach to quality control testing is to follow minimum regulatory guidelines, which are sparse and vague concerning consumables used in production.
- Many consumables are tested during the production process. This includes pressure tests for bags and filters either before or after production use.
- At least one company is consolidating designs for families of consumables in an effort to reduce the number of Stock Keeping Units (SKUs) they order from the supplier.
- In general, all consumables which have product contact are considered critical and are treated with similar quality assurance programs including supplier quality questionnaires, manufacturing site audits, quality agreements, and other business contracts.
- Short lists of preferred suppliers are maintained and new consumables to be used for production are required to be sourced from among these preferred suppliers.
- Information about the entire supply chain is collected and archived "down to the mine" whenever possible.

- The frequency and depth of supplier audits is generally increasing and the training of professional auditors is also intensifying and focusing on specific quality risks.
- Quality issues for each family of consumables from each supplier are monitored on a yearly basis and the intensity of quality assurance efforts are modulated based on the quality history for that supplier.
- Due to the expanded resources and time devoted to auditing, there is an effort to share audit results among biopharmaceutical manufacturers.
- Efforts to ensure supplier compliance with change notification requirements is increasing with many biopharmaceutical manufacturers improving communication and expectations for what changes require notification.

These initiatives show a dedication to Quality Assurance activities including supplier audits, quality questionnaires, and agreements which are helpful in maintaining confidence in the suppliers' general quality systems. There is less attention given to Quality Control methods in which the quality of the consumables can be tested before production use because the guidance is limited and requirements are few. There remains a need for a risk management strategy which can provide direction and prioritization for implementing additional quality controls.

Identification testing methods within Novartis

In addition to many of the Quality Assurance activities listed above, Novartis BioPharmOps is also implementing identification testing on multiple families of consumables using external spectroscopy tools. These tools, which are non-destructive to the consumable material, allow the material composition (especially for polymers) to be identified based on the spectrum of molecular vibrations observed with a transmission or reflection probe. Like a fingerprint, the spectrum is unique to a material or a blend of materials and can be used to confirm the correct material composition and in some cases the presence or absence of contaminants, thus reducing the risk of accepting a consumable which can leach unqualified chemical compounds into the product stream. This method includes three modes, mid-infrared or Fourier Transform Infrared (FTIR), near infrared (NIR), and Raman spectroscopy. FTIR is already used for testing some drug substance containers and NIR has been developed for the membranes of some filters and the film resin of some bags. Raman spectroscopy is used for testing the identity of raw material powders. The following table, adapted from a white paper published by a handheld Raman spectroscope manufacturer, provides a brief summary of the advantages and disadvantages of each mode [23].

Table 1. Comparison of spectroscopic identification modes.

	FTIR	NIR	Raman
Selectivity	High, directly interpretable peaks	Low, peaks are not directly interpretable	High, directly interpretable peaks
Interference	Strong interference with water	Interference with water, signal impacted by physical attributes like hardness, porosity	Fluorescence creates interference
Sampling	Requires direct sample contact	Standoff sampling through glass and plastics	Standoff sampling through glass
Portability	Typically large laboratory devices	Handheld devices are available	Handheld devices are available
Method Development	Sample compared to single reference spectrum	Chemometric methods, multiple samples required to create extensive library of references	Sample compared to single reference spectrum

External spectroscopic methods, if developed correctly, can be useful for detecting material errors and significant contaminations which may lead to product contamination; this can be done non-destructively on an appropriate number of batch samples. They are generally limited, however, by the specificity of the measurement. Low concentration contaminants, foreign materials outside of the measurement spot, or compounds which respond outside of the measurement band, may not be detectable with these methods. In summary, external spectroscopic identification is a feasible method to reduce risk for some failure modes and demonstrates a Quality Control approach which is complementary to a supplier quality risk management system for consumables.

Summary

The various methods from Novartis and other biopharmaceutical manufacturers described in this section provide options for mitigation activities to reduce risk in unique cases. These activities, and others to be explored later, can be implemented where they are most appropriate and economically feasible.

3 Failure Mode Categorization

3.1 Objectives

The first step in the development of the present risk management system is risk identification. If we were given a short list of articles which was assumed to be static over time, the risk identification task would normally involve exploring potential failure modes for each article one at a time. However, the site for which this system is being developed uses a few hundred consumables in its production system and more are added every year. Pursuing all unique failure modes for all consumable articles presents an intractable task.

Therefore, a risk identification system is required which enables all potential failure modes for all current and future consumables to be systematically predicted and sufficiently defined to perform risk assessment on each consumable article. In this case, the objective is the categorization of the various failure modes which have been observed and which are possible within consumables. The categorization has the following requirements:

1. Identify a comprehensive list of possible failures which have a potential product quality impact
2. Define a system in which all possible failure modes from all consumables can be categorized for comparing the total risk associated with each failure mode.
    a. The categories must be cumulatively exhaustive and mutually exclusive
    b. The categories must be detailed enough to allow analysis of their likelihood and effects.
    c. The categories must be broad enough to allow efficient assessment of all consumable articles

3.2 Failures Observed in Consumables

Failure mode data was collected from experienced production and quality experts at the Huningue manufacturing site, deviation reports from production, supplier complaints issued by the site, and other biopharmaceutical companies through the BPOG consortium. The following list presents a condensed form of the failure modes recorded which are related to consumable quality.

- An incorrect raw material used in a consumable component which leads to leaching of an unqualified chemical compound into the product.
- A container is mislabeled. Huningue receives a consumable intended for another use, possibly with the same form factor.

- Raw material used in consumable (i.e. plastic or resin) is contaminated with foreign material and leaches into product stream
- Storage solution for a filter is not formulated correctly leading to introduction of foreign chemicals into the product stream
- Filter releases fibers from membrane into the product stream
- Particle from manufacturing (e.g. bag cutting) adheres to consumable and is introduced into the product stream
- Cross-contamination of a chemical or particle from another product using the same equipment or facilities
- Bottle wall is not thick enough causing bottle to have insufficient mechanical strength.
- Lubricant or another chemical from the manufacturing process leaks onto the consumable
- Mold release or other additives are not adequately cleaned off before use
- Foreign particle (dust, fiber, etc.) is transferred onto consumable from environment, testing, handling, packaging, or compromised container during shipping or storage
- Inadequate sterilization or microbiological contamination post-sterilization
- Microbiological contamination from the manufacturing environment with no post-production sterilization.
- Consumable is assembled incorrectly (e.g. filter membrane inverted, seal is not complete)
- Leak in a seal of a bag, bottle, connector, or tubing leading to lost product or allowing foreign contaminants into the product. Leak can occur from many sources:
  - Poorly fitting components
  - Damage to a component or bag film
  - Incomplete sealing
  - Faulty assembly during manual operation
- Leak in a filter leading to contamination of product from process materials (particles, chemicals, or microbes).

The Pareto chart below shows the number of complaints which are issued to the suppliers of consumables from 2004 to 2012 regarding quality issues. In general, a complaint is issued when a consumable is received which does not conform to the specifications or which generates a deviation in the process. By far the greatest number of complaints stems from leaks in storage bags. The effect of these leaks can be small, as in the case of purification buffer storage, or very costly, as in the case of contamination of drug substance. It should be noted that supplier complaints are most common among failure modes which are

most detectable with the current systems. Many potential non-conformances are not currently detectable at any production stage and thus they would not generate a supplier complaint. In at least one case, a consumable with a critical non-conformance was used in production and the deviation was not detected until a letter from the supplier was received explaining the error.

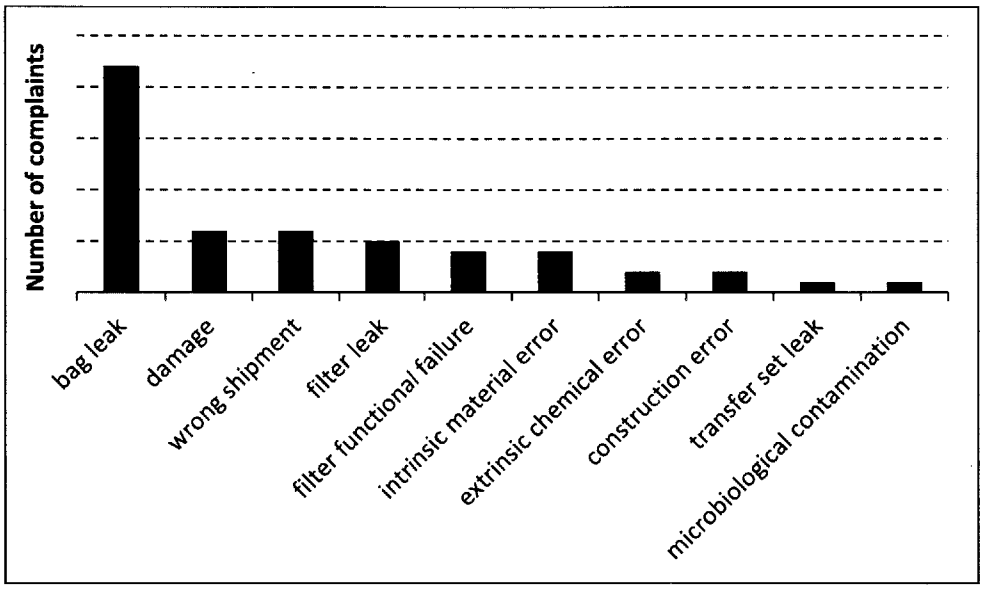

Figure 8. Pareto of non-conformances in consumables which generated supplier complaints from 2004 to 2012.

3.3 Failure Modes and Effects

In an effort to determine the effects and relationships between these many failure modes, a high level fault tree analysis was performed, illustrated in Figure 9. In this analysis, the most generic failure event, "defect in Drug Substance (DS) quality", serves as the root. For each node, all possible causes were deduced and Boolean logic used to determine the possible sources. At the first branch, the distinction is made between the two primary quality defects, purity and potency. At the next branch within purity, the three basic types of contamination are considered. For each of these, the source is either intrinsic, that is materials which are normally present in the process, or extrinsic, that is foreign materials. And from each of these branches, all possible sources are considered, including consumable, environment, and raw materials. From the main potency branch, two main causes are considered, process deviations which would cause malformation of the protein and interference reducing the activity of the protein molecule by inhibiting the active binding sites. Within process deviations, the source can be process equipment, raw material errors, or test sample errors. Potential sources for these errors are expanded in the tree. This method does not, however, independently evaluate relative severity of the events. Within the contaminant interference branch, the source can be internal to the process or from foreign material.

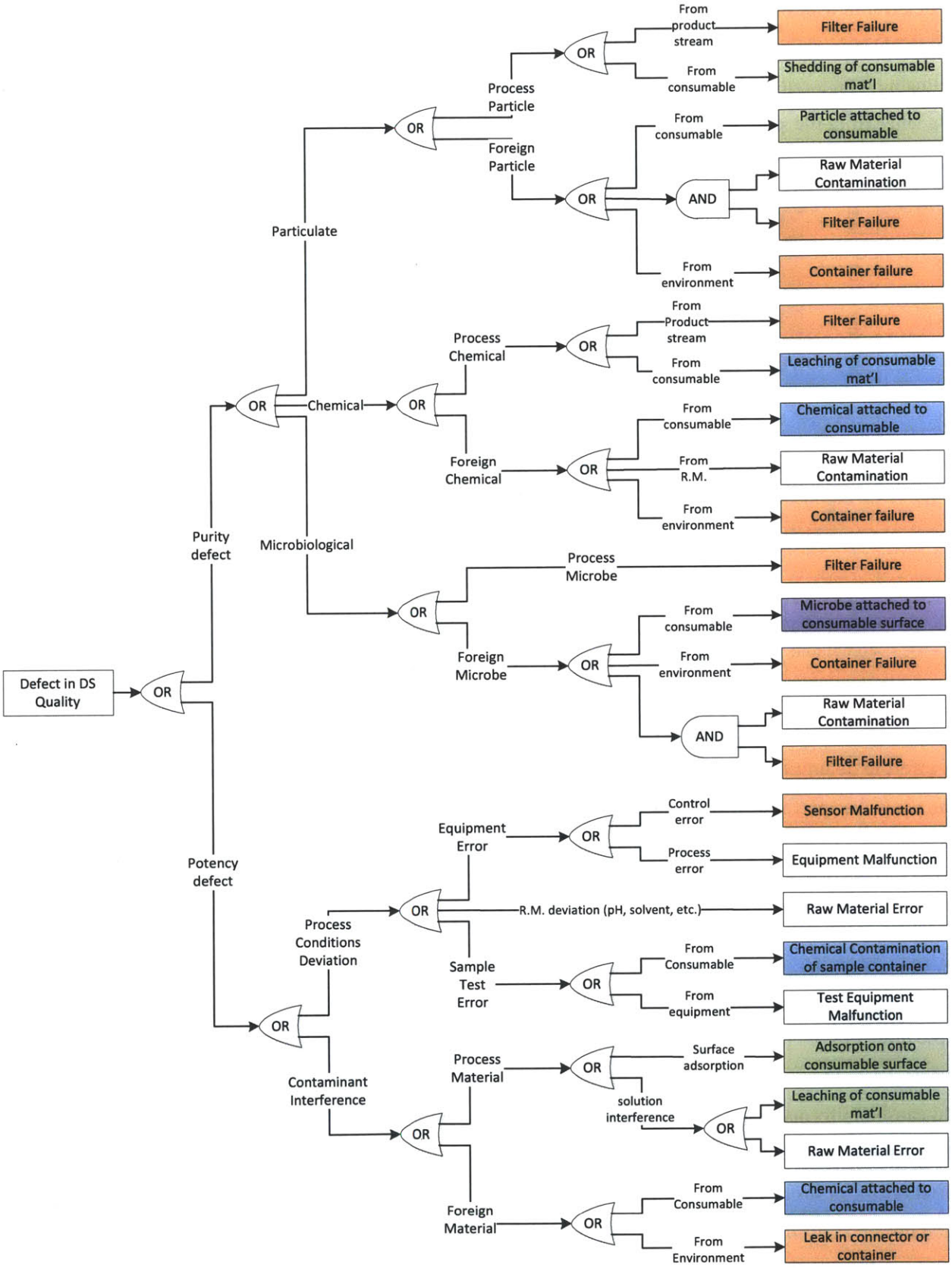

Figure 9. Drug Substance quality defect fault tree.

Categorizing the Failure Modes

The output of this fault tree analysis is a high-level list of potential sources for the ultimate drug substance defect. This list was cross-referenced with the failure modes brainstormed and listed above to confirm that all potential failure modes are captured in these broad categories. Furthermore, the defect sources which were related to consumable quality defects were categorized into four broad groups including chemical contamination (blue), particulate contamination (green), microbiological contamination (purple), and functional errors (orange). It should be noted that functional errors appear in many of the branches indicating that the function of some consumables has a potential impact on product quality through several paths.

Although the fault tree shows many routes of failure for potency defects, we will exclude it from the rest of our analysis because the risk to patient safety is considered very low. Sufficient systems are in place to monitor the potency of the drug at several stages during production and the final concentration of Active Pharmaceutical Ingredient (API) which is pharmacologically potent is well-controlled in the final formulation of the drug. Thus, a defect from any consumable which has a potential impact on the drug molecule will ultimately have no patient safety risk. In addition, the types of defects which would affect drug potency are considered very rare by process experts at the production site. Thus, we have rationale to exclude these effects from our analysis on the grounds that the severity and the likelihood are sufficiently low to make the total risk negligible.

Within the chemical contamination and particulate contamination failure modes, the mechanisms which lead to quality defects are diverse and require separate treatment for the purposes of risk assessment. For chemical contamination, the leaching of a chemical compound from a polymer component of a consumable must be treated separately from a foreign chemical attached to the surface of the consumable because the impact of the contamination, the root causes, and the methods for detection are unique to each. Therefore, we distinguish between intrinsic and extrinsic sources of chemical contamination. Likewise, the sources for particulate from a consumable may be from the material itself or it may be from a foreign particle which becomes attached to the consumable. The root causes, effects, and detection of these two sources are unique and must be treated differently. For microbiological and functional failures, however, the source of the error is irrelevant to the effect and the detection of the error and there is therefore no need to separate the source into unique failure modes. Table 2 presents these six resulting failure modes which are later defined more formally and which are used in the subsequent risk assessment.

Table 2. Consumable failure mode categories.

	Chemical Contamination	Particulate Contamination	Microbiological Contamination	Functional Failure
Intrinsic	Unqualified chemical leaches from material	Particle is shed from component material	Microbe attached to the consumable	Consumable has a defect which compromises its primary function
Extrinsic	Foreign chemical attached to consumable	Foreign particle attached to consumable		

Defining the Failure Modes

Since these failure modes serve as the basis for our risk assessment, they require more formal definitions and examples to aid the developer in accurately building the risk model and the user in performing the analysis and interpreting the results. These definitions are built on the assumption that the consumables have already been qualified in a "normal" condition for use in biopharmaceutical production and that these failure modes represent a deviation from the expected materials, handling, and processing which were previously qualified.

Unqualified Leaching: An error in a component material of the consumable leads to leaching of internal chemicals into the process stream which are of an unqualified volume or composition, i.e. an excessive volume of chemicals or unknown chemicals are released. *Examples: mix-up or contamination of raw material at the supplier, deviation in manufacturing process reduces binding or curing of resins.*

Particle Shedding: An error in the component material of the consumable leads to a release of intrinsic particles from the material into the process stream. *Examples: mix-up or contamination of raw material at supplier, deviation in manufacturing process reduces binding or curing of resins, insufficient cleaning.*

Foreign Chemical: A foreign chemical which is not a component of the consumable becomes attached to the exterior of the consumable and then is released into the process stream. *Examples: cross-contamination of manufacturing equipment, lubricant leak, spray from nearby process, insufficient cleaning.*

Foreign Particle: A foreign particle becomes attached to the exterior of the consumable and then is released into the process stream. *Examples: cross-contamination of*

manufacturing equipment, environmental particles from abrasion, cutting operations, clothing, skin, hair, paper, insufficient cleaning.

Microbiological: A microbiological entity becomes attached to the consumable and then is released into the process stream. *Examples: insufficient cleaning of manufacturing equipment, contamination of raw materials, cross-contamination during handling, insufficient sterilization or sanitization.*

Functional Failure: The consumable fails to perform its primary function due to an error in construction or damage. *Examples: leak in bag seal, leak in tubing connection, filter membrane damaged or installed incorrectly.*

3.4 Discussion

We have defined a standard set of failure modes which may be used in the risk assessment of consumables. By first generating a list of all potential and historically observed failures and subsequently performing a fault tree analysis which includes all listed failures, these failure mode categories are cumulatively exhaustive and mutually exclusive. This provides a system in which all future observed failure modes may be placed into exactly one of these categories for subsequent risk assessment. In addition, the categories are sufficiently narrow to enable an analysis of the likelihood of failure and the severity of the effects and in so doing enable the comparison of risk among consumables for each failure mode. Lastly, the six defined categories are broad enough to allow efficient and standardized analysis, removing the burdensome risk identification task of the individual consumable task from the analyst. In establishing these standard failure modes, which are applicable to each consumable, the risk assessment may also be standardized as will be presented in the next chapter.

4 Development of Risk Assessment Method

4.1 Objectives

Following risk identification, a comprehensive risk management system requires the assessment of each of these risks. In the context of consumables quality, this assessment is to be performed on each consumable article individually according to the standard failure modes defined in the previous chapter. The following objectives are established based on requirements from regulatory authorities, production and quality managers, and the risk analysts who will ultimately use this method.

Outputs prioritize risks for mitigation decision-making

The outputs of the risk assessment method must provide a relative assessment of the risks among all consumables assessed such that they can be prioritized for the implementation of mitigation actions. It should be adaptable to various mitigation options which may be implemented internally in the form of additional incoming control testing or inspections, additional in-process testing, cleaning procedures, etc. or implemented at the supplier in the form of improved quality systems, improved controls, additional testing, etc. Specific mitigation options are discussed in Chapter 5. The output should enable direct comparison of consumables and of the failure modes within each consumable, that is, the assessment should distinguish which failure modes within each consumable present the highest risk. In addition, the output must be at least semi-quantitative to enable prioritization of a large set of consumables.

Provide justification and rationale

Regulatory authorities require rationale and justification for accepting certain risks and mitigating others. With regard to consumables quality and receiving inspections, the ICH states that "the lack of on-site testing for [processing aids] should be justified and documented," [3]. Therefore, if the risk assessment will be used to accept certain risks, it must provide formalized documentation which can be archived and reviewed as rationale for those decisions. This rationale should be made once for all subsequent analyses within an accompanying guidance document as well as in signed and approved documentation for each iteration of the analysis.

Performed in an efficient tool

The risk assessment method must be implemented into a tool which is capable of performing the analysis according to reasonable and understandable rules in a manner which is efficient for the analyst. Because several hundred consumables will ultimately be assessed, the analytical burden should be alleviated by semi-automated calculations which are pre-defined and can be subsequently applied to all consumables

based on the variables unique to each. In an electronic tool, this can be achieved by formulas which take specific attributes as inputs and automatically calculate the risk levels as outputs.

Consistent results among users

Lastly, the risk assessment tool must provide consistent results among users and over time. Since several analysts will be required to perform the assessment depending on the articles they are familiar with (the Huningue site produces multiple products on multiple lines) and since new articles are added each year, the tool must generate outputs which are not analyst-dependent. This further necessitates pre-defined rules to guide the assessment such that the input choices are independent of the analyst's judgment. Furthermore, the tool must be robust against entry errors and it must be protected against modification after approval and signature.

4.2 Risk Assessment Method

Risk Assessment Process

All of the objectives discussed above led the author to develop a risk assessment tool based on an FMEA framework with pre-determined rules and calculations to determine the Severity, Likelihood, and Detectability of each failure mode for each consumable. The FMEA framework allows risk from multiple failure modes to be analyzed according to three relevant risk dimensions and provides a semi-quantitative output to guide management decisions for risk acceptance and mitigation. It is especially useful for systematically approaching the factors which affect the overall risk in manageable analytic pieces and synthesizing these factors in a summary score. In a traditional FMEA analysis, a team of experienced staff collaboratively grade each risk dimension for each failure mode based on their judgment and expertise. In the context of consumables quality, as discussed above, the task of performing a traditional FMEA is intractable since the users are diverse, there are several hundred articles to be analyzed, and new articles are added frequently. Therefore, it is preferable to define certain rules once for a standard risk assessment developed in collaboration with all of the appropriate work functions such that future risk assessment can be performed efficiently and consistently.

In the risk assessment method presented in this chapter, the assessment is performed on each consumable one at a time, analyzing the risk associated with each of the six failure modes and generating a report. The report contains a semi-quantified level of risk which can then be prioritized and compared against pre-defined decision thresholds for determining if the risk is acceptable. If not, implementation actions can be implemented to reduce the risk and the assessment can be repeated until the risk level is acceptable for each failure mode. The following diagram describes the workflow for this tailored and standardized assessment process.

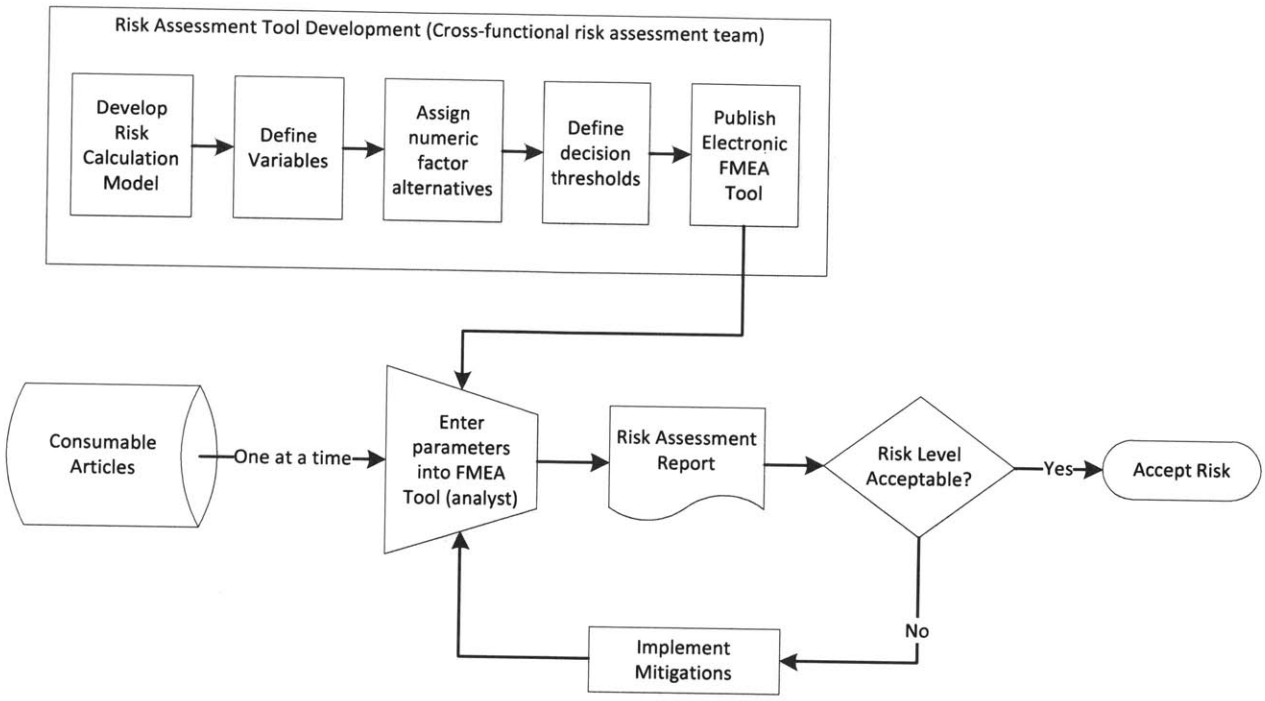

Figure 10. Risk assessment workflow

Risk Assessment Tool

Following the basic FMEA framework, the Severity, Likelihood, and Detectability of each failure mode are analyzed and the scores from these dimensions are multiplied to obtain the Risk Priority Number (RPN), a measure of overall risk. The scores are non-dimensional and in the present tool they are calculated using pre-defined formulas which take as inputs various attributes for each consumable. The output of the tool is, therefore, one RPN for each of the six failure modes for each consumable. The diagram below illustrates this combination of attributes which constitute Severity, Likelihood, and Detectability scores which are combined into the RPN according to each failure mode. The mathematical models for generating these scores are discussed in the remainder of this chapter.

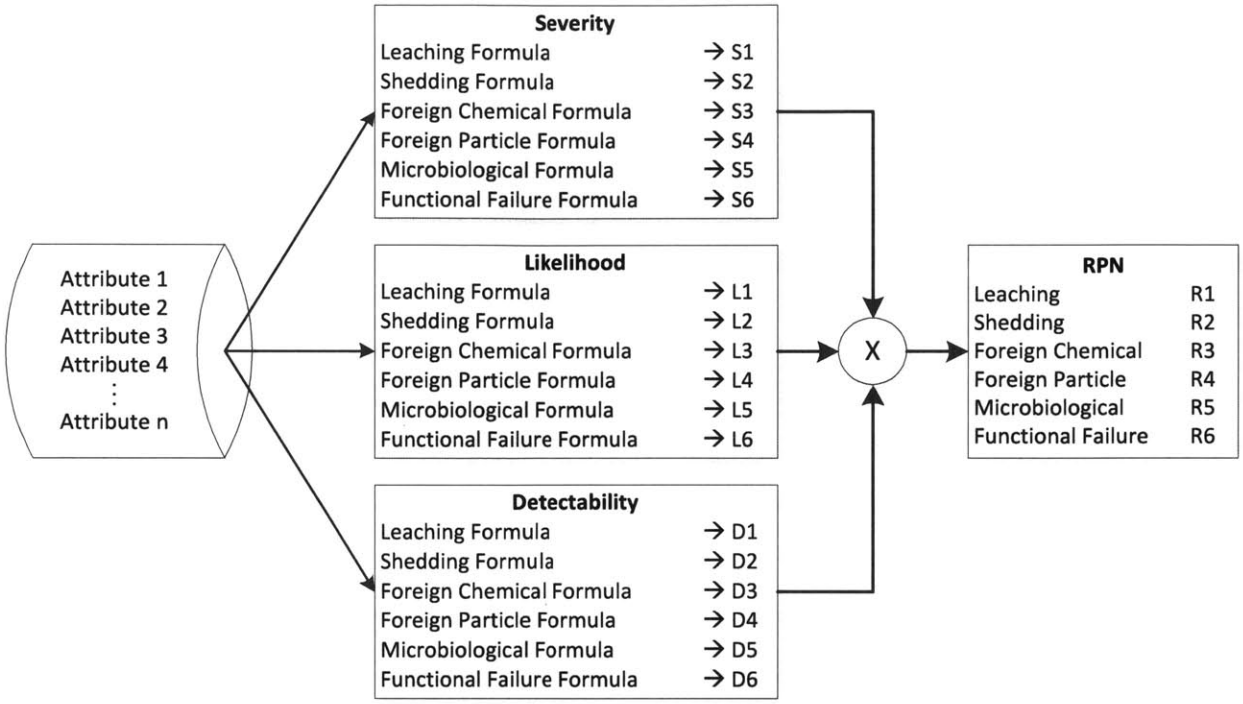

Figure 11. FMEA risk assessment tool diagram. The "X" symbolizes the multiplication of each failure mode risk dimension for the RPN calculation. For example, R1 = S1 × L1 × D1.

