Application of Failure Mode and Effect Analysis (FMEA) for Process Risk Assessment

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Process validation is required by current good manufacturing practice (cGMP) regulations for finished pharmaceuticals. The scope of process validation includes clean-in-place (CIP), steam-in-place (SIP), mixing, hold time, and manufacturing process variations. With today's biopharmaceutical companies faced with the challenge of reducing validation costs — but in an environment that demands increased compliance with cGMP — applying the same process validation requirements to every process would consume enormous resources.

The FDA's initiative in Pharmaceutical cGMPs for the 21st Century is a science- and risk-based approach to product-quality regulation. That approach enhances the industry's ability to focus on identifying and controlling critical factors affecting process and product quality. The Q7A GMP guide for active pharmaceutical ingredients (APIs) requires validation of critical processing steps determined to affect the quality and purity of an API. A risk assessment should be performed to identify and assess risks within a process and to its personnel and mitigate against those risks. In basic terms, it aims to identify what can go wrong with a system, the likelihood of that occurrence, and its potential impact (1).

Once risks are identified and assessed, risk-reduction measures can be introduced. This process serves to address intolerable risks, focus validation efforts, and maximize the business value of a system.

Table 1: Severity rating

Rating	Description
S = 1 (very low)	No known severity, defect can be corrected without batch loss/ manufacturing delay
S = 2 (low)	Action/alert, manufacturing delay including medium/buffer lot rejection, no product batch rejection
S = 3 (moderate)	Product batch rejection, rework/reprocessing
S = 4 (high)	Customer complaints for defects/dissatisfaction, reportable regulatory problems
S = 5 (very high)	Failure affects safety and regulatory compliance, customer complaint for major defects (e.g., hospitalization or death)

Table 2: Occurrence rating

Rating	Description
O = 1 (very low)	Remote probability of occurrence (e.g., failure rate 0–1 in 100)
O = 2 (low)	Low probability of occurrence (e.g., failure rate 2–3 in 100)
O = 3 (moderate)	Moderate probability of occurrence (e.g., failure rate 4–6 in 100)
O = 4 (high)	High probability of occurrence (e.g., failure rate 7–9 in 100)
O = 5 (very high)	Very high probability of occurrence (e.g., failure rate ≥10 in 100)

Table 3: Detection rating

Rating	Description
D = 1 (very high)	Controls almost certainly will detect the existence of a failure (e.g., real time monitoring such as temperature, pH, conductivity)
D = 2 (high)	Controls have a good chance of detecting the existence of a failure (e.g., final WFI rinsate conductivity in CIP)
D = 3 (moderate)	Controls may detect the existence of a failure (e.g., bioreactor microbial contamination or visual detection of product residues after CIP)
D = 4 (low)	Controls more likely will not detect the existence of a failure (e.g., multiproduct batch-to-batch carryover for inadequate cleaning or change in contamination profile in raw materials)
D = 5 (very low)	Controls very likely will not detect the existence of a failure (e.g., sterility failure in sterile product fills)

This article shows the application of failure mode and effect analysis (FMEA), a risk analysis tool, for determining which critical processes require validation and at what level of effort. FMEA is a preventative tool that uses a bottom-up approach to identify all potential failures of a product, process, or system before use and assesses the effects or consequences

of the identified failure modes. It documents each potential failure mode, its effect in the next level, the cause of failure, and current controls.

A cross-functional team comprising quality, manufacturing, and technical experts is required to perform a process FMEA. The team determines risk levels for occurrence, severity, and detection. A high risk-priority number (RPN) requires full-scale process validation and routine revalidation, and a low RPN requires abbreviated process validation and minimal or no revalidation. Because risk ratings (values) can be subjective based on inputs from team members, a method of rating pharmaceutical processes is presented here to minimize variations.

