Guidelines for Risk-Based Changeover of Biopharma Multi-Product Facilities

Rob Lynch, David Barabani, Kathy Bellorado, et al.

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GUIDELINES FOR RISK-BASED CHANGEOVER OF BIOPHARMA MULTI-PRODUCT FACILITIES

Authors:
ROB LYNCH, (GSK)
DAVID BARABANI, (Pfizer)
KATHY BELLORADO, (Pfizer)
PETER CANISIUS, (AbbVie)
DOUG HEATHCOTE, (AbbVie)
ALAN JOHNSTON, (Amgen)
NED WYMAN, (AZ)
DEREK WILLISON PARRY*

ABSTRACT: In multi-product biopharma facilities, the protection from product contamination due to the manufacture of multiple products simultaneously is paramount to assure product quality. To that end, the use of traditional changeover methods (elastomer change-out, full sampling, etc.) have been widely used within the industry and have been accepted by regulatory agencies. However, with the endorsement of Quality Risk Management (1), the use of risk-based approaches may be applied to assess and continuously improve established changeover processes. All processes, including changeover, can be improved with investment (money/resources), parallel activities, equipment design improvements, and standardization. However, processes can also be improved by eliminating waste. For product changeover, waste is any activity not needed for the new process or that does not provide added assurance of the quality of the subsequent product. The application of a risk-based approach to changeover aligns with the principles of Quality Risk Management. Through the use of risk assessments, the appropriate changeover controls can be identified and controlled to assure product quality is maintained. Likewise, the use of risk assessments and risk-based approaches may be used to improve operational efficiency, reduce waste, and permit concurrent manufacturing of products.

KEYWORDS: Quality risk management, Risk, Risk management, Changeover, Change-out.

Introduction

With the growth of biopharma product pipelines and the desire to improve operational efficiency as well as reduce the cost of goods sold (COGS), companies seeking to improve operational efficiency are in constant pursuit of streamlining their operations. An area of opportunity for improved efficiency is product changeover. For this paper, changeover is defined as the activities specifically performed to mitigate cross-contamination of products (e.g., changeover sampling, line clearance, elastomer change-out, etc.). Activities that may occur during changeover (i.e., calibrations, planned maintenance, and change controls), though essential to manufacturing, are considered outside the scope. Product changeover is a process that prepares and configures the facility and equipment for the next manufacturing process, and includes actions taken to protect the subsequent process against contamination from the previous process. Historically, the changeover between two products within a multi-product facility has created a great deal of operational inefficiency. With the use of risk-based tools and supporting data, the changeover activities of multi-product facilities can be significantly reduced and, under well-controlled and characterized operations, concurrent manufacturing may be achieved. Specifically, the change-out of small parts and elastomers as well as the collection of changeover cleaning samples may be significantly reduced or eliminated. This article is primarily intended for the manufacture of bulk biological drug substance; however, the principles may be applied to finished drug product as well.

Changeover Overview

It is a regulatory expectation by various boards of health to verify the cleanliness of equipment between campaigns of different products to eliminate the risk of cross-contamination. “Contamination of a starting material or of a product by another material or product
must be avoided” (2). Additionally, “control measures to remove the organisms and spores before the subsequent manufacture of other products” (3) must be in place in a multi-product facility. These references emphasize that preventing cross-contamination is paramount in a robust changeover process so as not to adversely affect the safety, identity, strength, purity, or quality of the subsequent product.

The scope of changeover is typically limited to non-dedicated product contact equipment (e.g., cell culture/fermentation, purification, and filling operations.) Process support areas (media and buffer preparation) may not be changed over, as this equipment does not contact any product containing material that would necessitate verification of removal. In addition, the introduction of single-use equipment to the process stream can also reduce the scope of changeover, as this equipment is disposed of after use and does not require verification of cleanliness.