4.3 Severity Calculations

4.3.1 Severity Scale

Severity is the magnitude of the effects of a potential failure on product quality which is related to patient quality in this context. Since this risk assessment is particularly concerned with understanding potential failures which could have a significant business impact, we can limit the scope of our severity assessment to those failures which may have a patient safety impact. We can then define a numeric 1, 5, 9 Severity score corresponding to potential patient safety impact for the three contamination types.

Chemical

The Product Quality Research Institute (PQRI) has established a Threshold of Toxicological Concern (TTC) of 1.5 µg daily intake based on a review of the acute toxicity of various chemical compounds and various regulatory agency recommendations [6]. This establishes our threshold for low severity, that is under 1.5 µg daily intake, the severity of contamination is defined as low.

Particulate

US Pharmacopeia <788>, Particulate Matter in Injections, describes limits and methods for detecting particulates in injectable solutions. For small-volume injections, up to 6000 particles between 10 and 25 μm in diameter are allowed [24]. Depending on the density of the particles, this is approximately 10 to 100 μg of particulate matter per dosage container, or about an order of magnitude higher than the limit for chemical contaminants.

Microbiological

Microbiological contamination may be measured as a concentration of bacterial endotoxin, a toxic protein released from bacteria upon cell wall burst. FDA guidelines for endotoxins in injectable drugs provides a limit at 5.0 Endotoxin Units (EU) per kilogram of body weight [25]. Assuming a 60 kg human, this translates to 300 EU, or approximately 30 μg, per daily dosage.

The following table defines the Severity scoring scale based on these limits. This severity scale is not linear with respect to quantity of contaminant because the toxicity of all potential contaminants lies within a very wide range, depending on its composition.

Table 3. Severity scoring scale

Score	Meaning	Patient Safety Risk
1	Low Severity	No influence on product quality or safety is expected. Potential contaminants introduced or allowed due to consumable non-conformance are removed before patient use or the introduced quantity is negligible (under lower threshold for contaminants).
5	Intermediate Severity	Intermediate effect on product quality or safety. The quantity of contaminants potentially introduced or allowed due to consumable non-conformance is small, but certain contaminants may be harmful to some patients.
9	High Severity	Severe effect on product quality or safety. The quantity of contaminants potentially introduced or allowed due to consumable non-conformance is large, and will likely be harmful to patients.

4.3.2 Severity Calculation Models

Generic contamination model

Based on this defined severity scale, we can establish a mathematical model to calculate the Severity score for each failure mode. For all contaminations, the potential toxicity to the patient is related to the volume of contaminant which would ultimately be administered to the patient. The volume of a material that could be present in a dose of product is a function of the quantity of the material released into the

process stream, the dilution factor, the clearance rate of all applicable filters, and the number of doses per batch. We can use the following formula to calculate total contaminant volume in each dose:

$$V = \frac{Q * D * (1 - C)}{N}$$

Where V is the volume of contaminant in each dose

Q is the quantity of contaminant released from the consumable

D is the dilution factor between the point of contamination to the final drug product (0 to 100%)

C is the clearance rate (0 to 100%)

N is the number of doses per batch

This generic model applies to all failure modes, but these variables must be decomposed into relevant sub-variables for each failure mode in order to perform the analysis for each consumable. The following sections describe this decomposition for the various failure modes.

Quantity released for leaching

Leaching has been sufficiently studied and documented at Novartis to allow us to establish a set of variables on which we can base the quantity released calculation. The quantity of material which could possibly leach from a consumable and into the production process is a function of its total surface area (a larger consumable can release more leachates, quantity released is proportional to the number of consumables used in production), the material properties (certain materials release more leachates than others), sterilization processes (sterilization increases leaching rate), the usage conditions including time, pressure, and agitation (all of which increase leaching rates), and composition of the product (pH, temperature, solvent strength). Material properties, sterilization, usage conditions, and product composition can all be considered dimensionless factors. Then by establishing a constant release rate per unit area based on an assumption of leaching quantity in the worst case conditions, we can estimate the quantity of a leachate released by the consumable:

$$Q = WorstCaseReleaseRate * SA * Material * Sterilization * UsageConditions * Composition$$

The worst case release rate constant is derived from information regarding a case of a non-conforming filter that was analyzed during a deviation investigation. In this case, a non-conforming binding resin was used in the filter membrane and instead of binding to the fibers by strong covalent bonds, the resin was

found to bind to the cellulose fibers with weak Van der Waals interactions which were more readily broken. During investigational studies, this resulted in a large amount of resin leaching into water when flushed at a rate similar to the conditions used in production. A leaching curve was obtained by mounting a sample of the membrane in a test fixture, flushing injectable water in small volume increments, and measuring the concentration of the resin in the effluent using a UV detector. The leaching curve was obtained for both conforming and non-conforming samples as seen in the graph below.

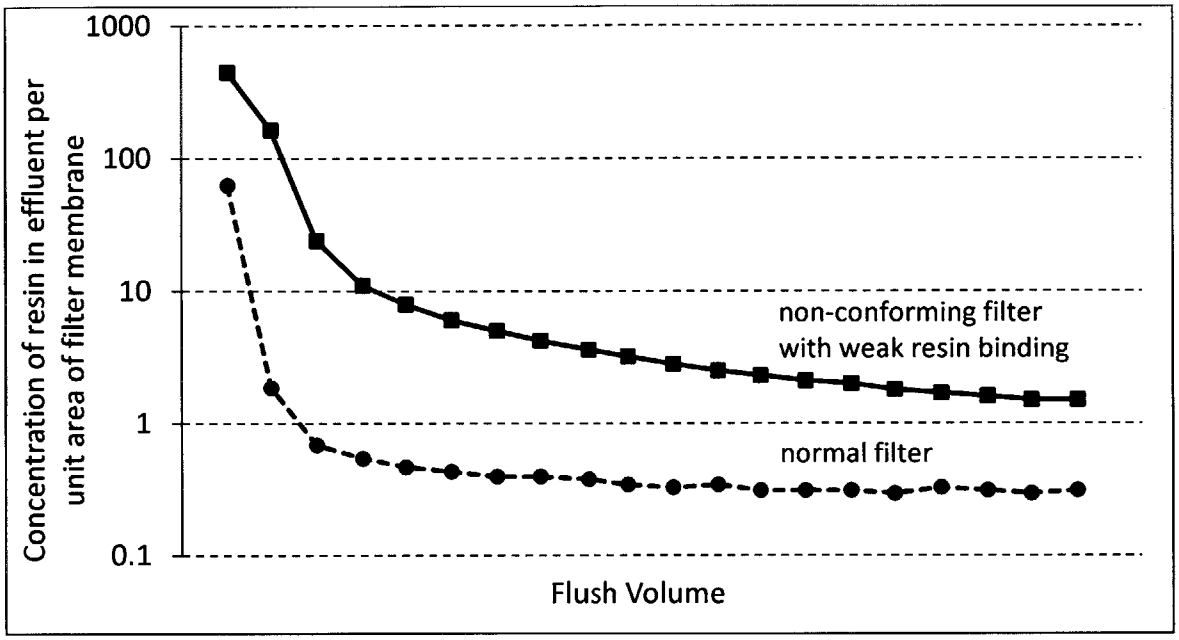

Figure 12. Leaching curves for normal and non-conforming filters. The non-conforming filter is made with an incorrect resin that leaches at a higher rate. By integrating under the curve, we can estimate a worst-case volumetric release rate per unit surface area.

By integrating under this curve we can calculate the total volumetric quantity of conforming resin released by this filter during its use in production (after flush to final rinse). We can treat this as the worst case leaching quantity because of the combination of conditions which lead to this release rate including bonding strength, material properties, sterilization, and usage conditions. Under other conditions, the volume of contaminant released is reduced from this worst case volume. We can define a set of dimensionless conditions factors on a 0 to 1 scale such that, when multiplied by the surface area and worst case release rate, the formula provides an estimate of the quantity of material released into the system.

Dilution factor for leaching

The amount of unqualified material that is present in the final drug product is reduced from the total released quantity due to dilution. The amount of dilution depends on the contact that the consumable has with the final drug product. For example, all leachates from a drug substance container will be present in the final patient dosage because there are no dilutive processes after the drug is stored in the container. On the other hand, leachates from a purification buffer container are diluted in the buffer before they are introduced into the process stream. Except in the case of the final purification buffers and excipients, the buffer is not included in the final product so the amount of contaminant transferred to the patient's dosage is diluted. As can be seen in the figure below, during clarification, purification, and ultrafiltration/ diafiltration (UF/DF) steps, impurities are rinsed out with these purification buffers and media mixtures. In general, leachates which contact the protein are not diluted and leachates with indirect contact have some varying degree of dilution. We can therefore assign a relative dilution factor to each level of product contact which a consumable has with the process with 1 being undiluted and 0 being fully diluted.

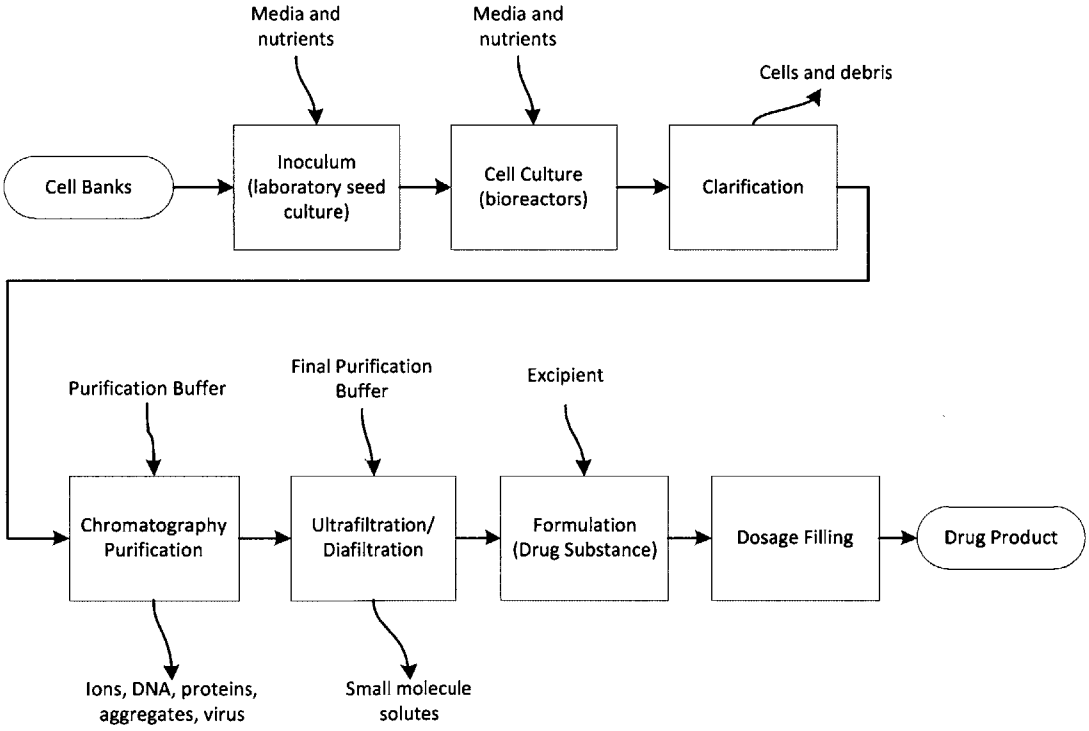

Figure 13. Generic biopharmaceutical manufacturing process showing inputs and outputs.

Clearance Rate

The biopharmaceutical manufacturing process has various filtration steps which are designed to remove impurities from the product, as can be seen in the figure above. In general, however, the process is designed to remove known impurities which are introduced during normal processing and it is not

qualified to remove unknown or unexpected impurities. Therefore, although we expect the chromatography and UF/DF processes to remove many chemical species which could be present from a non-conformance, we cannot depend on any chemical clearance in our risk assessment. However, the size-exclusion filters in place are designed to remove particles including some microbes and so we can establish clearance rates for these potential contaminants based on the process step where the consumable is used. If there is a sterile filter downstream of the consumable, the clearance rate is high and the total amount of contaminant in the final patient dosage is low.

Clearance can also occur through rinsing of the consumable before it contacts the product. As can be seen in Figure 12, the volume of material released by the filter membrane significantly decreases as a function of the volume of fluid which is forced through it. Thus by flushing a consumable before use, much of the non-conforming material can be removed instead of being introduced into the product stream. This effect is even more pronounced for foreign chemicals and particles which are bound more loosely to the consumable surface.

Number of Doses per batch

The volume of contaminant that a patient will receive is proportional to the concentration of contaminant in the batch, which itself is inversely proportional to the total volume of the batch. The drugs produced at any given facility are produced in various batch sizes and in various concentrations, making it impossible to calculate the actual contaminant volume. However, we can calculate the worst case number of doses in a batch based on the minimum volume of the batch and the maximum daily dosage for any given patient as

$$N = \frac{Minimum\ Batch\ Volume * Minimum\ Concentration}{Maximum\ Daily\ Dosage}$$

The following table illustrates two possible scenarios. Note that the minimum number of doses may be lower, and therefore the relative amount of contaminant given to the patient may be higher, even with a larger batch.

Table 4. Examples of Number of doses calculation.

Minimum Batch Volume	Minimum Drug Concentration	Maximum Daily Dosage	Minimum Number of Doses
1,000 L	100 mg / L	1,000 mg	100 doses
100 L	100 mg / L	10 mg	1,000 doses

This minimum number of doses may be applied to a particular production line, in cases where the use of a consumable is limited to one line, or it can be applied to the entire facility in cases where the consumable may be used on multiple production lines.

Normalization of variables for severity calculation

We have demonstrated a quantitative model for approximating the volume of a contaminant introduced into a drug but the model may be normalized for easier integration into a risk assessment tool and for broader applicability for all failure modes. The worst case release rate and the minimum number of doses per batch can be combined into one constant and the clearance rate can be converted into an allowance rate defined as (1 – clearance). We can then normalize the model to our highest risk articles for each failure mode to a scale of 0 to 1. The severity risk calculation model then becomes:

$$SeverityIndex = QuantityReleased * DilutionRate * AllowanceRate$$

where each variable is composed of one or more sub-variables whose factors can be scaled from 0.1 to 1. A factor of 0 should not be assigned because it would automatically reduce the Severity score to 0. The variable's numerical factor is selected from a set of options based on the particular attribute for the consumable. For example, the variable "material" includes the attribute set "fibers without resin", "fibers with resin", "amorphous polymer", "crystalline polymer", "metal", and "glass" each with their own assigned numerical factor. For a depth filter, the primary material is fiber with resin and a factor of 1 is assigned for the material variable.

The full collection of variables, each affecting the quantity released, dilution rate, or allowance rate, are listed in Table 6 and the attribute sets and corresponding factors are listed in the subsequent section. Based on this collection of variables, the severity calculation for each failure mode can be generalized to:

$$SeverityIndex = \prod_{i=0}^{n} S_i \quad \forall \ S_i \in [0.1,1]$$

where S_i is an individual factor corresponding to an attribute selection and n is the total number of variables for the given failure mode. Since the maximum Severity index is 1.0 (all factors are selected as 1), a severity score (1, 5, or 9 points) can be assigned based on the index according to the following rules.

Table 5. Transformation rules for Severity index to Severity score.

Severity Level	Severity Index	Severity Score
Low Severity	0.001 to 1/3	1 point
Medium Severity	1/3 to 2/3	5 points
High Severity	2/3 to 1	9 points

The Severity analysis process is illustrated in the diagram below.

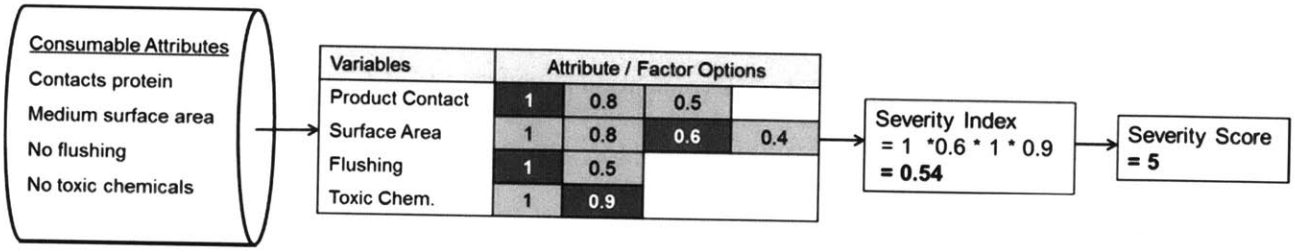

Figure 14. Severity Score calculation diagram. The consumable attributes are chosen from a list of possible options, each with a pre-defined numerical factor. The factors are multiplied to obtain the Severity Index, which is converted to the Severity Score.

4.3.3 Detailed Explanation of Severity Factors

Factors which affect Severity by Failure Mode

The following table lists the variables which are applicable for each failure mode. The attribute options for each variable are explained in the subsequent tables.

Table 6. Factors which affect the severity score by failure mode.

Failure Mode	Severity Calculation Factors	Rationale
Unqualified Leaching	• Product contact • Material • Surface area • Usage conditions • Product composition • Flushing or rinsing • Sterilization/sanitization	As explained above, the quantity of leached chemicals released from the consumable is a function of the material properties, surface area, conditions of use, and sterilization or sanitization. Dilution is a function of product contact. Clearance is a function of flushing, but there can be no assumption of chemical clearance by filtration anywhere in the process so process step is not considered in the analysis of this failure mode.

Failure Mode	Severity Calculation Factors	Rationale
Particle Shedding	• Product contact • Material • Surface area • Usage conditions • Sterilization/sanitization • Flushing or rinsing • Downstream filtration	The quantity of shed particles released from the consumable is a function of the material properties (particularly if fibrous), surface area (larger area leads to more shedding), conditions of use (pressure, agitation, and long term storage can lead to shedding), and sterilization or sanitization (weaken the fiber-resin bonds). Dilution is a function of product contact since particles may be diluted in buffers with indirect contact. Clearance may occur through a downstream particle filter or with pre-use rinsing.
Foreign (External) Chemical	• Product contact • Surface area • Flushing or rinsing • Toxic chemicals at supplier	The quantity of foreign chemicals that can be held and released from the consumable is only a function of its surface area (larger area can hold more contaminant) since we cannot reasonably predict the source or nature of the foreign chemical. Dilution is a function of product contact. Flushing or rinsing can clear chemical contaminants but there is no assumption of chemical clearance anywhere in the process. In addition, the presence of any toxic chemicals at the supplier increases the potential hazardous nature in the case of a contamination.
Foreign (External) Particle	• Product contact • Surface area • Flushing or rinsing • Downstream filtration	The quantity of foreign particles that can be held and released from the consumable is only a function of its surface area (larger area can hold more particles) since we cannot predict the source or nature of the particles. Dilution is a function of product contact. Clearance may occur through a downstream particle filter or with pre-use rinsing.
Microbiological Contamination	• Product contact • Sterilization/sanitization • Downstream filtration	The quantity of microbes (and therefore endotoxin) that may be released from the consumable is a function of the sterilization and/or sanitization processes which are performed before the consumable is used. Dilution is a function of product contact. Clearance may occur through a downstream particle filter or with pre-use rinsing.

Failure Mode	Severity Calculation Factors	Rationale
Functional Failure	• Consumable Function • Product contact	The quantity of contaminants which would be allowed into the product in the case of consumable functional failure is related to its primary function. For example, the failure of a sterilizing filter has a more severe impact that the failure of a raw material dispensing tool. The impact of a functional failure also depends on the contact it has with the product. For example, a leak in a bag containing DS is more severe than a leak in a bag containing buffer because potential contaminants will be diluted if the consumable has only indirect contact with the product.

Quantity Released Variables and Factors

The tables in this section list the numerical factors assigned to each attribute for each variable related to the quantity of contaminant released into the production system. These factors were developed by relative comparison with the other attributes in collaboration with production specialists experienced with these consumables. The definitions and rationale for each factor can be found in Appendix 2.

The consumable function factors listed below are based on a scale in which 1 represents a critical function relating to product quality and 0.1 represents a function which has negligible product quality impact.

Table 7. Factors for the Function variable.

Function	Factor
Storage	1
Bioburden Reduction	1
Virus Removal	1
UF/DF	1
Clarification	0.7
Material Transfer	0.7
RM dispensing	0.3
Air filtration	0.3
Sampling	0.1

The material factors listed below are based on a scale in which a score of 1 represents a great amount of contaminant potentially released and 0.1 represents a negligible amount of contaminant potentially released.

Table 8. Factors for the Material variable.

Material	Leaching Factor	Shedding Factor
Fiber without resin	0.5	1
Fiber with resin	1	1
Amorphous Polymer	1	0.1
Crystalline Polymer	0.8	0.1
Glass	0.4	0.1
Metal	0.1	0.1

Table 9. Factors for the Total Surface Area variable. In this table, the total surface area is the product of the number of this consumable used for a single batch and the surface area in contact with the solution (buffer, excipient, protein pool, or DS). If fluid recirculates through the consumable, it should be considered in the Total Surface Area.

Total Surface Area	Size Definition	Factor
$< 10\ cm^2$	Very small	0.2
10 to $100\ cm^2$	Small	0.4
100 to $1{,}000\ cm^2$	Medium	0.6
0.1 to $1.0\ m^2$	Large	0.8
$> 1.0\ m^2$	Very large	1.0

Table 10. Factors for the Toxic Chemicals at Supplier variable.

Toxic Chemicals at Supplier	Foreign Chemical Factor
Yes	1
No	0.8

Table 11. Factors for the Sterilization/Sanitization variable.

Sterilization/ Sanitization	Intrinsic Factor	Microbiological Factor
Supplier Sterilization	1	0.5
Internal Sanitization	1	0.3
Internal Sterilization	1	0.1
None	0.9	1

The usage conditions factors listed below are based on a scale in which a score of 1 represents conditions which lead to the maximal amount of contaminant released and 0.1 represents conditions which do not lead to significant contamination.

Table 12. Factors for the Usage Conditions variable.

Usage Conditions	Leaching or Shedding Factor
Filtration	1
Storage	1
Flow through	0.6
Brief	0.2

The product composition factors, listed below, are based on a scale in which a score of 1 represents production materials which lead to maximal leaching or shedding and a score of 0.1 represents production materials which lead to negligible leaching or shedding.

Table 13. Factors for the Product Composition variable.

Product composition	Leaching Factor	Shedding Factor
Harsh Solutions	1	1
Mild Solutions	0.9	0.9
Solids	0.5	1

Dilution Variable and Factors

The tables in this section describe the numerical factors assigned to each attribute for the product contact variable which are related to the dilution of potential contaminants in the production system. These factors were developed by relative comparison with the other attributes by production experts experienced with these consumables.

Table 14. Factors and rationale for the Product Contact variable.

Product Contact	Contamination Factor	Functional Factor
Drug Substance	1	1
Excipient	1	0.8
UF/DF Buffer	1	0.8
Protein Pool	1	0.8
Purification Buffer	0.7	0.5
Raw Materials	0.7	0.5
USP Contact	0.5	0.3
None	0.1	0.1

Clearance Variables and Factors

The tables in this section describe the numerical factors assigned to each attribute for the variables which are related to the clearance of potential contaminants from the production system. These factors were

developed by relative comparison with the other attributes by production experts experienced with these consumables.

Table 15. Factors and rationale for the Flushed/Rinsed variable.

Flushed / Rinsed	Intrinsic	Extrinsic
Yes	0.9	0.5
No	1	1

Table 16. Factors and rationale for the Downstream Filter variable.

Downstream Filter	Particle Factor	Microbiological Factor
Yes	0.1	0.4
No	1	1

Multiple Components

In many cases, consumables have multiple material components which may contribute to the overall risk profile and which need to be considered separately. For example, filters normally include a fibrous membrane with a polymer casing and core and elastomeric gaskets; bags normally include tubing and connectors. Because the quantity of contaminants released by leaching and shedding is dependent on the material and surface area, these two failure modes must be analyzed for each component material in the consumable. Although most variables are common to the entire consumable, the material, total surface area, and usage conditions are particular to the individual component.

4.3.4 Results from Representative Consumables

The severity calculation model described above was applied to a pilot group of 48 consumables from the Huningue production facility. These consumables are considered "critical" because of their contact with the product in downstream processes (clarification through drug substance filling) as evaluated through a preliminary criticality analysis. The ten attributes described above were collected for each of these consumable articles and the severity assessment rules were applied to obtain the severity profile displayed in the histogram below.

The severity scores for Leaching and Functional Failures are relatively high, as can be expected due to the nature of the articles used for this pilot assessment. Critical consumables generally have a high degree of product contact with a large surface area, and the list is entirely composed of filters and storage containers. In addition, because they are used in downstream processes, they carry substantial risk in the case of a functional failure.

Shedding, foreign particulate, and microbiological severity scores are relatively low because most consumables have at least one sterile filter in process steps downstream which would remove particles and most microbes. Those consumables which are used after sterile filters are generally sterilized or sanitized, reducing the microbiological risk.

Lastly, foreign chemical scores are intermediate, corresponding with the observation that all filters are flushed before use, thereby clearing some of the contaminant before it enters the product stream.

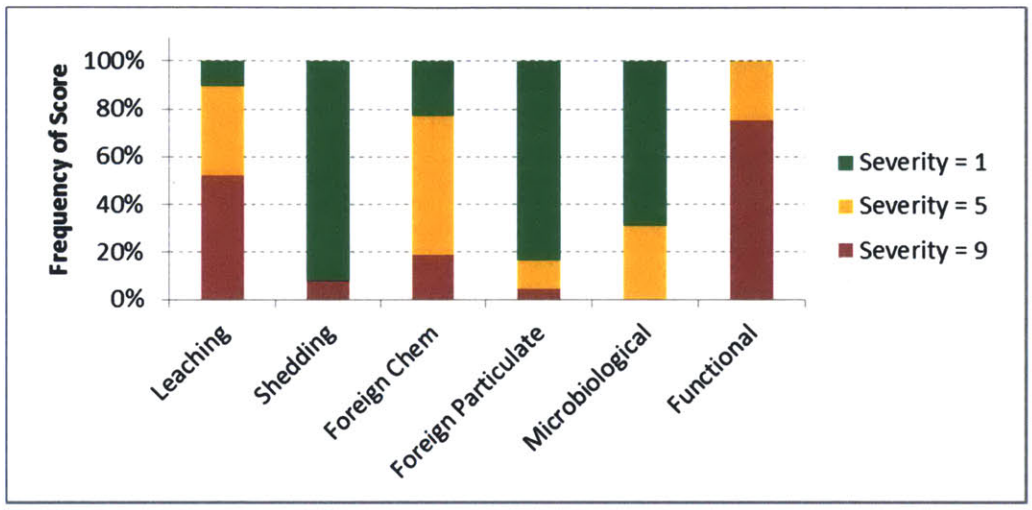

Figure 15. Histogram of Severity scores for pilot group of 48 consumables. The assessment was only performed for the largest material component for each consumable.

4.3.5 Sensitivity Analysis

The sensitivity of the severity calculation to the various inputs indicates for which variables the factor definition and selection are most significant. If the model is insensitive to a particular variable, uncertainty or error in that variable may have only a small impact. On the other hand, uncertainty or errors in highly influential variables may have significant impact on the severity calculation. We can empirically evaluate the influence of each input variable on the likelihood calculation for each failure mode by analyzing the correlation between variables and failure mode index from the given data set for critical consumables. Table 17 shows the coefficients of correlation (Pearson product-moment correlation coefficient, r) which were calculated for each failure mode-variable combination. The most highly correlated variable for each failure mode are displayed in Figure 16.

In general, the correlations are relatively weak (only four of sixty r values are above 0.75) indicating that most individual variables are not highly influential in the data set. In addition, the data are highly clustered at certain input values and often do not cover the whole range of possible input values. For example, the Usage Conditions and Toxic Chemicals at Site variables include only one numerical level in this data set and consequently have no correlation with any of the failure mode indexes. Therefore,

although the correlation evaluation can show relative influence in this data set, it cannot be generalized to evaluate the sensitivity of the broadly applicable mathematical model for all possible data sets.

