

# Reducing Complexity In Biomanufacturing Operations Through Single-Use Assemblies

by

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B.S. Chemical Engineering, Columbia University, 2005

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


Master of Business Administration  
and  
Master of Science in Chemical Engineering

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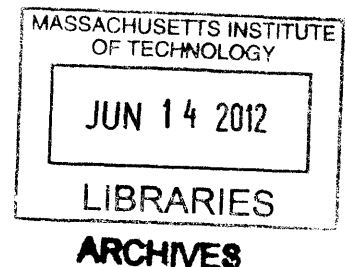
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## **Abstract**

Novartis Vaccines and Diagnostics operates a centralized equipment cleaning and preparation suite at a vaccine production facility in Marburg, Germany. The ~100 pieces of multi-use stainless steel, glass, and plastic equipment prepared at this centralized pretreatment suite all need to be disassembled, cleaned, reassembled, sterilized, shipped, and tracked. This highly complex cycle is problematic because of the coordination cost, possibility of assembly errors, and lack of operational flexibility. Additionally, the multi-use assemblies were designed as long as 20 years ago, and newer, more reliable alternatives exist.

The goal of this project is to evaluate the hypothesis that replacing multi-use assemblies with single-use assemblies will reduce production risk and costs of goods sold of vaccines by reducing operational complexity.

To understand the impact of adopting single-use assemblies, the one-time cost of switching (e.g. regulatory filings, validation studies, operational costs) are weighted against the potential for operational savings and risk reduction or transfer to vendors. The current-state variable costs and risks are evaluated with a cost model that accounts for variable equipment cost, operator cost, autoclave cost, and washer costs. Future state variable costs are determined through a request for proposal (“RFP”) process with vendors. Novartis Vaccines and Diagnostics had previously conducted failure mode and effect analyses (“FMEA’s”), and the critical and potentially critical risks affected by adopting single-use assemblies were reassessed.

It is possible to reduce the complexity of pretreatment operations with single-use assemblies. Adopting the four of the assemblies studied in this project would reduce the number of components processed in a year by 40% and the number of unique components by 10%. Many critical or potentially critical risks, such as labeling, assembly, sterilization, transportation, and storage of assemblies will be transferred to third-party vendors. Because these vendors specialize in the production of single-use assemblies, they can invest in more costly capital equipment and processes such as higher class clean rooms and gamma sterilization. Some single-use assemblies will have a lower variable operating cost, while others will increase operating costs. Thus, new assemblies fall into three categories in a decision making framework: 1) Reduced risk and cost, 2) Pay for risk reduction, and 3) Continue with current state. Assemblies in categories 1 and 2 should be modernized from multi-use to single-use, while assemblies in category 3 should remain multi-use.

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To my parents, **Marjorie Alfano** and **Ronald Alfano** – your steadfast commitment to our family is an inspiring role model for me. The values and skills you taught me during our years of homeschooling and discussions around the dinner table or on family vacations are fundamental to all of my achievements, including this thesis.

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# **1 Introduction and Thesis Overview**

## **1.1 Problem Description and Motivation**

While traditional biomanufacturing facilities have relied almost entirely on multi-use stainless steel, plastic, or glass equipment, single-use systems are increasingly common in modern facilities. Indeed, literature on the topic states that 86% of contract manufacturing organizations and 63% of product manufacturers have improved facility performance via single-use devices (Langer, 2011). Often cited examples of improved performance include reduced processing time and greater manufacturing capacity, reduced capital equipment expense, reduced process development time, reduced validation time and cost, and reduced product change over time (Fuller & Pora, 2008).

Disposable, or single-use, systems can be integrated into operations to a widely varying extent. The positive extreme is a new facility laid out to exploit all the advantages of single-use systems. Such a design would reduce or eliminate autoclave suites, washing machines suites, and high-quality utilities but would add bag handling systems and tube fusers (Hitchcock, 2010) (Peuker & Peuker, 2011). The facility would be simpler to operate than a traditional facility. While a traditional facility has mobile equipment that is constantly cycling through washing, preparation, sterilization, and production suites, the facility designed for single-use systems merely disposes of used equipment and installs new equipment for each use. Similarly, traditional facilities require a clean-in-place and sterilize-in-place cycle for permanent, stainless steel equipment between manufacturing runs, while a facility designed for disposable systems would simply swap out used liner bags and tubing manifolds for new ones. Several authors claim savings in capital expense of up to 41% and cost of goods sold reduction of up to 17% for these facilities (Sinclair & Monge, 2005). The advantages of single-use systems are most pronounced in clinical stage manufacturing facilities that are originally designed for single-use systems and in which new products and production processes are developed every year. Such facilities can realize the advantages of accelerated product change over and faster process development times.

However, many biomanufacturing facilities were designed for multi-use systems and manufacture an unchanging set of commercial stage products. These facilities are the negative extreme for single-use systems. They already contain the washer and autoclave suites and clean utilities required to process multi-use equipment and perform clean-in-place and sterilize-in-place services. Thus, legacy plants cannot easily realize the reduced capital equipment opportunity presented by single-use systems.

Likewise, if the facility is dedicated to a single product, it would not benefit as significantly from faster product change over. Finally, due to the extensive regulation of biopharmaceutical products, these facilities have high switching costs to adopt single-use systems. For example, numerous validation studies, regulatory filings, and operational changes are required to make this type of process change. Thus, it is not clear if the often cited advantages of single-use assemblies are applicable to these facilities.

This thesis aims to evaluate the opportunity for legacy facilities designed for multi-use equipment to adopt single-use assemblies. The thesis does not examine the impact of changing large equipment such as seed trains, bioreactors, stainless steel compounding vessels, or fillings lines. Rather, process changes are evaluated that do not require renovations to the building layout, such as replacing multi-use mobile equipment with single-use equipment. Examples of this equipment include bioprocess containers, upstream filter systems for the preparation of media and buffers, and tubing manifolds. Adopting single-use mobile equipment would reduce the load on washers and autoclaves, saving the variable cost of running the equipment. However, no major re-organization is assumed, so the facility will continue to bear the fixed costs of this equipment. Other operational savings will be realized in assembly time, process utility demand, and validation.

## **1.2 Thesis Statement**

This thesis document explores the hypothesis that the adoption of single-use mobile equipment such as bioprocess containers and upstream filter systems at a facility designed to process multi-use assemblies will result in a meaningful reduction in the complexity of operations, thereby reducing costs and improving product quality.

### **1.3 Thesis Contributions**

The literature contains many comparisons of facilities designed for multi-use assemblies versus single-use assemblies (Sinclair & Monge, 2005). However, this comparison is only relevant for a manager considering the design of a new facility. These new builds will be a small segment of global biomanufacturing capacity for many years to come. Thus, an evaluation of the impact of migrating from multi-use assemblies to single-use assemblies at an already operating facility addresses a gap in the literature.

### **1.4 Organization of Thesis Document**

This thesis is organized in six chapters

**Chapter 1: Introduction and Thesis Overview.** This chapter introduces the problem that the thesis addresses as well as the thesis hypothesis itself.

**Chapter 2: Company Background and Project Context.** This chapter discusses the aspects of operations at the Novartis Vaccines and Diagnostics Marburg complex that are relevant to the project.

**Chapter 3: Analytical Methodology.** This chapter describes the analytical approach used to evaluate the hypothesis.

**Chapter 4: Results.** This chapter presents the results of the method described in the previous chapter.

**Chapter 5: Conclusions and Recommendations.** This chapter discusses the results and implications for Novartis Vaccines and Diagnostics, including recommendations for changes in operations and additional study.

**Chapter 6: Bibliography.** This chapter reports the references cited in the thesis document.

### **1.5 Confidentiality**

The majority of the data gathered and analyzed for this thesis are confidential. Thus, sensitive cost data have been withheld from publication. Throughout this thesis document, the current state cost data have been generated to illustrate the analytical method and are not representative of the true costs borne by Novartis Vaccines and Diagnostics. The switching cost data presented are the author's best estimate of true costs.



## 2 Company Background and Project Context

### 2.1 Novartis Vaccines and Diagnostics

Novartis Vaccines and Diagnostics is the 5th largest vaccine company worldwide. It generated \$2.9 billion in revenue and \$1.1 billion in core operating income in 2010. The company employs ~5,400 employees and has major production facilities in America, England, Germany, India, and Italy. Novartis Vaccines and Diagnostics is a business unit of Novartis Group (Novartis Group, 2010).

### 2.2 Marburg Manufacturing Complex

The Marburg manufacturing complex produces a variety of vaccines for both bacterial and viral infectious diseases such as diphtheria, pertussis (whooping cough), rabies, seasonal influenza, tetanus, and tick borne encephalitis. The complex consists of three separate facilities, and the Goerzhausen II facility, pictured below in Figure 1, is the host for this thesis.