As a prelude to this article, an industry survey was conducted to assess the current practices and identify the key areas deemed to be opportunities to improve changeover. Survey results were collected from 15 representative companies and included products manufactured both internally and externally (contract manufacture). It also included manufacturing across the spectrum of potency from low-potency products (such as monoclonal antibodies) through medium- and high-potency (cytokines and tumor necrosis factors). A summary of the survey results for the current changeover practices and the percentage of companies currently following each of the practices is shown in Table I. The table shows the tasks associated with normal lot to lot (no product change) and the additional percentage of companies that perform the tasks during product changeover. The table is divided into three sections:

- Changeover activities performed (lot to lot/additional at product changeover)
- Release criteria (prior to starting the next lot/product)
- Samples collected (during lot to lot/product changeover)

The activities are ranked based on additional percentage performing each activity as part of product changeover.

This paper will discuss the optimization of changeover practices through the reduction of waste. Lean Six Sigma identifies eight forms of waste (Figure 1). Many, if not all, of these forms of waste may be present during traditional product changeover. In particular, this paper focuses on the elimination of waste associated with cleaning and verification of equipment cleanliness during product changeovers. Table II uses the lean forms of waste associated with changeover and identifies the benefits of applying risk-based changeover approaches.

Optimization of a changeover practice is the process of determining the most efficient and effective method to achieve the product changeover from Product A to Product B without adversely affecting the quality and safety of Product B. A robust risk program can be used to drive changeover optimization to assure the appropriate actions and controls have been established and executed to defend the quality and safety of Product B.

The results in Table I show that there is variability in the changeover activities performed by survey respondents, with “equipment cleaning” the only activity performed by all. So what actions are really needed and which are not?

Risk assessments (RAs) are an industry-accepted tool to establish the changeover requirements. The RA defines the criteria that need to be met during the changeover, the potential threats to meeting these criteria, and the controls (design and procedures) needed to mitigate, control, or detect these threats.

Cleaning and protection of the next process from contamination are major quality concerns during the changeover process. There are many potential contamination threats to the coming product associated with changeover.

The RA allows a systematic assessment of each potential threat and how each of these threats is mitigated controlled (design, cleaning, procedures, documentation) and/or how the threat to quality is detected before it can affect the marketed product (sampling, verification, inspection).

All of the items listed in Table I are types of controls; the opportunity for optimization is to define—based on the quality threat— which of these controls is actually needed to defend and demonstrate that the quality of the next process will not be
affected by the changeover processes. This also ensures that the changeover activities are commensurate with the threats to quality.

With robust risk assessments, companies can provide a solid defense that can support reduction in changeover activities. This may include the following:

- Elimination or reduction of elastomer change-out
- Elimination or reduction of elastomer change-out
- Elimination or reduction of changeover sampling
- Reduction of line clearance activities
- Concurrent manufacture of multiple products within a single manufacturing area

It is important to realize that, if using risk assessment to justify a reduction in changeover, the risk assess-