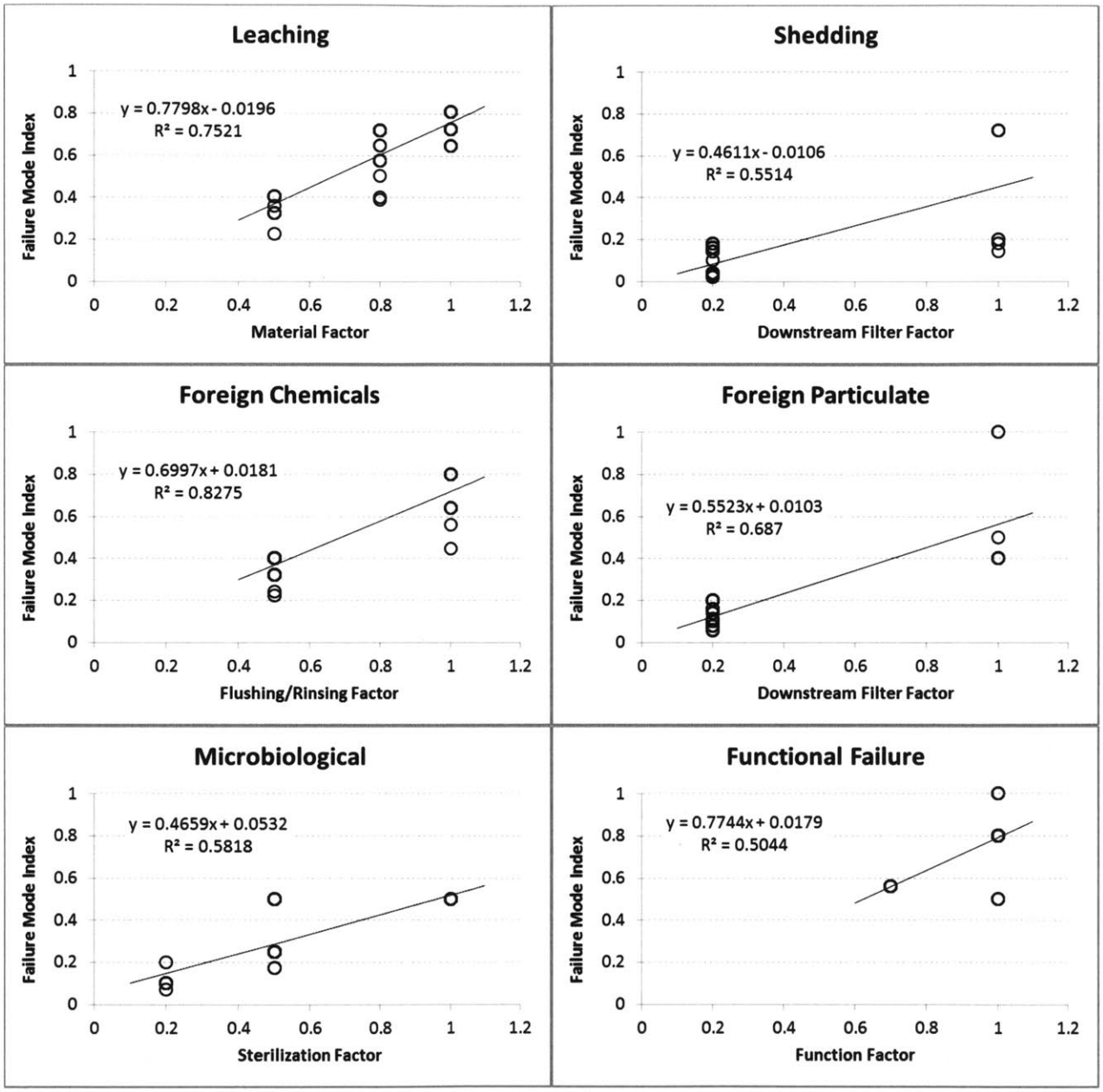

Figure 16. Likelihood scatterplots for selected variables showing a least squares linear regression between the most correlated variable and the overall failure mode index based on the correlation coefficient (r) in the table below.

Table 17. Correlation coefficient of variable and failure mode factor. The intensity of the cell color corresponds to the strength of the correlation.

	Leaching	Shedding	Foreign Chemicals	Foreign Particulate	Microbiological	Functional Failure
Surface Area	0.62	-0.27	0.34	0.01	0.07	-0.01
Usage Conditions	0.00	0.00	0.00	0.00	0.00	0.00
Product Composition	-0.23	0.00	-0.13	-0.08	-0.06	0.06
Sterilization	0.19	0.10	-0.02	-0.12	0.76	-0.54
Downstream Filter	-0.31	0.74	-0.07	0.83	0.50	0.44
Material	0.87	-0.55	0.02	-0.22	0.00	-0.25
Product Contact	0.37	0.13	0.10	0.12	0.30	0.50
Flushing/Rinsing	0.10	-0.31	0.91	0.31	-0.15	0.20
Function	-0.28	-0.04	0.23	0.23	-0.51	0.71
Toxic Chemicals at site	0.00	0.00	0.00	0.00	0.00	0.00

Because of the clustering and lack of coverage of the range of possible inputs, it is also useful to evaluate the sensitivity of the model theoretically. Since the severity calculation is simply the product of several numerical factors, each variable inherently has the same weight within the severity score calculation. However, some variables have a large range of possible values compared to others, allowing them to have more influence on the calculation. For example, the consumable Function factor can be selected from a range between 0.1 and 1.0 whereas the Toxic Chemicals on Site factor includes only 0.8 and 1.0. So the severity calculation is more sensitive to the function of the consumable than the manufacturer's use of toxic chemicals because of the relative magnitude of risk reduction that the function attribute can provide. Table 18 below lists the relative influence of each variable on each failure mode based on the range of its possible inputs and it shows possible severity index reductions from 10% to 90%, depending on the factor.

Table 18. Influence of factors on severity calculation. The percentage values represent the effect that the factor can potentially have on the severity index due to the range of possible input values. For example, a factor of 0.8 represents a 20% decrease in the severity index. The intensity of the color in each cell indicates the relative influence.

	Leaching	Shedding	Foreign Chemicals	Foreign Particulate	Microbiological Contamination	Functional Failure
Surface Area	-80%	-80%	-80%	-80%		
Usage Conditions	-80%	-80%				
Product Composition	-50%					
Sterilization	-10%	-10%			-80%	
Downstream Filter		-80%		-80%	-50%	
Material	-90%	-80%				
Product Contact	-50%	-50%	-50%	-50%	-50%	-70%
Flushing/Rinsing	-10%	-10%	-50%	-50%		
Function						-90%
Toxic Chemicals at site			-20%			

From the values above, we can see that the severity calculation for leaching and shedding is highly sensitive to surface area, usage conditions, and material while relatively insensitive to sterilization and rinsing/flushing. This is expected since the quantity of material leached or shed is highly dependent on the material, under certain conditions, and is proportional to the surface area of the material. Conversely, sterilization and flushing/rinsing have a relatively minor impact on the quantity of material that could leach or shed from a consumable. The severity of shedding and foreign particulate is highly sensitive to the presence of a downstream filter which will remove most particles which could be released from the consumable. The severity of a foreign chemical or particulate contamination is also highly sensitive to the surface area since a large consumable is able to transfer a greater volume of contaminant into the production system. These failure modes are also moderately sensitive to product contact and flushing/rinsing, both of which relate to the dilution of any possible contaminants. The model's sensitivity is reasonable because there is no way to guarantee the removal of chemical or particulate contamination by dilution. The severity of microbiological contamination is most sensitive to the sterilization process, which reflects the best way to ensure the removal of microbes from the consumable and prevent introduction into the production system. Once the microbes are introduced, they are difficult to completely remove, contributing to the intermediate sensitivity of the downstream filter and product contact factors. Lastly, the severity of functional failures is highly sensitive to the function of the consumable and quite sensitive to the product contact. The strong influence of both of these factors is

reasonable since a functional failure is only critical if the function and the use location of the consumable is critical.

4.3.6 Uncertainty Analysis

The effect of uncertainty in these assigned factors was also evaluated using a probabilistic simulation. Since the factors described above are difficult to derive theoretically or empirically, we must accept some uncertainty in the absolute magnitudes. The numerical factors were assigned by teams of experienced personnel and through relative comparison with other factors within the same variable. Therefore, we can assert that the factors are in correct relative order, but the absolute magnitude of each factor is imprecise, but within a certain range of likely values. If we claim that the "real" factor is within ± 0.2 points from the defined factor with 95% confidence, then we can use the normal probability function with mean equal to the defined factor and standard deviation equal to 0.102 to estimate the relative probability distribution of the "real" factor (Figure 17). The normal distribution assumes that that the likelihood of overestimation is equal to the likelihood of underestimation in the factors. In addition, the probability of gross mis-estimation is non-zero and will be captured in the analysis.

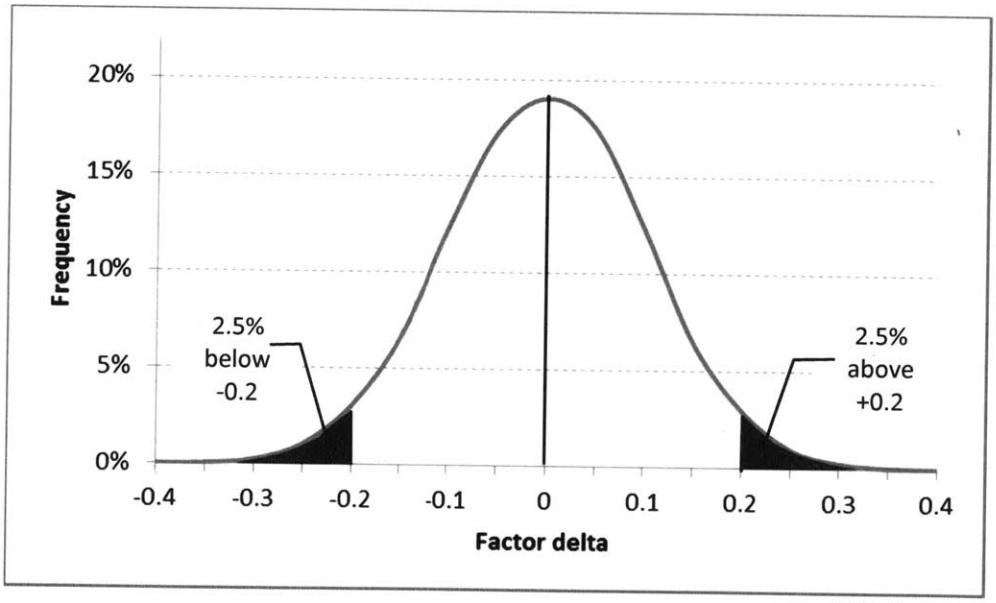

Figure 17. Probability distribution for factor delta during uncertainty analysis. Normal distribution with $\mu = 0$ and $\sigma = 0.102$.

Using a Monte Carlo simulation based on this probability distribution, we can generate the probability distribution of the Severity score outputs with the modeled uncertainty. Because Severity is binned into scores of 1, 5, or 9, the model is expected to exhibit some inherent stability. Only when the severity factor (0 to 1) crosses the threshold into another third will the score change. Therefore, it is most useful to

evaluate the stability of our model in the presence of uncertainty by counting the number of Severity scores which have increased or decreased for each run. The uncertainty simulation was implemented in a Visual Basic script running in Microsoft Excel. For each simulation run, each variable factor was modified individually by a delta randomly generated by the normal distribution described above. The Severity score was calculated for all failure modes for each simulation run and stored in a 10,000 run-long array. The Severity scores for each failure mode were then compared to the scores generated from the pre-defined factors and the number of increased and decreased scores was counted. Figure 18 shows the Severity score change distributions for each failure mode. Runs which appear to the left of "0" indicate that the scores decreased and runs which appear to the right of "0" indicate that the scores increased. Since there are 48 consumables in this pilot data set, the maximum number of score changes is 48.

In this context, the model is considered stable when the effect of uncertainty in the input factors has minimal effect on the score output. Unqualified Leaching and Foreign Chemical Severity scores appear to be the most unstable while Shedding, Foreign Particulate, Microbiological Contamination, and Functional Failure scores demonstrate highly stable behavior. The Severity scores for Shedding and Foreign Particulate are very stable, as can be seen by the high frequency of runs which generated 0 to 9 score changes (98 and 94% respectively). This indicates a high degree of confidence in the scores even in the presence of uncertainty in the factors. Microbiological Contamination Severity scores demonstrate high stability in approximately 83% of the runs but the model also generates score increases in 30 consumable articles or more in 10% of runs. The data shows that this jump in scores occurs when the three relevant factors (sterilization, downstream filter, and product contact) all have positive deltas in the run. In other words, if these three factors were all underestimated in this model, the actual Severity scores should be higher. Otherwise, the model is stable for this failure mode. Functional Failure exhibits a similar bimodal behavior in that the model is stable in most cases (65% of runs) but when the two relevant factors (function and product contact) are both decreased in the run, the scores of more than 20 consumable articles can decrease.

The Severity scores for Leaching and Foreign Chemicals are more unstable. On average, Leaching scores decrease for 19 consumable articles and Foreign Chemicals scores decrease for 7 articles with random uncertainty. This instability is due to the greater number of factors which are included in the Severity calculation combined with the relatively high number of 5 and 9 scores in these failure modes. As described above, when two or three factors are sufficiently low in a particular run, the product of the factors can then reduce the overall Severity factor enough to decrease the score for a large number of consumable articles. In addition, when there are many 9 scores in the standard model, there is less opportunity to increase the scores than to decrease in the presence of symmetric uncertainty.

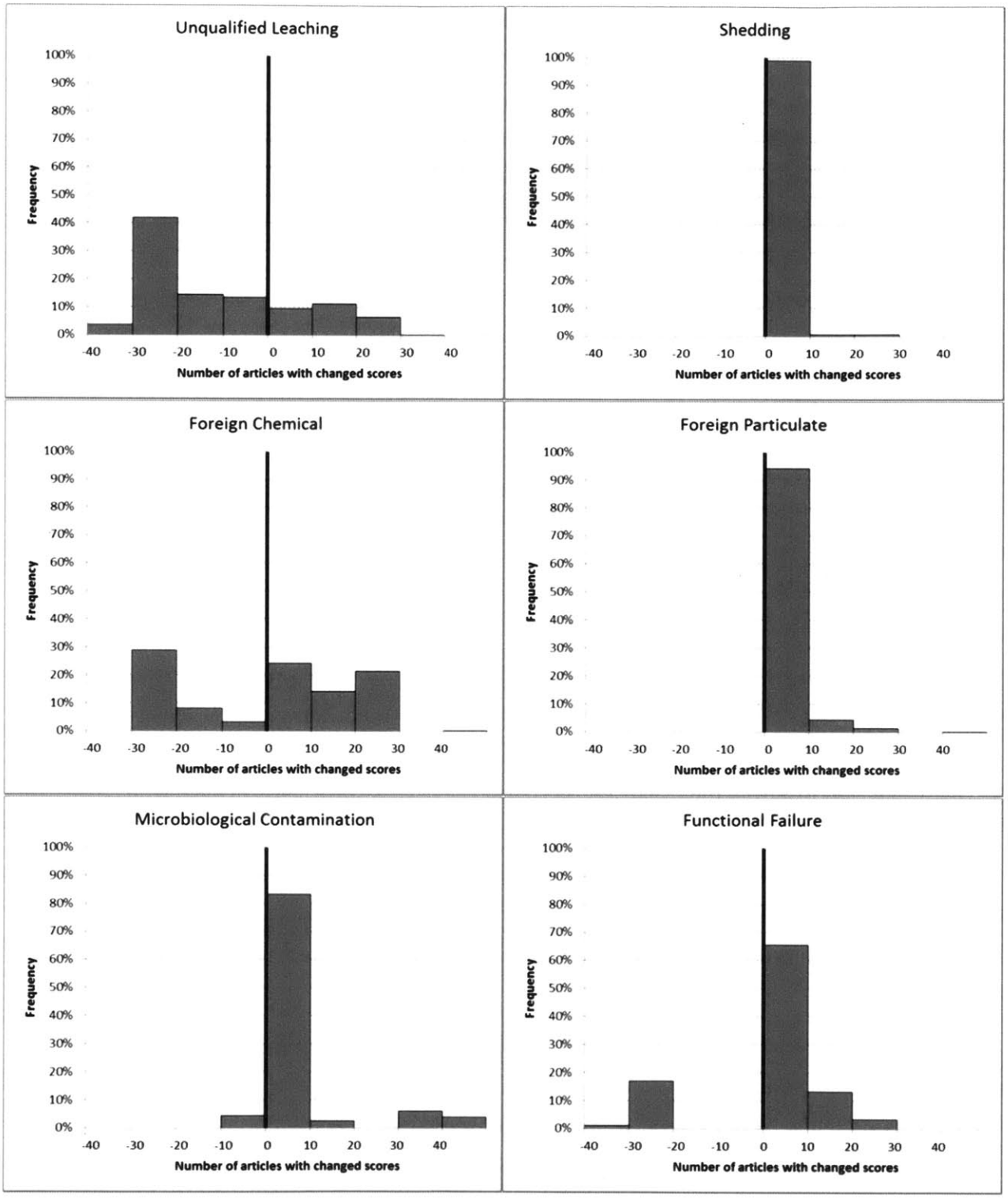

Figure 18. Stability of Severity scores with uncertainty in the model factors from a sample of 48 consumable articles. Each histogram shows the distribution of the number of articles for which the Severity score decreased (negative numbers) or increased (positive numbers) based on 10,000 runs with uncertainty in the factors simulated by a delta from the standard factor from a normal distribution with $\mu = 0$ and $\sigma = 0.102$. Note for interpretation: a scenario in which 10 to 19 articles had decreased scores would appear in the bin between -20 and -10. A scenario in which 0 to 9 articles had increased scores would appear in the bin between 0 and 10.

4.4 Likelihood Calculations

4.4.1 Variables Affecting Likelihood

The Likelihood risk dimension is an estimation of the relative probability that the manufacturer will produce a consumable with a non-conformance. As supplier quality control tests are addressed in the Detectability dimension, we restrict this analysis to all operations prior to final quality inspections. Although a precise quantification of the probability of non-conformance may be impossible to determine since many non-conformances go undetected or unreported by the supplier, we can estimate relative likelihood of non-conformance among suppliers and consumables using certain manufacturer-related metrics. This diverges from the notion of a probabilistic risk analysis in which the frequency of failure is estimated but it brings internal consistency to the evaluation. A relative analysis is unable to provide an absolute quantification of expected monetary loss, but it is nonetheless useful for our objective to prioritize risks and mitigate the riskiest items first. In particular, it allows us to compare suppliers along multiple dimensions in an effort to evaluate the risk of failures for the consumables they provide. Therefore, the purpose of this Likelihood analysis is to determine the relative probability of failure with metrics which are available for each consumable and the corresponding manufacturer. In the context of consumables non-conformance, we can use complexity, general manufacturer quality systems, and specific quality controls to estimate the likelihood of failure.

Consumable Complexity

The probability of consumable non-conformance is approximately proportional to the complexity of the consumable components and the manufacturing processes required to produce it. As an approximation, we can use the number of raw materials which comprise a consumable to assess the probability of failure of a material error, i.e. that an error in a raw material will be present in the final consumable. If we make the simplifying assumption that raw material errors are independent events, then the probability that there is at least one material error is the complement of the probability of no material errors, which itself is the product of the probability of conformance for all materials. If we use the simplifying assumption that each raw material has the same probability of failure, the probability of non-conformance in the whole consumable can be expressed as

$$P\ (nonconformance) = 1 - [1 - P(material\ failure)]^N$$

Where N is the number of raw materials comprising the consumable and *P(material failure)* is the probability that a raw material will have a failure. Figure 19 below shows the relationship between N and the overall probability of non-conformance in the consumable for three different levels of failure rates (1, 2.5, and 5%). At low failure rates, it can be seen that the probability of non-conformance is approximately

linear with respect to the number of component raw materials. Since the probability that any given raw material will fail is low, we can say that the probability of consumable non-conformance from raw material failure is approximately proportional to the number of raw materials. Using the same logic, we can say that the probability of non-conformance due to failures in manufacturing processes is proportional to the number of manufacturing processes involved in producing the consumable. If we consider the number of materials and the number of manufacturing processes together as a measure of complexity, then we can scale the Likelihood score with a complexity factor which is particular to each consumable type. Complexity affects the probability of non-conformance for material and functional failures, i.e leaching, shedding, and functional failure modes but not for microbiological contamination.

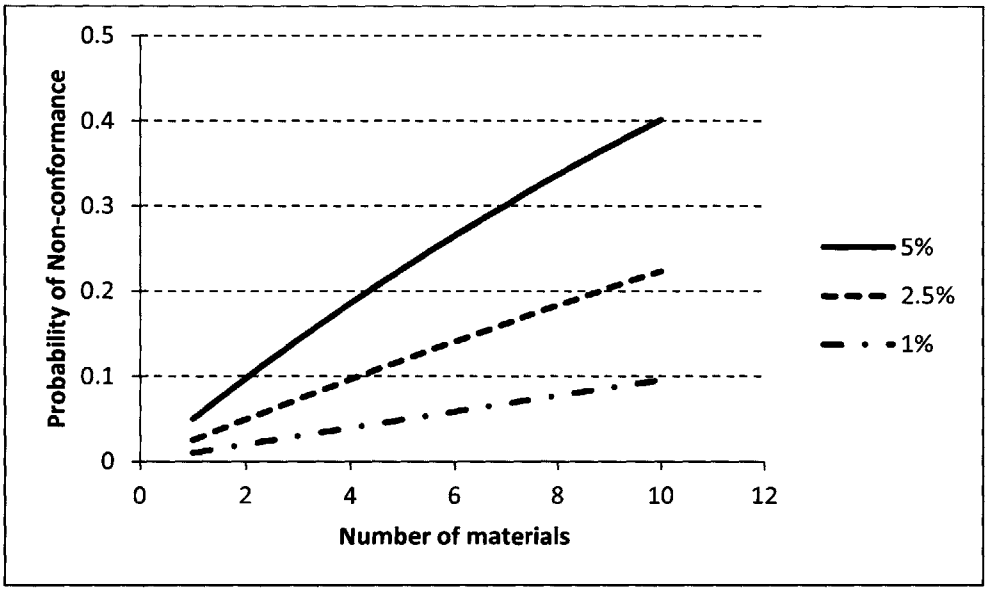

Figure 19. The relationship between the number of materials and the probability of failure in at least one material comparing three different failure rates.

General quality systems

The relative probability that the supplier will produce a consumable with a non-conformance is also related to the general quality systems in place at the manufacturer. Regulatory agencies and pharmaceutical manufacturers assess the general quality systems of consumable suppliers through audits and quality questionnaires in order to ensure suppliers meet minimum quality requirements. These general quality metrics include Good Manufacturing Practices (GMP), dedication of facilities and equipment to individual products, documentation systems, customer complaint handling, change control, and sub-supplier control. Although none of these systems can be tied to probabilistic failure events, they collectively contribute to a manufacturing environment which will experience fewer failures. For example, the probability of a raw material error is affected by the supplier's visibility and control over its sub-suppliers, the handling of raw materials in the warehouse to prevent contamination, labeling and

picking processes to reduce the risk of mix-up, segregation of conforming and non-conforming material, line clearance between lots, and traceability of raw material by manufacturing lots. These manufacturing system attributes are all evaluated by third party quality audit programs (such as ISO), regulatory body audits (such as FDA), and pharmaceutical manufacturer supplier audits (Novartis run), and we can use the outcome of these audits to collectively evaluate the risk of material error leading to a leaching non-conformance.

In addition, Novartis' history with the supplier gives us further evidence for evaluating the risk of failure. A manufacturer which has open complaints tied to non-conformances in consumables recently supplied is at higher risk for generating repeat failures because the non-conformance is evidence that their quality systems are generally inadequate to prevent these non-conformances. Lastly, a facility which is dedicated to only one product or one family of products has a lower risk of producing a non-conforming consumable because there is less opportunity for material mix-up, cross-contamination, manufacturing equipment set-up problems, and operator training shortcomings. Collectively, we can say that the probability of a failure event is lower when the supplier's quality systems are better established, which can be estimated from the combination of the quality system metrics described in Table 22. Because the general quality attributes each affect the relative probability of failure, we can assign a factor to each attribute which will increase or decrease the Likelihood score.

Failure mode-specific quality controls

In addition to the general quality systems described above, the relative probability of non-conformance is related to some attributes which are specific to certain failure modes. For example, the suppliers' testing of raw materials reduces the risk of leaching and shedding because it reduces the probability that an incorrect material is used in the production of the consumable. However, it is not applicable to foreign contaminants or functional failures and it should not be included in the Likelihood calculation for these. The list of specific quality questions which are applicable for the likelihood calculations of particular failure modes is provided in Table 23 and is comprised of questions that are found in the supplier quality questionnaire. In this way, these attributes for the consumable manufacturer are readily available and the Likelihood analysis can be performed efficiently.

Likelihood calculation model

The Likelihood score should be calculated as the product of the several variables indicated above because the variables are probabilistically independent and because a multiplicative model appropriately amplifies the effect of combinations of factors. For example, if two independent factors both increase the probability of failure by 30%, the combined increase in probability is 69% (1.3×1.3). Since these

attributes affect or reflect multiple probabilistic events with varying amounts of impact, each attribute should be assigned a numeric factor according to the response from the supplier or from Novartis' history with the supplier. If we normalize the factors around the standard expectations for a biopharmaceutical consumable supplier, and establish these expected characteristics with a factor of 1, we can define the scale for each factor such that likelihood-increasing factors are given values above 1 and likelihood-decreasing factors are below 1. The calculation of the Likelihood index is the product of several independent factors defined as

$$LikelihoodIndex = \prod_{i=0}^{n} L_i \quad \forall \; L_i \in [0.5,2]$$

where all L_i are the individual factors corresponding to the attributes which contribute to the likelihood score for each failure mode and n is the total number of variables for the given failure mode. The factors are all constrained between 0.5 and 2.0 such that any factor can halve or double the Likelihood index. In order to keep the scale consistent among the failure modes, an equal number of the most influential factors were chosen for each failure mode. These are listed in Table 20.

4.4.2 Likelihood Scale

A combined Likelihood index of 1.0 is considered standard and should correspond to an intermediate Likelihood score of 5, meaning that the relative probability of failure is intermediate. When the Likelihood index is below a pre-defined threshold due to good quality systems, indicating reduced probability of failure, the Likelihood score can be reduced to 1. When the index is above a pre-defined threshold due to poor quality systems, indicating increased probability of failure, the Likelihood score should be raised to 9. The individual numerical factors for each attribute were defined by a group of experienced quality assurance and quality control specialists wherein a factor of 1.0 was given for those attributes which are expected or normal among suppliers. Factors above or below 1.0 were defined according to the expected impact of the attribute to the likelihood of failure. After initial definition, the factors were adjusted such that the range of possible Likelihood indexes was equal (e.g. 0.3 to 3) for each failure mode.

Once the factors had been defined, the pilot set of 48 consumables was assessed using the available historical and quality questionnaire data in order to establish the thresholds for determining Likelihood scores. The threshold was determined such that approximately 10% of articles received a "Low Likelihood" score and 10% of articles received a "High Likelihood" score. The remaining 80% are assigned a "Medium Likelihood" score. This definition ensures that a relatively small number of consumables are given low likelihood scores which could lead to a low overall risk rating despite high

severity and poor detectability. Based on the distribution shown below, the lower threshold is set at 0.75 and the upper threshold is set at 1.25. As expected due to the definition of the factors, the mean Likelihood factor is 1.0.

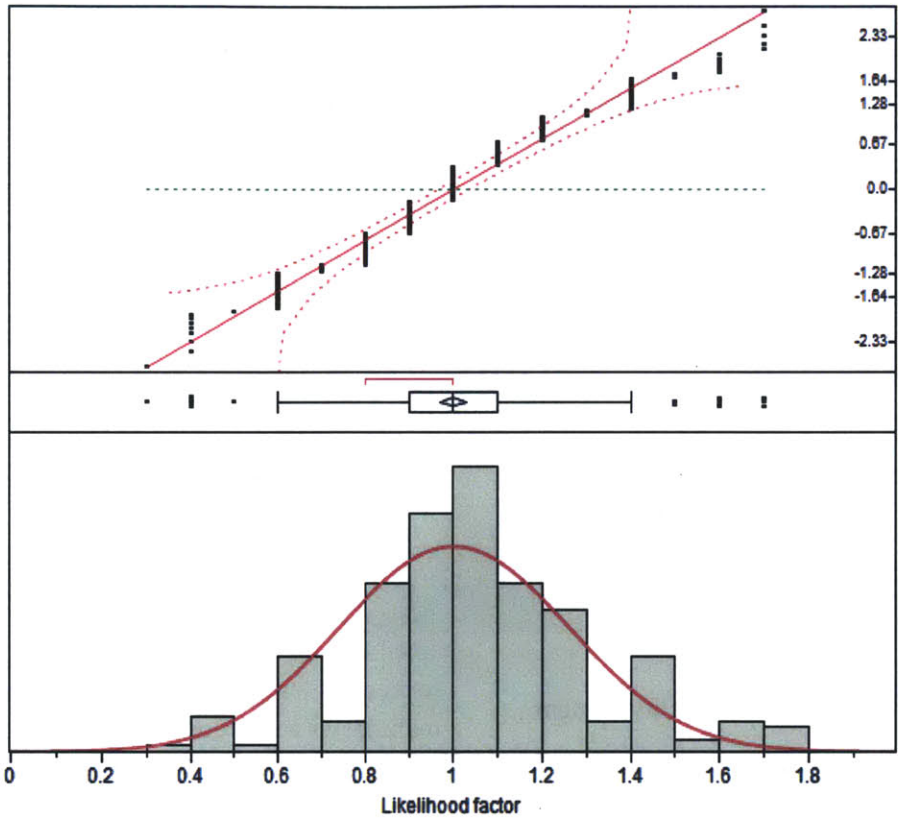

Figure 20. Distribution of Likelihood factors and normal quantile plot showing normality evaluation. Generated by JMP 10.0.0.

Therefore, a likelihood score (1, 5, or 9 points) can be assigned based on this likelihood index (0.3 to 3.0) according to the following rules.

Table 19. Transformation rules for Likelihood index to Likelihood score.

Likelihood Level	Likelihood Index	Likelihood Score
Low Likelihood	< 0.75	1 point
Medium Likelihood	0.75 to 1.25	5 points
High Likelihood	> 1.25	9 points

The process for determining the Likelihood score is illustrated below.