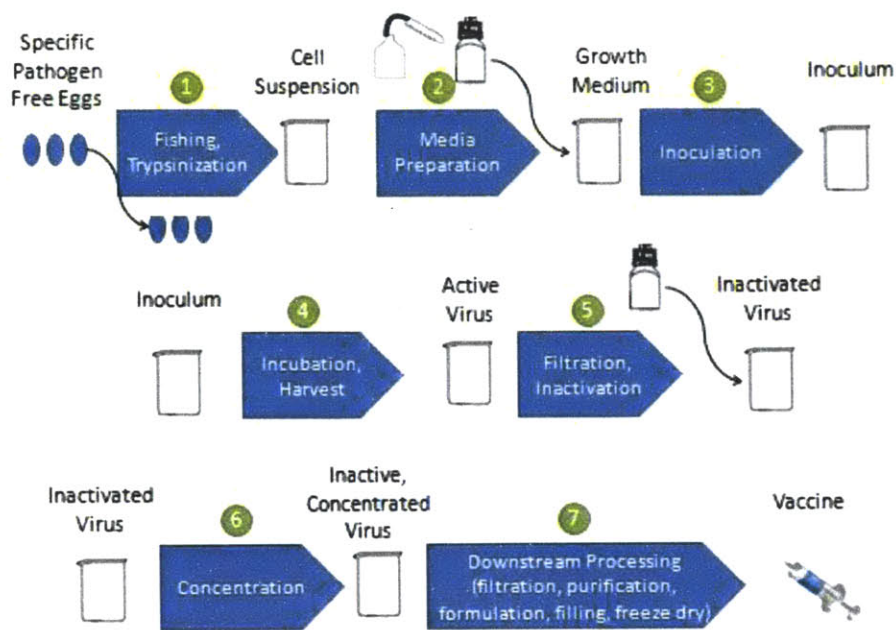
**Figure 1, Aerial Photograph of Goerzhausen II Facility**

The Goerzhausen II facility has a centralized pretreatment suite to process mobile, multi-use equipment. The processing cycle for multi-use equipment is described in Section 2.5, Mobile Assembly Process Flow

Diagram. This facility also houses a centralized media and buffer preparation area, a warehouse, production lines for tick borne encephalitis and rabies vaccines, and a production line for inorganic adjuvant. The pretreatment suite and the media and buffer preparation suites service both Goerzhausen II and the other facilities in the Marburg manufacturing complex.

### **2.3 Vaccine Manufacturing Process Overview**

The vaccine production process is typically described as consisting of upstream processing, downstream processing, formulation, and fill / finish (National Institute for Bioprocess Research and Training, 2012). Upstream processes include fishing (for egg-based vaccines), media preparation, inoculation, incubation, harvest, inactivation, and concentration, as depicted in Figure 2, Upstream Vaccine Manufacturing Schematic. Upstream processing yields a crude form of the antigen(s) that will be part of a vaccine. Downstream processing consists of filtration and purification unit operations such as various chromatography methods, and yields purified antigen. Formulation is the process of combining drug substances such as antigens and buffers to make the final drug product. Fill / finish is the process of filling a vial or syringe with the drug product, and produces a salable product (National Institute for Bioprocess Research and Training, 2012).



**Figure 2, Upstream Vaccine Manufacturing Schematic**

Figure 2, Upstream Vaccine Manufacturing Schematic, depicts an example of the upstream production process for rabies vaccine and was chosen to illustrate an egg-based production process. As it shows, mobile equipment is necessary to support the production process at several unit operations. For example, the growth medium is made by adding human albumin, polygeline, and antibiotics to the cell suspension. This process requires mobile bioprocess containers to transfer the cell suspension and the other components of the growth medium. Similarly, mobile bioprocess containers are required to handle the  $\beta$ -propiolactone that is used for virus inactivation (Food and Drug Administration, 2012).

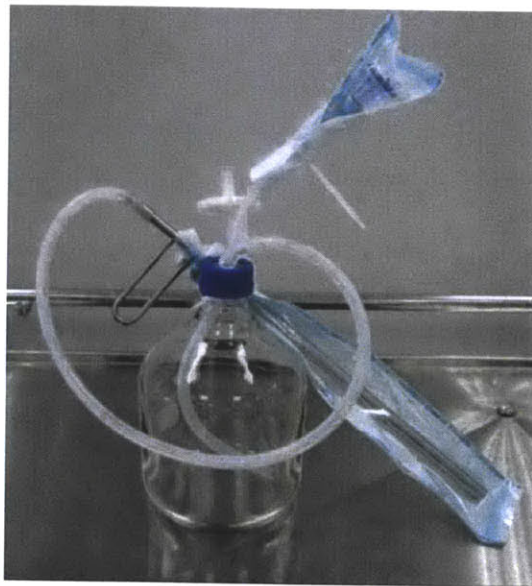
## 2.4 Description of Assemblies and Their Use

This thesis document evaluates the opportunity to replace six multi-use mobile assemblies with single-use assemblies. These six assemblies were prioritized from the complete set of ~200 assemblies on the basis of their comparatively higher variable cost or risk. They were also selected as representative examples of a broad set of assemblies, so that conclusions reached for these six assemblies could be extended to other similar assemblies. Four of these six assemblies are used in the rabies vaccines production process and

potentially for the production of other vaccines. Figure 2 is referenced in the introduction of these four assemblies to illustrate their position in the overall upstream manufacturing process.

#### **2.4.1 Cell Suspension Transfer Assembly**

Figure 3 below depicts an assembly used to transfer the cell suspension from one room to another. It is used in process step #2 shown in Figure 2, Upstream Vaccine Manufacturing Schematic. To fill the bioprocess container, the stainless steel pipette is inserted into a bottle containing the cell suspension and a slight vacuum is applied to the bottle, causing the cell suspension to be drawn up the pipette and into the container. The tubing is then sealed and the bottle is transferred aseptically to the next room for processing.

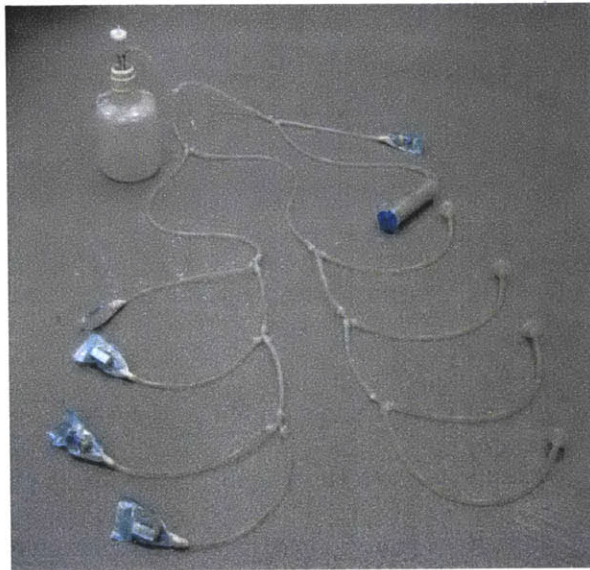


**Figure 3, Cell Suspension Transfer Assembly**

#### **2.4.2 Filter System**

The centralized media and buffer suite at Goerzhausen II prepares numerous solutions for use in several production processes. These solutions are typically mixed in batches 100's of liters large, and the filter system pictured in Figure 4, is used to process these large batches. The media and buffers are filtered to ensure their quality, and the first run of the filter is collected in the Nalgene bottle for disposal. The

remaining solution is then directed through the tubing manifold and aliquotted into smaller containers for use in the production process. For the rabies vaccine production process, medium 3, which is used in process step #3 in Figure 2, is prepared in this way. The filter system is used to process several other media and buffers as well.

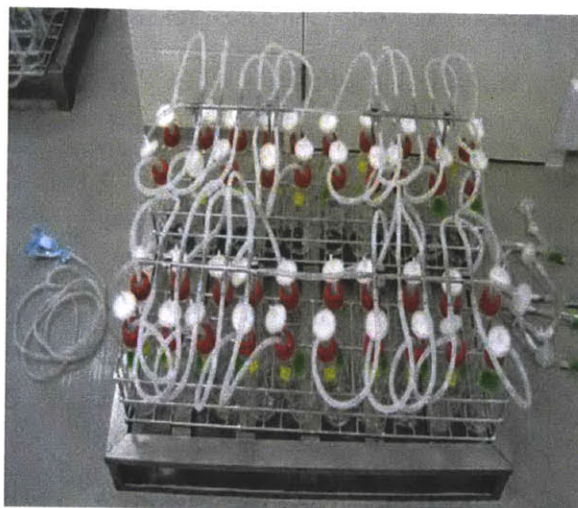


**Figure 4, Filter System**

### **2.4.3 Glass Bottles Assembly**

Figure 5 below pictures the glass bottles assembly. This equipment consists of glass bottles that contain media or buffers for use in the production process, a tubing manifold with silicon siphons that aliquots a large batch of media or buffers into the glass bottles, and sample flasks for quality control testing.

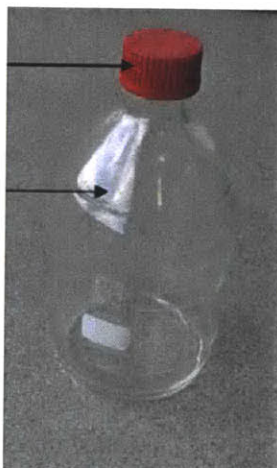
Trypsinization medium is filled into this assembly and is used in process step #1 in Figure 2, Upstream Vaccine Manufacturing Schematic, to remove the extracellular matrix encasing the cells so that they behave properly during the inoculation and incubation process. Other media and buffers are also filled into the assembly for rabies and other vaccine production.



**Figure 5, Glass Bottles Assembly**

#### **2.4.4 Simple Glass Bottle**

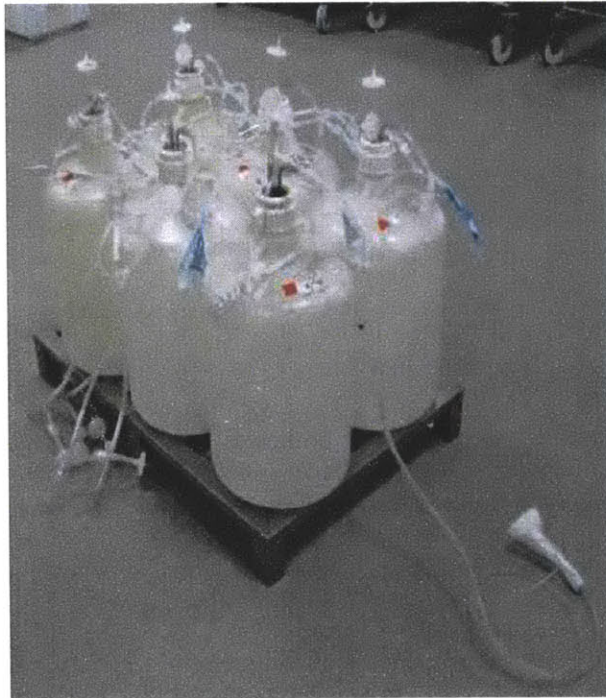
The simple glass bottle depicted in Figure 6 below is used in 28 distinct processes at the Marburg complex. Three of these processes relate to rabies vaccine production: this bottle is filled with tryptose phosphate solution, an ingredient of medium 3; phenol red, a pH indicator; and phosphate buffered solution, a pH buffer.