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**TABLE I**

Summary of Survey Practices

<table>
<thead>
<tr>
<th>Survey Question</th>
<th>Response</th>
<th>Always—Lot to Lot</th>
<th>Additional—Product Changeover</th>
</tr>
</thead>
<tbody>
<tr>
<td>In direct product contact equipment/areas—what changeover activities do you perform normally (regular lot to lot) and during product changeover?</td>
<td>Execute cleaning cycles</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Collect cleaning samples (rinse, swab, or both)</td>
<td>40.0%</td>
<td>93.3%</td>
</tr>
<tr>
<td></td>
<td>Remove all materials or impose material restrictions from previous lot (clearance)</td>
<td>20.0%</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>Change liquid filters</td>
<td>60.0%</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>Remove all documentation from previous lots</td>
<td>40.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Equipment cleaning after maintenance</td>
<td>66.7%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Change probes/instruments (pH, dissolved oxygen)</td>
<td>26.7%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Move equipment into and out of the area</td>
<td>33.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Change vent filters</td>
<td>46.7%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Attach hardcopy equipment status labels</td>
<td>66.7%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Facility area cleaning—after maintenance activities or as part of changeover</td>
<td>40.0%</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>Update product status in automation</td>
<td>53.3%</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>Post/update signs on area entrances</td>
<td>33.3%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>Environmental sampling requirements</td>
<td>46.7%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>Install parts/perform set-up</td>
<td>53.3%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>Change elastomers</td>
<td>0.0%</td>
<td>53.3%</td>
</tr>
<tr>
<td></td>
<td>Change flex hoses</td>
<td>20.0%</td>
<td>53.3%</td>
</tr>
<tr>
<td></td>
<td>Test/verify equipment configuration and settings</td>
<td>20.0%</td>
<td>53.3%</td>
</tr>
<tr>
<td></td>
<td>Change equipment/piping configuration</td>
<td>0.0%</td>
<td>46.7%</td>
</tr>
<tr>
<td></td>
<td>Request STAT (immediate) sample analysis from laboratories</td>
<td>20.0%</td>
<td>40.0%</td>
</tr>
<tr>
<td></td>
<td>Perform special environmental sampling</td>
<td>0.0%</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>Run special automation changeover recipes</td>
<td>6.7%</td>
<td>26.7%</td>
</tr>
<tr>
<td></td>
<td>Execute special equipment changeover cleaning cycles</td>
<td>6.7%</td>
<td>26.7%</td>
</tr>
<tr>
<td>What “release” criteria must be met before the next process batch can be started in this shared direct product contact equipment—both for lot to lot and for product changeover</td>
<td>Equipment inspection</td>
<td>53.3%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Area inspection—all changeover criteria met</td>
<td>6.7%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Equipment cleaning sample results needed</td>
<td>13.3%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Quality release (signature)</td>
<td>26.7%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Quality review of documentation</td>
<td>33.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>Facility cleaning confirmation</td>
<td>20.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>Return to service or equivalent sign off</td>
<td>20.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>Environmental monitoring sample results needed</td>
<td>20.0%</td>
<td>40.0%</td>
</tr>
<tr>
<td></td>
<td>No restrictions (just operators executing procedures)</td>
<td>26.7%</td>
<td>26.7%</td>
</tr>
<tr>
<td>What samples do you take, for verification of equipment cleaning - both normally (lot to lot) and for product changeover.</td>
<td>Total organic carbon (TOC)—rinse</td>
<td>63.6%</td>
<td>90.9%</td>
</tr>
<tr>
<td></td>
<td>Visual—through sight-glass (non-intrusive)</td>
<td>81.8%</td>
<td>81.8%</td>
</tr>
<tr>
<td></td>
<td>Visual—Intrusive (open system)</td>
<td>54.5%</td>
<td>72.7%</td>
</tr>
<tr>
<td></td>
<td>Conductivity</td>
<td>72.7%</td>
<td>72.7%</td>
</tr>
<tr>
<td></td>
<td>TOC—swab</td>
<td>45.5%</td>
<td>63.6%</td>
</tr>
<tr>
<td></td>
<td>Bioburden</td>
<td>45.5%</td>
<td>63.6%</td>
</tr>
<tr>
<td></td>
<td>Endotoxin</td>
<td>45.5%</td>
<td>63.6%</td>
</tr>
<tr>
<td></td>
<td>Product-specific assay</td>
<td>18.2%</td>
<td>27.3%</td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td>9.1%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>No sampling or verification</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Note: The data was also analyzed to compare the differences in practices between manufacturers handling high- and medium-potency products versus low-potency products but showed no significant differences and is not presented.
ment must be defendable. By building up technical documents to support this defense, it is possible to demonstrate control while minimizing activities.

Figure 2 is an overview of the types of defenses that can be established to support a reduced changeover effort. Each of the elements in the diagram is discussed in the following sections. A risk assessment will use inputs defined in Figure 2 to determine the relative risk associated with the controls established within a given organization. Once the risks and controls are understood, higher level risks may be mitigated with additional controls or may dictate more traditional changeover practices if accepted. Figure 3 depicts an example of the outputs from a risk assessment including potential changeover benefits. As with

Lean Six Sigma waste.