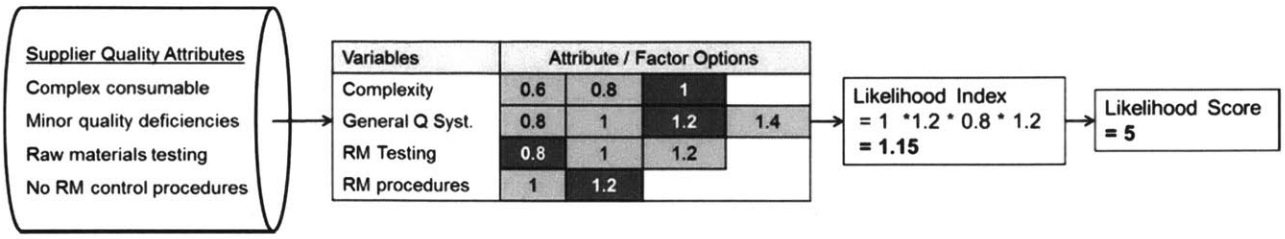

Figure 21. Likelihood score determination diagram. The quality system attributes (including consumable complexity) determine the factors which are multiplied to obtain the Likelihood index which is transformed into the Likelihood score.

4.4.3 Detailed Explanation of Likelihood Calculations

Factors Specific to Each Failure Mode

The following table lists the attributes which are applicable to each failure mode. The General Quality System attribute is the product of five factors which are listed in the General Quality History table (Table 22).

Table 20. Factors which are applicable to each failure mode for the Likelihood calculations.

Failure Mode	Likelihood Calculation Attributes	Rationale
Unqualified Leaching	• Complexity • General Quality System • Raw material testing • Raw material control procedures	The likelihood of unqualified chemical leaching (excessive leaching quantity or hazardous material) is a function of the complexity of the consumable because of the opportunities for material mix-up or process deviations, the supplier's quality systems and history with Novartis, and the specific controls which involve raw material usage at the site.
Particle Shedding	• Complexity • General Quality System • Raw material testing • Manufacturing processes validated	The likelihood of a material error which leads to shedding is a function of the complexity of the consumable because of the opportunities for material mix-up or process deviations, the supplier's quality systems and history with Novartis, and the specific controls which involve raw material usage at the site and manufacturing processes.
Foreign (External) Chemical	• General Quality System • Dedicated equipment • Cleaning procedures for equipment • Cleaning processes validated	The likelihood that a foreign chemical will be attached to the consumable is a function of the manufacturer's general quality systems and the specific controls they have in place to prevent or reduce chemical cross-contamination like cleaning processes and dedicated equipment.

Failure Mode	Likelihood Calculation Attributes	Rationale
Foreign (External) Particle	• General Quality System • Cleanroom manufacturing • Cleaning procedures for equipment • Cleaning processes validated	The likelihood that a foreign particle will be attached to the consumable is a function of the manufacturer's general quality systems and the specific controls they have in place to prevent or reduce particulate attachment like cleanroom manufacturing and cleaning processes.
Microbiological Contamination	• General Quality System • Cleanroom manufacturing • Equipment surfaces monitored microbiologically • Cleaning procedures for equipment	The likelihood of a microbiological contamination is related to the general quality system of the manufacturer and their specific controls including manufacturing in a cleanroom, proactive monitoring of equipment surfaces for microbiological contamination, and cleaning procedures for equipment.
Functional Failure	• Complexity • General Quality System • Dedicated equipment • Validated manufacturing processes	The likelihood of a functional error is related to the complexity of the consumable because of the opportunities for human error, process deviations, or damage. Functional errors are also related to the supplier's quality systems and history with Novartis, the use of dedicated equipment at the manufacturer, and the control the manufacturer has on their processes.

Consumable Type Complexity

The following table lists the complexity scores for the consumable types which are used in biopharmaceutical production. These scores are derived from a combination of the number of component materials in the consumable and the complexity of manufacturing operations required to produce them. The rationale for each factor is provided in Appendix 3.

Table 21. Complexity factors for each consumable type.

Product sub-group	Factor
Bags	1
Depth Filter	1
UF/DF membrane	1
Hollow fiber nanofilter	1
Column filter cartridge	0.8
Syringe filter	0.6
Air filter	0.6
Transfer sets and connectors	0.6
Bottles	0.5
Other	0.5

General Quality History

The first three questions in the following table are extracted from the standard supplier quality questionnaire and the last two questions are tracked by the Novartis quality assurance department. The rationale for each factor is provided in Appendix 3.

Table 22. General quality system metrics and associated factors.

Question	Response and Factor
Has the facility been audited by a local or international health authority?	Yes: 0.9 No: 1
Has the facility been awarded any national or internationally recognized quality standard certification?	Yes: 0.9 No: 1
Does the manufacturer manufacture other products than this in the facility?	Yes: 1.1 Same Family: 1 No: 0.8
Is there an open complaint with this manufacturing site or are there ongoing actions linked to major or critical points?	Yes: 1.2 No: 1
What was the outcome of the last Novartis audit?	Good: 0.6 Satisfactory: 1 At risk: 1.4 None: 1.2

Specific Quality Controls

The following table lists questions which appear in the supplier quality questionnaire and are pertinent to the relative probability of specific failure modes. The rationale for each factor is provided in Appendix 3.

Table 23. Specific quality controls and associated factors for the Likelihood calculation.

Question	Response and Factor
Does the manufacturer use dedicated equipment for the production of this product?	Yes: 0.8 Same Family: 1 No: 1.2
Does the facility test all raw materials?	All: 0.8 Some: 1 No: 1.2
Is this product manufactured in a cleanroom environment?	Yes: 1 No: 1.2
Does the facility monitor the equipment surfaces microbiologically?	Yes: 0.9 No: 1
Are there cleaning procedures in place for each area and piece of equipment?	Yes: 1 No: 1.2
Does the site have procedures that define the control of raw materials?	Yes: 1 No: 1.2
Are the manufacturing processes validated?	Yes: 1 No: 1.2
Are the cleaning processes validated?	Yes: 0.8 No: 1

4.4.4 Results from Representative Consumables

The histogram below shows the Likelihood scores which were obtained from the analysis described above performed on a sample set of 48 consumables. It can be seen that the majority of consumables (approximately 80%) are given scores of 5, 10% are given scores of 1, and 10% are given scores of 9.

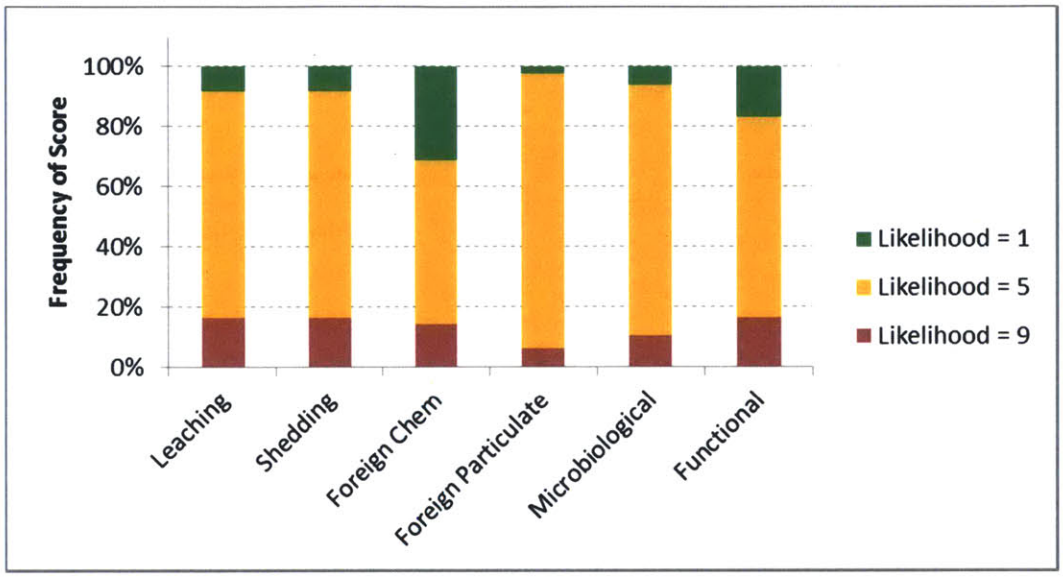

Figure 22. Likelihood score results from the pilot set of 48 consumables.

4.4.5 Sensitivity Analysis

The sensitivity of the likelihood calculation to the various selection variables can indicate for which variables the factor definition and selection is most influential. As described in the Severity calculation section, we can empirically evaluate the influence of each input variable on the likelihood calculation for each failure mode by analyzing the correlation between variables and failure mode index from the given data. The coefficients of correlation (Pearson product-moment correlation coefficient, r) were calculated for each failure mode-variable pair and are presented in Table 24. Figure 23 shows scatterplots of the most highly correlated variable for each failure mode.

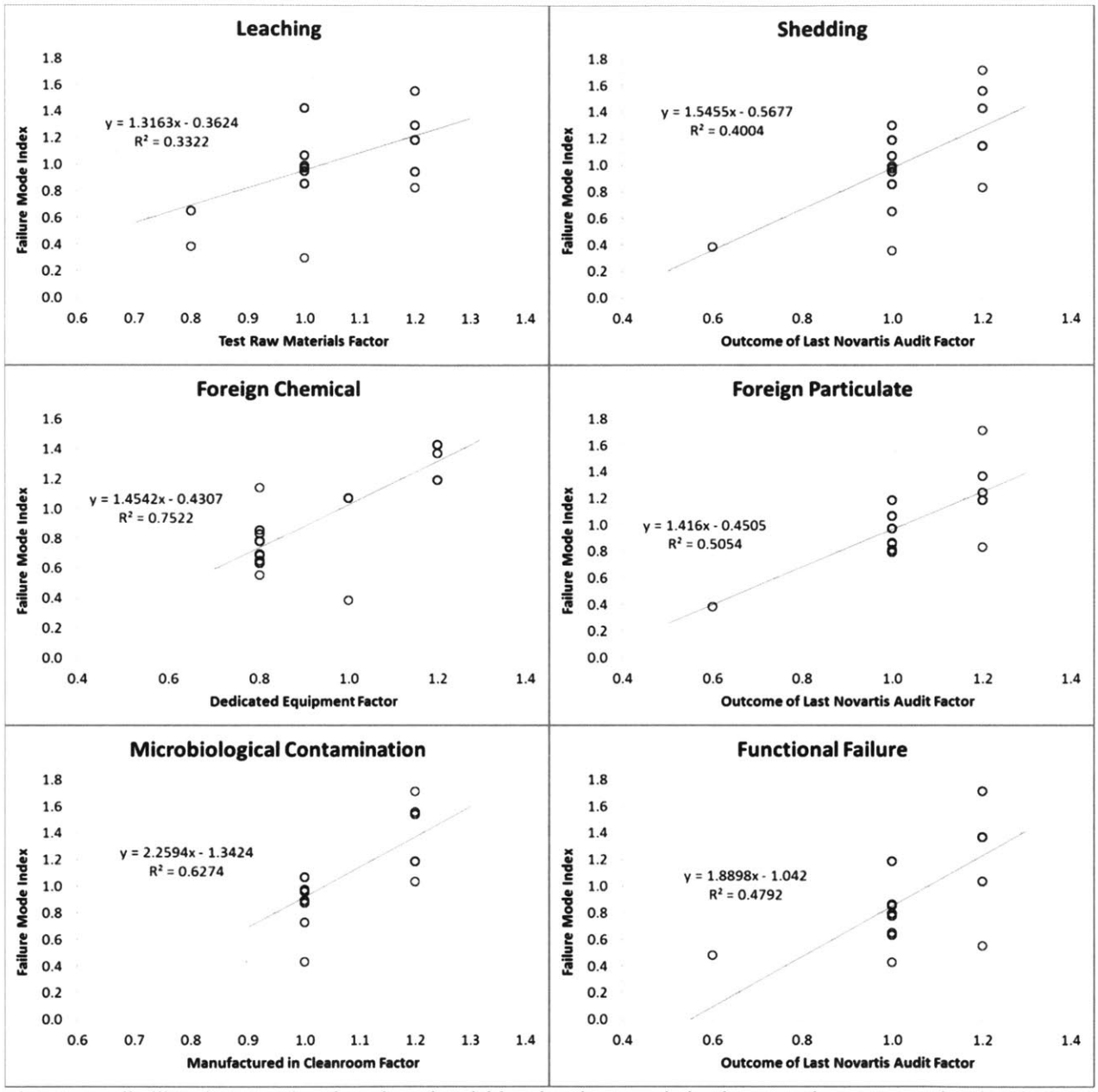

Figure 23. Likelihood scatterplots for selected variables showing correlation between the most correlated variable and the overall failure mode index based on the correlation coefficient in the table below.

Table 24. Correlation coefficient values from correlation of variable and failure mode factor. The intensity of the cell color corresponds to the strength of the correlation.

	Leaching	Shedding	Foreign Chemical	Foreign Particulate	Microbiological Contamination	Functional Failure
Health authority audit	0.32	0.40	0.16	0.10	0.42	0.36
Quality Standard Certification	-0.37	-0.37	-0.28	-0.44	-0.36	-0.22
Manufacture other products	0.18	0.24	0.56	0.47	0.32	0.43
Open complaint	0.35	0.26	-0.04	0.26	0.18	0.02
Outcome of last Novartis audit	0.50	0.63	0.60	0.71	0.74	0.69
Dedicated Equipment	-0.22	-0.09	0.87	0.50	0.34	0.65
Test Raw Materials	0.58	0.51	-0.29	-0.14	0.22	-0.09
Manufactured in cleanroom	0.29	0.29	0.31	0.57	0.79	0.40
Monitor surfaces microbiologically	0.13	0.15	0.16	0.43	0.61	0.12
Cleaning procedures	0.00	0.00	0.00	0.00	0.00	0.00
Control of raw materials	0.00	0.00	0.00	0.00	0.00	0.00
Manufacturing processes validated	-0.14	0.12	0.65	0.48	0.30	0.45
Cleaning processes validated	-0.46	-0.36	0.47	0.39	-0.11	0.09
Complexity	0.55	0.45	-0.39	-0.14	-0.03	0.13

Similarly to the Severity data set, these r values are relatively low (only two of 84 are above 0.75) indicating generally poor correlation between the input factors and Likelihood indexes in the given data set of critical consumables. Again, the data are highly clustered at certain input values and often do not cover the whole range of possible input values. For example, the Cleaning Procedures and Control of Raw Materials variables include only one level in this data set and have no correlation with any of the failure mode indexes.

Due to these limitations in the given data set, it is also useful to analyze the sensitivity of the mathematical model theoretically. As discussed in the Severity chapter above, the range of possible input values indicates the potential influence each variable has on the Likelihood calculation. Some variables may reduce the Likelihood index by only 10% and others have a larger range such that they may reduce the index by up to 70%. Table 25 below lists the relative influence of each variable on each failure mode based on the range of its possible inputs.

Table 25. Influence of factors on likelihood calculation. The percentage values represent the effect that the factor can potentially have on the likelihood index. For example, a factor of 0.8 represents a 20% decrease in the likelihood index. The intensity of the color in each cell indicates the relative influence.

	Minimum factor	Maximum factor	Possible Influence of Variable on Failure Mode Likelihood index					
			Leaching	Shedding	Foreign Chemicals	Foreign Particulate	Microbiological Contamination	Functional Failure
Health authority audit	0.9	1.0	-10%	-10%	-10%	-10%	-10%	-10%
Quality Standard Certification	0.9	1.0	-10%	-10%	-10%	-10%	-10%	-10%
Manufacture other products	0.8	1.1	-20%	-20%	-20%	-20%	-20%	-20%
Open complaint	1.0	1.2	+20%	+20%	+20%	+20%	+20%	+20%
Outcome of last Novartis audit	0.6	1.2	-40%	-40%	-40%	-40%	-40%	-40%
Dedicated Equipment	0.8	1.2			±20%			±20%
Test Raw Materials	0.8	1.2	±20%	±20%				
Manufactured in cleanroom	1.0	1.2				+20%	+20%	
Monitor surfaces microbiologically	0.9	1.0					-10%	
Cleaning procedures	1.0	1.2			+20%	+20%	+20%	
Control of raw materials	1.0	1.2	+20%					
Manufacturing processes validated	1.0	1.2		+20%				+20%
Cleaning processes validated	0.8	1.0			-20%	-20%		
Complexity	0.3	1.0	-70%	-70%				-70%

From the values above, we can see that the model is moderately sensitive to the outcome of the last Novartis audit across failure modes. This is reasonable, since the audit is the most direct way for Novartis to evaluate the quality systems of the supplier and it is a good predictor of future quality. On the other hand, audits by health authorities and other quality standard organizations are only indirect measures of a manufacturer's quality systems and have less influence in calculation of the likelihood of failure. The complexity factor presents the largest range of possible values and therefore the highest influence in the likelihood calculation for Leaching, Shedding, and Functional Failures. This is also reasonable since it is the only factor which accounts for the large range in form factors used in biopharmaceutical production. However, since this factor is significantly more influential than the others, care should be taken when defining or redefining the values and when evaluating consumables during the risk analysis. Aside from the complexity and Novartis audit outcome factors, all other factors have the potential to increase or decrease the likelihood index by 10 or 20%, indicating that the model is less sensitive to these factors.

4.4.6 Uncertainty Analysis

The effect of uncertainty in the attribute factors on the Likelihood calculation was evaluated using the same Monte Carlo simulation as described for the Severity section above and implemented in Visual Basic embedded within a Microsoft Excel spreadsheet. In each of 10,000 simulations, the attribute factors for each variable was randomly adjusted based on a normal probability distribution with $\mu = 0$ and $\sigma = 0.102$. The number of score changes for the 48 sample consumable articles was determined for each simulation run and the distribution of these score changes is provided for each failure mode.

As can be seen in the distributions below, the Likelihood calculation model is generally unstable in the presence of uncertainty. A stable mathematical model would demonstrate minimal change in the output scores when exposed to uncertainty in the inputs. In less than 50% of the simulation runs, fewer than 10 articles have changed scores for all failure modes. This instability is due to the large number of factors that are involved in the Likelihood calculation which, when combined, can contribute to a large deviation in the Likelihood factor and leading to a change in Likelihood score. With more factors, the probability that several are significantly underestimated or overestimated is increased. In addition, the window defined for assigning a score of 5 is relatively narrow (Likelihood factor 0.75 to 1.25), and thus the threshold for uncertainty causing a change in score is relatively low.

Although this model appears unstable in the current implementation, it is robust to systematic under- or over-estimation in the factors. The score determination limits were artificially defined in order to produce a Likelihood score distribution where 80% of articles received a score of 5. If a combination of several factors was underestimated in the model and required subsequent adjustment, the determination limits would also have been adjusted to maintain the prescribed ratio and the scores would be largely unchanged. Therefore, the model should be evaluated for its robustness against uncertainty in a small number of factors, not combinations of many factors. In cases where only 1 or 2 factors are over or underestimated, an average of 77% of articles are unchanged compared to 53% in which all factors are uncertain. This demonstrates that the model is more robust to uncertainty in a small number of factors.

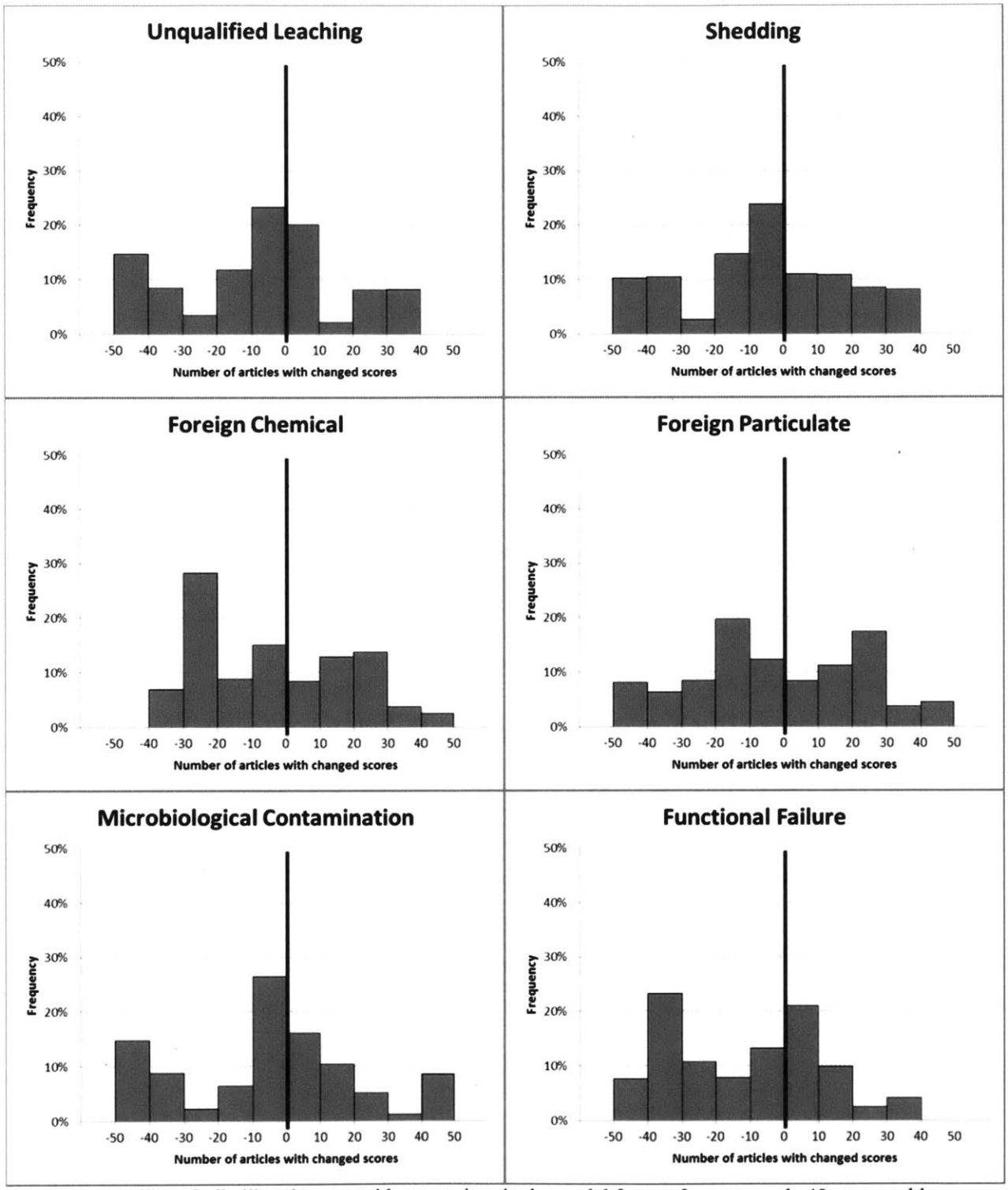

Figure 24. Stability of Likelihood scores with uncertainty in the model factors from a sample 48 consumable articles. Each histogram shows the distribution of the number of articles for which the Likelihood score decreased (negative numbers) or increased (positive numbers) based on 10,000 runs with uncertainty in the factors simulated by a delta from the standard factor from a normal distribution with $\mu = 0$ and $\sigma = 0.102$. Note for interpretation: a scenario in which 10 to 19 articles had decreased scores would appear in the bin between -20 and -10. A scenario in which 0 to 9 articles had increased scores would appear in the bin between 0 and 10.

4.5 Detectability Evaluation

4.5.1 Detectability Scale

The Detectability score is an estimation of the relative probability that a given non-conformance will be detected by the supplier or internally. In most cases, the test or inspection is performed before the consumable is used in production, thus preventing the contamination of a batch which could lead to the loss of that batch. In the case of filter integrity, however, Novartis often performs post-use integrity testing to ensure proper functionality of the filter throughout the processing of the whole batch.

The determination of the Detectability score is based on factors pre-defined scores for many tests and inspections which are already in place according to the failure modes for which they are applicable. An examination of the tests and inspections that various suppliers perform on consumables reveals that some tests are highly sensitive to a broad range of potential non-conformances and therefore greatly reduce the risk of impact to the drug product. Other tests are applicable to particular failure modes but are only able to detect a subset of the possible non-conformances because of high detection limits or because the limited detection scope. These tests reduce the overall risk some, but not to the same extent. The table below defines the Detectability definitions and corresponding scores.

Table 26. Detectability scale and scoring definitions.

Detectability Level	Detectability definition	Score
High Detectability	Applicable and sensitive. The test or inspection will detect all or almost all potential consumable non-conformances.	1 point
Medium Detectability	Applicable but not sensitive. The test or inspection will detect some of the potential non-conformances.	5 points
Low Detectability	None applicable. There are no tests or inspections which will detect any non-conformances.	9 points

Test Article impact on Detectability

The detection of non-conformances is dependent on the representativeness of the test articles. When an applicable and sensitive test is performed on a number of samples which are statistically representative of an entire lot of consumables, the risk of non-conformance for that whole lot is greatly reduced. However, if the test samples are not representative because they are too few or because the batch is not homogeneous, the remainder of the lot remains at risk of non-conformance. Thus, when the test article is not representative of the lot, the Detectability score should not be as advantageous as the same test on a representative sample. The following table defines the various test articles and implications for the Detectability scores.

Table 27. Test article effect on Detectability scores.

Test Article	Criteria	Score	Rationale
100%	All articles in the manufacturing lot are tested	Full score (1 or 5)	When all articles or representative batch samples are tested, the probability of detecting a failure is high. When the test is sensitive, a score of 1 is given. When the test is not sensitive, a score of 5 is given. The appropriate sample size should be based on a statistical approach like Acceptable Quality Level (AQL).
Batch Sample	Samples from the batch are representative of that batch. That is, a representative sample from each sub-group of a heterogenous batch, or a statistically significant quantity of a homogeneous batch	Full score (1 or 5)	
Audit Based	The test is performed on an audit basis or samples which are not representative of the batch.	Add 4 (5 or 9)	If the test article is not representative of the batch (i.e. audit basis or non-representative sample), the probability of detecting a failure is reduced. If the test is sensitive, a score of 5 is given and if not sensitive, a score of 9 is given.
None	No tests are done which are applicable to this failure mode.	9	When no test is performed which is applicable to this failure mode, a score of 9 is given.

4.5.2 Detectability Analysis process

For each consumable article, the Detectability Analysis involves the following process:

1. List all tests and inspections performed on the consumable from the supplier Certificate of Analysis (or Certificate of Compliance) and from internal test procedures.
2. For each test, record the test article according to the table above.
3. For each test, look up the appropriate score for each failure mode from the pre-defined table below. If the test is not pre-defined, evaluate the applicability and sensitivity of the test and define scores for each failure mode.
4. Based on the test article, adjust the score if necessary.
5. For each failure mode, record the best score (minimum number) for each failure mode among all of the listed tests. This is the Detectability score.

4.5.3 Detailed Explanation of Detection Opportunities

The following table lists the tests and inspections which have been evaluated and given pre-defined scores. Rationale is provided in Appendix 4.

Table 28. Detectability scores for various tests and inspections. These scores assume the test article is 100% or a representative batch sample of the consumable lot. If more than one test is performed, the minimum Detectability score from these is selected.

Test Description	Leaching	Shedding	Foreign Chemicals	Foreign Particles	Microbiological	Functional
Direct functional test (e.g. leak test for bags, bacteria retention or post-use integrity tests for bioburden reduction filters, Gold Nanoparticle test for nanofilter, solute marker passage test for UF/DF membranes)						1
Indirect functional test (e.g. pressure drop test for filters)						5
Dimensional inspection						5
Total organic carbon and conductivity test on flush (USP <643> and <645>)	1		1			
Oxidizable substances test on flush (legacy USP test)	1		1			
Extractable ions test (supplier method)	5		5			
Organic weight (0.25% max), Ca, Fe, and Color after flush (supplier method)	5		5			
Visual inspection for particles and chemicals (no flush)			5	5		
Visual inspection for particles after flush		5		5		
Particle count by machine or visual under microscope after flush		5		1		
LAL endotoxin test or Bioburden test by ISO 11737 method by filtration					1	
Membrane fiber release test		1				
Non-volatile residue, residue on ignition, heavy metals tests	5		1			
External spectroscopy material ID test	1	5				
Mass spectroscopy peak confirmation on extract or flush	1		1			

4.5.4 Results from Representative Consumables

The Detectability analysis described above was applied to a sample of 48 consumable articles used by Novartis. As can be seen in the histogram below, among the six failure modes, the Detectability scores are the best for Functional Failures. For most of these sample articles, the function is critical to the quality of the drug due to filtration or storage, and some degree of testing has already been implemented to ensure performance. On the other hand, the risk of particle shedding has not been previously evaluated in depth and thus few tests have been implemented to detect potential non-conformances.

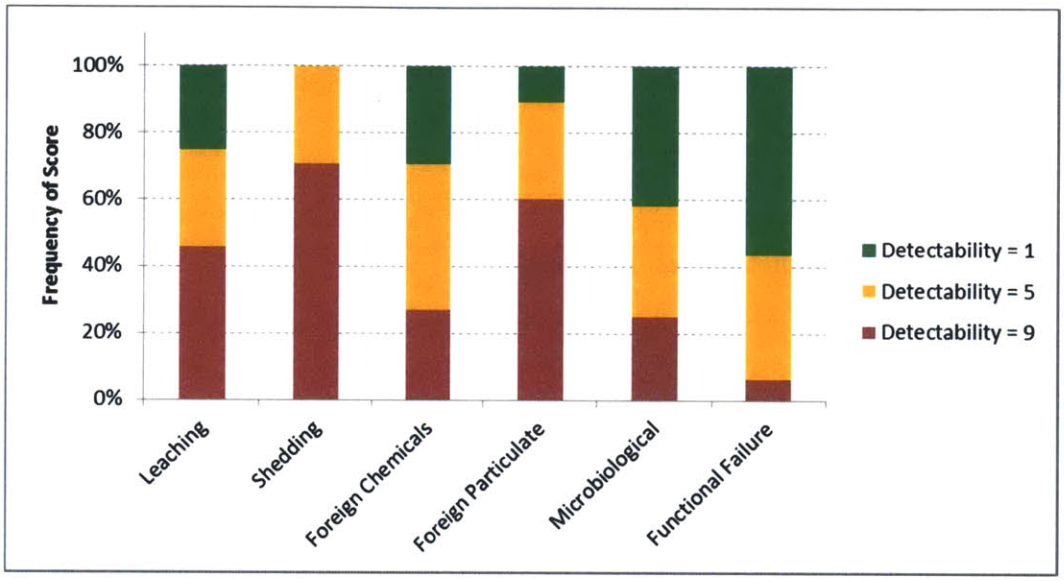

Figure 25. Detectability score results from the pilot set of 48 consumables.