The illustrations below provide examples of FMEAs for general processes of CIP, SIP, mixing, hold time, and manufacturing process variations. Because of differences in process details and the need for confidentiality, I am presenting general applications. Based on specific process details, you can tailor these examples to meet your company's individual needs. Therefore, the FMEAs presented in this paper are for demonstration only. Also, because judgment and experience will vary, you can't be confident that all auditors will accept your risk assessment. Companies need to set their own approaches and prepare to defend their decisions.

Table 4: FMEA for bioreactor CIP

System Description: Bioreactor CIP **Date:**
References:
Compiled by: **Reviewed by:**

Process Function	Potential Failure Mode	Potential Effects Next Level	Severity (S) Rating (1–5)	Potential Causes of Failure	Current Controls	Occurrence (O) Rating (1–5)	Failure Detection Method	Detection (D) Rating (1–5)	RPN (1–125)
Removal of process residues	Fails to reduce residues to acceptable level	Medium for bacterial growth, interference with fermentation, product loss for undesirable carry-over	3	Ineffective cycle parameters (contact time, flow rate, temperature, pressure)	Spray ball coverage study, cycle development, control of cycle parameters	3	Visual check for residues, WFI rinsate conductivity/ pH/TOC	3	27
			3	Residues dried too long (ineffective cycle)	Control of cycle parameters, maximum dirty hold	3	Visual check for residues, WFI rinsate conductivity/ pH/TOC, dirty hold time	3	27
			3	Fail to achieve cycle parameters (contact time, flow rate, temperature, pressure)	Validated control system, control of cycle parameters, PM for heat-exchanger and pump	2	Verification of cycle parameters	1	6
			3	Fails spray coverage, damaged or clogged spray balls	Spray ball coverage study, SOP for the installation of spray balls	2	Spray balls check before installation	2	12
			3	Detergent pump malfunction or leaks	Pump PM program	2	Verification of cycle parameters and detergent concentration	1	6
Reduce bioburden load	Presence of microbial contamin ation and endotoxin in process stream	Product loss due to contamination	3	Distribution of contaminants, no significant microbial reduction by CIP	Caustic or acid wash, final WFI rinse, validated SIP/ sterilization of components	2	Verification of complete drainage, bioburden monitoring of feed RO and WFI	2	12
Removal of cleaning solution with final WFI	Undesirable presence of cleaning reagents	Presence of cleaning residues in product stream	3	Inadequate WFI rinse (WFI flow and time)	Nontoxic and highly soluble cleaning components, control of WFI flow rate and time	2	Final WFI rinse pH/ conductivity	2	12
Clean hold	Presence of microbial contamination and endotoxin in product	Product loss due to contamination	3	Proliferation of microbial contaminants	Complete drainage/air purge, validated SIP/ sterilization of components	2	Verification of dry surface, controlled air in room and closed tank	2	12

FMEA Format and Definitions

An FMEA requires no unique format. This allows a company the flexibility to adapt the format to its biologics applications.The tables herein present forms with appropriate columns for the failure mode and its effect and severity rating. Each occurrence rating is followed by the cause of the failure and control-in-place. Failure detection precedes detection ratings. I prefer to complete these analyses in two stages: identifying risk (potential failure, effect, cause, control, and detection methods) and reviewing identified risks and assigning appropriate ratings.

Failure: A failure mode represents a situation resulting in an undesirable effect that may ultimately pose a hazard or inconvenience to an end user. Failure modes are potential ways in which an item may fail to perform its intended function. A failure mode can be thought of in the context of a customer complaint or loss of a function (problems, errors, risks, concerns). Examples of potential

failure modes include failures to open, overheating, low yields, leaking, contaminations, and so on.

Effect: Each failure mode can have several potential consequences. Failures can affect products, processes, systems, or customers. In the case of a process FMEA, documentation should include the estimated impact of a failure on the process step under review as well as on downstream steps. For example, a failure at the medium mixing step will affect medium preparation as well as the fermentation. **Cause:** A cause is the mechanism that triggers a failure. Any one failure mode may have several causes. Each cause should be documented.