<table>
<thead>
<tr>
<th>Changeover Waste</th>
<th>Examples</th>
<th>Changeover Waste Benefit</th>
</tr>
</thead>
</table>
| Waiting          | • Equipment availability  
                  | • Sample results  
                  | • Elastomer change-out  
                  | • Sample collection  
                  | • Facility downtime | • Equipment scheduling improved  
                  |                      | • Sampling reduced or eliminated  
                  |                      | • Elastomer change-out reduced or eliminated  
                  |                      | • Testing reduced or eliminated  
                  |                      | • Facility efficiency improved |
| Inventory        | • Sampling (swabs/vials) materials  
                  | • Cleaning materials  
                  | • Elastomers inventory  
                  | • Water (cleaning) usage  
                  | • Packaging materials | • Reduced raw material consumption  
                  |                      | • Reduced cleaning detergent consumption & waste water treatment  
                  |                      | • Reduced elastomer consumption  
                  |                      | • Reduced water consumption and waste water  
                  |                      | • Reduced packaging waste |
| Talent           | • Unnecessary sample collection & testing  
                  | • Unnecessary elastomer change-out | • Re-allocate resources  
                  |                      |                      | • Improves changeover efficiency  
                  |                      | • Eliminates waste due to waiting |
| Motion           | • Unnecessary sample collection & testing  
                  | • Unnecessary elastomer change-out | • Fewer errors/defects  
                  |                      |                      | • Eliminates unnecessary movement  
                  |                      | • Improves changeover efficiency |
| Extra Processing | • Unnecessary sample collection & testing  
                  | • Unnecessary elastomer change-out  
                  | • Extra cleaning due to sample collection  
                  | • Over production of materials (e.g., media/buffer) | • Reduces resource constraints  
                  |                      |                      | • Reduces raw material consumption  
                  |                      | • Improves changeover efficiency  
                  |                      | • Reduces raw material waste |
| Defects          | • Extra cleaning due to sampling  
                  | • Reduced system integrity due to elastomer change-out  
                  | • Increased risk contamination due to elastomer Change-Out | • Reduces or eliminates rework  
                  |                      |                      | • Reduces or eliminates scrap  
                  |                      | • Reduces waste due to waiting |
| Transportation   | • Unnecessary staging and replacement of elastomers  
                  | • Unnecessary staging and replenishment of cleaning detergents | • Reduces transport of elastomers  
                  |                      |                      | • Reduces the transport of cleaning detergents |
Figure 2

Risk-based changeover process flow diagram.
Figure 3

Risk-based changeover flowchart (example).
all risk assessments, risk tolerance will vary from organization to organization and will result in differing levels of potential benefits. Guidance for Quality Risk Management and representative case studies can be found within PDA Technical Reports 54 (4) and 54-4 (5).

New Product Introduction

The introduction of new products, or new product introductions (NPIs), to a multi-product facility poses unique challenges to existing changeover processes of validated products. As a result, more traditional changeover activities may be required. Because the validation of NPIs may be incomplete, the execution of cleaning validation/verification is a major component of the NPI process. Small-scale studies are used to assess the product to be introduced into the manufacturing facility. These include coupon recovery studies, cleanability studies and degradation/denaturation, and inactivation as discussed below. The findings of these small-scale studies determine the level of the commercial-scale cleaning validation/verification work required to demonstrate that the validated cleaning processes remove any residual material to acceptable levels. These acceptance levels are determined to verify that potential residual Product A remaining would not be expected to affect the safety or product quality of Product B.

Without the controls of validated cleaning processes and routine monitoring, the use of risk-based changeover practices for new products is impractical. Based upon product knowledge, small-scale studies, and cleaning validation, risk-based changeover practices may be implemented for future campaigns.

Changeover Assessments

The sections that follow identify activities which may be considered and leveraged to support a risk-based changeover. In addition to these, your organization may have additional program data that may be leveraged to support further risk-based changeover practices.

Recovery Studies

The use of rinse and swab recovery studies in support of cleaning validation is routinely performed. These studies demonstrate how the soil of interest (cleaning agents, product, or process) adheres to the representative materials of construction (MOC) throughout the manufacturing process. These studies can be used to support that the residues are easily solubilized so if present within a system they will be present in rinse water samples collected at the system outlet or on swab samples of equipment surfaces. These studies support the use of single-point sampling as well as the collection of swab samples of the actual equipment surfaces. In addition, the studies demonstrate that the residues are readily removed from elastomer and gasket materials and are a critical element supporting a risk-based approach to the change-out of elastomers (e.g., gaskets, o-rings, valve diaphragms, etc.).