4.6 Risk Evaluation

4.6.1 Risk Priority Number

With all of the risk dimensions calculated, we can now evaluate the overall risk for each consumable article in order to prioritize actions and decisions for risk mitigation. According to the standard FMEA formulation, the Risk Priority Number (RPN) is a representation of the overall risk level and is calculated as the product of Severity, Likelihood, and Detectability. Because the present implementation uses 1, 5, and 9 scores for each dimension, the RPN ranges from 1 to 729. Within this range, we can broadly categorize the risk levels for further mitigating action. Since we have limited our analysis of each risk dimension to "Low", "Medium", and "High" risk, there is a small set of scenarios which we must consider for our overall evaluation (1, 5, 9, 25, 45, 81, 125, 225, 405, 729, see Figure 7). Mathematically, all RPN scores up to 81 points require at least one risk dimension to be "Low". For reasons which are explained in the subsequent section, we define these scores as having "Low" priority for mitigation of the

failure mode of an individual consumable article. The only way to obtain a score of 125 points is to have "Medium" risk in all dimensions. We can define this score as having "Medium" priority. All RPN scores above 125 points are obtained by a product of "High" and "Medium" scores in all three dimensions yielding a "High" priority.

4.6.2 RPN Score Scenario Explanations

The following table describes the various scenarios which take place at the thresholds between priority levels and summarizes the rationale for determining outcome. When the RPN is lower than 81, the Priority Levels is inherently Low and when the RPN is higher than 225, the Priority Level is inherently High, and so these scenarios do not need to be explored.

Table 29. Risk Priority Number scenarios and rationale for priority level determination.

Severity	Likelihood	Detectability	RPN	Priority Level	Rationale
9	9	1	81	Low	Although this kind of failure has very severe consequences and is likely to occur, it is almost certain to be detected and therefore there is low risk that a non-conforming consumable will be used and impact product quality. Therefore these risks are Low Priority for mitigation action.
1	9	9	81	Low	This kind of failure has low impact on product quality, regardless of how often it occurs. Therefore these risks are Low Priority for mitigation.
9	1	9	81	Low	The impact of this failure to product quality is very severe and there is no mechanism in place to detect it. However, the risk is low because manufacturer is among the best 10% of all manufacturers analyzed during the generation of this method and therefore the likelihood of failure is low.
5	5	5	125	Medium	In this scenario, the failure has a moderate severity, moderate likelihood, and moderate detectability. In summary, it is possible that a non-conformance of this type would occur and have an impact on product quality. Due to the uncertainty in this evaluation method, the risk may be justified to be acceptable based on factors which were not considered in the assessment. This risk is Medium Priority for mitigations.

Severity	Likelihood	Detectability	RPN	Priority Level	Rationale
9	5	5	225	High	This kind of failure, if it occurs, will have a severe impact on product quality and the existing controls are not sufficient to consistently prevent it. Therefore it is High Priority for implementation of a mitigation which will improve detectability or reduce the likelihood of failure (more difficult).
5	9	5	225	High	This kind of failure may have an intermediate impact on product quality, and it is more likely to occur based on the supplier's quality systems. Mitigation is High Priority to reduce the likelihood that the failure will occur or improve the opportunity to detect this failure before production use.
5	5	9	225	High	This failure may have an intermediate impact on product quality and is somewhat likely to occur. However, there are no controls in place to prevent use of this non-conforming consumable so the risk is High Priority to improve the detection of failures.

4.6.3 Comparison Between Granular and Discrete Analyses

By constraining the scores of each risk dimension to 1, 5, or 9 as opposed to using a granular 1 through 10 scale, we incur some risk of mis-categorizing certain risks due to rounding. To understand this effect, a granular RPN score was generated for the 48 sample consumable articles using unrounded Severity and Likelihood scores from the raw mathematical formula (Detectability scores are defined on a discrete scale and could not be "granularized"). These granular RPN scores were then rounded to the nearest discrete RPN. As can be seen in Figure 26 below, the discrete analysis produces 15% more 45 scores and 3-4% fewer 81, 125, 225, and 405 scores. With respect to priority levels, this translates to a 7% decrease in High Priority risks, a 3% decrease in Medium Priority Risks, and a corresponding 10% increase in Low Priority Risks compared to the granular analysis. Although the author believes this small underestimation of Medium and High Priority risks is acceptable, this effect should be understood when adopting this risk assessment method.

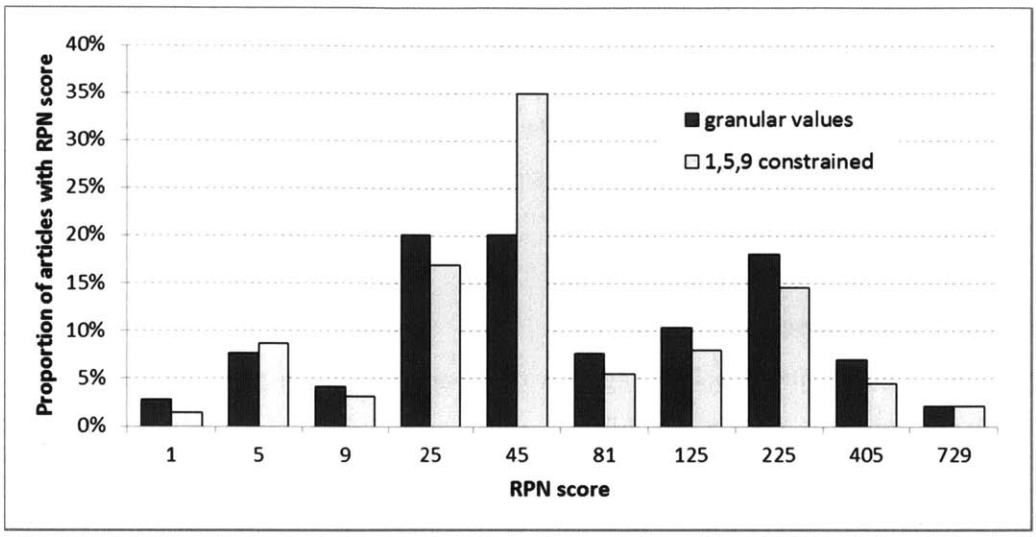

Figure 26. Comparison of RPN scores obtained by assigning granular values versus discrete scores (1, 5, or 9) for each risk dimension.

4.7 Validation of Results

4.7.1 Comparison with Historical Failures

In an effort to determine how accurately this risk assessment process predicts risk due to non-conformances, we can compare the estimated priority levels with the non-conformances which have been observed historically at Novartis. Among the 48 sample consumables described above, 19 have been cited in a non-conformance which generated a supplier complaint since 2006 [1]. Of these 19 articles, 15 were given a High Priority risk assessment rating in the failure mode which ultimately failed. The remaining 4 articles which experienced a non-conformance were given a Low Priority rating due to the good Detectability of the failure mode. That is, the test or inspection which enabled the non-conformance to be detected and generate the supplier complaint was sufficient to prevent the non-conforming material from being used to produce drug for human use and therefore the overall risk is sufficiently low to not require mitigation actions. Therefore, we can say that the Type II error, the probability of assigning a low risk priority to a high risk item, is low.

However, the Type I error, the probability of assigning a high risk assessment to a low risk item, is difficult to estimate for two reasons. First, the limited history of the facility with many of these consumables means that there has been limited opportunity for failure and a lack of non-conformances with product quality impact does not indicate a low risk of future failures. Second, because all High

[1] This count includes those consumables for which another article in the same family (i.e. same form factor and purpose but different specifications for materials, dimensions, or attachments) has been involved in a non-conformance.

Priority risks necessarily have intermediate or poor Detectability scores, any non-conformances previously created would likely not have been detected and therefore would not have initiated a deviation leading to a supplier complaint. Although 22 of the 29 articles which did not generate supplier complaints were given High Priority risk assessments, we cannot say that the Type II error is high because the true failure rate is unknown.

4.7.2 Correlation with Experts' Opinions

The outcomes of this risk assessment tool also agree with the opinions of various quality experts who are familiar with these consumables. To evaluate this, a workshop was conducted in which representatives from Quality Assurance and Quality Control collaborated to perform a qualitative risk assessment on a sampling of nine representative and varied consumable articles based on all of the data that is used by the automated risk assessment tool. The team was asked to rate the risk for each failure mode as High, Medium, or Low based on the given data for each article. The ratings and rationales were recorded and compared with the output of the risk assessment tool.

In summary, 67% of the responses matched the tool output, 28% deviated by one grade (Low versus Medium or Medium versus High), and 6% were given Low responses whereas the tool gave High priority output. The tool's overestimation of the risk in these cases is a more conservative approach in which mitigation actions may be implemented where the quality staff would not normally require them. The possibility of risk overestimation should be weighed against the improvements in efficiency and repeatability that this risk assessment tool provides before implementing it. In the cases where the tool provided outcomes different from the expert opinions by one grade, the tool underestimated risk for about half of the risks, most of which were given a Low Priority by the tool and Medium priority by the experts. These underestimates may be due to information about specific supplier or internal quality controls which were not weighted as heavily by the experts as by the risk assessment tool.

Because of the possibility of risk underestimation described above, the author recommends that this risk assessment tool be implemented on a small group of consumables and the output reviewed in detail by a varied group of experienced users during a pilot phase. Discrepancies between expected outcome and the output of the tool should be resolved and new non-conformances observed in consumables should trigger appropriate adjustment in the tool (starting with numerical factor definitions). This pilot phase is described in greater detail in the next section.

4.8 Implementation of Risk Assessment Tool

4.8.1 Formulation Into an Automated Template

Risk assessment worksheet

In order to ensure that the calculations are performed correctly and to reduce the calculation burden for the hundreds of consumables which need to be analyzed, this risk assessment method has been implemented in an automated Excel worksheet (screenshots included in Appendix 1). This worksheet is to be completed for each consumable article. It takes all applicable consumable information as inputs from the user and automatically calculates the Risk Priority Number for each of the six failure modes. It also includes fields for recording a mitigation plan in order to reduce the necessary risks to an acceptable level.

The score for each risk dimension is calculated on dedicated pages. The first page of the worksheet includes text fields for recording identifying information about the consumable and pull-down menus to select the attributes relating to the severity calculation. The consumable production usage and attributes with corresponding factors for the severity score calculation are all pre-defined in tables; when the attribute is selected, the factor is included in the formula. When all fields are completed, the score is automatically calculated. The second page performs the Likelihood analysis. Similarly, all supplier quality attributes and corresponding factors are pre-defined in tables and are included in the Likelihood score formula when selected. The third page performs the Detectability analysis in which the user selects the specific tests and inspections that are performed and the minimum factor is chosen for each failure mode. The fourth page performs an additional severity and detectability analysis for secondary and tertiary components in the Leaching and Shedding failure modes. These modes are material-specific and as such, the fields in this section pertain only to the unique properties of the secondary materials. If no secondary or tertiary materials are entered, the fields remain grayed-out and the Severity and Detectability scores are not calculated. The last page collects the scores from each dimension and calculates the Risk Priority Number for each failure mode, including secondary materials. The RPN is automatically color-coded based on the priority level as described above. A text field below provides space for the user to record a mitigation plan for those failure modes with medium or high Priority levels. Finally, the user can enter the RPN scores in the as-mitigated state to demonstrate that the mitigation plan will reduce the risk levels to an acceptable level.

The implementation of this risk assessment also meets the usability and security needs of the various users. Because it is formatted in Excel, multiple users can share a common form and complete it based on their unique expertise. The automation of the calculations and drop down menus ensures not only that the calculations are performed correctly and consistently, but also allows the user to enter a great amount of

information very quickly. If the data for any given consumable is at hand, the completion of the risk assessment form and the risk calculations require less than two minutes. In addition, the entries of the worksheet are protected such that only expected values can be entered and the formulas cannot be changed by unauthorized users. Once the formulas are fully validated, the worksheet may be locked and stored in an accessible location for future use. The worksheet is formatted for printing or saving into a portable document format (*pdf*) file in which the various specialists responsible for completing the risk assessment can digitally sign the document and archive it in a protected digital folder to meet Good Manufacturing Practice requirements.

Dashboard visualization of risk

In addition, a dashboard worksheet was developed with a Visual Basic script to collect the scores from all risk assessment worksheets and to provide an accessible visual summary of the risk mitigation priorities. On the first sheet, all consumable articles and the corresponding risk level for each dimension is collected and color-coded for rapid evaluation. The second sheet graphically displays the current and as-mitigated risk levels. This tool is especially useful for managers to understand the various needs in the collection of consumables and to allocate resources effectively toward the mitigation of high priority risks. The diagram below illustrates the hierarchy of tools which together provide a complete description of the risk associated with consumables. Screenshots of these tools can be seen in Appendix 1.

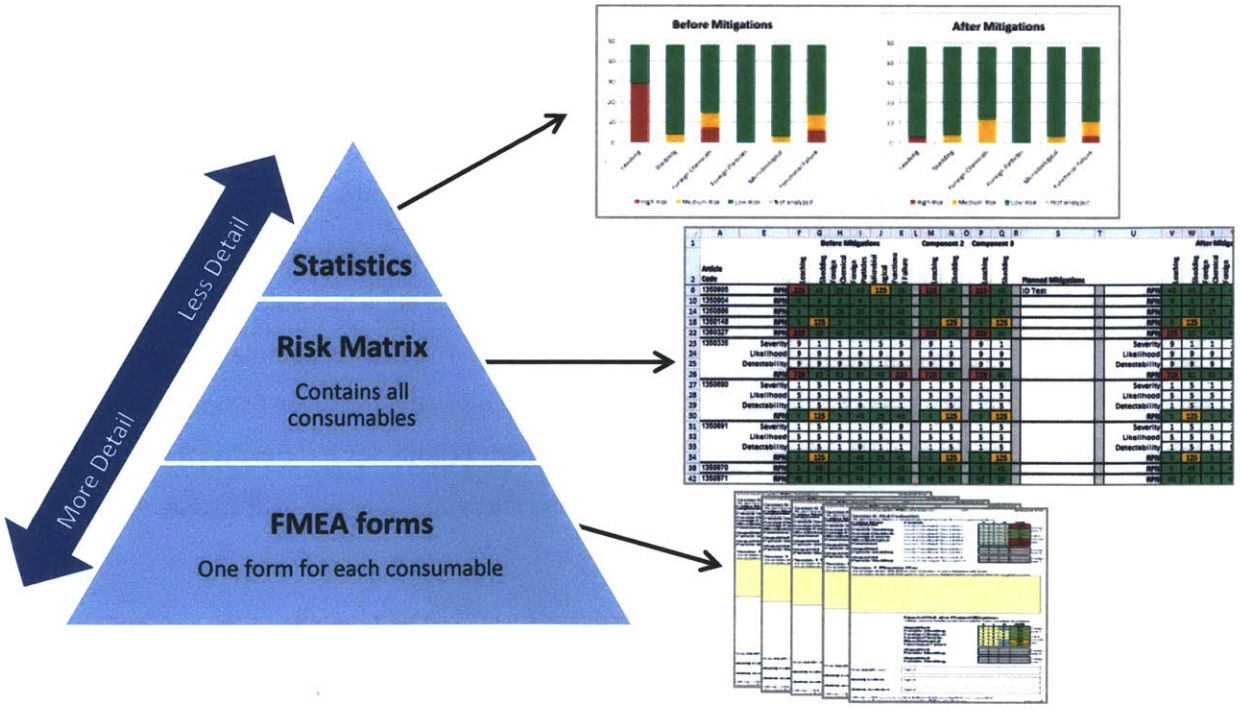

Figure 27. The hierarchy of Excel tools involved in the risk assessment and visualization.

4.8.2 Risk Assessment Workflow

The first step in the Risk Assessment process is the completion of the assessment worksheet. Although the Quality Control department is ultimately responsible for the management of the risk assessment and the implementation of the mitigation activities, input is also required from the consumable user in production, and the Quality Assurance department. Because the consumable user (an experienced process expert) is most familiar with how the consumable is used in production and the various materials and properties of the consumable, they are responsible for completing the Severity analysis section on the first page of the worksheet. A Quality Assurance specialist is responsible for completing the Likelihood analysis section, on page 2, because they have the information pertaining to the quality systems of the supplier in the quality questionnaire and the history of audits and complaints. The Detectability section, page 3, is completed by a Quality Control specialist who has access to the certificates of analysis provided by the supplier and is knowledgeable about internal tests and inspections. Entries for secondary components should be completed by the consumable user and the Quality control staff. Because this worksheet is implemented in Excel, the three functionalities responsible for its completion can share the form in a common file location.

After the analyses for the three risk dimensions have been completed, the risk evaluation is automatically calculated in the last page of the worksheet. The Quality Control specialist is responsible for completing a risk mitigation action plan when necessary (the requirements for mitigation actions are described in the next chapter). The plan should include specific actions which address the various risk areas in order to reduce the risk priority to an acceptable level. These plans should reduce the scores of one or more risk dimensions and these planned scores should be recorded in the "as-mitigated" RPN tables below the action plan field.

When the risk assessment form has been completed, it should be reviewed fully by all three analysts and saved to a *pdf* file type. The Excel form is formatted to print each sheet as a page with a date and time stamp in the header. Using a plug-in for electronic signatures in Adobe Reader®, each specialist should then sign the form and archive the completed form in a protected network folder. This folder is managed by the Quality Assurance department which prevents the modification or deletion of documents once they have been saved. When a form needs to be modified, the Excel version may be modified, saved to another *pdf*, electronically signed, and archived as an updated version in the same folder as the original form. Figure 28 below diagrams the flow for this risk assessment process.

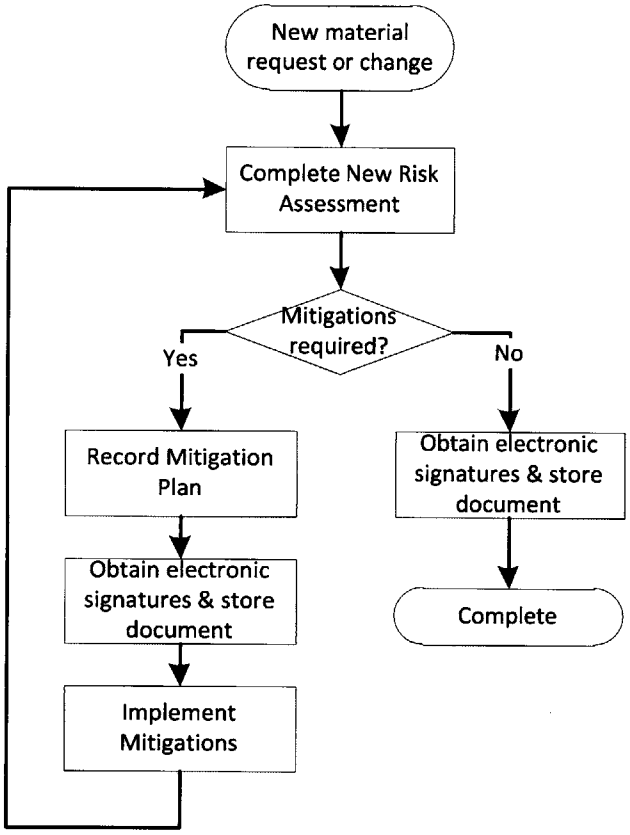

Figure 28. Flow diagram for the risk assessment process.

4.8.3 Pilot on Critical Consumables

As described previously, a pilot of this risk assessment process was implemented on a sample of 48 critical consumable articles in order to refine the method before application to the whole list of several hundred articles. These pilot consumables were selected using a criticality assessment decision tree which categorizes consumables into three levels based on the level of product contact and the process step in which it is used. The decision tree is shown in Figure 29 with terms defined in Table 30. Because these consumables have significant contact with the drug in downstream processes, they inherently have the greatest potential impact on product quality. Therefore, performing the risk assessment on these articles also serves to address the highest priority risks first even while the method is being perfected.

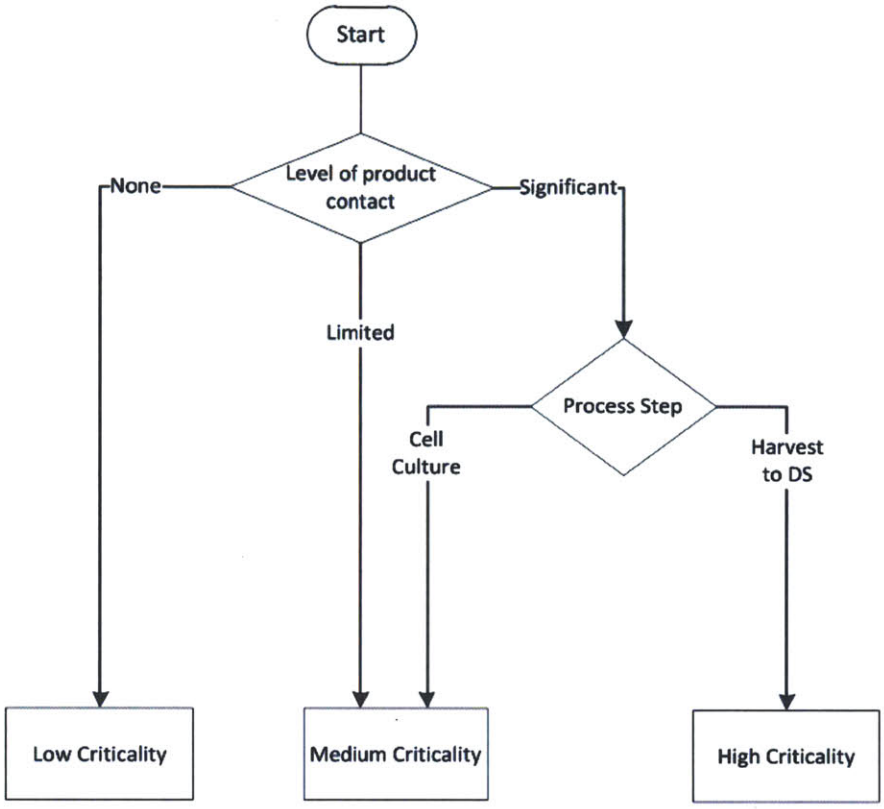

Figure 29. Criticality Assessment decision tree. The High Criticality articles are used for the pilot implementation of the risk assessment. Definitions are provided in Table 30.

Table 30. Definition of the levels for the criticality assessment.

Product Contact	
None	– No product contact (e.g. gloves, air filters) – Contact with samples only
Limited	– Small surface (e.g. transfer tubes, connectors, sensor probes), – Short contact duration (e.g. raw material dispensing), – Indirect contact: consumables without contact with the protein used before the last purification step (e.g. buffer storage bag, buffer filter)
Significant	– Large surface or long contact duration with the protein. That is, all bags, bottles, and filters that contacts the protein. – Consumables having significant contact with buffers used during the last purification step (UF/DF buffers filters & bags)
Process Step	
Cell Culture	All cell culture processes including consumables used during cell bank manufacturing (MCB or WCB).
Harvest to DS	All processes from harvest to drug substance.

The Risk Priority Number, calculated as described above for each failure mode for each consumable, is classified into three priority levels which are illustrated in the stacked histogram below. Because the Leaching and Shedding risk is evaluated for secondary and tertiary materials, the total number of evaluations is higher than for the other failure modes. Proportionally, there is a large number of articles with a high leaching risk because there are few established methods to detect leaching before production use. Similarly, consumables which are not rinsed before use (particularly storage bags), present a high Foreign Chemical risk because few articles undergo thorough pre-use testing. Functional failures also present a high number of High Priority articles because of the criticality of their use in the process and the difficulty of performing pre-use inspections on many articles (especially large storage bags). Comparatively, the risk of Shedding and Foreign Particles is low because there are few articles which could introduce particles to the product after the final filter. The risk of Microbiological contamination is even lower because most articles are supplied sterile or are sterilized or sanitized on site.

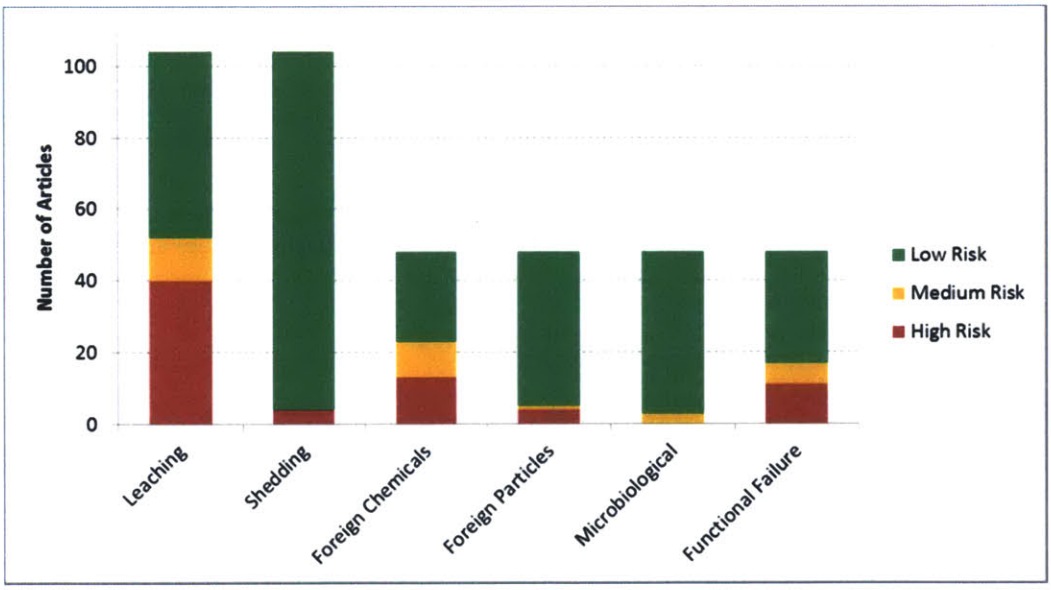

Figure 30. Risk Priority Number results from pilot consumable articles.

4.9 Discussion

This risk assessment method and collection of tools meets all of the objectives pre-defined at the beginning of this chapter.

Outputs prioritize risks for mitigation decision-making

The Risk Priority Number calculation provides a semi-quantitative evaluation of the overall risk according to the various failure modes and provides a prioritization of the risks for implementation of

mitigation actions. Recommendations are presented which require action for High Priority articles and tools have been developed for the efficient visualization of a summary of risk levels that enable managers to allocate resources to risk mitigation activities.

Report guides the setting of specifications

The risk assessment worksheet, which is saved as a report, can guide the process of setting specifications because it records all supplier and internal controls in one consistently-formatted location. This process is described in the following chapter.

Provide justification and rationale

Justification and rationale for mitigation decision making is accomplished in two ways. First, a procedure has been written to accompany the standard assessment form which includes all of the rationale for the choice of the factors described in the sections above. If necessary, this reviewed and released procedure can be referenced to provide justification to a regulatory agency. Second, the forms themselves provide evidence that a rational and systematic process was followed to perform the risk analysis and determine a course of action.

Performed in an efficient tool

The Excel worksheet makes the risk assessment process efficient due to the use of selection fields which restrict the entry parameter to a pre-defined list of factors. The scores for each risk dimension and the overall RPN are automatically calculated, reducing the calculation burden and the risk of error. With all relevant information available, only two minutes are required to complete the form for a new consumable.

Consistent results among users

Because the selection fields are restricted to characteristics which air paired with pre-defined numerical factors and the calculations are formulated and protected within Excel, the tool provides consistent risk analysis results among multiple users. Once protected, the numerical factors are not adjustable and users have access only to pull down menus to select characteristics (such as material). The accompanying procedure defines each selection field unambiguously and sufficiently to aid the user in the correct selection for any given article. As implemented and tested for the pilot articles, the tool accounts for all possible responses for all articles. The only opportunity for subjective analysis is for tests or inspections which have not been pre-defined in the form and which must be entered manually and given a Detectability score.

5 Mitigation Decision-Making

5.1 Objectives

With the risk assessment complete, we can implement mitigations to reduce the overall risk according to the prioritization established. A structure which can be systematically applied for risk reduction must meet the following objectives.

Define a rules-based protocol for decision-making

The mitigation decisions should be structured in a clear and rational system to reduce ambiguity and to provide justification for those risks that are accepted and those that are mitigated. In addition, a well-defined system aligns expectations across the organization and communicates the goals and targets for risk reduction.

Identify possible actions to reduce risks efficiently

Within each of the three risk dimensions involved in the assessment, many mitigation actions are available. The development of a pre-defined list of possible mitigations allows managers to efficiently select actions which are effective and applicable to multiple articles. Therefore, this list should include options to address the most common outstanding risks.

Define a process for specification setting

Novartis needs a way to define specifications for all consumables in order to ensure each lot of received consumables meets production quality needs. These specifications should be established based on the specific controls, tests, and inspections which are in place to prevent non-conforming articles from being used in production.

