DESIGNING A BETTER SINGLE-USE FACILITY

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With the right tool, single-use facility design can benefit from a proactive review of facility, systems, design intent and risk.

Although single-use, disposable technologies (SUTs) have been around for decades, continued development and implementation of this innovative process technology is needed to help accelerate the advancement of biopharmaceutical drug development.

SHARED RISK, SHARED REWARD

Responding to global market demand is increasingly a part of successful manufacturing strategy. SUTs promote capacity and production schedule flexibility, up to the 2,000L bioreactor batch and perfusion production scale. In addition, reliable process replication across global manufacturing networks and effective technology transfers to contract manufacturers are provided. The ability to use disposable and similar equipment configurations, and the same materials for production equipment at the process development and commercial-scale phases, also simplifies process scale-up and can accelerate time to market. The disposable platform greatly reduces time spent in cleaning validation.

In SUT processing trains, a portion of processing risk and quality control is shifted to the disposable systems manufacturer. Single-use technologies are also proving adept at delivering compliant, flexible cGMP manufacturing process platforms with improved production titers at many commercial scales. According to a 2015 BioPlan Associates study of the biopharmaceutical manufacturing space, more than 90% of biopharmaceutical facilities use single-use/disposable technologies. Also, manufacturers and suppliers consider both disposable and stainless-steel options when planning their manufacturing strategies.[1] Although some low-production titers of mAb scales may require stainless steel production at 20,000L batch volumes, many of the platforms work with perfusion and batch scale at multiple 2,000L scale and orphan drugs at the 2,000L and 500L disposable scale.

GETTING IT RIGHT THE FIRST TIME

For companies implementing SUT-based manufacturing strategically, assessing accurately the costs and benefits associated

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A NICE INSIGHT SUPPLEMENT

with implementing the technology optimally is critical. Regardless of existing or green-field facility project plans, facility design 'performance' can benefit from a proactive review of facility, systems, design intent and risk.

With years of experience conducting SUT risk assessments, we began to recognize a pattern. There are some engineering design quality approaches that can identify and quantify SUT process-associated risk, suggest mitigation strategy, and thus manage their impact to a minimum. It was recognized that to evaluate operational risk and forecast process performance accurately, an effective repeatable methodology was called for.

A SHARPER TOOL

Framed by a Failure Mode and Effects Analysis (FMEA) analytical structure, our analysis incorporates M+W Group's Single-Use Design (SUD) template to create a high-quality systematic review and risk assessment tool for evaluating SUT biotechnology facilities.

The SUD tool documents key process operations and ties them to specific processing parameters. In our client's experience this has proven to be an invaluable evaluation tool, bringing insight into the full potential of a given SUT process design decision, or when incorporating a new SUT-based process into current operations.

Regardless of what might be motivating the adoption, successful SUT implementation requires a comprehensive understanding of the design space and the quality structure applied to maintain control.

The SUD tool presents a structured approach for evaluating SUTs. Taking a life-cycle approach to product process design and production, the SUD tool rubric sets out a six-part evaluation sequence to structure the analysis:

1. **Establish the quality system**
2. **Define the design space**
3. **Document the design space**
4. **Perform a risk-based FMEA analysis**
5. **Perform sensitivity analysis on risk data**
6. **Finalize and fix the design approach**

There are many quality systems already established, but SUT processing guidelines are less established. Regardless, QbD life-cycle methodology may provide one of the stronger approaches to implementing an SUT quality system regime. Biopharmaceutical manufacturers are outsourcing the design space more and more. Quality attributes have to be met both by the drug manufacturer within the facility and by the SUT manufacturer as well, and both are tasked with characterizing their products and understanding the effect of leachables, leachable byproducts and similar, so as to not affect product quality. Additionally, documenting the reproducible performance of process activities can boost confidence in the manufacturing process.