When recovery studies have been conducted for all products and MOC, a matrix can be created that generically suggest worst-case MOC for each product as well worst-case MOC across products. The data associated with recovery studies become valuable inputs to risk assessments determining the extent of elastomer change-out and reduced sampling.

Cleanability Studies

Bench-scale cleanability studies are performed prior to introducing a new soil in to the manufacturing facility to give assurance that the existing cleaning cycle(s) will be effective. These studies are common in the industry, as referenced by the Parenteral Drug Association (PDA): “Generally, the cleaning effectiveness of the existing system for new soils can be tested by performing laboratory experiments using coupons of relevant materials. These experiments can be designed to test both the effectiveness of the proposed cleaning regimen and the relative difficulty of cleaning the new soils that have already been introduced to the plant” (4).

A well-designed cleanability study will assess the manufacturing process conditions and soil(s) as well as the cleaning cycle(s). During testing, both the soil and cleaning cycles can be manipulated to further challenge the effectiveness of the cleaning cycle(s). While the primary goal of these studies is to determine if the process soil is a new-worst case situation and that the cleaning cycles are appropriate, the data also indirectly supports changeover. Through demonstrating that the process soils are cleanable at the laboratory scale, the risk associated with decreasing or eliminating elastomer change-out or changeover sampling may be assessed.
Product Degradation/Denaturing/Inactivation

For multiproduct equipment cleaning validation, cleaning acceptance limits for residual process materials are typically set based upon the product dosage and/or health-based exposure limits such as acceptable/permitted daily exposure (ADE/PDE) or threshold of toxicological concern (TTC) of Product A. These values are used to calculate the maximum allowable carryover (MAC) of residue from Product A to Product B. However, the activity of biological products such as monoclonal antibodies and therapeutic proteins rapidly degrade/denature when exposed to pH extremes and/or heat, and thereby become pharmacologically inactive (5, 6). When product degradation and inactivation can be demonstrated, the relative risk of product-to-product carryover is significantly reduced. From a risk-based perspective, demonstration of degradation/inactivation lowers the associated risk of foregoing elastomer change-out and drastically reduces or eliminates the primary risk of product carryover between products. Furthermore, when product inactivation is demonstrated and cleaning validation has been completed, the requirement for changeover sampling may be assessed to reduce or eliminate sampling. By reducing or eliminating elastomer change-outs and changeover sampling, the overall waste (e.g., material disposal, equipment and resources availability) associated with changeover is reduced.

Product Toxicity/Potency

It is important to ensure that the potent or toxic process soil risk can be reduced during product changeover in order to prevent cross-contamination into the subsequent or concurrent product being manufactured within the facility. If process soils are toxic or highly potent, then additional safeguards need to be considered in order to ensure pure, safe, and effective product for patients. Safeguards that can be taken include product-dedicated equipment, use of cleaning cycles that degrade or denature process soils, and/or product/component-specific assays.

It is also important to understand the impact of the cleaning cycles on the toxic or potent process soil. If the cleaning cycle degrades, denatures, or in some manner eliminates the potent or toxic aspect of the process soil, and this can be proven, then the cleaning acceptance criteria can be set using a non-specific limit rather than a specific assay. In addition, proving that the toxic or potent component has been degraded or denatured allows for product contact equipment to be shared and not dedicated to a product. This also allows for other methods for calculating acceptance criteria to be used (8, 9). If removal of toxic or highly potent residues is demonstrated, changeover activities of associated equipment may be reduced based on risk assessments.

Cleaning Validation/Verification

Cleaning validation establishes documented evidence that a cleaning system (including cleaning equipment, cleaning cycles, and associated procedures) performs as expected and that the parameters of the cleaning cycle are adequate to ensure process equipment is cleaned in an effective and consistent manner. With scientific guidance from the laboratory-scale cleanability studies, the validation may be applied in a grouping approach to multiple products that are proven through laboratory-scale cleanability studies to be less challenging to clean. The advantage to changeover gained through cleaning validation is the potential reduction and/or elimination of the need to perform extensive sampling at each changeover, thereby reducing changeover time.