**Figure 6, Simple Glass Bottle**

#### **2.4.5 Nalgene Bottles Assembly**

The Nalgene bottle assembly depicted in Figure 7 below is used in the production process for tick borne encephalitis vaccine, but it is not used for rabies vaccine manufacturing. Like the glass bottles with silicon siphons assembly, this assembly consists of containers, a tubing manifold, and sample flasks. Growth media is filled into this assembly and is used during the incubation process for tick borne encephalitis vaccine manufacturing.



**Figure 7, Nalgene Bottles Assembly**

#### **2.4.6 Diphtheria Crude Toxoid Assembly**

The diphtheria crude toxoid container pictured in Figure 8 below is used in the production process for diphtheria vaccine, but it is not used in the rabies vaccine production process. It consists of a filter housing with filter cartridge, 50 liter concentrate bottle, and two sample flasks. Pre-washed diphtheria toxoid is filtered through the capsule then filled into the 50 liter container. Samples are taken after filtration for quality control analysis.

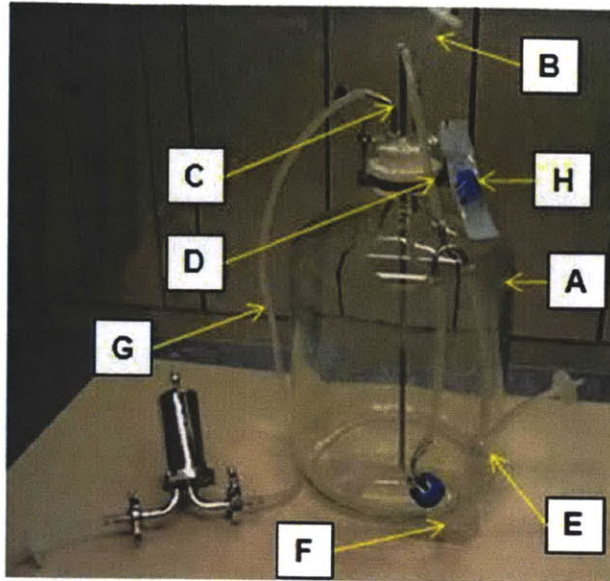


Figure 8, Diphtheria Crude Toxoid Assembly

## 2.5 Mobile Assembly Process Flow Diagram

All of the multi-use assemblies processed in the pretreatment suite of the Goerzhausen II facility, including the multi-use assemblies introduced in Section 2.4, cycle through the facility according to the process described in Figure 9, Process Flow Diagram of Multi-Use Assemblies.

- Step #1: A customer uses the assembly, making it dirty, which is indicated by red shading for the assembly.
- Step #2: The pretreatment suite disassembles the dirty equipment.
- Step #3: Dirty multi-use components are loaded onto wash carts in a validated loading pattern, and single-use components are disposed of.
- Step #4: The wash carts are placed in the washing machine, and the components are cleaned, as indicated by the white components.
- Step #5: The clean components are put together into the assembly that will be used by a customer. New single-use components are added from storage where appropriate.



- Step #6: The completed assemblies are loaded onto an autoclave cart and sterilized, indicated by the green shading of the assembly.
- Step #7: The assemblies are packed and shipped to a warehouse or customer for use.

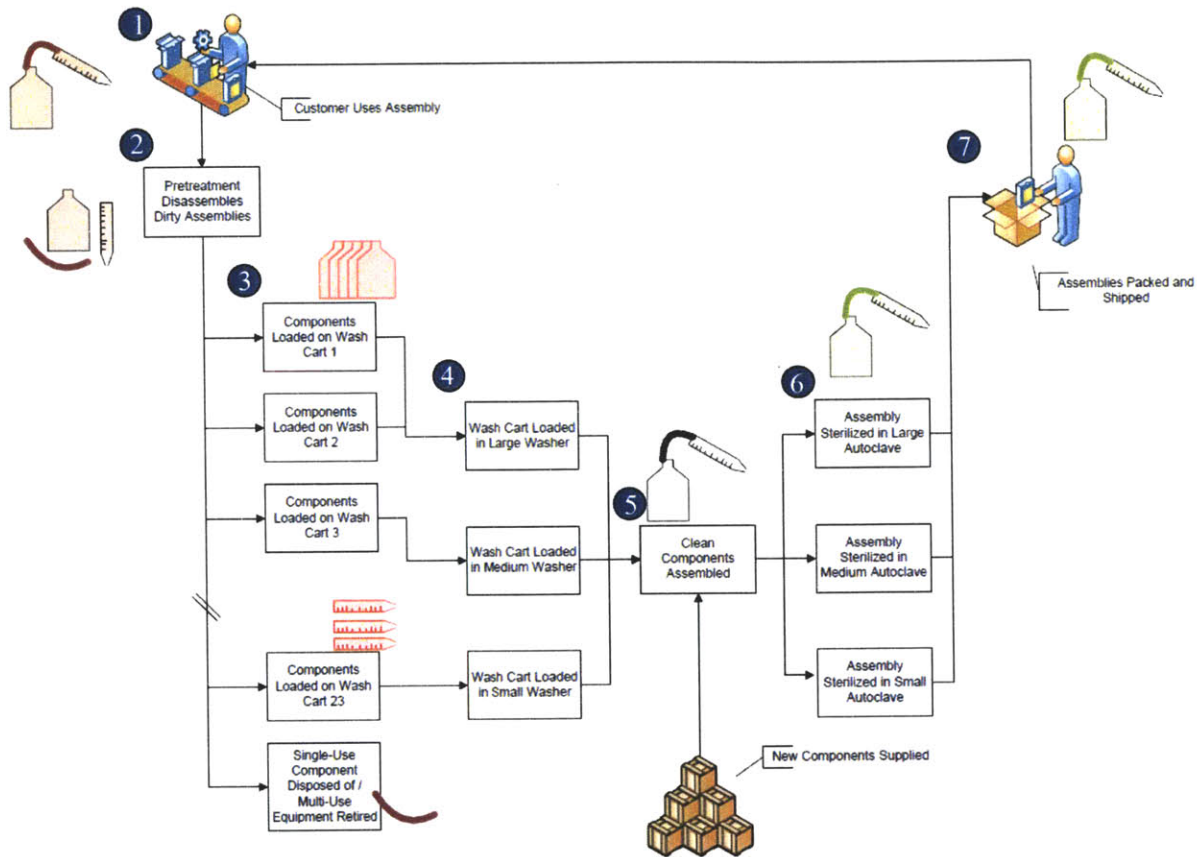


Figure 9, Process Flow Diagram of Multi-Use Assemblies

### **3 Analytical Methodology**

#### **3.1 Overview of Approach**

Novartis Vaccines and Diagnostics faces a choice for every multi-use assembly processed at Goerzhausen II, including the six assemblies introduced in Section 2.4. Given the constraints of this project, that choice is limited to two options: 1) continue using the incumbent, multi-use assembly or 2) replace the incumbent, multi-use assembly with a single-use alternative. Either choice imposes certain costs and risks on the company.

- Choice 1, the current state, requires operating the pretreatment suite to disassemble, wash, reassemble, sterilize, and ship equipment.
- Choice 2, the potential future state, entails certain switching costs to change the production process and relies on third party vendors to supply the new, single-use assemblies.

Thus, the company faces a tradeoff of paying one-time switching costs to realize potential operational savings and risk reduction.

The relevant financial figure of merit for both the current state and future state is the yearly variable operations cost. The capital expense for the pretreatment suite and equipment like washers and autoclaves is already committed, and the company will incur the sunk costs associated with the pretreatment suite such as depreciation of the washers, autoclaves, and clean utilities if it selects choice #1 or choice #2. Because of the design of the facility and the production process, the pretreatment suite cannot be repurposed easily to meet some other business need. Furthermore, it is beyond the scope of this project to redesign the facility to use only disposable mobile equipment. Thus, these sunk, or fixed, costs associated with the pretreatment suite should not be considered when evaluating the choices. Stated another way, if several or even the majority of the multi-use assemblies are replaced with single-use assemblies, the fixed costs allocated to the multi-use assemblies will simply be redistributed over a smaller number of assemblies.

Novartis Vaccines and Diagnostics uses a Failure Mode and Effect Analysis (“FMEA”) risk assessment tool, a method originally pioneered by the United States military. FMEA is a reliability task that should be implemented during the design phase of a mission or production process. It is a method to “systematically evaluate and document, by item failure mode analysis, the potential impact of each functional or hardware failure on mission success, personnel and system safety, system performance, maintainability, and maintenance requirements” (Department of Defense, 1980). This thesis project relied on recently conducted FMEA’s and a re-evaluation of risks associated with the potential future state.

Depending on circumstances, other figures of merit may be relevant to evaluate. For example, if the market demand for a particular product exceeds a company’s production capacity, the adoption of single-use assemblies may not only improve operational costs and risk but also allow the company to generate more revenue. This additional revenue would be realized if a production constraint could be relaxed by adopting single-use assemblies. Such an advantage is not relevant for the Goerzhausen II facility because its output capacity significantly exceeds market demand for its products.