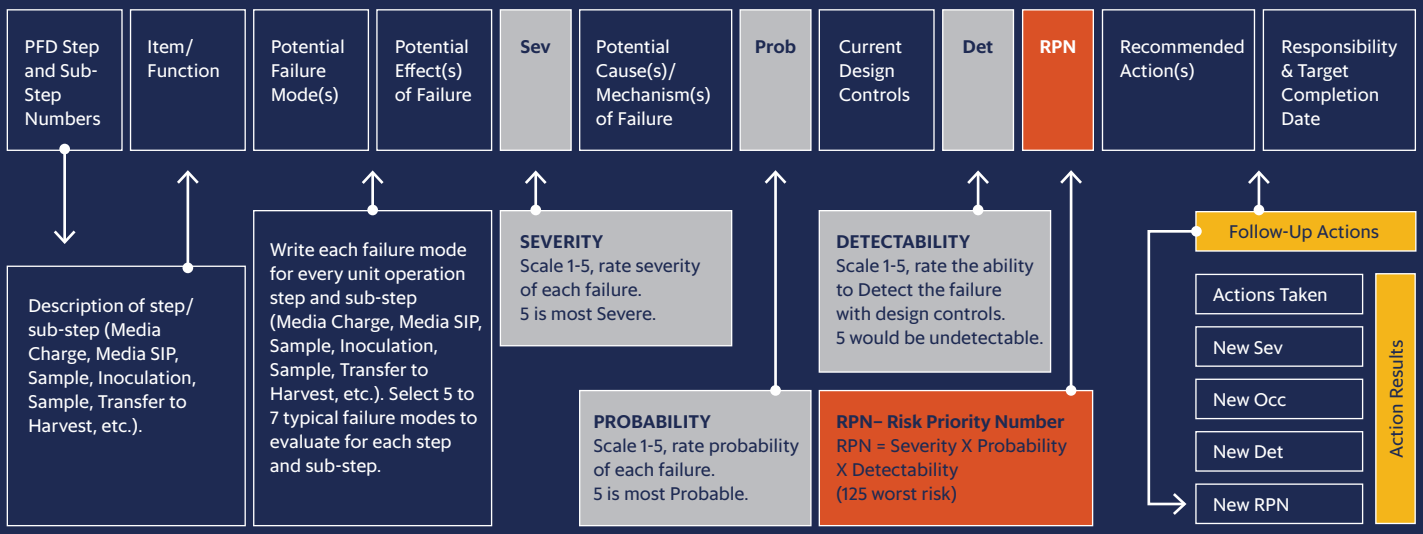
DOCUMENTING THE DESIGN SPACE

A Process Flow Diagram (PFD) is elemental to the process and can facilitate discussion and documentation of the testing studies needed to define the product's design space. Here, it has proven effective to engage SUT suppliers in a discussion involving their production processes and product design space, which are now integral to the biopharmaceutical process design.

To provide the most utility, a PFD (combined with the process description) should portray clearly the process and support functions that affect product quality and identify all process streams to document process and utility flows. The PFD facilitates documenting the steps prescribed by the SUD template and to be evaluated within the FMEA template. Note that this is an expansion of the PFD role. The goal in developing the PFD in this case is to define the process needs

TABLE 1

Potential Failure Mode and Effects Analysis (Design FMEA)



USE OF THE SUD TOOL CAN **DOCUMENT THE KEY PROCESS OPERATIONS** AND TIE THEM TO SPECIFIC PROCESSING PARAMETERS.

and work out those details – the ones that can add significant cost savings to the process design.

The requirement of the PFD in building the SUD template is to capture all the critical steps and operations that pose a risk within the model process to be included in the evaluation. Therefore raw material, heat-up, cool-down, reactions, transfers, changeover, etc., all must be captured in the PFD stream identifications so that the operation can be evaluated within the SUD template and FMEA analysis.

COLLECTING INFORMATION FOR THE SUD TEMPLATE

The SUD template is used to document all critical attributes of the process facility. Here, process steps are walked through while adding details to the steps identified in the PFD. The steps, sub-steps and sub-sub-steps will cover all areas of risk for the inventory, including set-up, run and retirement of the process(es). The process is followed from raw materials through final Vial Fill/Packaging, Bulk Fill/Storage, Freeze-Thaw and Shipment.

FMEA is a tried and true methodology that M+W Group has used successfully for many years. The tool provides an ideal format to compare process parameters identified within the SUD template with the associated risks identified in the FMEA analysis. This numerical evaluation of risk, including thorough cross-references to process details, offers tremendous transparency of all the potential issues SUT implementation may present.

RISK EVALUATION

Selecting failure modes carefully is critical to a successful FMEA, as is consistent, fair evaluation of each of the tasks or functions with potential for risk mitigation. Best practice recommends that the project team evaluating the risk also be involved in brainstorming the failure modes. This will only add to the understanding of the FMEA template prior to filling out the risk evaluation.

Common failure modes familiar to SUT process engineers often considered in M+W Group analysis include:

- **Power Loss**
- **Operator Error**
- **Adverse Leachable**
- **Bag Tear/Leak**
- **Tube or Fitting Wear or Leak**
- **Over Pressure**
- **Material Compatibility**

Although strictly ensuring uniform, consistent ratings is not possible, M+W Group employs a five-point system to help minimize the guessing between hazard ratings. To be effective, we try to keep evaluation simple. For example, address the risk as "it is," "it is not" and "it may be." By starting at this point, using a 5, 3 or 1, then the degrees can be determined (4 or 2 leaning one direction or another). It is best to filter the list to include all of one failure mode so that the evaluator's frame of mind does not wander during the evaluation. Noting carefully what is being considered in the risk ranking can help to make the evaluations more consistent during the evaluation.

It is key that no mitigation is included during the first evaluation, as this would unfairly reduce the perceived risk. The Risk Priority Number (RPN) is established by multiplying the Severity (S) times the Probability (P) times the Detectability (D).

RPN = S × P × D

The max RPN value of 125 can be obtained.

Note that S is the most difficult parameter of RPN to improve. P may be improved, although typically this parameter has already been optimized. Detectability is the most likely parameter to improve through testing or PAT integration.

RISK MITIGATION

Once the FMEA evaluation is completed, the SUD template is expanded with the FMEA failure modes per evaluation step and then updated with the FMEA RPN values. The product of S and P forms a fairly firm value of risk. For executive and operations managers using this methodology, one can provide a distinct line between acceptable risk and unacceptable risk.

Facility design can benefit from a proactive review of facility, systems, design intent and risk. Once accomplished, potential risk-mitigation plans can be put in place to reduce the risk to acceptable limits. Use of the SUD tool can document the key process operations and tie them to specific processing parameters. For M+W Group, this has proven to be a valuable evaluation tool when reviewing the economic suitability and quality potential of integrating SUTs into the existing process or incorporating SUTs into an entirely new process. P

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Mr. Carlson has more than 30 years of industrial process engineering experience. His expertise is in process development and production operations, process and facility design, integration of manufacturing expertise, process engineering, process control and cGMP compliance, providing an ideal background for quality facility and process design. Mr. Carlson's four years of operations experience at DuPont followed by 26 years of design experience with architectural and engineering companies has involved bridging communication across executive, scientific and operations levels of organizations.

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