Cleaning verification is the process of collecting evidence to demonstrate that the equipment is properly cleaned. Cleaning verification is typically used where there are not sufficient process lots to perform validation, or in support of investigations, as well as during product changeover. The challenge with verification is that to fully demonstrate that the residues have been removed from all surfaces, extensive sampling (rinse and swab) throughout the equipment is required. This often necessitates disassembly and/or intrusive actions that can significantly add to changeover times, especially when lock-out/tag-out and other safety requirements (e.g., confined space tank entries) and post-sample re-cleaning are factored in. Therefore, if cleaning validation has not been completed and cleaning verification is performed to support changeover, the reduction or elimination of changeover sampling and elastomer change-out are more difficult to justify.

Routine Monitoring

Routine monitoring of cleaning cycles is required to provide ongoing evidence that the cleaning processes are effective in ensuring the equipment is clean and
suitable for use. “Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production” (7). This is the core principle behind lifecycle management of cleaning processes. This is supported by the statement, “Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results” (8). Both statements emphasize that validation does not end upon completion of performance qualification (PQ) and that it is important to periodically verify that the cleaning processes are still operating as originally qualified as part of lifecycle management.

As part of lifecycle management, a cleaning monitoring program verifies the cleanliness of equipment on a pre-determined frequency (quarterly, yearly, etc.) based on risk or usage. The same assays utilized during PQ are typically used to verify that the cycles are still working as intended. These data can be utilized to identify trends in cleaning processes or to re-evaluate current acceptance criteria.

Changeover cleaning verification and cleaning monitoring are similar, as the equipment is verified as clean using the same (or similar) analytical testing in addition to a visual inspection; they are also linked in an inversely proportional way. For example, a strong cleaning monitoring program could lead to reduced sampling during changeover as the cleaning monitoring team demonstrates and documents control of the cleaning processes throughout the year. Conversely, if a facility undergoes multiple changeovers in a year, these data could be used to support cleaning monitoring and reduce the number of samples required for that program.

In addition to cleaning monitoring, other aspects of lifecycle maintenance can include preventive maintenance, re-validation, and change controls. Each of these programs ensures that the equipment is operating as intended and any changes do not negatively affect the validated state of the equipment.

“Inspection of equipment for cleanliness immediately before use” (9) is a specific requirement of the U.S. Food and Drug Administration. This inspection is routinely performed by manufacturing personnel following clean-in-place (CIP) and prior to subsequent manufacturing steps. This is an additional safeguard that can provide real-time feedback of the effectiveness of the lifecycle management program.

Changeover Sampling

With a robust data set encompassing the topics previously covered, changeover sampling can be risk-assessed for reduction and/or elimination. A combination of data points including equipment complexity, materials of construction, cleanability/recovery, degradation/denaturing, and cleaning validation may be used to assess typical changeover sampling operations. In high-risk applications, typical changeover sampling (rinses and swabs) may still be necessary. However, in low- and medium-risk application, a reduction or the elimination of changeover sampling will likely be scientifically justifiable. Table III provides examples of risk-based changeover activities.

This is especially true for organizations that have actively implemented process analytical technology (PAT) to actively monitor and control critical process parameters (CPPs) associated with cleaning processes. The use of in-line and at-line technologies—for example, total organic carbon (TOC), conductivity, etc.—that enable proactive control of cleaning processes may be leveraged to reduce or eliminate typical changeover sampling methods.

With the reduction or elimination in changeover sampling, several modes of waste are minimized. Resources are freed up to attend to other activities, quality control (QC) testing is decreased, equipment is released in a timely manner, and the overall efficiency of changeover may be significantly improved without impact to product quality.

Elastomer Change-Out

Historically, the change-out of elastomers was an essential component of product cross-contamination protection during changeover. Through the replacement of elastomers, multi-product facilities assured cross-contamination of product from elastomer surfaces was eliminated. However, using risk-based approaches and other supporting data, the requirement of elastomer change-out to mitigate product cross-contamination is being revisited.