## **3.2 Current State Assessment**

### **3.2.1 Current State Cost Assessment**

As explained in Section 3.1, the key financial figure of merit is yearly variable operations cost. This cost can be calculated for a single assembly in the current state using the two equalities reported in Equation 1, Yearly Variable Operations Cost.

$$\begin{aligned}
 \text{Yearly Variable Operations Cost} &= [\text{Standard Variable Cost}] \times \text{Yearly Volume} \\
 &= [\text{Standard Variable Labor Cost} + \text{Standard Variable Materials Cost} \\
 &+ \text{Standard Variable Washer Cost} + \text{Standard Variable Autoclave Cost}] \times \text{Yearly Volume}
 \end{aligned}$$

**Equation 1, Yearly Variable Operations Cost**

The yearly variable operating cost is calculated by multiplying the standard variable cost of preparing the assembly once with the yearly volume of the assembly. The second equality shows that the standard variable cost of preparing the assembly once consists of four components:

- Standard variable labor cost, as described in Equation 2
- Standard variable materials cost, as described in Equation 3
- Standard variable washer cost, as described in Equation 4
- Standard variable autoclave cost, as described in Equation 5

There are many ways to account for costs, and this method is based on Novartis Vaccines and Diagnostics management's accounting. It is a helpful method because it makes apparent the costs for key activities in the pretreatment suite. Other, equally valid approaches exist.

Equation 2 below reports the standard variable labor cost for each assembly. This cost is calculated by summing the time required for all of the processing steps with the variable cost of labor.

$$\begin{aligned}
 &\text{Standard Variable Labor Cost} \\
 &= \left[ \begin{array}{c} \text{Time for Disassembly, Cleaning, Endoscopy, Assembly, Filter Test, Integrity Test,} \\ \text{Autoclave, Wrapping, Transportation} \end{array} \right] \\
 &\times \text{Variable Cost of Labor}
 \end{aligned}$$

**Equation 2, Standard Variable Labor Cost**

Equation 3 below reports how to calculate the standard variable materials cost for each assembly.

*Standard Variable Materials Cost*

$$= \sum_{\text{All Components } i \text{ in Assembly}} \frac{\text{Cost Per Component } i \times \text{Number of Units of Component } i \text{ in Assembly}}{\text{Number of Times Component } i \text{ is Used Before Retirement}}$$

**Equation 3, Standard Variable Materials Cost**

This equation takes the cost of buying the component, multiplies it by the number of those components used in an assembly, and divides it by the number of times that component is used before retirement. For example, the equation can be applied to air vent filters for the glass bottles assembly in Figure 5 as follows:

- Cost per air vent filter = €2.56
- Number of air vent filters in assembly = 49
- Number of times air vent filter is used before retirement = 1
- Cost of air vent filters for this assembly = €2.56 X 49 / 1 = €125.44

This computation must be completed for each component in an assembly to yield the standard variable materials cost for the assembly.

Equation 4 below reports the method to compute the standard variable washer cost for each assembly.

*Standard Variable Washer Cost*

$$= \sum_{\text{All Components } i \text{ in Assembly}} \frac{\text{Component } i \text{'s \% of Wash Cart} \times \text{Variable Cost of Full Wash Cart Load}}{\text{Expected Wash Cart Utilization}}$$

**Equation 4, Standard Variable Washer Cost**

In this formula, Variable Cost of Full Washer Cart Load includes utilities, waste disposal, maintenance, and validation variable costs. The computation must be run for every component of a given assembly.

The washing process is highly regulated, and Novartis Vaccines and Diagnostics is required to validate the washing process for the worst-case load for each wash cart. Figure 10 and Figure 11 below show the validated worst-case load for two wash carts. The worst case load is a wash cart completely full of soiled equipment. In practice, the wash carts will typically be run partially loaded, so if the cleaning process is effective for a worst-case, or full load, it is also validated for a partial load. Wash carts are run partially loaded because the soiled equipment has a maximum dirty hold time and the number of each component circulating in the facility requires prompt washing.

Equation 4, Standard Variable Washer Cost can be applied to the 3 liter glass flask represented by the large yellow bottle in Figure 10 as described below.

- 3 liter glass flask's percent of wash cart: 6%
- Variable cost of full wash cart load: €213.15
- Expected wash cart utilization: 50%
- Standard variable washer cost for 3 liter glass flask = 6% X €213.15 / 50% = €23.67

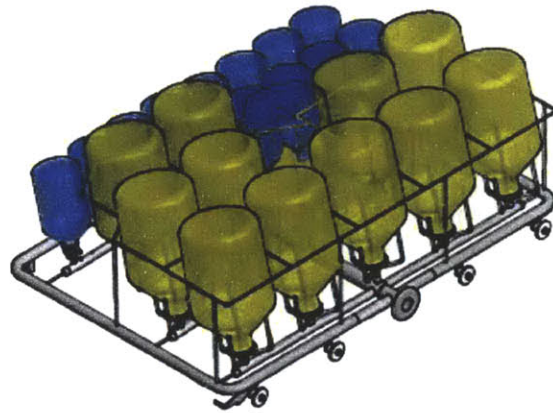


Figure 10, Worst Case Wash Cart Loading Example #1

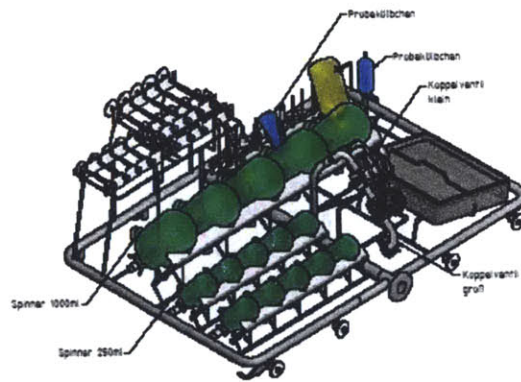


Figure 11, Worst Case Wash Cart Loading Example #2

Equation 5 below reports the method to calculate the standard variable autoclave cost for an assembly. As with the washer costs, the variable cost of an autoclave load includes utilities, waste disposal, maintenance, and validation.

*Standard Variable Autoclave Cost*

$$= \frac{\text{Assembly's\% of Autoclave Load} \times \text{Variable Cost of an Autoclave Load}}{\text{Expected Autoclave Load Utilization}}$$

**Equation 5, Standard Variable Autoclave Cost**

Unlike the standard variable materials cost or washer cost, which are based on individual components of an assembly, the autoclave cost is calculated directly for the assembly itself because only a completed assembly is sterilized, as depicted in Step #6 of Figure 9. Figure 12 and Figure 13 below show two examples of worst-case loads for autoclave carts.



**Figure 12, Autoclave Cart Loading Example #1**





**Figure 13, Autoclave Cart Loading Example #2**

Equation 5 can be applied to the glass bottles assembly depicted in Figure 12 as described below:

- Glass bottles assembly percent of one autoclave load: 30%
- Variable cost of one autoclave load: €77.67
- Expected autoclave load utilization: 50%
- Standard variable autoclave cost for glass bottles with silicon siphons assembly:  $30\% \times €77.67 / 50\% = €46.60$

### **3.2.2 Current State Risk Assessment**

As part of the commissioning of the Goerzhausen II facility, Novartis Vaccines and Diagnostics conducted FMEA's. An FMEA is an iterative process performed during the design phase of a manufacturing process. The process below was employed at Novartis Vaccines and Diagnostics, and is an adaptation of the United States military's approach (Department of Defense, 1980).

- Step 1: Determine all failure modes, or the way a failure occurs and its impact on equipment and operations
- Step 2: Evaluate the severity of the failure mode, or the worst potential consequences in terms of property or product damage or system damage. Assign a numerical value “SEV” using Table 1.

Severity (“SEV”) Score	Description
1	Small failure, that will probably not be recognized during process and has no visible impact on the product
2	Small failure, that is recognized during process and has only minor impact on product quality, safety and potency
3	Moderate failure, that leads to a fair decrease in process performance and fair impact on quality, potency and safety (leads to a major deviation report)
4	Critical failure, that leads to a severe impact on product quality, potency, safety (leads to critical deviation report and product recall)
5	Critical failure, that leads to loss of many batches and has a direct and extremely high impact on product quality, potency and safety (leads to critical deviation report and product recall)

Table 1, Severity Score Guideline

- Step 3: Evaluate the probability of the failure mode and assign a numerical value “PROB” using Table 2.

Probability (“PROB”) Score	Description
1	Very low probability
2	Low probability
3	Moderate probability
4	High probability
5	Very high probability/ failure almost unavoidable

Table 2, Probability Score Guideline

- Step 4: Evaluate how likely the failure event will be detected. Assign a numerical value “DETEC” using Table 3.

Detectability (“DETEC”) Score	Description
1	Process failure will be detected in every case
2	Detection very probable
3	Detection probable
4	Low probability of detection
5	Failure cannot be detected

Table 3, Detectability Score Guideline

- Step 5: Calculate the Risk Priority Number (RPN) using Equation 6. Note, the severity score is squared because there are high safety risks for the patient if a severe failure occurs.

$$RPN = SEV^2 \times DETEC \times PROB$$

Equation 6, Risk Priority Number (“RPN”) Formula

- Step 6: Assess the criticality of the failure using Table 4.

RPN Range	Criticality Assessment
$RPN \leq 24$	Not critical
$25 \leq RPN \leq 74$	Potentially critical
$75 \leq RPN$	Critical (immediate danger)

Table 4, Criticality Assessment Guideline

The output from this process is a registry of failure modes and their cognate RPN #'s.