5.2 Mitigation Actions for Priority Levels

A protocol for implementing mitigation actions for certain risks can be defined using the three risk Priority Levels described above. Because resources are limited to implement mitigation activities for all risk areas, the author recommends a policy to accept the risks (according to each failure mode for a particular consumable article) which are evaluated as Low Priority and to focus time and money on the higher risk items. For High Priority risks, Novartis should require mitigation activities to be implemented reducing the overall risk to an acceptable level. The Medium Priority risks are not inherently acceptable since there is an intermediate probability that a failure with intermediate consequence will occur. But since these risks are not High Priority, mitigations should not be automatically required lest they distract

resources from those risks which necessitate the most immediate attention. In addition, the author recognizes some inherent uncertainty in the numerical factor definitions for all possible risks which could lead to a mis-categorization for a small proportion of risks. Therefore, those risks which are evaluated as Medium Priority should be qualitatively re-evaluated by the risk assessment team to determine if the risk is acceptable or if it requires mitigation. These rules correspond to the recommended bands described in ISO 31010.

Thus, the RPN scores can be binned into overall priority levels and actions as follows:

- RPN < 125 Low Priority Acceptable risk
- RPN = 125 Medium Priority Requires detailed evaluation to accept or mitigate risk
- RPN > 125 High Priority Mitigation action required

Within all of the risk areas evaluated, about 74% are acceptable, 8% require detailed evaluation, and 18% require mitigation.

5.3 Mitigation Options

In order to obtain the most risk reduction benefit with the available resources, Novartis should aggregate mitigation actions and develop methodologies which are applicable to as many articles as possible. In many cases, the articles share a common form factor or are from a single manufacturer product family and therefore specific test methods are often applicable to multiple articles. In this section, a partial list of possible mitigation opportunities is presented and the number of consumable articles which would benefit from this action is stated. The implementation of each of these actions will automatically reduce the RPN for a specific risk because it affects the score of at least one risk dimension. Rather than targeting those articles with the highest RPN scores first, the author recommends development of those actions which have the broadest risk-reduction opportunity first.

5.3.1 Supplier Mitigations

The following mitigation options may be implemented through interaction with the supplier. It should be understood that these additional activities may increase the manufacturing cost of the consumable and this should be compared with the cost of internal method development and controls to ensure the quality of received materials.

Audits and certifications

Although the performance of audits by Novartis or third party agencies does not directly reduce the risk of failure, the absence of audit results causes Novartis to assume a higher risk in the absence of evidence of effective controls. Similarly, favorable audit outcomes or quality system certifications provide confidence that the supplier meets certain quality standard expectations. Thus, for consumables which have no audit on file or have an unfavorable outcome, Novartis may perform an on-site manufacturer audit to reduce the likelihood of non-conformance.

Resolving open complaints and actions

Open complaints with the supplier increases the risk of future failure because it provides evidence against the integrity of their quality systems. The closure of these complaints requires action within the manufacturer to close gaps and address the specific quality concerns. Therefore, the overall risk of failure may be reduced by implementing these actions which are adequate to close the complaints. This may be sufficient to reduce the risk for at least one article but may also be used in conjunction with other mitigations to further reduce overall risk.

Improved quality controls

The Likelihood analysis calculation takes many supplier quality control factors into account and the improvement of one or a combination of these will reduce the risk profile of targeted failure modes. Although improving one control is insufficient to change the prioritization of any risks in the pilot sample, a combination of improvements may be helpful for at least one of the 48 pilot articles.

Increased test frequency

Supplier tests are often performed on samples from a batch or on an audit basis at periodic intervals. In many cases, the manufacturer's test is adequate to detect non-conformances in a unit but it is not performed frequently enough to provide statistical confidence that a lot of consumables is wholly conforming. In those cases where the necessary test is performed only periodically or on a non-representative sample, the testing interval or sample size may be increased to improve the detectability of the non-conformance in a lot. The widely used Acceptable Quality Limit (AQL) method may be used to determine the appropriate sample size based on an acceptable rate of failure and the lot size. Increasing the test frequency or sample size may reduce risk for at least eleven of the pilot articles.

Expansion of established test methods

In some cases, a specific test or inspection method may be transferred to other products in the same family as one for which it is already performed. In addition, effective test methods currently performed at

one supplier may be implemented at other suppliers. These approaches are possible for fiber release tests, particle counting, visual inspections, pressure leak tests, the Total Organic Carbon test, and filter particle capture tests.

5.3.2 Internal Mitigations

The following mitigation activities may be implemented internally. Whenever possible, it is preferable to perform tests and inspections in Quality Control laboratories so that non-conformances can be isolated and corrected with the supplier quickly and efficiently. In cases where the test is destructive and the consumable is expensive, it may be more appropriate to perform the test or inspection using production equipment in the installed position just prior to or just after production use.

Visual inspections

Visual inspections may be defined in the specifications for each article and can include checks for physical integrity of seals or component interfaces, the presence of visible particles, or the presence of foreign chemicals. Although these inspections are generally not as sensitive as an instrumented detection method, they may be sufficient to reduce the risk to an acceptable level in some cases. This is an inexpensive and immediately implementable opportunity to improve detection for at least five of the pilot articles. The specifications should describe in detail the types of failures the technician is inspecting.

Particle counting

The presence of particles in drug product is a common reason for product loss or even recall because sufficiently large particles, even if very low in concentration can be visible to customers and harmful if injected. Because it is a well-known problem, drug manufacturers have implemented particle counting techniques at various locations in the production process. When considering the risk of particulate release from consumables, however, the task is not straightforward because the particles cannot be readily observed while still on the consumable. The most effective way to test for particulate release is to perform a flush or a rinse step and then a particle count. Most filters are rinsed before use and the effluent may be collected to detect particulates through at least two possible methods. First, commercial particle counters use light disruption to detect particles in automated systems with flow control. These can be highly sensitive to sub-micron particles. Alternatively, a sample from the effluent may be inspected under a microscope by a human inspector. Bags, which are generally not rinsed before use, may need to undergo sacrificial testing in which batch samples are filled with pure water and the particle counting conducted on the extract. At least one supplier currently performs a similar test on high value bags used for drug storage. A particle test is applicable and useful for about five of the 48 pilot articles.

Residue tests

Novartis currently performs a suite of USP <661> tests on drug substance storage bags and bottles to detect the possible presence of organic and inorganic chemicals and heavy metals. The risk of chemical contamination can be high for bags which contain protein pool or other production materials earlier in the process, and these residue tests can be broadened to those articles without incurring significant method development costs. The testing costs may be significant, however, accounting for the time of quality control specialists and the sacrifice of the test samples. This group of tests can reduce the risk of chemical contamination for about seven storage bag articles.

Spectroscopic identification testing

Novartis has begun implementation of spectroscopic identification testing for one family of depth filters and similar methods may be appropriate to detect material errors leading to failures for other families of consumables as well. External spectroscopy requires benchtop or handheld equipment with an emitter/detector head, analyzer, and software to interpret the absorption spectrum which is collected. For benchtop test units, the consumable or a sample is placed under the emitter head and a spectrum is collected and analyzed on a local laptop. Handheld test units can perform the detection and analysis within a small device with a screen. Once the sample spectrum is collected, it is automatically compared to a reference library of spectra which have been previously collected from conforming materials. Peaks which do not correspond to those in the reference spectra indicate the presence of chemical compounds in the sample which are unexpected and unqualified. These compounds pose a significant leaching risk when used in production. This test is sensitive to bulk material deviations but not for foreign chemicals which may be located on small surfaces.

There are two main external spectroscopy technologies which are commonly used for non-destructive material testing. Raman spectroscopy measures the frequency spectrum of Raleigh scattering upon incidence of laser light to a depth of 8-10 mm. Impurities below 5% can be detected but fluorescent compounds interfere with the method causing it to be unsuitable for certain families of polymers. Near infrared (NIR) spectroscopy measures the absorption spectra of organic materials by reflecting an infrared beam off a surface. Due to the reflection mode, the sensitive depth is only 1-3 mm but the method is suitable for fluorescent polymers and mixes. Whereas Raman spectroscopy generates a unique peak for every compound present in the material and requires a very small reference library, the broad peaks are not identifiable in an NIR spectrum and therefore the reference library must be large enough (at least 10 units) to enable automated comparison. Thus, the method development costs for NIR are higher than for Raman but the cost per sample is comparable between the methods.

For all of the reasons listed above, the author recommends implementing Raman spectroscopy for consumables with high leaching risk, comprising non-fluorescent polymers, in which the materials are externally accessible. When internal materials also require testing to reduce the leaching risk, the consumable may be destroyed to access those materials or an extraction method may be used, as described below. This type of testing can reduce the risk of leaching for about seventeen consumable articles.

Total Organic Carbon test

USP <643>, Total Organic Carbon (TOC), is a proven and established test for determining the concentration of organic compounds in a solution. It replaces the legacy USP Oxidizable Substances test which was binary (pass/fail) instead of providing numeric output [26]. The TOC test is capable of detecting organic carbon down to approximately 500 parts per billion (ppb) and provides quantitative output which can be used to determine if unqualified compounds are present. Although the identity of these compounds may not be elucidated by this method alone, it is sensitive enough to provide article-to-article or lot-to-lot comparison of the quantity of organic materials leached from a material. For consumables that release a quantity of chemicals below the toxicological safety concern limit, the composition of leachates is unimportant and we can use the TOC test result to verify that the leachates are low risk. If the normal quantity of chemicals leached from conforming consumables are above the total concentration limit, these compounds have already been qualified for human use and are therefore acceptable. In this case, the TOC test may be used in a monitoring and control method to detect if the concentration is higher than expected, indicating the presence of an unqualified compound or an unexpected concentration of a qualified compound.

Because Novartis already has TOC equipment available in the production area and because the method requires analysis of a fluid flush, this method would be best implemented on fluid which is collected after the filters are rinsed on production equipment. The test results could be verified before the consumable contacted the protein pool. In this way, the test is non-destructive and can be implemented on 100% of articles if deemed necessary. This method may be possible to reduce the risk of leaching and foreign chemical contaminations for sixteen consumable articles, but more investigation needs to be conducted to determine if sample effluent can be taken from the production system for the TOC test.

Mass spectroscopy

Mass spectroscopy is a well-known laboratory method used to identify and measure the concentration of compounds in a solution. To analyze a sample, less than one mL of solution is passed through the laboratory equipment which ionizes and measures individual peaks for each compound. The sample is

generated similarly to a TOC test sample, either by an extraction or collecting a fluid flush during the pre-use rinse. Whereas the TOC test requires a production-simulating volume of purified water for the extraction to determine if unacceptable levels of chemicals will be released, an extract for mass spectroscopy can be generated with a small extract volume because the compounds are readily identified like a fingerprint of the solution. In addition, an extraction, although normally destructive to the consumable, can utilize more aggressive solvents to increase the extraction rate and identify very low concentration contaminants. This is especially useful for filters which have internal components that are inaccessible to external spectroscopy and when the production fluid flush is inaccessible.

The most immediate and economic use is for detecting potential contaminants in ultrafiltration/ diafiltration (UF/DF) cartridges. The cartridge is delivered and stored in a unique solution, a mix of water and glycerin to keep the membrane fully wetted before use. The fluid acts as an extraction solution and a fingerprint of the cartridge materials and any potential foreign chemicals can be collected by performing a mass spectroscopy test on a small sample. The sample can be collected with a syringe through the cartridge packaging and the hole resealed to prevent contamination. In this way, the test is non-destructive. Testing may be done at a contract laboratory test facility that conforms to Good Manufacturing Practices.

A proof of concept test was conducted on two families of UF/DF filters to determine if mass spectroscopy was sufficiently sensitive to distinguish between filters from different manufacturers. A set of particle mass peaks are generated for each chromatography peak and the collection of the most prominent mass peaks serve as the fingerprint for a filter. Extraneous peaks indicate the presence of unqualified compounds that could contaminate the drug product. The images below are taken from the proof of concept tests performed using Novartis laboratory equipment on two UF/DF samples and show the unique fingerprint of each sample. This test may reduce the leaching and foreign chemical risk for all five UF/DF filters currently used in production.

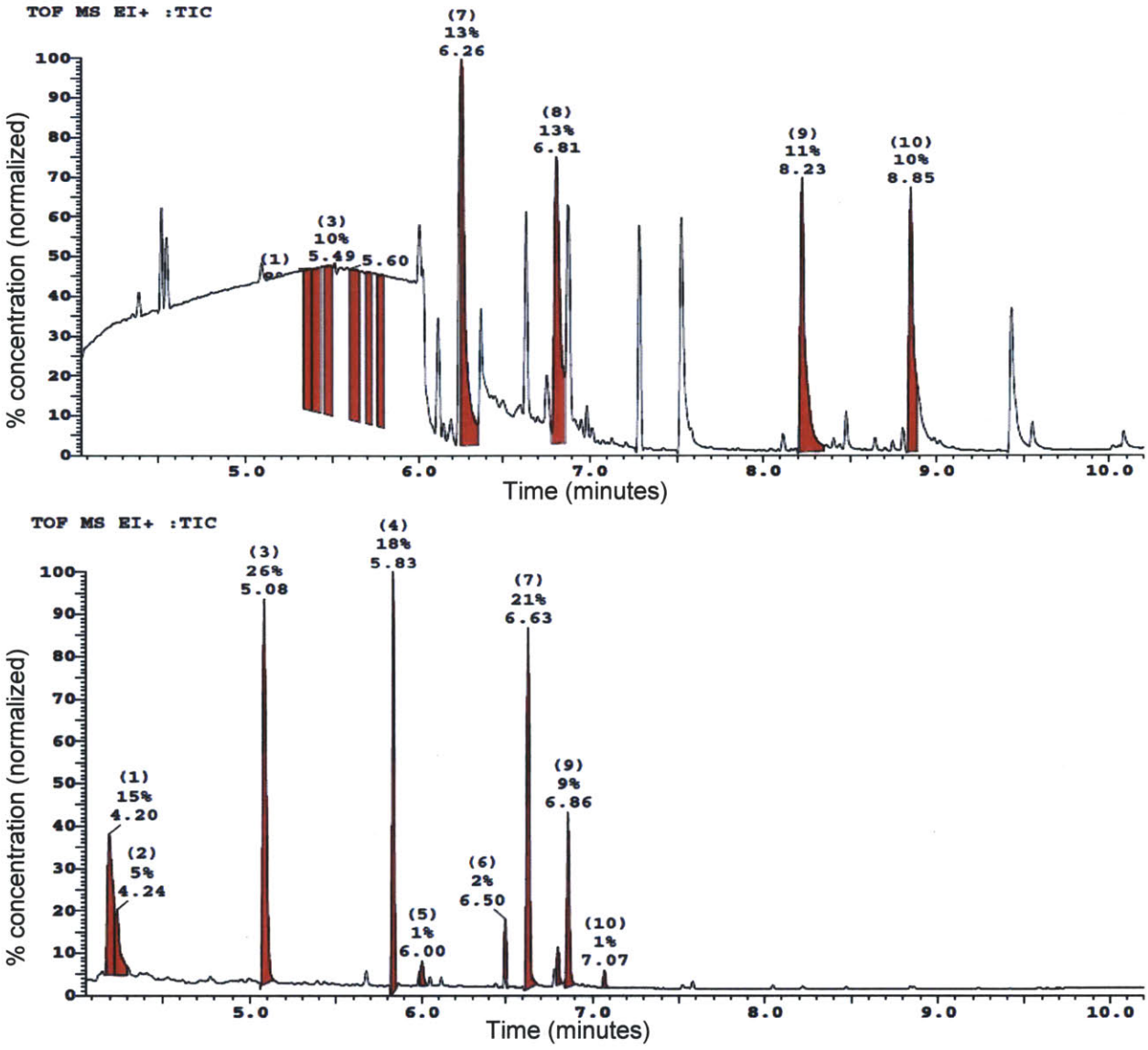

Figure 31. Sample gas chromatography mass spectroscopy data from UF/DF sample solutions from Supplier A (top) and Supplier B (bottom). The GC/MS peaks serve as fingerprints for a consumable.

Pressure leak tests

Storage bags, especially those which contain the protein pool or finished drug substance, often have a high risk of leaking and very few have adequate tests in place to prevent leaky articles from being used in production. Instead, the bags are inspected for leaks after they are filled and when a leak is found, extensive tests are performed on the contents to ensure they are not contaminated. This leads to added testing costs, production downtime, and lost product. Leak tests performed before production use can prevent these non-conformance costs.

Currently, at least one supplier performs an online leak test on storage bags for 100% of units using filtered air held at elevated pressure for a defined time. This test can be replicated at the supplier for other

bag articles or internally at Novartis to ensure quality. Very large storage bags, which are particularly susceptible to leaks, may be difficult to set up and test using this method. Development of a suitable method may require significant resources but can reduce the risk of leaking for about twelve consumable articles.

5.3.3 Mitigation Results

If all of the mitigations described above are implemented, all of the High Priority risks and most of the Medium Priority risks will be reduced to an acceptable level.

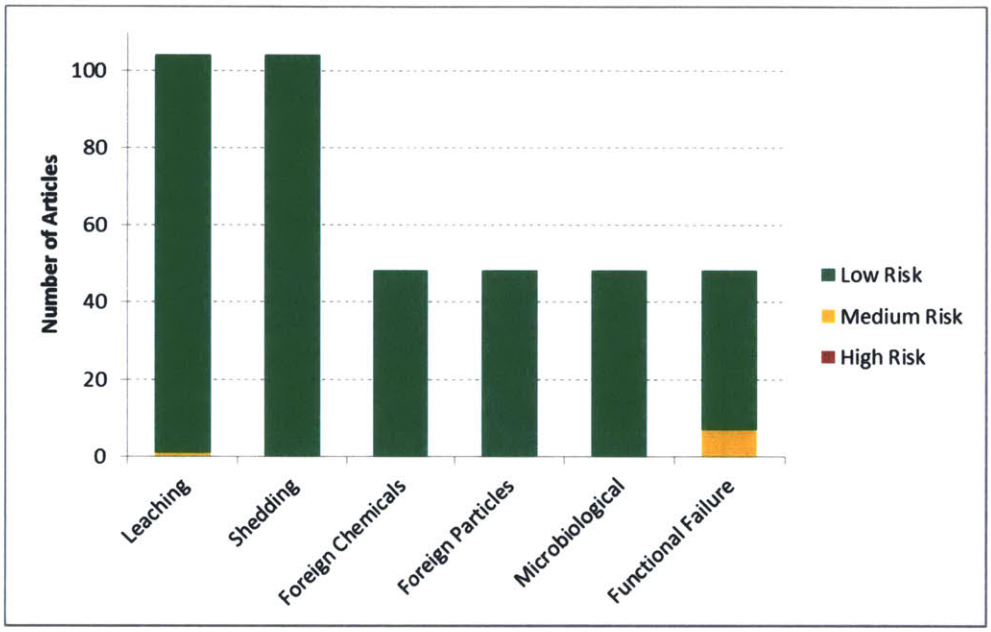

Figure 32. Potential risk profile if all recommended mitigations are implemented.

5.3.4 Long-Term Risk Reduction Strategies

The risk mitigation strategies described above are targeted for reducing the Likelihood of failure and improving Detectability, but risk can also be reduced by reducing the Severity of potential failures by performing improved pre-use cleaning procedures, avoiding exposing consumables to harsh solutions, and only using sterilized or sanitized consumables. Although these mitigations are difficult to implement on products which have already been qualified, they can be applied to new products during development.

In addition, a company-wide effort to consolidate the total number of consumable articles used can enable Novartis to devote more resources to ensuring high quality. Other drug manufacturers have begun similar initiatives and in some cases have reduced the number of SKUs used in a family of filters by 67% by standardizing connections and configurations. This increases the lot sizes of received consumables, reducing cost and enabling more thorough testing.

5.4 Defining Specifications

The risk assessment and mitigation decision processes provide the necessary information to define specifications for each consumable article. This includes supplier manufacturing and test specifications and internal inspection requirements, which can be separated into two specification documents or combined into one, which is referenced during the receipt and testing of incoming lots of consumables.

5.4.1 Supplier Specifications

The supplier Certificate of Conformance for each article includes all test and inspection criteria the manufacturer uses for release of each lot of consumables. Currently, most consumables are accepted at receipt if the supplier's Certificate of Compliance (CoC) shows that the lot conforms to all supplier specifications, but the tests and inspections listed are not verified against any internal specification or requirements. Thus, an omission on the CoC will not be discovered and the quality of a lot of consumables cannot be effectively ensured. During the Detectability analysis of the risk assessment, the CoC is collected and reviewed, and those criteria which have implications for the drug quality may be directly used in defining the internal receipt specifications. In this way, future lots of consumables will be referenced against the current specifications on which the risk assessment is based.

5.4.2 Test Specifications

Internal tests and inspections

Internal specifications for additional tests and inspections to be performed by the Quality Control department should be defined using those tests and inspections which are already performed in addition to those which are required as risk mitigation activities. The specifications should only be revised after a new test method is fully validated so specific tests are not required before they can be implemented, causing an internal non-compliance.

Sample size determination

For tests and inspections which require representative batch samples to ensure quality, Novartis should use the Acceptable Quality Limit (AQL) method described in ANSI/ASQ Z1.4 instead of the "square root of lot size (n) plus one" method that is currently employed. The later method, although widely adopted by pharmaceutical manufacturers, is not a statistically derived method and requires large sample sizes when the lot size is small [27]. For destructive tests and consumables which cost tens of thousands of dollars, this cost may prohibit the adoption of many kinds of tests. For example, for a lot size of ten consumables (a small but common lot size in the industry), the sample size under the square root of n plus one rule requires five test samples, or 50% of the lot (3.16 + 1, round up to 5). This effectively doubles the cost of

the consumable even before considering the test costs. Alternatively, the AQL method uses a statistical approach to derive a number of samples based on the manufacturer's willingness to accept a certain small percentage of failures. This acceptance limit can be modulated based on the manufacturer's risk tolerance, but a typical value is 0.16% (accept lot on zero failures, reject lot on at least one failure, 95% confidence). The lookup tables provided in the standard for General Level I require just two samples for lot sizes between two and fifteen units [28]. The graph below shows that the sample size required under the AQL method is lower for small lot sizes, but the two methods converge at larger lot sizes.

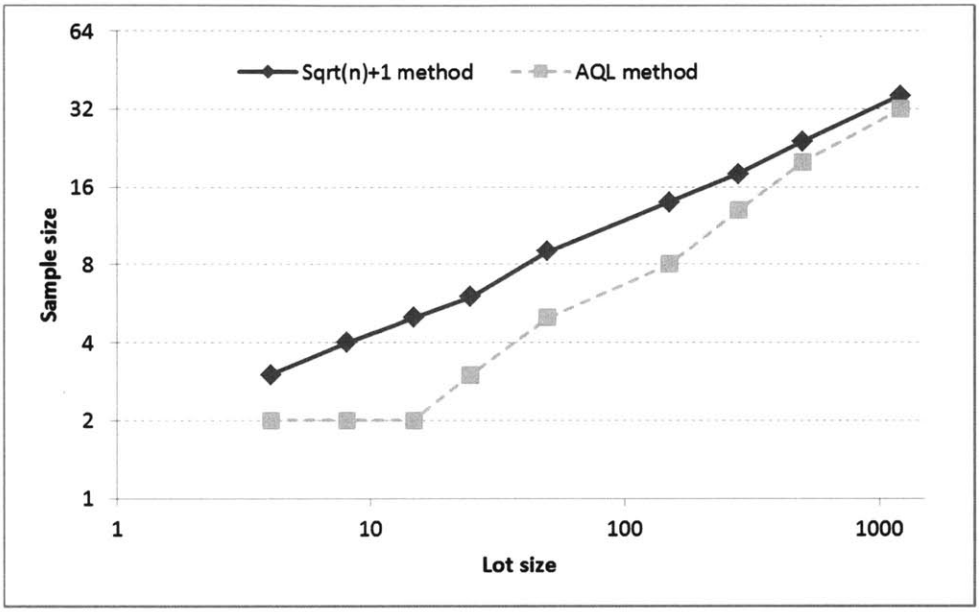

Figure 33. Comparison of sample size requirement between sampling methods.

It should be noted that all consumable suppliers engaged during this project use the AQL method to determine their sample sizes.

5.5 Business Process Integration

5.5.1 First Time Risk Assessment on New Consumables

The risk assessment and mitigation processes are first being implemented on a pilot group of critical consumables as described previously. After the risk assessment process is implemented on the pilot articles and has been tested for three to six months, it should undergo thorough review before being implemented for the remaining consumables. This review should be performed by a team of production and quality experts who have become familiar with the risk assessment tool and assessment outcomes. The risk levels collected in the dashboard should be reviewed for each article to determine if the result matches expectations and the history of non-conformances. Where discrepancies exist between the

expected and the calculated scores for any risk dimension, the numerical factors should be adjusted to align the outcomes. If this adjustment is insufficient to achieve the needed results, the thresholds between 1, 5, and 9 scores may be modified. Changes to the calculation models should be avoided. In addition, the review team should also take the opportunity to make any necessary changes to the Excel worksheet to improve its functionality.

After the review and necessary revisions, the risk assessment process should be applied to all remaining consumable articles. Mitigations should be applied where required and specification documents written for all articles, constituting a complete library of risk assessments and specifications.

5.5.2 Triggers for Review

Several events may trigger the completion or review of a consumable risk assessment. Whenever a new consumable article is introduced into the production system, a new risk assessment form should be completed while the supplier is being approved. Depending on the novelty of the consumable and the supplier, the lack of supplier quality history may warrant enhanced controls for a defined period until a sufficient quality history has been established to reduce the controls. When necessary, risk mitigations should be implemented before the first set of specifications is defined. If an article is used for a new application such as a new part of the process or for a new drug product, the risk assessment should be reviewed and updated taking into account the highest impact application of the consumable. Normally, the use of an article in a more downstream process will lead to a more severe impact in the event of a consumable non-conformance. Supplier changes, such as manufacturer location, vendor changes, or new audit outcomes, should also prompt an update of the risk assessment worksheet as well as internal events such as the implementation of mitigation activities or new quality issues which are discovered.

5.5.3 Continuous Improvement and Review

The risk assessments and tools should also be reviewed based on a periodic schedule. This review should be more frequent in the first years after its implementation to remove imperfections from the system. As described above, a team of experienced specialists should review the risk assessment tools thoroughly at these intervals and adjust as necessary to ensure accurate and efficient operation. In addition, the details in each of the risk assessments for each consumable should be reviewed for accuracy. Acknowledging that not all changes that should trigger a review will be detected, the periodic reviews should also compare the current supplier quality systems and CoCs with those referenced in the last risk assessment.

6 Conclusions

6.1 Review of the System

6.1.1 Failure Modes

This work has presented a categorization system for the failure modes that may be observed in consumables that could lead to contamination of the drug product. These six failure modes allow the various risks presented by several hundred consumables to be sufficiently analyzed, compared and prioritized. They cover the three major types of contamination, chemical, particulate, and microbiological and also provide for functional failures which could indirectly lead to contamination. In this way they are cumulatively exhaustive – all possible supplier non-conformances are captured in these categories. They are also broad enough to allow efficient analysis and applicability to all consumable articles. It should be noted that each failure mode can have several root causes and several effects on the quality of the product.

6.1.2 Risk Assessment

With the risk assessment method presented in this work, all of the various risks can be quantified and prioritized using a modified FMEA framework. In order to ensure consistent outcome among different users and provide for efficient analysis of the six failure modes of several hundred articles, the method has been implemented in an Excel worksheet where the risk is estimated using semi-automated calculations. Quality Control, Quality Assurance, and production specialists are responsible for completing the analysis of the risk dimensions pertaining to their function – QC completes the Detectability section, QA completes the Likelihood section, and production experts complete the Severity section. Each of these risk dimensions is calculated using a pre-defined set of factors which are particular to the consumable, its application in production, and the supplier. The product of all three provides a Risk Priority Number which is used to prioritize the various risks for mitigation. We have defined the decision thresholds for this RPN such that low priority risks are accepted, allowing resources to be directed only toward those items which present the highest risk of contamination.

Qualitative and quantitative evaluation of this method demonstrates that the output of the tool agrees with the expectations of experienced specialists and provides consistent results among individual users. With the Excel-based automation, it is capable of performing a full risk assessment in less than two minutes, the time required to complete the form with the consumable-specific information. In addition, the assessment output is robust to small errors in the calculation assumptions but is sensitive to the factors which are believed to have significant influence on the risk profile.

Lastly, the visualizations provide management with a tool to understand the current risk areas, make mitigation and resource allocation decisions, and observe progress over time. In summary, this risk assessment method provides a systematic way to prioritize risks for mitigation and documents the rationale that leads to risk acceptance or control.

6.1.3 Risk Mitigation

With the established risk assessment system, Novartis can implement mitigations commensurate with the magnitude of the risk. In cases where the RPN is intermediate, the application of a test or inspection with relatively insensitive detection limits may be sufficient to reduce the risk to an acceptable level whereas a more sensitive test may be required for higher risk items. In addition, risk areas may be grouped such that a single mitigation action may be applied to multiple consumables, reducing the risk adequately while developing only one new test method. In this way, resources can be allocated to obtain the best outcome for an investment.

Eleven mitigation opportunities, both internal and at suppliers, have been investigated and presented in this work which together can eliminate the high priority risk areas. Some of these opportunities require little upfront investment (e.g. visual inspections) while others will require significant investment in equipment and method development (e.g. mass spectroscopy, bag leakage tests). In cases where a test method may be destructive to the sample, a new method for sample size determination has been presented which is statistically valid and economically feasible.