Elastomers must comply with USP Class VI and the materials of construction must be compatible with the existing manufacturing processes. Selection and utilization of elastomers are critical to ensure not only effective cleaning and steaming of the process equipment, but also to avoid leaching during normal oper-
Valve diaphragms are evaluated for a smooth surface finish and components that minimize wear from repeated toggling or use. The selection of elastomer materials of construction ensures that they are suitable for use in a multi-product environment and that a comprehensive training program is in place to ensure elastomers are installed, maintained, and handled in a manner that reduces the potential for elastomer failure and subsequent potential product cross-contamination.

As noted above, soil cleanability of new or modified product and process materials is determined through bench-scale cleaning evaluations. Using this data, a risk assessment may be conducted to minimize or eliminate elastomer change-out from one product to the next. Once assessed, the need for elastomer change-out may be based on defined preventive maintenance intervals (10).

**Closure Analysis**

“Closure analysis is a type of a risk assessment that should focus on the probability and severity of exposing a process system to the surrounding environment before, during, and after the process operations” (11). The International Society for Pharmaceutical Engineering (ISPE) Baseline Pharmaceutical Engineering Guide, Volume 6, provides guidance on performing closure analysis. The ISPE guide breaks the process into three fundamental phases: Review and Selection → Calculations and Definitions → Outcome.

Although closure analysis is typically performed to assess viral and microbial control within the process, the principles may be applied to the risk of simultaneous manufacture of multiple products. In the context of changeovers, closure analysis can be used to identify unit operations with sufficient controls to permit concurrent manufacturing. Systems or processes are defined as being briefly exposed, closed, functionally closed, or open. Once the systems and processes have been defined, an assessment may be performed to determine which unit operations have adequate controls to permit concurrent manufacturing. Concurrent manufacturing allows the simultaneous manufacture of multiple products within a well controlled area. From a lifecycle perspective, the changeover path to concurrent manufacturing may occur incrementally. When closure analysis has been completed and all

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<th>System/Buffer Tank</th>
<th>Changeover Controls</th>
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<tbody>
<tr>
<td>Low</td>
<td>Cleanability/Recovery Studies</td>
<td>Changeover sampling eliminated Elastomer change-out eliminated Concurrent manufacturing possible</td>
<td>Sampling materials, collection, and testing eliminated Elastomer raw materials eliminated Resources are freed to focus on other changeover activities System immediately available Preparation of new product medias justifiable</td>
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<tr>
<td>Medium</td>
<td>Cleanability/Recovery Studies</td>
<td>Changeover sampling reduced or eliminated Elastomer change-out reduced or eliminated Concurrent manufacturing possible Use of SMED principles</td>
<td>Sampling materials, collection, and testing reduced or eliminated Elastomer raw materials reduced or eliminated Resource loading improved Changeover efficiency improved System availability improved Simultaneous production of second product justifiable</td>
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<tr>
<td>High</td>
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<th>TABLE III Risk-Based Changeover Examples</th>
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<td>System/Buffer Tank</td>
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controls required by quality risk assessments have been assessed and are in use, concurrent manufacturing may be implemented. With each new product, the process must be performed; however, data can be leveraged, potentially shortening the process.

Once the requisite data has been generated to support concurrent manufacturing, logistical efficiencies are also necessary to facilitate concurrent manufacturing. The staging of changeover parts must be both efficient and timely. Sufficient trained resources must be available to guarantee the efficient changeover between products. Tools such as single-minute exchange of die (SMED) may be used to improve logistical changeover efficiency. In an ideal state, sufficient controls are in place, cleaning processes are validated, products are non-toxic and non-potent, and product degradation has demonstrated that the requirement for changeover may be minimized or even eliminated.