### 3.3 Future State Cost Assessment

#### 3.3.1 Future State Cost Assessment

For both the future state and current state, the key financial figure of merit is yearly variable operations cost. In the future state, the variable costs calculated by the method described in Section 3.2.1 are not relevant. Instead, costs will be driven primarily by the price that third party vendors charge to supply single-use assemblies. New variable costs will also be incurred for waste disposal of the single-use assemblies.

Numerous companies are capable of supplying sterilized, ready to use, disposable assemblies, including Applied Critical Fluids, ATMI, Merck Millipore, Sartorius Stedim, St. Gobain, and others. These companies and others were invited to participate in a Request For Proposal (“RFP”) process to provide drop-in replacements for the current, multi-use assemblies. The costs determined by the RFP process drive the future state cost assessment.

### **3.3.2 Future State Risk Assessment**

As with the current state risk assessment, an FMEA method was used to evaluate future state risks. In this case, the current FMEA was used as a baseline, and process changes associated with single-use assemblies were evaluated for their impact on the RPN #'s.

## **3.4 Switching Cost Estimation**

### **3.4.1 Regulatory Switching Cost Estimation**

The production of human vaccines is a highly regulated process. Filing requirements are determined by a variety of agencies, depending on the location in which a product is sold. The Food and Drug Administration (“FDA”) governs the vaccine industry in the United States. The European Medicines Agency has harmonized the evaluation of vaccines in the European Union, but member states still maintain national medicine regulatory bodies. These regulatory organizations oversee many aspects of the biotechnology and pharmaceutical industry such as clinical trial design, manufacturing processes, and commercial practices.

The regulatory requirements of the FDA are discussed as an example of the filing requirements for vaccine manufacturing. The FDA has issued numerous guidance documents pertaining to chemistry, manufacturing, and controls that specify what information about the manufacturing process must be disclosed in filings. In the case of changing a manufacturing process by adopting single-use assemblies, the filing requires fall into the three categories below (Food and Drug Administration, 1997).

- 1) changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which require submission of a supplement and approval by FDA prior to distribution of the product made using the change
- 2) changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change
- 3) changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which are to be described by the applicant in an annual report

The following process was used to determine the regulatory switching costs of adopting a single-use assembly:

- Step 1: Determine what products would be affected if the current, multi-use assembly were replaced by a single-use assembly.
- Step 2: Determine if the change has a substantial, moderate, or minimal chance to have an adverse effect on each product. Examples of changes with a substantial chance of adverse effects include those that affect downstream processes like final filtration or formulation or solutions used directly in formulation.
- Step 3: Estimate the cost to prepare and submit the required regulatory filings. The cost of any required validation studies is not included in regulatory switching costs, but instead is accounted for directly in the validation switching cost, as described in Section 3.4.2.

This process was completed for each of the six assemblies for the major regulatory regions of the United States, the European Union, and Japan.

### 3.4.2 Validation Switching Cost Estimation

The FDA defines “process validation” as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product (Food and Drug Administration, 2011). A list of potential validation studies and their purposes are reported in Table 5.

Validation Study Name	Study Purpose
<b>Extractable and Leachable Study</b>	Determine what compounds will leach from the assembly or could be extracted from the assembly and contaminate the drug substance during assembly use. The assembly may still be fit for use if these compounds will not adversely affect product quality and will be sufficiently removed before final filling (Colton, 2008).
<b>Cell Compatibility Study</b>	Determine if cells used in production will be adversely affected by a material
<b>Shelf Life Study</b>	Determine the length of time a product will retain its quality under a certain set of storage conditions
<b>Media / Buffer Hold Study; Closure Integrity Test</b>	Ensure sterilization, aseptic filling, and closing operations are reliable and aseptic (Food and Drug Administration, 2004)

Table 5, Validation Studies Descriptions

The process of determining validation switching costs is very similar to the process of determining regulatory switching costs and is described below.

- Step 1: Determine what products would be affected if the current, multi-use assembly were replaced by a single-use assembly
- Step 2: Determined if the change affects a critical solution or process. Examples of critical processes include downstream processes like final filtration or formulation. An example critical solution is one used directly in formulation.
- Step 3: Determine what validation studies are prudent in light of the potential product impact.
- Step 4: Estimate the costs of validation studies for each assembly.

Costs were estimated to include raw materials to generate the media or buffer, management time to design the validation study and review the data, operator time to conduct the experiment, third party contractor costs.

### **3.4.3 Operations Switching Cost Estimation**

Operations switching costs consist of test runs and training runs with the new assembly, materials costs to prepare the solutions for test runs, and personnel time to conduct risk assessments, amend standard operating procedures, and process change control. The operations switching costs were estimated based on precedent comparable changes in the manufacturing process.

## **4 Results**

### **4.1 Current State Results**

#### **4.1.1 Current State Costs**

The method described in Section 3.2.1 was used to evaluate the current state costs for the diphtheria crude toxoid container, the cell suspension transfer assembly, and every assembly used by the media and buffer preparation area (this group includes the other four assemblies described in Section 2.4). This analysis yielded a large data set, and the costs for high-cost assemblies are displayed in Figure 14 below. Each stacked column represents a unique assembly, and the variable cost composition can be visualized through the four different colors, one each for material, operator, autoclave, and washer variable costs. The assemblies are grouped by type, and the six different types outlined in green, blue, brown, red, yellow, and orange cover the overwhelming majority of the yearly variable costs for assemblies for the media and buffer preparation area plus the diphtheria crude toxoid container and the cell suspension transfer assembly. As stated in Section 1.5, the cost data presented throughout this thesis document has been generated to illustrate the analytical method and are not representative of the costs borne by Novartis Vaccines and Diagnostics.



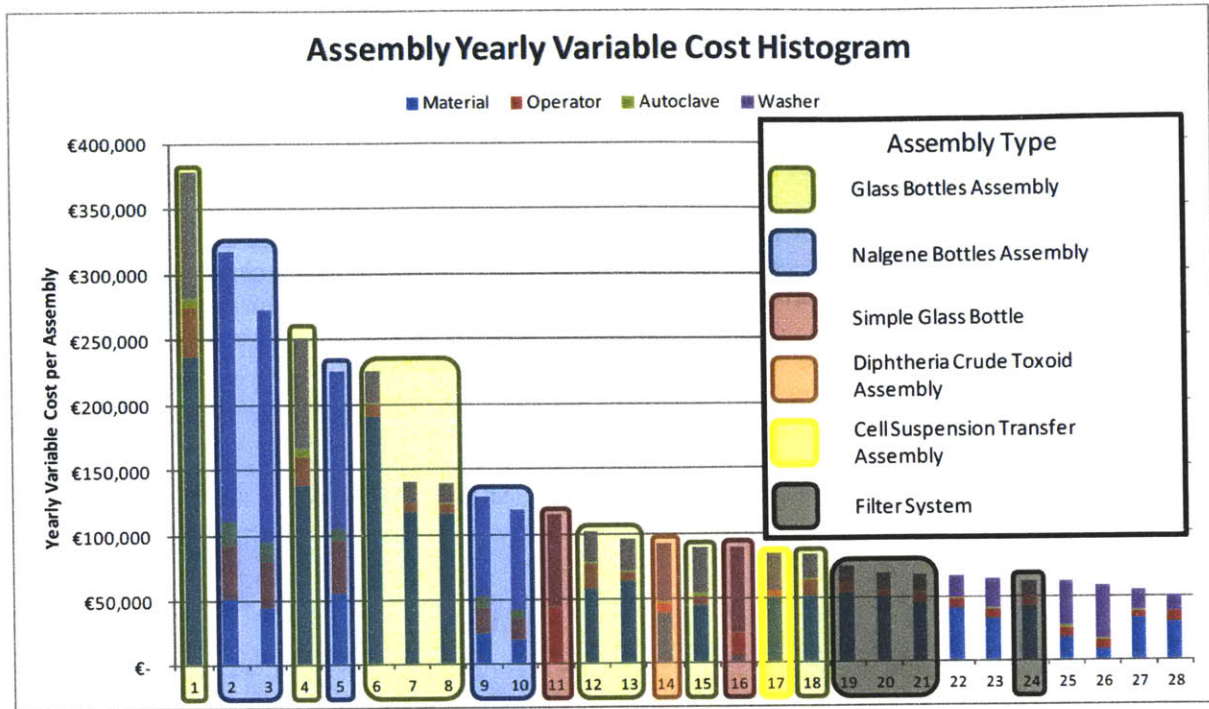


Figure 14, Current State Costs

Because these six types of assemblies drive substantially all of the variable costs, representative members of the assemblies were selected for further evaluation, including a risk assessment, switching cost assessment, and future state risk and cost assessment. Those assemblies and their corresponding types are:

- 1) Glass bottles assembly, described in Section 2.4.3, type highlighted in green in Figure 14
- 2) Nalgene bottles assembly, described in Section 2.4.5, type highlighted in blue in Figure 14
- 3) Simple glass bottle, described in Section 2.4.4, type highlighted in red in Figure 14
- 4) Diphtheria crude toxoid container, described in Section 2.4.6, highlighted in orange in Figure 14.
- 5) Cell suspension transfer assembly, described in Section 2.4.1, highlighted in yellow in Figure 14
- 6) Filter system, described in Section 2.4.2, type highlighted in brown in Figure 14

The variable cost composition for the assemblies provides insight about what operations are most variable cost intensive. For the glass bottles assembly, the primary driver is the single-use silicon siphons, which

represent 54% of the yearly variable costs for this assembly. For the Nalgene bottles assembly, the primary cost, 65% of the total, is washing the multi-use components such as Nalgene bottles and stainless steel siphons. For the simple glass bottle, washing costs dominate the total variable cost. The primary cost driver for the diphtheria crude toxoid container is the washing cost of the flask and stainless steel components, followed by the material cost of the filter. The primary cost driver for the cell suspension transfer assembly is the single-use silicon siphon system that connects the pipette to the container. For the filter system, costs are driven primarily by the cost of the filter itself. This analysis shows that in general, autoclave variable costs are nearly negligible and that material costs often are the largest contributor to total variable cost.