Controls: The control column on these forms reflects controls currently in place (or that will be in place) to prevent, detect, or reduce the impact of a field failure. Controls are aimed at preventing and detecting causes and failures. Emphasis is placed on prevention rather than on detection of failures.

Detection Method: This refers either to detection of the root cause of a failure or to the actual failure.

Table 5: FMEA for bioreactor SIP

System Description: Bioreactor SIP **Date:**
References:
Compiled by: **Reviewed by:**

Process Function	Potential Failure Mode	Potential Effects Next Level	Severity (S) Rating (1–5)	Potential Causes of Failure	Current Controls	Occurrence (O) Rating (1–5)	Failure Detection Method	Detection (D) Rating (1–5)	RPN (1–125)
Sterilization	Insufficient sterilization	Product loss due to contamination	3	Low temperature, short cycle time	Control of temperature and cycle time	4	Temperature monitoring, F_0 calculation	4	48
			3	Poor steam quality	Qualified clean steam supply	3	Steam temperature and pressure monitoring	2	18
Tank cool down after SIP	Tank cooling rate is too slow	Production delay	2	Poor heat transfer	Filtered air flow, control of cooling step	2	Temperature monitoring	1	4
Maintain sterile environment	Contamination inside the tank	Bioreactor contamination, product loss, production delay	3	System leak, ingress of contamination from nonsterile air	Air filtration, pressure test, positive tank pressure	2	Tank pressure monitoring	3	18

Table 6: FMEA for mixing of medium and buffer solutions

System Description: Mixing of medium and buffer **Date:**
References:
Compiled by: **Reviewed by:**

Process Function	Potential Failure Mode	Potential Effects Next Level	Severity (S) Rating (1–5)	Potential Causes of Failure	Current Controls	Occurrence (O) Rating (1–5)	Failure Detection Method	Detection (D) Rating (1–5)	RPN (1–125)
Dissolution of solution components	Inaccurate amount of components	Solution discard for not meeting specification	2	Balance malfunction, operation error	Balance calibration program, batch record	2	Calibration, component verification	2	8
	Undissolved components	Solution discard for not meeting specification	2	Inadequate mixing speed and time, inappropriate pH/temperature	Soluble components, control of mixing speed and time, pH/temperature control	2	Control check of pH/temperature, mixing speed and time, visual check (turbidity)	2	8
pH adjustment	Out-of-specification pH/conductivity	Solution discard for not meeting specification	2	Malfunction of pump, meter, sensor, and control system	PM for pump and meter, sensor calibration, control system validation	2	pH/conductivity monitoring	1	4

A Practical Risk Rating Method for Biologics

Process risk traditionally has been measured through reliability engineering and statistical methods. Because of its complexity, FMEA has extracted those basic principles without technical mathematics (**2**). FMEA is being increasingly used in the medical device, pharmaceutical, and biopharmaceutical industries. There is, however, no guideline for its use in the biologics industry to minimize variability in assigning risk ratings. I am proposing here a new rating method that combines regulatory considerations with safety and technical aspects. Various rating scales could be used, such as a scale of 1–5, 1–10, or 1–100%. In this discussion I use a scale of 1–5 for all ratings.

Severity Ratings: Table 1 shows how severity ratings can be defined. Severity (S) is assessed based on the impact of failure to the system and customers.

• Is this failure likely to lead to product rejection?

• Will failure lead to a reportable regulatory problem (such as adverse events, error and accident reports, and stability failures)?

• Does this failure directly affect patient or operator safety?

The impact is documented in the "Potential Effects" column of the FMEA form. Severity increases as product moves downstream (e.g., from cell culture medium preparation to sterile fills).

Occurrence Ratings: Table 2 describes occurrence ratings. Occurrence (O) is related to the probability that a specific cause will be present; that occurrence should be determined with respect to the current controls. Determination is made of the probable occurrence of a cause, not of the failure mode — the probability that the cause will lead to a failure.