Viral Reduction and Segregation

Another consideration of risk-based changeover is the viral reduction and viral segregation controls of the process. Viral reduction studies are typically performed to demonstrate the ability of cleaning processes, steam-in-place (SIP) or autoclave processes, to reduce viral loads to acceptable levels. The studies may be used to assess the risk associated with changeovers in which pre-viral inactivation portable equipment are moved to post-viral inactivation steps. Dependent on the viral reduction studies and viral controls, a risk assessment of the need for elastomer change-out may be performed to prescribe the appropriate level of elastomer change-out. For systems such as portable tanks that incorporate SIP unit operations, the need for elastomer change-out may not be necessary. However, for systems that are incapable of SIP operations, the change-out of elastomers as well as other decontamination processes must be considered and may be required.

Disposable Technology

The use of disposable technology in biologics manufacturing allows for the complete adoption of risk-based changeover principles by eliminating the sources of potential product carryover: the permanent stainless steel, glass, or acrylic surfaces that require cleaning in between use and the elastomer surfaces that require replacement for absolute assurance of residual product removal.

With disposable technology, the permanent surfaces are replaced by disposable plastic surfaces with inherent appurtenances that enable process control of the contents. Current examples include single-use bioreactors (SUBs), single-use mixing systems (SUMs), and disposable skids for depth filtration, chromatography, and ultrafiltration.

The advantage of disposable technology, aside from the elimination of cleaning, is the minimizing of movable parts and piping connections, which reduces the need for change-out of gaskets, o-rings, valve diaphragms, and other elastomers. By being entirely non-product contact, the replacement of any elastomeric surfaces on disposable equipment is dictated by a PM schedule only and is not required during product changeover, further enabling the implementation of risk-based changeover practices.

Examples of Risk-based Application

The examples provided in Table III and Figure 3 are not intended to explicitly define the changeover requirements for the systems discussed; they merely provide a general guidance on what the application of risk assessments to determine changeover controls may permit. The level of risk tolerance and product-specific considerations of those performing the assessments may result in different outcomes than those shared below. The intent is to demonstrate how the guidance may be generically applied.

Conclusion

Traditional changeover philosophies and methods are being revisited as the needs of the industry have changed over time. Current regulatory guidance supports the use of appropriate, scientifically justified, risk-based changeover methods, some of which have been outlined in this article. Utilizing a risk-based approach supported by a strong data set comprised of items such as bench-scale studies, cycle validation, and lifecycle management, the efforts and inefficiencies of the traditional changeover model can be reduced. However, any reduction in changeover activities must be able to be readily defended to demonstrate that the appropriate product carryover controls are in place to ensure both product and patient safety.

Glossary

Briefly Exposed—Open processes containing process and/or product components that are rendered closed by...
means of an appropriate closing process (e.g., media and buffer operations) (12).

Carryover—Contaminants detected in process streams arising from insufficient removal of contaminating components from previous manufacturing steps or batches (14).

Changeover—The steps taken for switching multi-product equipment from the manufacture of one product to the manufacture of a different product (13).

Closed System—A process system that is designed and operated such that the product is never exposed to the surrounding environment. Additions to and draws from closed systems must be performed in a completely closed fashion. Sterile filters may be used to provide effective barriers from contaminants in the environment. A system is closed (or isolated from the environment) when the risk of contamination to the product or process cannot be mitigated by housing the operation in a bioburden-free or particulate-free environment (14).

Crossover—Contamination of a system by components or contaminants found in neighboring system. Crossover typically occurs with open processes sharing environments. Crossover can also occur when there is a breach of integrity of a closed system in an environment shared with an open process or when there is a breach in integrity of two closed processes (14).

Functionally Closed—Process systems that may be opened but are “rendered closed” by a cleaning, sanitization, and/or sterilization process that is appropriate or consistent with the process requirements, whether sterile, aseptic, or low bioburden. These systems shall remain closed during production within the system (14).

Open Process—A process that is exposed to the environment and therefore requires environmental conditions to mitigate the risk of contamination from the environment (14).

Product Changeover—Procedural steps taken for switching from the manufacturing of one product to another product (16). The program by which the processing area is cleared of supplies and components used in the manufacture of a previous product and then readied for production of a new product. This often includes parts changeover and/or special cleaning to eliminate cross-contamination (17).

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Conflict of Interest Declaration

The author(s) declare that they have no competing interests.

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