In summary, the current state aggregate yearly variable costs for the six assemblies evaluated are described in Table 6. As stated in Section 1.5, the cost data presented throughout this thesis document has been generated to illustrate the analytical method and are not representative of the costs borne by Novartis Vaccines and Diagnostics.

Assembly	Yearly Variable Cost
Glass Bottles Assembly	€378,000
Nalgene Bottles Assembly	€318,000
Simple Glass Bottle	€115,000
Diphtheria Crude Toxoid Assembly	€92,000
Cell Suspension Transfer Assembly	€84,000
Filter System	€74,000

Table 6, Current State Aggregate Yearly Variable Cost for Multi-Use Assemblies

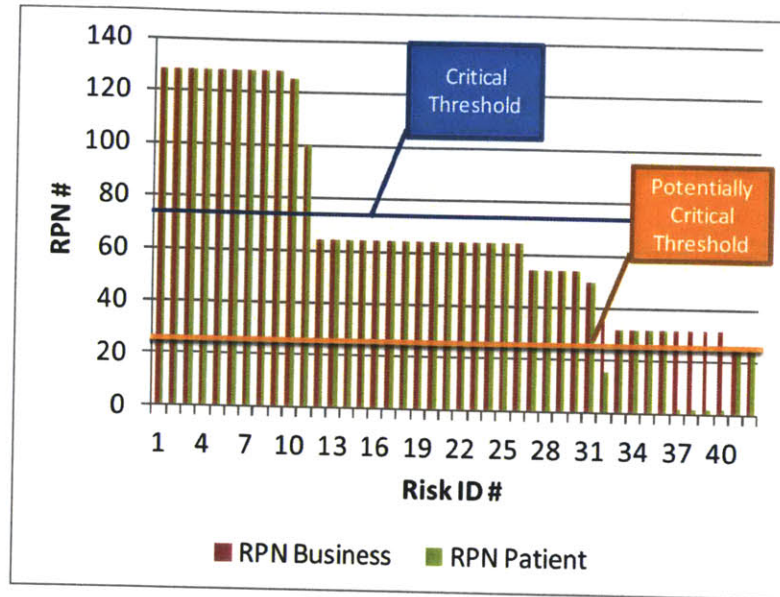
#### 4.1.2 Current State Risks

The critical risks identified to date that will be affected by the adoption of single-use assemblies are primarily in the pretreatment suite, rather than in the use of the assembly during a manufacturing run. Thus, the same set of risks is generally applicable to all six evaluated assemblies. These risks include labeling, assembly, sterilization, transportation, and storage of assemblies and are reported in Table 7. The RPN # threshold for a critical risk is 75. Any failure mode assigned an RPN # greater than 75 requires some corrective action.

Process Step	Process Control Parameter	Failure	Potential Effect(s) of Failure	Possible Cause of Failure	RPN Business	RPN Patient
<b>Labeling</b>	correct labeling of equipment	mix up of labeling trackers	equipment not labeled acc. to the selected cleaning program	operator failure	128	128
<b>Assembly</b>	correct assembly acc. to process requirements	incorrect assembly	assembly incomplete	customer SOP incorrect	128	128
<b>Loading carts (steam sterilizer)</b>	sterility	incorrect/not validated loading	equipment unsterile	Incorrect SOP (not conform to validation)	128	128
<b>Steam sterilizer</b>	validated sterilization procedures	equipment damaged, visually not detectable	equipment unsterile	operator failure	128	128
<b>Steam sterilizer</b>	validated sterilization procedures	equipment damaged, visually not detectable	equipment unsterile	instrument failure	128	128
<b>Delivery to ZMB</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	operator failure	128	128
<b>Delivery to ZMB</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	equipment failure	128	128
<b>Passing out airlock</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	operator failure	128	128
<b>Passing out airlock</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	equipment failure	128	128
<b>Warehouse</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	operator failure	128	128
<b>Warehouse</b>	equipment is undamaged	equipment is damaged	damage is not detected, equipment available to customer	equipment failure	128	128
<b>Receiving</b>	Equipment not infectious	Equipment infectious	hazard for of operators	contamination of delivered infectious equipment not detectable	125	125
<b>Receiving</b>	Equipment not infectious	Equipment infectious	washer contaminated	decontamination by customer not sufficient	100	100

**Table 7, Risk Assessment Summary**

These relevant critical risks and potentially critical risks that have RPN #'s between 128 and 25 are visualized below in Figure 15.



**Figure 15, Typical Assembly Risk Profile, Current State**

To better understand the risks associated with production, a query was run on the source of product write offs during the period from 2009 through 2011. The data from this query is presented below Figure 16. This figure shows that ~73% of inventory write offs occur because of the self-life was exceeded or the material was obsolete. Write offs that could be related to the risks associated with multi-use assemblies include “Process Deviation” (3%), “Batch Fail, Other” (2%) and “Batch Fail, Sterility” (1%).

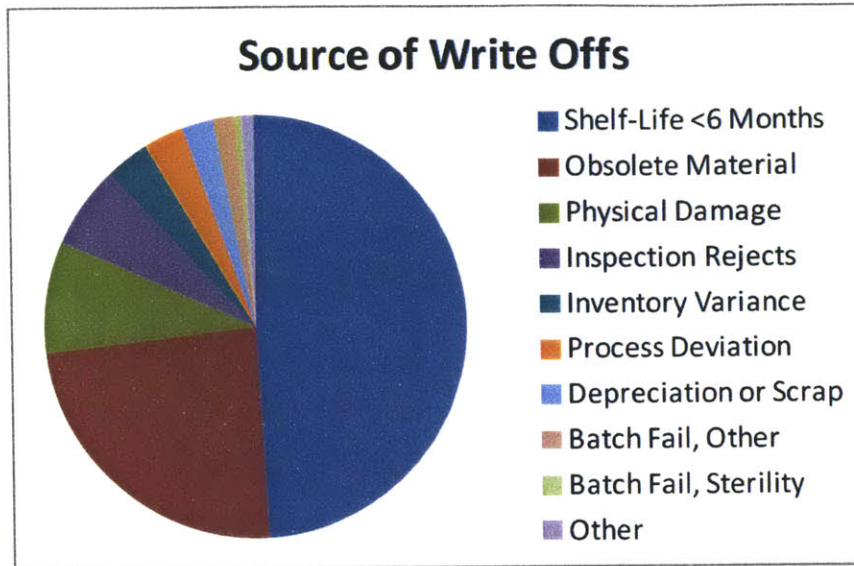


Figure 16, Source of Write Offs for 2009 - 2011

#### 4.1.3 Current State Complexity

The number of unique components used by all the assemblies in the media and buffer suite is 85.

The total yearly number of components processed for all the assemblies in the media and buffer suite is approximately 78,000.

### 4.2 Future State Results

#### 4.2.1 Future State Costs

The future state aggregate yearly variable costs for the six assemblies evaluated are described in Table 8. As stated in Section 1.5, the cost data presented throughout this thesis document has been generated to illustrate the analytical method and are not representative of the costs borne by Novartis Vaccines and Diagnostics.

Assembly	Yearly Variable Cost
Glass Bottles Assembly	€330,000
Nalgene Bottles Assembly	€487,000
Simple Glass Bottle	€78,000
Diphtheria Crude Toxoid Assembly	€120,000
Cell Suspension Transfer Assembly	€73,000
Filter System	€60,000

Table 8, Future State Aggregate Yearly Variable Costs for Single-Use Assemblies

#### 4.2.2 Future State Risks

In this preliminary analysis, adopting single-use assemblies is projected to meaningfully reduce risk associated with the pretreatment suite. Figure 17 below depicts the same set of risk events graphed in Figure 15. The reduction in risk, as determined by preliminary FMEA analysis is clear, as the number of critical risks fell from 11 to 5 and the number of potentially critical risks fell from 31 to 19. Examples of risks that have been reduced include “mix up of labeling trackers” (RPN # drops from 128 to 32) and “incorrect unsterility” (RPN # drops from 128 to 64).

This future state FMEA is preliminary and can be supplemented by a historical evaluation of deviations in the pretreatment suite. Many of the risks with the current state would be transferred to a vendor in the future state. For example, instead of Novartis labeling assemblies and sterilizing them in-house, a third party vendor would provide that service in the future. Until Novartis is able to conduct a thorough audit of the potential vendor, the future state FMEA must be regarded as preliminary and subject to revision as more data on the vendor’s quality system are available. In fact, Novartis may actually face an increase in risk because it would no longer control the preparation of the single-use assemblies. Furthermore, the information from the forward-looking FMEA can be supplemented by past performance data. This historical data in Figure 16, the Source of Write Offs”, indicates that these failure modes have not been a significant source of scrap in the last three years of operations. Specifically, the scrap due to unsterile assemblies or particles is below 1% of total scrap, and the cost was modest compared to the cost of the assemblies themselves. Thus, although the preliminary FMEA projects very clear risk reduction, that positive finding must be moderated by the preliminary nature of the future state assessment and the low cost of historic deviations that are likely to be ameliorated by single-use assemblies.