Occurrence ratings will vary from facility-to-facility based on process design and performance. These ratings are based on 100 so that enough field data can be collected in a reasonable time to determine an appropriate rating.

Detection Ratings: Table 3 describes detection ratings. Detection (D) refers to the ability of a failure to be detected before a customer detects or

experiences its effects. How easily can the failure be detected before it happens or before the next step begins? Detection can focus either on the root cause of failure or on the actual failure. Assuming that causes of all failures are identified, detection is based on the cause of each failure listed in an FMEA.

FMEA Examples

The following examples show how risks can be assessed for bioreactor CIP, SIP, mixing, hold time, and process variations.

Bioreactor CIP: Table 4 shows an FMEA for bioreactor CIP. A severity rating of 3 is based on contamination and product loss in a single product facility, a number that is likely to be higher in a multiproduct facility. The occurrence rating is based on experience with CIP systems, so that can change with new information. The detection rating varies based on detection method such as 1 for pH (real time), 2 for visual (end of cycle), and 3 for QC testing.

Removal of undesirable residue is the most challenging aspect of bioreactor CIP. Microbial contamination presents a lesser risk because of SIP and other controls. This FMEA is intended for initial validation. The process of revalidation, for which the focus is maintaining a validated state, will be different from that of initial validation.

Bioreactor SIP: Table 5 shows an FMEA for a bioreactor SIP. Note that this FMEA can be expanded to include piping, location, port, and valve for validation study design. The severity rating of 3 is based on contamination/product loss and 2 for production delay. The occurrence rating is based on experience with the SIP system, so it can change with new information. The detection rating varies based on detection methods, such as 1 for temperature (real time), 3 for pressure data in a sterile environment, and 4 for indirect biokill (temperature) monitoring. Because maintaining a sterile environment is paramount, sterilization is the most challenging aspect of this bioreactor SIP.

Mixing of Fermentation Medium and Purification Buffer: Table 6 shows an FMEA for mixing media and buffers. (Maintaining a well mixed, homogeneous, condition is assessed in the hold time FMEA.) A severity rating of 2 was assigned based on the potential for medium/buffer loss that

Table 7: FMEA for medium and buffer hold time

System Description: Medium and buffer hold time **Date:**
References:
Compiled by: **Reviewed by:**

Process Function	Potential Failure Mode	Potential Effects Next Level	Severity (S) Rating (1–5)	Potential Causes of Failure	Current Controls	Occurrence (O) Rating (1–5)	Failure Detection Method	Detection (D) Rating (1–5)	RPN (1–125)
Maintain homogeneous condition	Precipitation or settling	Solution discard for not meeting solution composition	3	Undissolved component, settling	0.2 µm filtration, control of mixing	1	Turbidity	1	6
			3	Changes in pH/conductivity/temperature	Control of pH, temperature, and mixing	2	pH/conductivity/temperature monitoring	3	18
Avoid microbial contamination	Microbial contamination	Solution discard for not meeting specification	3	Exposure to contamination	Validated SIP and CIP, inlet, and vent filters	2	Bioburden test, filter integrity	3	18

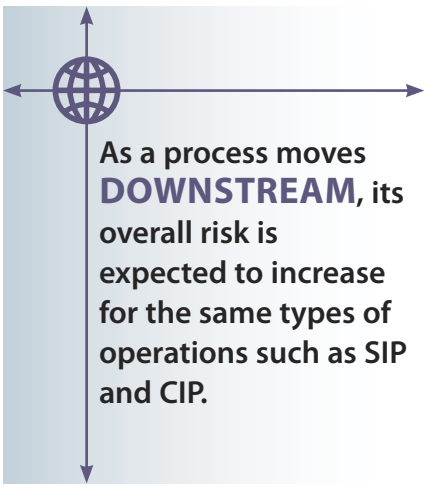
Table 8: FMEA for fermentation process variations