Lastly, this risk assessment and mitigation process enables specifications to be defined for each consumable systematically. In this way, the supplier and internal controls are maintained throughout the life of a product.

6.1.4 Pilot Implementation

The methods described above have been implemented in a pilot group of 48 consumables. Preliminary risk assessments have been completed and some mitigation activities are underway. Specifications are being drafted based on the recommendations established in this work. The pilot is intended to provide initial direction for reducing contamination risk while debugging and refining the method for future use. The Quality Control department is currently responsible for the completion of the risk assessments and implementing enhanced controls. A team of QC specialists currently owns the tools and documentation for this process and will collaborate with QA and production for the remainder of the pilot and the expansion into other areas.

6.2 Future Work

6.2.1 Implementation and Expansion

Initial Release

After the pilot phase is complete, a thorough review of the system, processes, and outputs will be conducted by an experienced team before releasing the tools and documentation for operational use all across the Novartis BioPharmOps organization. This initial release will include the risk assessment forms, operating procedure, and reference to the system in associated procedures such as the supplier approval procedure. An implementation plan will be drafted showing the gaps between the newly released requirements and the current documentation. Since the risk assessment forms are completed during the pilot phase, these gaps should be limited to the remaining consumables.

Expansion to other consumables

Whereas the pilot is applied to all high criticality consumables (48), it will be expanded to all medium criticality consumables as well. Although the risk profile of these consumables is expected to be lower due to their limited contact with the product and use during upstream processes, the greater number of them (more than 200) will lead to a significant assessment burden and mitigation action requirement. Many of the mitigation actions previously implemented will be applicable to these, however, and the need to develop novel test methods should be limited. Low criticality consumables do not need to be assessed because they have negligible impact to product quality.

6.2.2 Continuous Improvement

This tool should be reviewed and revised at pre-defined periods (the author recommends every six months initially, and every two years after the first two years) and at certain quality event triggers discussed previously. In particular, when non-conformances are discovered which were not identified by the current controls, the risk assessment tool should be reviewed to see if any parameters need to be modified to implement more appropriate controls. In short, this method should be used as a draft and refined as Novartis learns more about consumable contamination risks.

6.2.3 Broader Applicability

Spare parts and equipment

Novartis managers have perceived an opportunity to apply this method to spare parts and equipment used in production. This should be possible with some modification to the tools because the same failure modes generally apply to these components. For equipment, the functional failure mode may need to be

separated into several distinct modes to effectively capture the various sources and impact of a failure on product quality. Because there are thousands of articles defined as spare parts, the automation of this method may be especially suited for rapid risk assessment. The author recommends first developing a criticality assessment to prioritize those articles which require a more detailed assessment.

Raw Materials

Risk assessment may be applied to raw materials using the framework presented in this work although the particular calculations and tools are not directly applicable. Raw materials present slightly different risks and a variation on the failure mode categories needs to be identified and defined. The major contamination families (chemical, particulate, and microbiological contaminations) are still applicable and each raw material has a particular function in the production process which has implications on drug product quality. The Severity calculation, which currently evaluates the relative quantity of contaminant that could be present in the final drug product, is largely applicable to raw materials although the material-related factors would need to be modified. The Likelihood calculation, which evaluates the quality systems of the supplier, may be similar for raw material suppliers, but the controls which are failure mode specific would need to be modified. Lastly, the Detectability calculation can be easily translated to raw material assessment with a new set of pre-defined tests and inspections. In summary, the method and the structure of the tools may, with some work, be modified to be applicable to raw materials. The need for this is not as great as for consumables since the risks associated with raw materials are better understood and appropriate test methods are already in place. Nonetheless, a systematic method does provide documentation and justification advantages over the current *ad hoc* processes. The implementation of a risk assessment system may provide a particularly valuable opportunity for future internships.

Other Risk Assessment Applications

Lastly, this approach is applicable in any case where a risk assessment must be performed for many articles by multiple people or over a long period of time. Although the failure modes, calculations, tools, and mitigations may not be appropriate for other applications, the process used to develop these methods is broadly applicable. Whereas traditional risk assessment requires a group of experienced specialists to brainstorm failure modes and qualitatively evaluate them for the various risk dimensions, the systematic method described in this work can make the process efficient for large numbers of articles and robust over time and among individual analysts. The following process provides a template for developing a rules-based risk assessment system and can be adapted for many applications.

1. Categorize and standardize failure modes
2. Develop the mathematical risk calculation model
3. Define variables that affect risk (example: material)
4. Identify alternatives within each variable (example: metal)
5. Assign a numeric factor to each alternative (example: metal = 0.2)
6. Test on known articles & rework factors to obtain expected output
7. Define decision thresholds on overall risk values
8. Implement risk mitigations to reduce risk to acceptable levels
9. Define specifications to maintain requirements over time

7 References

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Appendix 1: Risk Assessment Worksheet and Dashboard

XXXXX.01_Consumables FMEA Form_v01_50500043.xlsx v 01 1/26/2013 21:28

CONSUMABLES RISK ASSESSMENT FORM

Section 1: Identifying Information

	Fill in:
Novartis Article Code	
Description	
Company Name of Supplier	
Supplier Material Trade Name	
Supplier Reference Number	
Supplier Manufacturing Site Location	
Consumable Type (e.g. column filter cartridge)	Depth Filter
Purpose/Function (e.g. clarification of protein pool)	clarification of protein pool

Section 2: Severity Analysis

*Complete this section for **the largest** component of the consumable which contacts the product. Smaller components, if applicable, can be entered in Section 5.*

Component Description *(eg. Filter membrane)*: Filter membrane — **Component 1**

Property	*Select:*	**Factor**	
Consumable Function	Clarification	0.7	A1 functionality
Product Contact	protein pool	1	A2a contamination
		0.8	A2b functionality
Component Material	fiber with resin	1	A3a leaching
		1	A3b shedding
Total Surface Area	very large (> 1 m2)	1	A4 contamination
Usage Conditions	filtration	1	A5 intrinsic
Product Composition	Mild Solutions	0.9	A6 intrinsic
Sterilization / Sanitization	none	0.9	A7a intrinsic
		1	A7b microbiological
Flushed or Rinsed	Yes	0.9	A8a intrinsic
		0.5	A8b extrinsic
Sterile filter downstream	Yes	0.1	A9a particulates
		0.4	A9b microbiological
Toxic Chemicals at Supplier	No	0.8	A10 foreign chemicals

Failure Mode	**Factor Formula**	**Factor (0 to 1)**		**Severity [1,5,9]**	
Unqualified Leaching:	A2a * A3a * A4 * A5 * A6 * A7a * A8a	0.7	→	9	Severity1
Particle Shedding:	A2a *A3b *A4 *A5 * A7a *A8a *A9a	0.1	→	1	Severity2
Foreign Chemical:	A2a * A4 * A8b * A10	0.4	→	5	Severity3
Foreign Particle:	A2a * A4 * A8b * A9a	0.1	→	1	Severity4
Microbiological Contam.:	A2a * A7b * A9b	0.4	→	5	Severity5
Functional Failure:	A1 * A2b	0.6	→	5	Severity6

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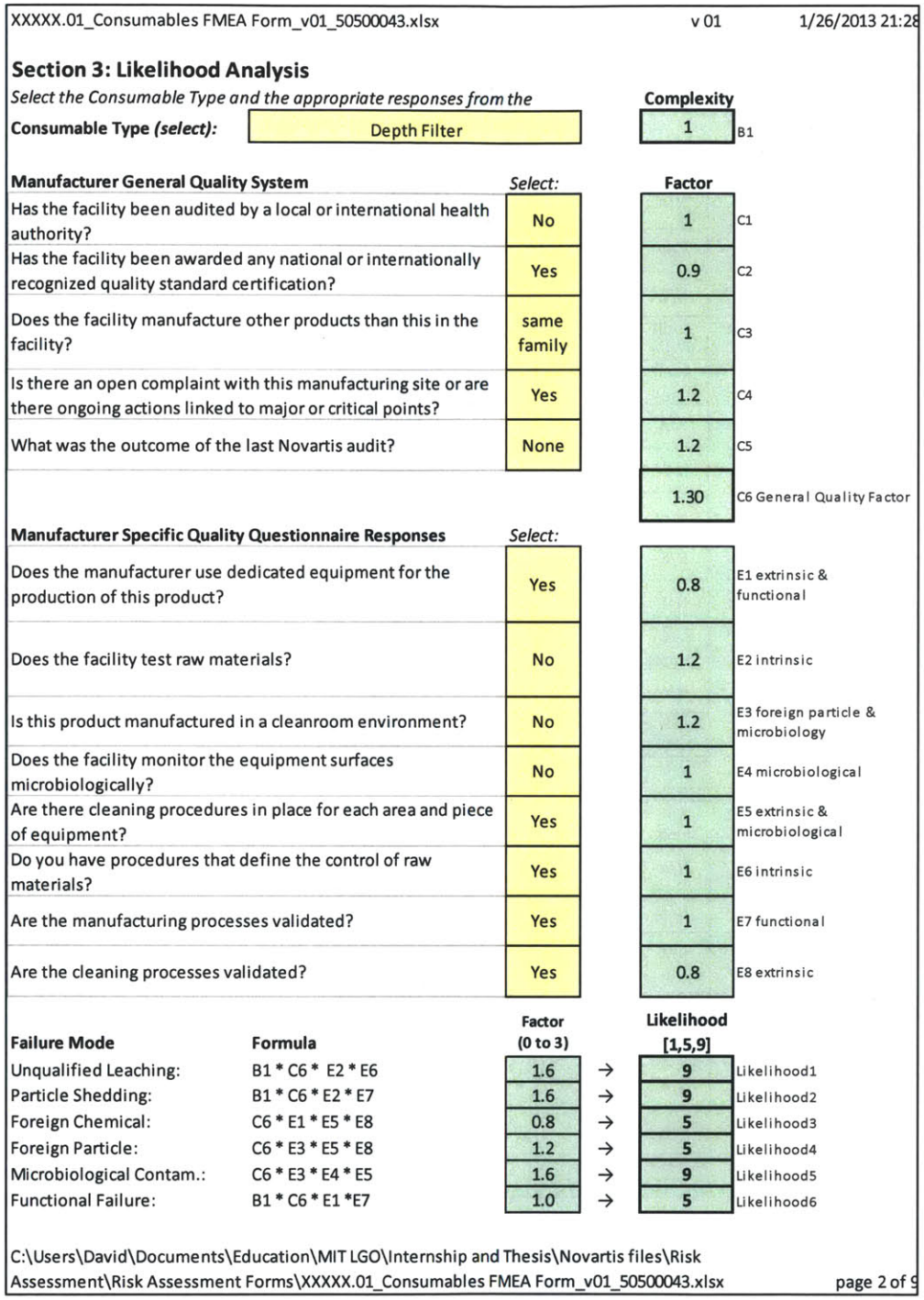
Figure 34. Page 1 of the Risk Assessment Excel worksheet. This page includes yellow text fields for identifying information and yellow selection fields for entering consumable usage and material properties for the Severity analysis. The green fields are automatically calculated.



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Section 3: Likelihood Analysis

Select the Consumable Type and the appropriate responses from the

Consumable Type *(select):*	Depth Filter	**Complexity**	1	B1

Manufacturer General Quality System	*Select:*	**Factor**	
Has the facility been audited by a local or international health authority?	No	1	C1
Has the facility been awarded any national or internationally recognized quality standard certification?	Yes	0.9	C2
Does the facility manufacture other products than this in the facility?	same family	1	C3
Is there an open complaint with this manufacturing site or are there ongoing actions linked to major or critical points?	Yes	1.2	C4
What was the outcome of the last Novartis audit?	None	1.2	C5
		1.30	C6 General Quality Factor

Manufacturer Specific Quality Questionnaire Responses	*Select:*		
Does the manufacturer use dedicated equipment for the production of this product?	Yes	0.8	E1 extrinsic & functional
Does the facility test raw materials?	No	1.2	E2 intrinsic
Is this product manufactured in a cleanroom environment?	No	1.2	E3 foreign particle & microbiology
Does the facility monitor the equipment surfaces microbiologically?	No	1	E4 microbiological
Are there cleaning procedures in place for each area and piece of equipment?	Yes	1	E5 extrinsic & microbiological
Do you have procedures that define the control of raw materials?	Yes	1	E6 intrinsic
Are the manufacturing processes validated?	Yes	1	E7 functional
Are the cleaning processes validated?	Yes	0.8	E8 extrinsic

Failure Mode	**Formula**	**Factor (0 to 3)**		**Likelihood [1,5,9]**	
Unqualified Leaching:	B1 * C6 * E2 * E6	1.6	→	9	Likelihood1
Particle Shedding:	B1 * C6 * E2 * E7	1.6	→	9	Likelihood2
Foreign Chemical:	C6 * E1 * E5 * E8	0.8	→	5	Likelihood3
Foreign Particle:	C6 * E3 * E5 * E8	1.2	→	5	Likelihood4
Microbiological Contam.:	C6 * E3 * E4 * E5	1.6	→	9	Likelihood5
Functional Failure:	B1 * C6 * E1 *E7	1.0	→	5	Likelihood6

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Figure 35. Page 2 of the Risk Assessment Excel worksheet. This page includes the selection fields for completing the Likelihood analysis. The yellow fields are inputs and the green fields are automatically calculated.

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Section 4: Detectability Analysis

Select the test article next to all relevant tests for this component. If there are additional tests which are performed but not listed, enter them in the available section below.

Supplier Tests and Inspections	select:	E. Leaching	F. Shedding	G. Foreign Chem.	H. Foreign Part.	I. Microbiological	J. Functional
Direct functional test (e.g. pressure leak test for bags; bacteria retention for filters)	N/A						N/A
Indirect functional test (e.g. pressure drop test for filters)	100%'						5
Dimensional inspection	N/A						N/A
Total organic carbon and conductivity test on flush (USP <643> and <645>)	Audit Based	5		5			
Oxidizable substances test on flush (legacy USP test)	Audit Based	5		5			
Extractable ions test (Pall method)	N/A	N/A		N/A			
Organic weight (0.25% max), Ca, Fe, and Color after flush (3M method)	N/A	N/A		N/A			
Visual inspection for particles and chemicals (no flush)	N/A			N/A	N/A		
Visual inspection for particles after flush	N/A		N/A		N/A		
Particle count by machine or visual under microscope after flush	N/A		N/A		N/A		
LAL endotoxin test or Bioburden test by ISO 11737 method by filtration	Batch Sample					1	
Membrane fiber release test (Millipore)	N/A		N/A				
N/A							
N/A							

Internal Tests and Inspections	select:	E	F	G	H	I	J
Non-volatile residue, residue on ignition, heavy metals, and buffer capacity tests	N/A	N/A		N/A			
External spectroscopy material ID test	N/A	N/A	N/A				
Mass spectroscopy peak confirmation on extract or flush	N/A	N/A		N/A			
Visual inspection for foreign chemicals and particles	N/A			N/A	N/A		
Indirect functional test (eg. visual inspection for bags)	N/A						N/A
Direct functional test (e.g. pressure leak test for bags, Gold Nanoparticle Test for nanofilter)	N/A						N/A
N/A							
N/A							

Failure Mode	Formula	Detectability [1,5,9]	
Unqualified Leaching:	minimum from Leaching column (E)	5	Detectability1
Particle Shedding:	minimum from Shedding column (F)	9	Detectability2
Foreign Chemical:	minimum from Foreign Chemical column (G)	5	Detectability3
Foreign Particle:	minimum from Foreign Particle column (H)	9	Detectability4
Microbiological Contam.:	minimum from Microbiological column (I)	1	Detectability5
Functional Failure:	minimum from Functional column (J)	5	Detectability6

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Figure 36. Page 3 of the Risk Assessment Excel worksheet..This page includes the selection fields for completing the Detectability analysis. The yellow fields are inputs and the green fields are automatically calculated

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Section 5: Secondary Components

Component 2 Description	polypropylene support structure		**Component 2**	
Component Material	crystalline polymer	0.8	A11a leaching	
		0.1	A11b shedding	
Total Surface Area	large (0.1 to 1.0 m2)	0.8	A12 contamination	
Usage Conditions	Filtration	1	A13 intrinsic	
Unqualified Leaching:	A2a * A11a * A12 * A13 * A6 * A7a * A8a	0.5	→ 5	Severity7
Particle Shedding:	A2a *A11b *A12 *A13 * A7a *A8a *A9a	0.0	→ 1	Severity8

Select the test article next to all relevant tests for this component.

		Leach	Shed
Total organic carbon and conductivity test on flush (USP <643> & <645>)	Audit Based	5	
Oxidizable substances test on flush (legacy USP test)	Audit Based	5	
Extractable ions test (Pall method)	N/A	N/A	
Organic weight (0.25% max), Ca, Fe, and Color after flush (3M method)	N/A	N/A	
Non-volatile residue, residue on ignition, heavy metals, buffer capacity	N/A	N/A	
External spectroscopy material ID test	N/A	N/A	N/A
Mass spectroscopy peak confirmation on extract or flush	N/A	N/A	
N/A			

Unqualified Leaching:	minimum from Leaching column	5	Detect7
Particle Shedding:	minimum from Shedding column	9	Detect8

Component 3 Description *enter "N/A" if there is none*	silicone gaskets		**Component 3**	
Component Material	amorphous polymer	1	A14a leaching	
		0.1	A14b shedding	
Total Surface Area	small (10 to 100 cm2)	0.4	A15 contamination	
Usage Conditions	Filtration	1	A16 intrinsic	
Unqualified Leaching:	A2a * A14a * A15 * A16 * A6 * A7a * A8a	0.3	→ 1	Severity9
Particle Shedding:	A2a *A14b *A15 *A16 * A7a *A8a *A9a	0.0	→ 1	Severity10

Select the test article next to all relevant tests for this component.

		Leach	Shed
Total organic carbon and conductivity test on flush (USP <643> & <645>)	Audit Based	5	
Oxidizable substances test on flush (legacy USP test)	Audit Based	5	
Extractable ions test (Pall method)	N/A	N/A	
Organic weight (0.25% max), Ca, Fe, and Color after flush (3M method)	N/A	N/A	
Non-volatile residue, residue on ignition, heavy metals, buffer capacity	N/A	N/A	
External spectroscopy material ID test	N/A	N/A	N/A
Mass spectroscopy peak confirmation on extract or flush	N/A	N/A	
N/A			

Unqualified Leaching:	minimum from Leaching column	5	Detect9
Particle Shedding:	minimum from Shedding column	9	Detect10

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Figure 37. Page 4 of the Risk Assessment Excel worksheet.This page includes the selection fields for completing Severity and Detectability analysis for secondary components. The yellow fields are inputs and the green fields are automatically calculated.

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Section 6: Risk Evaluation

The Risk Priority Number is automatically calculated from the scores generated above.

Failure Mode	Formula	S	L	D	RPN	
Unqualified Leaching:	Severity1 * Likelihood1 * Detectability1	9	9	5	405	Compo-
Particle Shedding:	Severity2 * Likelihood2 * Detectability2	1	9	9	81	nent 1
Foreign Chemical:	Severity3 * Likelihood3 * Detectability3	5	5	5	125	whole
Foreign Particle:	Severity4 * Likelihood4 * Detectability4	1	5	9	45	consumab
Microbiological Contam.:	Severity5 * Likelihood5 * Detectability5	5	9	1	45	le
Functional Failure:	Severity6 * Likelihood6 * Detectability6	5	5	5	125	
Unqualified Leaching:	Severity7 * Likelihood1 * Detectability7	5	9	5	225	Compo-
Particle Shedding:	Severity8 * Likelihood2 * Detectability8	1	9	9	81	nent 2
Unqualified Leaching:	Severity9 * Likelihood1 * Detectability9	1	9	5	45	Compo-
Particle Shedding:	Severity10 * Likelihood2 * Detectability10	1	9	9	81	nent 3

Section 7: Mitigation Plan

For all failure modes with RPN at least 225 points, record a mitigation plan below.

For all failure modes with RPN equal to 125, record a mitigation plan or a justification for acceptance below.

increase test frequency of TOC test
or ID test (only mitigates membrane leaching risk)

Expected Risk after Planned Mitigations

Change expected Likelihood and Detectability Scores assuming the planned

	S	L	D	RPN	
Unqualified Leaching:	9	9	1	81	Compo-
Particle Shedding:	1	9	9	81	nent 1
Foreign Chemical:	5	5	1	25	whole
Foreign Particle:	1	5	9	45	consumab
Microbiological Contam.:	5	9	1	45	le
Functional Failure:	5	5	5	125	
Unqualified Leaching:	5	9	1	45	Compo-
Particle Shedding:	1	9	9	81	nent 2
Unqualified Leaching:	1	9	5	45	Compo-
Particle Shedding:	1	9	9	81	nent 3

Consumable user: Signed:

Quality Control: Signed:

Quality Assurance: Signed:

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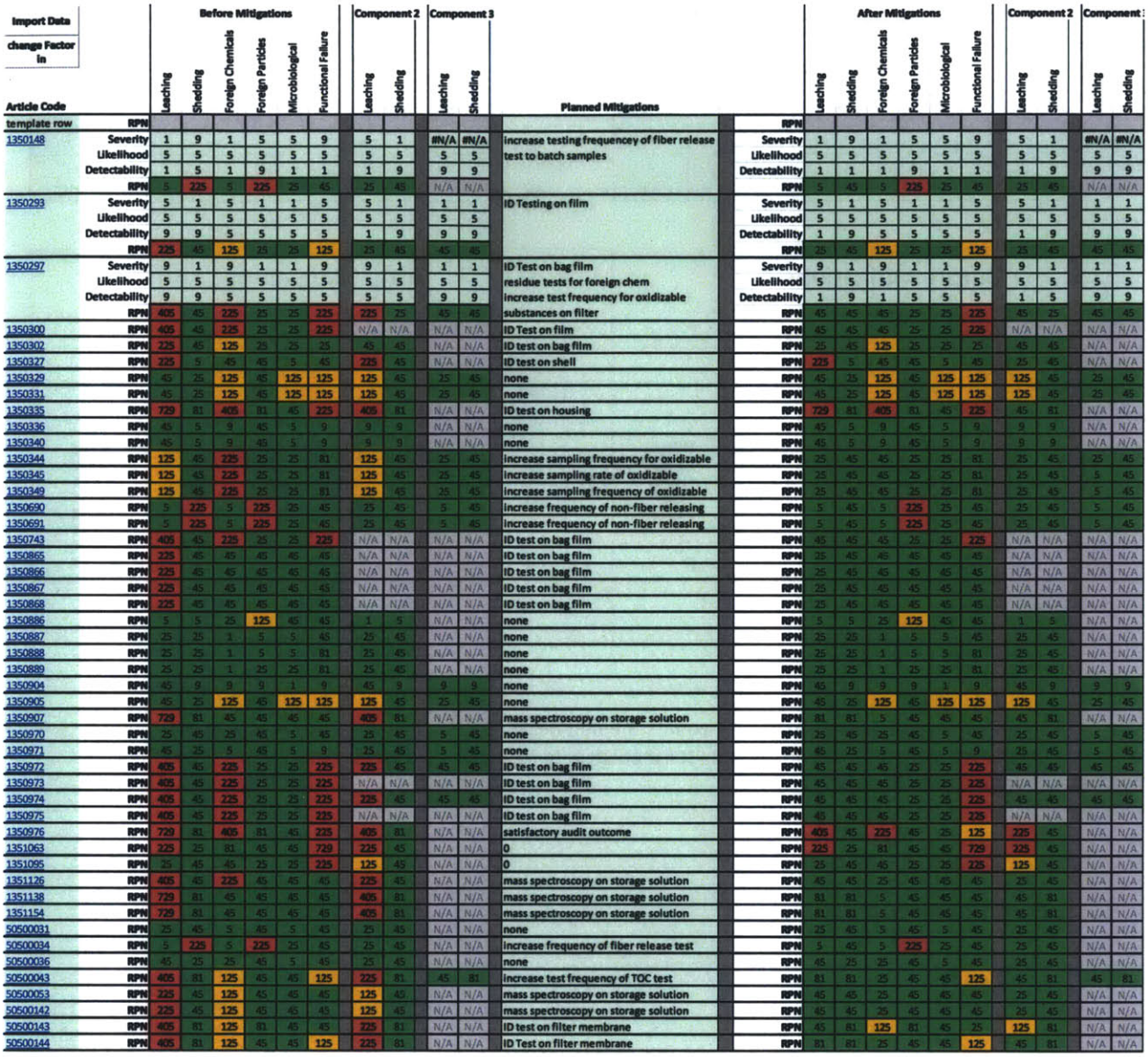
Figure 38. Page 5 of the Risk Assessment Excel worksheet. This page automatically performs the RPN calculations and includes a text field for entering a mitigation plan. The score changes corresponding to that mitigation plan can be entered in the tables below. Lastly, boxes for verification of this form are included for digital signature.