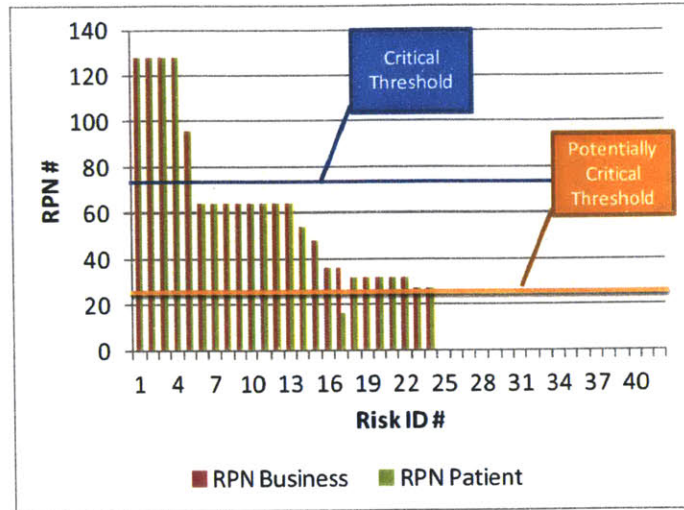


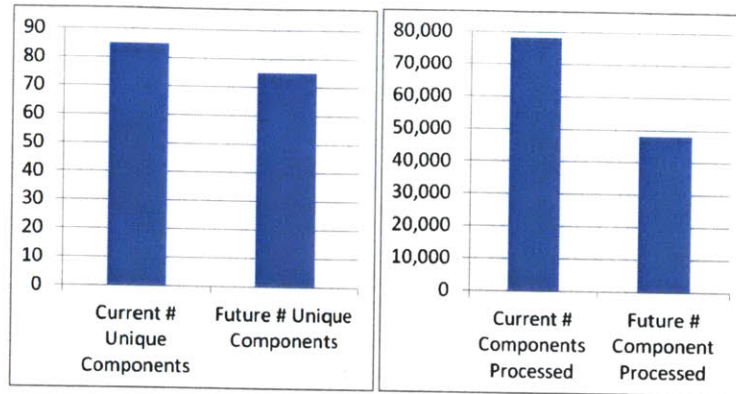
Figure 17, Typical Assembly Risk Profile, Future State

#### 4.2.3 Future State Complexity

It is possible to meaningfully reduce the complexity of operations in the pretreatment suite with single-use assemblies. This thesis document evaluates six assemblies, four of which are used in the media and buffer suite. Those four assemblies are:

- Glass Bottles Assembly
- Nalgene Bottles Assembly
- Simple Glass Bottle
- Filter System

Figure 18 below shows the impact of changing only these four assemblies. The number of unique components processed in the pretreatment suite for the media and buffer suite falls from 85 to 75 and the yearly number of components falls from 78,000 to 48,000.



**Figure 18, Complexity Analysis**

These figures understate the true opportunity for complexity reduction because they are based on changing only four of the assemblies used by the media and buffer suite. If a decision is made to change one of the four assemblies, it is probable that Novartis Vaccines and Diagnostics would change the other assemblies similar to it. For example, if the glass bottles assembly is a compelling candidate to switch to single-use, then the eight other similar assemblies highlighted in green in Figure 14 are likely to be compelling candidates as well.

At the time of publication, the complexity reduction associated with the cell suspension transfer assembly and the diphtheria crude toxoid assembly had not been evaluated.

### **4.3 Switching Cost Results**

#### **4.3.1 Regulatory Switching Costs**

The regulatory experts at Novartis Vaccines and Diagnostics determined that the regulatory filing requirements to adopt single-use assemblies were low to modest. Specifically, the determination is reported below in Table 9. A Type 1B Variation is in the second category of regulatory filings described in Section 3.4.1. It is a regulatory submission sent to FDA to request minor changes in a manufacturing process or its control. FDA has 30 days in which to respond, after which the change is considered approved and the part of the existing licensed process (BioPharm International, 2012).



Assembly	Regulatory Filing Requirement	Cost
Glass Bottles Assembly	Type 1B Variation	€10,500
Nalgene Bottles Assembly	None	€0
Simple Glass Bottle	Type 1B Variation for Multiple Facilities	€25,500
Diphtheria Crude Toxoid Assembly	None	€0
Cell Suspension Transfer Assembly	None	€0
Filter System	None	€0

**Table 9, Regulatory Filing Requirements and Costs**

### 4.3.2 Validation Switching Costs

The global head of process validation at Novartis Vaccines and Diagnostics performed an initial assessment of what validation studies would be required to adopt the single-use assemblies, using the method described in Section 3.4.2. Table 10 below reports what validation studies are prudent.

Description of Assembly	Validation Study
<b>Glass Bottles Assembly</b>	1) Media / buffer hold study (5X) 2) Extractable and leachable study 3) Closure integrity test
<b>Nalgene Bottles Assembly</b>	1) Media / buffer hold study (2X) 2) Closure integrity test
<b>Simple Glass Bottle</b>	1) Media / buffer hold study (6X) 2) Extractable and leachable study 3) Closure integrity test
<b>Diphtheria Crude Toxoid Assembly</b>	1) Shelf life study 2) Extractable and leachable study 3) Closure integrity text
<b>Cell Suspension Transfer Assembly</b>	1) Cell compatibility evaluation with vendor data 2) Closure integrity test
<b>Filter System</b>	1) Extractable and leachable study

**Table 10, Required Validation Studies**

The costs for these studies are reported graphically in Figure 19 below.

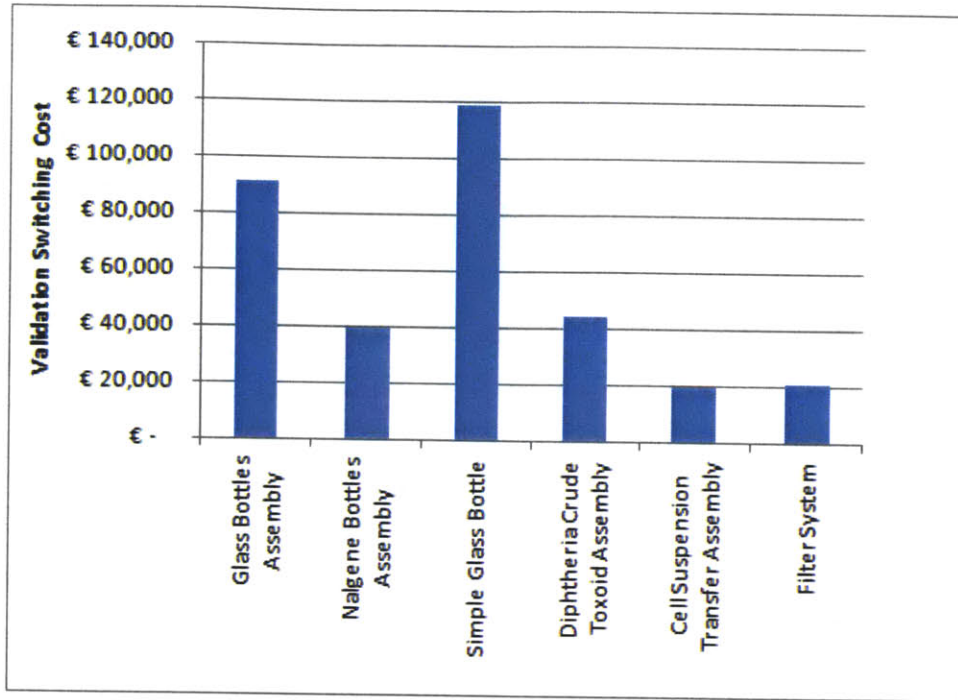


Figure 19, Validation Switching Costs

### 4.3.3 Operations Switching Costs

The operations switching costs were assessed using the method described in Section 3.4.3. Those costs are reported below in Figure 20.

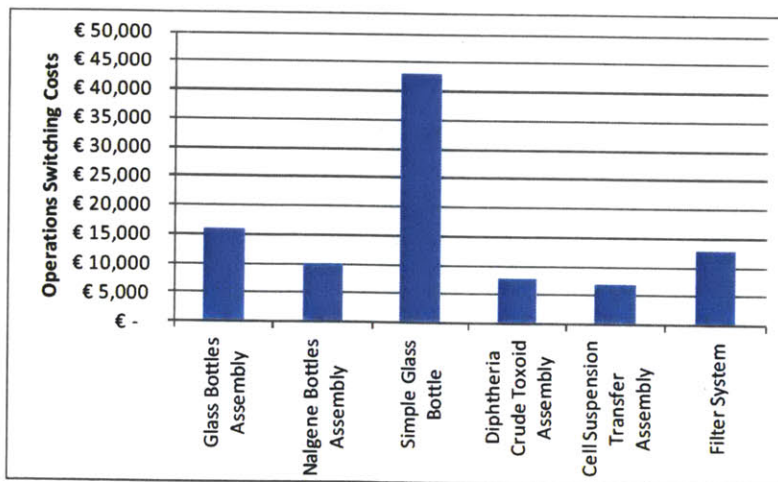


Figure 20, Operations Switching Costs

## **5 Conclusions and Recommendations**

### **5.1 Conclusions**

#### **5.1.1 Complexity Reduction Conclusions**

Adopting the 4 single-use assemblies used in the media and buffer suite would meaningfully reduce the number of unique components processed, from 85 to 75, and the total yearly number of components processed, from 78,000 to 48,000. The assemblies selected for analysis tended to have high yearly volumes, which in turn created high yearly variable cost. This selection bias explains why the yearly number of components processed fell more sharply than the number of unique components. As described in Section 4.2.3 it is reasonable to project that an entire family of multi-use assemblies, such as all the assemblies highlight in green in Figure 14, would be replaced by single-use alternatives. If this were to occur, the percentage reduction in the number of unique components would more closely match the percentage reduction in the total yearly number of components processed, because lower volume assemblies would be affected. This complexity reduction is desirable because it allows Novartis Vaccine and Diagnostics operators to focus on fewer tasks and reduces variability in the jobs performed.