Import Data / change Factor in		Before Mitigations						Component 2		Component 3		Planned Mitigations		After Mitigations						Component 2		Component 3	
Article Code		Leaching	Shedding	Foreign Chemicals	Foreign Particles	Microbiological	Functional Failure	Leaching	Shedding	Leaching	Shedding			Leaching	Shedding	Foreign Chemicals	Foreign Particles	Microbiological	Functional Failure	Leaching	Shedding	Leaching	Shedding
template row	RPN												RPN										
1350148	Severity	1	9	1	5	5	9	5	1	#N/A	#N/A	increase testing frequency of fiber release	Severity	1	9	1	5	5	9	5	1	#N/A	#N/A
	Likelihood	5	5	5	5	5	5	5	5	5	5	test to batch samples	Likelihood	5	5	5	5	5	5	5	5	5	5
	Detectability	1	5	1	9	1	1	1	9	9	9		Detectability	1	1	1	9	1	1	1	9	9	9
	RPN	5	225	5	225	25	45	25	45	N/A	N/A		RPN	5	45	5	225	25	45	25	45	N/A	N/A
1350293	Severity	5	1	5	1	1	5	5	1	1	1	ID Testing on film	Severity	5	1	5	1	1	5	5	1	1	1
	Likelihood	5	5	5	5	5	5	5	5	5	5		Likelihood	5	5	5	5	5	5	5	5	5	5
	Detectability	9	9	5	5	5	5	1	9	9	9		Detectability	1	9	5	5	5	5	1	9	9	9
	RPN	225	45	125	25	25	125	25	45	45	45		RPN	25	45	125	25	25	125	25	45	45	45
1350297	Severity	9	1	9	1	1	9	9	1	1	1	ID Test on bag film	Severity	9	1	9	1	1	9	9	1	1	1
	Likelihood	5	5	5	5	5	5	5	5	5	5	residue tests for foreign chem	Likelihood	5	5	5	5	5	5	5	5	5	5
	Detectability	9	9	5	5	5	5	5	5	9	9	increase test frequency for oxidizable	Detectability	1	9	1	5	5	5	1	5	9	9
	RPN	405	45	225	25	25	225	225	25	45	45	substances on filter	RPN	45	45	45	25	25	225	45	25	45	45
1350300	RPN	405	45	225	25	25	225	N/A	N/A	N/A	N/A	ID Test on film	RPN	45	45	45	25	25	225	N/A	N/A	N/A	N/A
1350302	RPN	225	45	125	25	25	25	45	45	N/A	N/A	ID test on bag film	RPN	25	45	125	25	25	25	45	45	N/A	N/A
1350327	RPN	225	5	45	45	5	45	225	45	N/A	N/A	ID test on shell	RPN	225	5	45	45	5	45	25	45	N/A	N/A
1350329	RPN	45	25	125	45	125	125	125	45	25	45	none	RPN	45	25	125	45	125	125	125	45	25	45
1350331	RPN	45	25	125	45	125	125	125	45	25	45	none	RPN	45	25	125	45	125	125	125	45	25	45
1350335	RPN	729	81	405	81	45	225	405	81	N/A	N/A	ID test on housing	RPN	729	81	405	81	45	225	45	81	N/A	N/A
1350336	RPN	45	5	9	45	5	9	9	9	N/A	N/A	none	RPN	45	5	9	45	5	9	9	9	N/A	N/A
1350340	RPN	45	5	9	45	5	9	9	9	N/A	N/A	none	RPN	45	5	9	45	5	9	9	9	N/A	N/A
1350344	RPN	125	45	225	25	25	81	125	45	25	45	increase sampling frequency for oxidizable	RPN	25	45	45	25	25	81	25	45	25	45
1350345	RPN	125	45	225	25	25	81	125	45	25	45	increase sampling rate of oxidizable	RPN	25	45	45	25	25	81	25	45	5	45
1350349	RPN	125	45	225	25	25	81	125	45	25	45	increase sampling frequency of oxidizable	RPN	25	45	45	25	25	81	25	45	5	45
1350690	RPN	5	225	5	225	25	45	25	45	5	45	increase frequency of non-fiber releasing	RPN	5	45	5	225	25	45	25	45	5	45
1350691	RPN	5	225	5	225	25	45	25	45	5	45	increase frequency of non-fiber releasing	RPN	5	45	5	225	25	45	25	45	5	45
1350743	RPN	405	45	225	25	25	225	N/A	N/A	N/A	N/A	ID test on bag film	RPN	45	45	45	25	25	225	N/A	N/A	N/A	N/A
1350865	RPN	225	45	45	45	45	45	N/A	N/A	N/A	N/A	ID test on bag film	RPN	25	45	45	45	45	45	N/A	N/A	N/A	N/A
1350866	RPN	225	45	45	45	45	45	N/A	N/A	N/A	N/A	ID test on bag film	RPN	25	45	45	45	45	45	N/A	N/A	N/A	N/A
1350867	RPN	225	45	45	45	45	45	N/A	N/A	N/A	N/A	ID test on bag film	RPN	25	45	45	45	45	45	N/A	N/A	N/A	N/A
1350868	RPN	225	45	45	45	45	45	N/A	N/A	N/A	N/A	ID test on bag film	RPN	25	45	45	45	45	45	N/A	N/A	N/A	N/A
1350886	RPN	5	5	25	125	45	45	1	5	N/A	N/A	none	RPN	5	5	25	125	45	45	1	5	N/A	N/A
1350887	RPN	25	25	1	5	5	45	25	45	N/A	N/A	none	RPN	25	25	1	5	5	45	25	45	N/A	N/A
1350888	RPN	25	25	1	5	5	81	25	45	N/A	N/A	none	RPN	25	25	1	5	5	81	25	45	N/A	N/A
1350889	RPN	25	25	1	25	25	81	25	45	N/A	N/A	none	RPN	25	25	1	25	25	81	25	45	N/A	N/A
1350904	RPN	45	9	9	9	1	9	45	9	9	9	none	RPN	45	9	9	9	1	9	45	9	9	9
1350905	RPN	45	25	125	45	125	125	125	45	25	45	none	RPN	45	25	125	45	125	125	125	45	25	45
1350907	RPN	729	81	45	45	45	45	405	81	N/A	N/A	mass spectroscopy on storage solution	RPN	81	81	5	45	45	45	45	81	N/A	N/A
1350970	RPN	25	45	25	45	5	45	25	45	5	45	none	RPN	25	45	25	45	5	45	25	45	5	45
1350971	RPN	45	25	5	45	5	9	25	45	5	45	none	RPN	45	25	5	45	5	9	25	45	5	45
1350972	RPN	405	45	225	25	25	225	225	45	45	45	ID test on bag film	RPN	45	45	45	25	25	225	45	45	45	45
1350973	RPN	405	45	225	25	25	225	N/A	N/A	N/A	N/A	ID test on bag film	RPN	45	45	45	25	25	225	N/A	N/A	N/A	N/A
1350974	RPN	405	45	225	25	25	225	225	45	45	45	ID test on bag film	RPN	45	45	45	25	25	225	45	45	45	45
1350975	RPN	405	45	225	25	25	225	N/A	N/A	N/A	N/A	ID test on bag film	RPN	45	45	45	25	25	225	N/A	N/A	N/A	N/A
1350976	RPN	729	81	405	81	45	225	405	81	N/A	N/A	satisfactory audit outcome	RPN	405	45	225	45	25	125	225	45	N/A	N/A
1351063	RPN	225	25	81	45	45	729	225	45	N/A	N/A	0	RPN	225	25	81	45	45	729	225	45	N/A	N/A
1351095	RPN	25	45	45	25	25	225	125	45	N/A	N/A	0	RPN	25	45	45	25	25	225	125	45	N/A	N/A
1351126	RPN	405	45	225	45	45	45	225	45	N/A	N/A	mass spectroscopy on storage solution	RPN	45	45	25	45	45	45	25	45	N/A	N/A
1351138	RPN	729	81	45	45	45	45	405	81	N/A	N/A	mass spectroscopy on storage solution	RPN	81	81	5	45	45	45	45	81	N/A	N/A
1351154	RPN	729	81	45	45	45	45	405	81	N/A	N/A	mass spectroscopy on storage solution	RPN	81	81	5	45	45	45	45	81	N/A	N/A
50500031	RPN	25	45	5	45	5	45	25	45	N/A	N/A	none	RPN	25	45	5	45	5	45	25	45	N/A	N/A
50500034	RPN	5	225	5	225	25	45	25	45	N/A	N/A	increase frequency of fiber release test	RPN	5	45	5	225	25	45	25	45	N/A	N/A
50500036	RPN	45	25	25	45	5	45	25	45	N/A	N/A	none	RPN	45	25	25	45	5	45	25	45	N/A	N/A
50500043	RPN	405	81	125	45	45	125	225	81	45	81	increase test frequency of TOC test	RPN	81	81	25	45	45	125	45	81	45	81
50500053	RPN	225	45	125	45	45	45	125	45	N/A	N/A	mass spectroscopy on storage solution	RPN	45	45	25	45	45	45	25	45	N/A	N/A
50500142	RPN	225	45	125	45	45	45	125	45	N/A	N/A	mass spectroscopy on storage solution	RPN	45	45	25	45	45	45	25	45	N/A	N/A
50500143	RPN	405	81	125	81	45	45	225	81	N/A	N/A	ID test on filter membrane	RPN	45	81	125	81	45	25	125	81	N/A	N/A
50500144	RPN	405	81	125	45	45	125	225	81	N/A	N/A	ID Test on filter membrane	RPN	81	81	25	45	45	125	45	81	N/A	N/A

Figure 39. Screenshot of the consumables risk assessment dashboard Excel worksheet. The color coded Risk Priority Number scores in the left-hand portion are as evaluated for all pilot articles. In the right-hand portion of the dashboard the expected scores are reported after planned mitigations are implemented. Each article can be expanded to show the Severity, Likelihood, and Detectability scores associated with each (as shown in the first 3 articles) or hidden to show only the RPN. The blue article code hyperlink loads the full risk assessment worksheet for the article when clicked.

Before Mitigations

	Leaching	Shedding	Foreign Chemicals	Foreign Particles	Microbiological	Functional Failure
N/A	40	40				
Low Risk	52	100	25	43	45	31
Medium Risk	12	0	10	1	3	6
High Risk	40	4	13	4	0	11

After Mitigations

	Leaching	Shedding	Foreign Chemicals	Foreign Particles	Microbiological	Functional Failure
N/A	40	40				
Low Risk	93	104	40	43	45	31
Medium Risk	5	0	6	1	3	7
High Risk	6	0	2	4	0	10

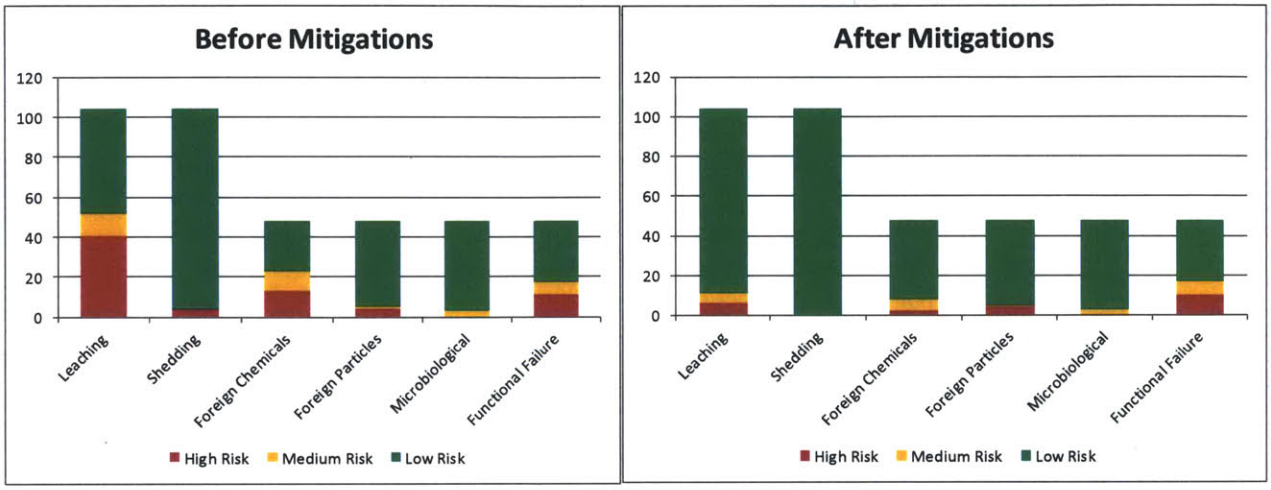


Figure 40. The statistics page of the dashboard counts the number of articles which fall into each of the priority levels and plots them in side-by-side histograms for managers to visualize the risk reduction before and after mitigations are implemented.

Appendix 2: Severity Factors Description and Rationale

Factors and rationale for the Function variable.

Function	Description	Factor	Rationale
Storage	The consumable is used to store a solution for longer than one day	1	The primary functions of a storage container are to prevent the solution from leaking out of the container and to protect the solution from external contaminants. In the case of containing the DS, a leak would mean the loss of product and the compromise of the purity of the product.
Bioburden Reduction	The consumable is used to reduce the bioburden of the solution. Does not include virus removal filters.	1	Bioburden reduction filters are based on size exclusion and are used throughout the system as a precaution against potential contaminants introduced through raw materials, other consumables, or the equipment. The failure of a bioburden reduction filter may allow a contaminant from raw materials or other consumables further down the product stream.
Virus Removal	The consumable is used to remove viruses in the protein pool. Also called nanofiltration	1	The virus removal filter is critical to the system for removing viruses which might have been present in the protein pool starting from cell culture. A failure in this filter will result in a viral contamination of the product.
UF/DF	The consumable performs ultrafiltration and diafiltration to remove impurities and concentrate the protein pool into the DS	1	The UF/DF membrane is critical to the system for removing small molecule impurities (salts, acids, bases, etc.) and for concentrating the DS into its delivery concentration. A failure in this filter will cause a contamination of the DS or affect the concentration of the formulation.
Clarification	The consumable is used to clarify the protein pool after cell culture by removing cell debris and other particulates	0.7	Clarification filters are intended to remove cell debris and other particulates from the protein pool directly after cell culture and centrifugation. A failure in the function of a clarification filter would lead to fouling of downstream filters but not a very large impact to product quality.

Function	Description	Factor	Rationale
Material Transfer	The consumable is used only to move material from one container to another (transfer tubes, connectors)	0.7	Consumables used for material transfer have an intermediate effect on product quality since a leak may mean loss of product or a small contamination from the environment.
RM dispensing	The consumable is used to gather, weigh, and dispense raw materials	0.3	The function of consumables used for dispensing of raw materials has a limited effect on product quality since a failure (e.g. leak) would not normally lead to a change in the amount of material dispensed.
Air filtration	The consumable is used for air filtration.	0.3	Air filtration has a limited effect on product quality since there is no direct product contact.
Sampling	The consumable is used to take a sample from the product stream	0.1	Consumables used for sampling have no effect on product quality since a failure in a sampling consumable would lead to another sampling.

Factors and rationale for the Material variable.

Material	Example materials	Leaching Factor	Shedding Factor	Rationale
Fiber without resin	Cellulose fibers	0.5	1	With no resin binder, bare fibers will not significantly leach. Fibrous materials may release fibers when flushed, leading to particulate content in the effluent.
Fiber with resin	Cellulose fibers with resin binder	1	1	Fibrous materials with resin binding agents may have a high degree of leaching especially if the resin does not covalently bind with the fibers themselves.

Material	Example materials	Leaching Factor	Shedding Factor	Rationale
Amorphous Polymer	Elastomers, PVC, PC, PS, PES	1	0.1	Amorphous polymers (including elastomers) leach more readily than crystalline polymers because the irregular structure does not hold chemicals as tightly. This is due to the additives in amorphous structures which are soluble and can be easily extracted compared to the additives in crystalline structures which are insoluble and not easily extracted. Polymers are not prone to shedding.
Crystalline Polymer	PE, PP, PET, PETG, PVDF, PTFE, HDPE, LDPE, EVAM	0.8	0.1	
Glass	Borosilicate	0.4	0.1	Glass is known to leach only in small amounts and in very harsh conditions and it is not expected to shed particulates into the system.
Metal	Stainless steel, aluminum	0.1	0.1	Metal does not readily leach or shed.

Factors and rationale for the Total Surface Area variable. In this table, the total surface area is the product of the number of this consumable used for a single batch and the surface area in contact with the solution (buffer, excipient, protein pool, or DS). If fluid recirculates through the consumable, it should be considered in the Total Surface Area.

Total Surface Area	Size Definition	Factor	Rationale
< 10 cm^2	Very small	0.2	Materials with large surface area in contact with the product have the potential to release more intrinsic chemicals (leaching) and particles (shedding). The leachables for any given material are generally proportional to its surface area. For extrinsic chemicals and particles, larger consumables have a greater capacity to hold contaminants, therefore their severity of potential contamination is higher.
10 to 100 cm^2	Small	0.4	
100 to 1,000 cm^2	Medium	0.6	
0.1 to 1.0 m^2	Large	0.8	
> 1.0 m^2	Very large	1.0	

Factors and rationale for the Toxic Chemicals at Supplier variable.

Toxic Chemicals at Supplier	Criteria	Foreign Chemical Factor	Rationale
Yes	The supplier uses Class 2 or Class 3 solvents, handles products of high activity or toxicity, or the product is sterilized with Ethylene Oxide.	1	The presence of these toxins at the supplier increases the potential toxicity of a foreign chemical in the case that the consumable is contaminated.
No	None of the above toxins are used.	0.8	

Factors and rationale for the Sterilization/Sanitization variable.

Sterilization/ Sanitization	Criteria	Intrinsic Factor	Micro-biological Factor	Rationale
Supplier Sterilization	The consumable is sterilized by the supplier	1	0.5	Sterilization breaks down the materials of the consumable making them more likely to leach or shed. Supplier sterilization reduces the microbiological risk some but insufficient dosage or sterile barrier breach could still allow microbiological contamination.
Internal Sanitization	The consumable is sanitized internally	1	0.3	Sanitization uses harsh chemicals which may break down the surface of the consumable increasing the rate of leaching and shedding.
Internal Sterilization	The consumable is sterilized internally by autoclave or sterilization in place	1	0.1	Sterilization breaks down the materials of the consumable making them more likely to leach or shed. Internal sterilization greatly reduces the microbiological risk significantly because there is less opportunity for post-sterilization contamination.

Sterilization/ Sanitization	Criteria	Intrinsic Factor	Micro-biological Factor	Rationale
None	The consumable is used non-sterile	0.9	1	The risk for leaching and shedding is slightly lower but the microbiological risk is higher with no sterilization.

Factors and rationale for the Usage Conditions variable.

Usage Conditions	Description	Leaching or Shedding Factor	Rationale
Filtration	The consumable's primary function is filtering the solution (filters)	1	The conditions acting on a material during filtration affect its rate of leaching and shedding. In a filter, pressures are generally high, and flow rates are high, leading to high leaching and shedding rates.
Storage	The consumable contains solution for greater than 1 day (bottles, bags)	1	In a storage container, the solution can be stored for a long period of time, leading to increased leaching and shedding rates. In many cases, storage containers have a broad range for the time a solution may be held and the worst case should be considered for this factor.
Flow through	The solution flows through the consumable but is not stored in it nor filtered by it (transfer tubes, connectors)	0.6	Consumables for which solutions just flow through have reduced risk for leaching and shedding since the pressures are not high and the solution does not contact the surfaces for a long duration.
Brief	The consumable only contacts the solution briefly (sampling or dispensing of raw materials)	0.2	Consumables with only brief contact have very little opportunity for leaching or shedding.

Factors and rationale for the Product Composition variable.

Product composition	Description	Leaching Factor	Shedding Factor	Rationale
Harsh Solutions	The consumable contacts harsh chemicals including strong acids (pH < 4) or bases (pH > 10), organic solvents, detergents, or high temperatures (>25°C)	1	1	Harsh chemicals promote leaching and shedding by breaking down weak chemical bonds at the surface of the consumables. High temperatures increase the rate of leaching and shedding due to higher chemical activity.
Mild Solutions	The consumable contacts solutions which are not harsh.	0.9	0.9	Mild solutions have a slightly reduced effect on leaching and shedding.
Solids	The consumable only contacts solids (e.g. powders).	0.5	1	Solids like powders have a very limited capacity to extract chemicals from a consumable. However, solids can have an abrasive effect on materials leading to high shedding quantities.

Factors and rationale for the Product Contact variable.

Product Contact	Description	Contamination Factor	Functional Factor	Rationale
Drug Substance	Consumable contacts the Drug Substance after UF/DF to filling in containers	1	1	Consumables which contact the excipient, protein pool, or DS have little opportunity for clearance, depending on the process step. Functional risk for the DS is highest because there are no downstream filters.
Excipient	Consumable contacts excipients	1	0.8	
UF/DF Buffer	Consumable contacts buffers used during the last purification step	1	0.8	

Product Contact	Description	Contamination Factor	Functional Factor	Rationale
Protein Pool	Consumable contacts the protein pool from centrifugation through the last purification step	1	0.8	
Purification Buffer	Consumable contacts buffers used during purification steps except the last one	0.7	0.5	Reduced risk of contaminating the final product since the buffers are not intended to remain in the DS. Most contaminants will be diluted and flushed from the system.
Raw Materials	Consumable contacts only raw material solutions or powders	0.7	0.5	Reduced risk of contaminating the final product since raw materials are not intended to remain in the DS (except excipients). Most contaminants will be diluted and flushed from the system.
USP Contact	Consumable contacts the product in upstream processes	0.5	0.3	Upstream contact carries very limited risk of quality problems in the DS since there is sufficient opportunity for clearance of contaminants and verification of protein quality.
None	Consumable has no contact with any of the above materials	0.1	0.1	Consumables with no contact have very limited impact to product quality.

Factors and rationale for the Flushed/Rinsed variable.

Flushed / Rinsed	Criteria	Intrinsic	Extrinsic	Rationale
Yes	The consumable is rinsed or flushed before use	0.9	0.5	Flushing is commonly used for filters, transfer tubes, and connectors to remove impurities. For filters, it has been shown to reduce the quantity of material leached from the consumable. For extrinsic materials, we can assume these are loosely bound to the external surfaces of the consumables and thus are more likely to be removed through rinsing.
No	The consumable is not rinsed or flushed before use	1	1	

Factors and rationale for the Downstream Filter variable.

Downstream Filter	Criteria	Particle Factor	Micro-biological Factor	Rationale
Yes	There is a size exclusion filter downstream to remove particulate and microbiological impurities	0.1	0.4	Size exclusion filters are efficient at removing particulates (including microorganisms) from the process stream. Therefore, if there is a filter downstream of the consumable in question the risk of particulate contaminants in the drug substance is greatly reduced. For microorganisms, the risk is reduced but not as significantly because microorganisms can release exotoxins into the process stream before they are filtered out.
No	There is no size exclusion filter downstream to remove particulate or microbiological impurities	1	1	

Appendix 3: Likelihood Factors Description and Rationale

Complexity factors for each consumable type.

Product sub-group	Factor	Rationale
Bags	1	Due to the multiple components and connections between them, and the manual processes required, the complexity is high.
Depth Filter	1	Many components and manual processes are required for the assembly of the depth filter.
UF/DF membrane	1	Several complex components and sensitive processes are required for the assembly of a UF/DF membrane.
Hollow fiber nanofilter	1	The components, materials, and manufacturing processes are highly complex for these hollow fiber filters.
Column filter cartridge	0.8	Many components and processes are required for the assembly of a column filter cartridge, but these are not as complex as depth filters.
Syringe filter	0.6	These filters are intermediately complex since they include several materials but are not highly sensitive.
Air filter	0.6	These filters are not complex since they include only a couple materials which are not highly sensitive.
Transfer sets and connectors	0.6	Transfer sets are intermediately complex since they require several materials and manual assembly processes.
Bottles	0.5	Bottles are not complex since their manufacturing processes are well known and only a couple materials are used.
Other	0.5	Other consumables include pipettes, syringes, dishes, stoppers, etc., which are not complex nor sensitive.

General quality system metrics and associated factors.

Question	Response and Factor	Rationale
Has the facility been audited by a local or international health authority?	Yes: 0.9 No: 1	An audit by a health authority provides evidence that the manufacturing site's quality systems have been tested and approved by an external body.
Has the facility been awarded any national or internationally recognized quality standard certification?	Yes: 0.9 No: 1	The quality system certification provides evidence that the manufacturing site's quality systems have been tested and approved by an external body.
Does the manufacturer manufacture other products than this in the facility?	Yes: 1.1 Same Family: 1 No: 0.8	A facility which is dedicated to one product will have a greater likelihood of producing high-quality consumables because of the reduced complexity of material handling, equipment change-over, and testing processes.
Is there an open complaint with this manufacturing site or are there ongoing actions linked to major or critical points?	Yes: 1.2 No: 1	A complaint to the manufacturing site indicates that there is a higher likelihood of an error occurring and not being discovered due quality systems of the site. Complaints which have been closed indicate improved quality systems.
What was the outcome of the last Novartis audit?	Good: 0.6 Satisfactory: 1 At risk: 1.4 None: 1.2	A recent Novartis is a good indicator of the quality systems of the manufacturing site. A good outcome is only given to sites with exceptional performance. A satisfactory outcome provides evidence that the general quality systems of the site are acceptable. An "at risk" outcome indicates that there are significant quality issues that could affect product quality. Not having an audit on file also increases the risk of a future non-conformance.

Specific quality controls and associated factors for the Likelihood calculation.

Question	Response and Factor	Rationale
Does the manufacturer use dedicated equipment for the production of this product?	Yes: 0.8 Same Family: 1 No: 1.2	The use of dedicated equipment for this product reduces the opportunity for cross-contamination with unqualified materials (extrinsic contamination) and improves the functional quality of the articles. Most manufacturers use dedicated equipment for a family of products.
Does the facility test all raw materials?	All: 0.8 Some: 1 No: 1.2	The testing of all incoming raw materials reduces the risk of contaminated materials which may comprise the consumable. Most manufacturers test some of their raw materials.
Is this product manufactured in a cleanroom environment?	Yes: 1 No: 1.2	The manufacture of a consumable outside a cleanroom environment increases the risk of particulates attaching on the surfaces of the consumable. Most suppliers manufacture their product in a cleanroom.
Does the facility monitor the equipment surfaces microbiologically?	Yes: 0.9 No: 1	The proactive monitoring of equipment surfaces for microbiology reduces the risk of microbiological cross-contamination.
Are there cleaning procedures in place for each area and piece of equipment?	Yes: 1 No: 1.2	Not having cleaning procedures for environment and equipment increases the likelihood for a foreign chemical or particulate to become attached to the consumable. Most suppliers have cleaning procedures in place.
Does the site have procedures that define the control of raw materials?	Yes: 1 No: 1.2	Not having procedures for raw material control increases the risk of intrinsic contaminations because it increases the risk of mixup or handling errors with the raw materials that comprise the consumable. Most suppliers have these procedures.
Are the manufacturing processes validated?	Yes: 1 No: 1.2	Not having validated manufacturing processes increases the likelihood of producing consumables with functional errors because the validation process tests the procedure for the various process conditions which affect the consistency and quality of production. Most suppliers have validated manufacturing processes.
Are the cleaning processes validated?	Yes: 0.8 No: 1	Validated cleaning procedures will remove extrinsic contaminations from the surfaces of the consumable. The validation will typically include confirmation of the removal of chemicals and particles the consumable is generally exposed to during manufacturing. Many manufacturers do not have validated cleaning procedures.

Appendix 4: Detectability Factors Description and Rationale

Detectability scores for various tests and inspections. These scores assume the test article is 100% or a representative batch sample of the consumable lot.

Test Description	Score By Failure Mode		Rationale
Direct functional test (e.g. leak test for bags; bacteria retention or post-use integrity tests for bioburden reduction filters, Gold Nanoparticle test for nanofilter, solute marker passage test for UF/DF membranes)	Leaching		Direct tests determine the performance of the consumable against a standard which is representative of its functional use for the manufacturing process. For filters, direct tests evaluate the ability of the filter to capture particles or solutes (e.g. bacterial retention test, solute marker test, or gold nanoparticle tests). Some filters can also be directly tested by a post-use integrity test in which pressure is measured across the filter (this is considered direct because it confirms no microbiological particles could have traversed the filter). For bags, a pressure leak test is a direct test for functionality.
	Shedding		
	Foreign Chem.		
	Foreign Particle		
	Microbiological		
	Functional	1	
Indirect functional test (e.g. pressure drop test for filters)	Leaching		Indirect tests ensure against failures which may compromise the quality of the product but are not testing the direct function of the consumable. For example, filters may undergo a pressure drop test as an indirect method of testing for porosity and leaks. It does not directly test for the effectiveness of the filtration membrane.
	Shedding		
	Foreign Chem.		
	Foreign Particle		
	Microbiological		
	Functional	5	
Dimensional inspection	Leaching		An inspection for key dimensions can detect non-conformances which may affect the fit of two parts together. Ill-fitting parts are likely to leak, leading to a functional failure. This is an applicable test in some cases, but not highly sensitive.
	Shedding		
	Foreign Chem.		
	Foreign Particle		
	Microbiological		
	Functional	5	
Total organic carbon and conductivity test on flush (USP <643> and <645>)	Leaching	1	The Total Organic Carbon and Conductivity Tests (USP <643> and <645>) repeatably detect organic and ionic chemical impurities down to 500 ppb. If performed on a flush of a filter with an appropriate volume, it will be able to detect a very small volume of contaminant which may have product quality impact. This is an applicable test for chemicals and highly sensitive.
	Shedding		
	Foreign Chem.	1	
	Foreign Particle		
	Microbiological		
	Functional		

Test Description	Score By Failure Mode		Rationale
Oxidizable substances test on flush (legacy USP test)	Leaching	1	The USP Oxidizable Substances Test is designed to detect chemical impurities of organic nature down to 500 ppb. If performed on a flush of a filter with an appropriate volume, it will be able to detect a very small volume of contaminant which may have product quality impact. This is an applicable test for chemicals and highly sensitive.
	Shedding		
	Foreign Chem.	1	
	Foreign Particle		
	Microbiological		
	Functional		
Extractable ions test	Leaching	5	The extractable ions test will detect ions which are extracted in solvents. It is only moderately sensitive because the acceptable range is large (1300 to 1800 mg/kg Ca for example) and it does not detect organic extractables.
	Shedding		
	Foreign Chem.	5	
	Foreign Particle		
	Microbiological		
	Functional		
Organic weight (0.25% max), Ca, Fe, and Color after flush	Leaching	5	The organic weight test will detect intrinsic and extrinsic chemicals of organic origin. The test limit is high (0.25%) and thus its sensitivity to detect small impurities is limited.
	Shedding		
	Foreign Chem.	5	
	Foreign Particle		
	Microbiological		
	Functional		
Visual inspection for particles and chemicals (no flush)	Leaching		A visual inspection on the consumable may detect foreign substances which are adhered to the surfaces of the consumable. Not all contaminants can be detected in this method since some interior surfaces are not accessible nor are all contaminants visible from the outside.
	Shedding		
	Foreign Chem.	5	
	Foreign Particle	5	
	Microbiological		
	Functional		
Visual inspection for particles after flush	Leaching		A visual inspection for particulates in a solution after a flush can detect internal foreign particles and those caused by shedding. The test is not highly sensitive when done visually.
	Shedding	5	
	Foreign Chem.		
	Foreign Particle	5	
	Microbiological		
	Functional		
Particle count by machine or visual under microscope after flush	Leaching		The particle count test will successfully detect extrinsic particles upon a flush since these are readily dislodged after a flush. It is less sensitive for detecting particulates from shedding because shedding usually occurs only in extreme conditions (long-term storage, abrasion, high pressure).
	Shedding	5	
	Foreign Chem.		
	Foreign Particle	1	
	Microbiological		
	Functional		

Test Description	Score By Failure Mode	Rationale
LAL endotoxin test or Bioburden test by ISO 11737 method by filtration	Leaching Shedding Foreign Chem. Foreign Particle Microbiological 1 Functional	The LAL endotoxin test is standard for detecting gram negative bacterial contaminations after sterilization. The bioburden test using growth on a filter flushed from an extract is also sensitive to microbiological contaminants.
Membrane fiber release test	Leaching Shedding 1 Foreign Chem. Foreign Particle Microbiological Functional	This test is performed on membrane samples to ensure no fibers are released. This test is applicable for shedding of fibrous materials. 21 CFR 210.3 (b) (6): "Nonfiber releasing filter means any filter, which after appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered."
Non-volatile residue, residue on ignition, heavy metals tests	Leaching 5 Shedding Foreign Chem. 1 Foreign Particle Microbiological Functional	These USP <661> tests are performed internally for the detection of extrinsic and intrinsic chemicals. The acceptance limit for non-volatile residues is 15 mg, and for residue on ignition is 5 mg for small samples which is not highly sensitive. The heavy metals test limit is approximately 10 ppm, which is sufficiently sensitive, but only for heavy metals. Since the test is not performed on a leaching sample, its detection sensitivity for leachates is low.
External spectroscopy material ID test	Leaching 1 Shedding 5 Foreign Chem. Foreign Particle Microbiological Functional	External spectroscopy testing for the verification of the identity of the material directly tests the major components of the material which may lead to leaching. It also tests the components of the material which may lead to shedding, but it is not a direct test for shedding since non-material identity properties can lead to shedding. It is not applicable for extrinsic chemical and particulate contaminations.

Test Description	Score By Failure Mode		Rationale
Mass spectroscopy peak confirmation on extract or flush	Leaching	1	A mass spectroscopy peak identification test is suitable for detecting leachates and foreign chemicals which are extracted from a consumable. For this test to be sensitive, the consumable must be extracted in a suitable solvent. After performing a mass spectroscopy on the extract, the peaks detected from the test article are compared to those detected for a standard. It is sensitive to contaminants down to 100 ppm.
	Shedding		
	Foreign Chem.	1	
	Foreign Particle		
	Microbiological		
	Functional		