#### **5.1.2 Cost and Risk Assessment Conclusions**

The results from the initial risk assessment indicate that adopting single-use assemblies will reduce the overall production risk for all six assemblies evaluated. This risk reduction will occur in the pretreatment suite that cleans, assembles, and sterilizes the assemblies. Critical risks that are likely to be mitigated include labeling, assembly, sterilization, transportation, and storage of assemblies. These risks would largely be transferred to the vendors who supply Novartis Vaccines and Diagnostics. Because these vendors specialize in the production of single-use assemblies, they can invest in more costly capital equipment and processes such as higher class clean rooms and gamma sterilization. However, these initial findings must be validated through vendor audits for confirmation.

Because the single-use assemblies are designed to be drop-in replacements for the multi-use predecessor assemblies, the operational risks associated with using them are largely unaffected. For example, sterile connections are generally made using Pall connectors, and this method will be conserved across the multi-use and single-use assemblies. Thus, the risk of an unsterile connection is unaffected by the decision to adopt these single-use assemblies.

Variable cost savings will be modest at best, and variable costs will increase for several of the assemblies. Figure 21 below compares the current state to future state costs and reports the one-time switching costs for each of the six assemblies. The net present value (“NPV”) and payback period associated with adopting each of these assemblies for 15 years with a 12% discount rate is computed from the data in Figure 21 and reported in Table 11. On one extreme, the single-use replacement for the glass bottles assembly has a positive NPV of €117,000 and a payback period of three years. On the other extreme, the single-use replacement for the Nalgene bottles assembly has a negative NPV of -€890,000 and will never pay for itself. Again, these cost data have been generated to illustrate the analytical method and are not representative of the true costs borne by Novartis Vaccines and Diagnostics.

The financial implications of adopting single-use assemblies would be substantially more favorable for a facility designed exclusively for single-use assemblies, as opposed to a mix of single-use and multi-use assemblies. In this case, the fixed costs associated with the pretreatment area would be avoided. These costs include the depreciation of washers and autoclaves and the higher capacity for clean utilities such as clean steam and water.

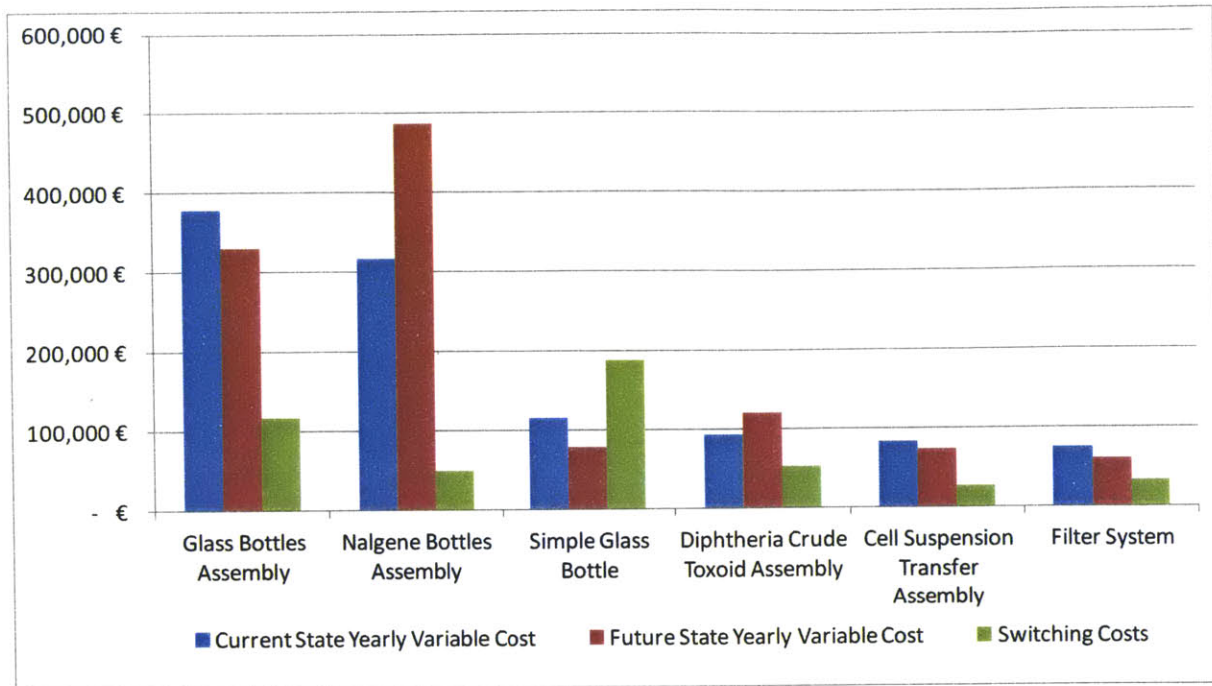


Figure 21, Future State Versus Current State Cost

Assembly Name	NPV	Payback Period (yr)
Glass Bottles Assembly	€138,000	2 yr
Nalgene Bottles Assembly	(€897,000)	N/A
Simple Glass Bottle	€17,000	5 yr
Diphtheria Crude Toxoid Assembly	(€187,000)	N/A
Cell Suspension Transfer Assembly	€32,000	2 yr
Filter System	€43,000	2 yr

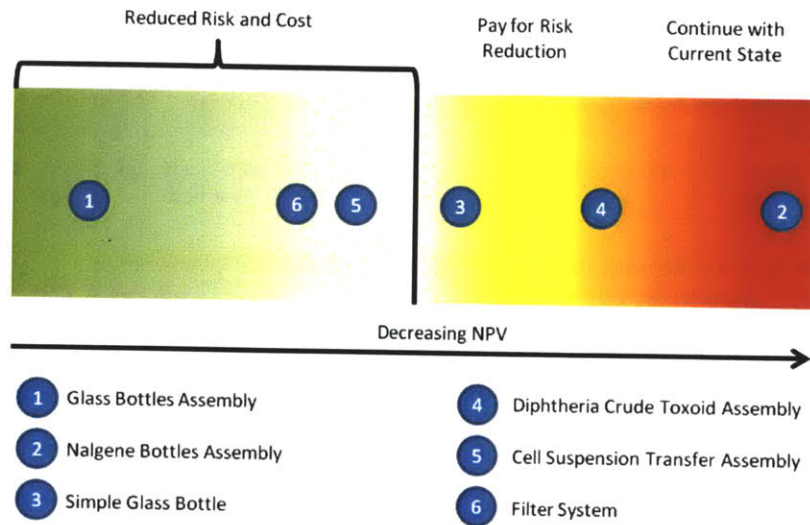
Table 11, Financial Evaluation of Single-Use Assemblies

It is possible to design a general decision making framework applicable to these six assemblies and all of the other assemblies used by Novartis Vaccines and Diagnostics. In general, assemblies fall into one of three categories described below and depicted graphically in Figure 22.

- 1) **Reduced Risk and Cost.** Adopting assemblies in this category will reduce both risk and cost.

The assemblies in this category should be switched from multi-use to single-use.

- 2) **Pay for Risk Reduction.** Adopting assemblies in this category will reduce risk but increase costs modestly. However, because the risk reduction is cost effective, these assemblies in this category should be switched from multi-use to single-use.
- 3) **Continue with Current State.** Adopting assemblies in this category is not a cost efficient way to reduce risk, and the multi-use assemblies should be used.



**Figure 22, Assembly Adoption Decision Making Framework**

## 5.2 Recommendations

Before Novartis Vaccines and Diagnostics makes any process changes, it must audit high priority vendors to confirm the initial risk reduction assessment.

Pending a successful audit of preferred vendors, Novartis Vaccines and Diagnostics should adopt single-use assemblies that reside in the two desirable categories of the decision making framework: “Reduce Risk and Cost” and “Pay for Risk Reduction”. The new assemblies should be adopted in a phased approach that allows Novartis Vaccines and Diagnostics to monitor the costs and risks associated with these new assemblies. Pending successful implementation of these assemblies, the remainder of the assemblies in the same family (e.g. for the glass bottles assembly, the remaining assemblies highlighted in green in Figure 14) should also be replaced with single-use assemblies.

For assemblies in the third category of the decision making framework, “Continue with Current State”, Novartis could consider a more ambitious process redesign or make no process change. The future state evaluated in this thesis document is one in which single-use assemblies are a drop-in replacement for the predecessor multi-use assemblies. For example, only rigid bioprocess containers were evaluated although flexible bags are also possible. As Novartis Vaccines and Diagnostics builds its relationships with single-use assembly vendors and experience with the products, the firm will be able to modify its production processes further. It is possible that the higher switching costs associated with specialized handling equipment to move flexible, liquid-filled bags are more than offset by the reduced operational costs of bags compared to rigid bottles.

### **5.3 General Implications**

The driving force behind adopting single-use assemblies at a legacy facility is the risk reduction associated with transferring critical risks to vendors who specialize in single-use assemblies and thus are able to invest in high cost equipment and processes that mitigate the risk of preparing the assemblies. Adopting single-use assemblies in some cases will save variable costs but in other cases will increase variable costs.

The analytical approach developed for this thesis project is generally applicable to evaluating a production process change to an existing facility. However, if the production process is modified to such an extent that the facility can be used for a new purpose or has an increased capacity because a bottle neck has been eliminated, this method is not applicable. Many production process decisions can be informed by this approach. In fact, Novartis Vaccines and Diagnostics will conduct a similar analysis for the production of diagnostics using this method.

### **5.4 Remaining Questions**

While this thesis document rigorously evaluates the merits of adopting certain single-use assemblies, the constraints set on those assemblies are selected with relatively little information about their implications.

Thus, Novartis Vaccines and Diagnostics now knows if drop-in replacement assemblies will be compelling, but it does not know if a more aggressive process modification would be preferable or not. For example, the company may consider investments in bag handling systems that enable the adoption of flexible bags to replace rigid containers.



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