System Description: Fermentation process variations **Date:**
References:
Compiled by: **Reviewed by:**

Process Function	Potential Failure Mode	Potential Effects Next Level	Severity (S) Rating (1–5)	Potential Causes of Failure	Current Controls	Occurrence (O) Rating (1–5)	Failure Detection Method	Detection (D) Rating (1–5)	RPN (1–125)
pH control	Fail to maintain pH	Product loss	3	Malfunction of pH control system	Process control of pH	2	pH monitoring	1	6
Temperature control	Fail to maintain temperature	Product loss	3	Malfunction of temperature control system	Process control of temperature	1	Temperature monitoring	1	3
Dissolved oxygen (DO) control	Fail to maintain DO	Product loss	3	Malfunction of DO control system	Process control of DO	3	DO monitoring	1	9
Cell growth	Process input parameters, raw materials	OOS cell growth	3	Failure to control process parameters at desired level, change in raw material	Procedure and computer control	3	Continuous monitoring	2	18
Product yield	Process input parameters, raw materials	Product loss for OOS yield, higher regulatory scrutiny	4	Fail to control process parameters at desired level, change in raw material	Procedure and computer control	3	End-of-run yield calculation	3	36
Maintain aseptic condition	Microbial contamination through aeration, medium feed, titrant feed, or sampling	Product loss due to contamination	3	Aeration filter failure	Filter quality check	2	Filter integrity, contamination check	3	18
			3	Medium filter malfunction or leaks	Filtration process and filter quality check	2	Filtration pressure, filter integrity, contamination check	3	18
			3	Titrant filter malfunction or leaks	Filtration process and filter quality check	2	Filter integrity, contamination check	3	18
			3	Sampling error	Steaming of the sample line	3	Contamination check (bioburden/microscopic)	3	27

Figure 9: Summary of severity, occurrence, and risk priority numbers

Process ID	Maximum Severity (S) Rating	Maximum Occurrence (O) Rating	Maximum Risk-Priority Number (RPN)
Bioreactor SIP	3	4	48
Process variations	4	3	36
Bioreactor CIP	3	3	27
Holdtime of medium and buffer solutions	3	2	18
Mixing of medium and buffer solutions	2	2	12



could delay production; the rating would be 3 if the mixing process caused product loss by actually failing to supply it on time. The occurrence rating is based on experience with the mixing process, which can change with new information. The detection rating varies based on detection methods such as 1 for pH/temperature (real time) and 2 for operator verification. Medium/buffer mixing for highly soluble products is a low-risk operation.

Hold Time: Table 7 shows an FMEA for medium and buffer hold times. A severity rating of 3 is based on medium/buffer loss during the hold that would cause product loss. The occurrence rating is based on experiences with medium/buffer hold times, so it can change with new information. The detection rating is 1 for pH/conductivity/temperature (real time monitoring) and 3 for turbidity testing. Note that turbidity testing may not be feasible for a solution in a very large tank. Medium/buffer hold poses a higher risk than the mixing step.

Fermentation Process Variations: Table 8 shows an FMEA for fermentation process variations. A severity rating of 3 is based on product loss and 4 for higher regulatory scrutiny. The occurrence rating is based on process experience, so this can change with new information. The detection rating is 1 for pH/conductivity/temperature (real-time monitoring) and 3 for delayed bioburden and filter integrity testing. Variation in product yield represents the highest risk, followed by the possibility of bioreactor contamination during sampling.

Adding Up the Columns

Table 9 summarizes risk priority numbers (RPN) and two additional columns for severity and occurrence ratings, in accordance with ISO 14971:2000 (**3**). In the previous examples, the RPN varies between 48 (bioreactor SIP) and 12 (mixing of medium and buffer). Stamatis proposed a common scale for overall risk: RPN 1–17 minor risk, RPN 18–63 moderate risk, RPN 64–125 major risk (**2**).

As a process moves downstream, its overall risk is expected to increase for the same types of operations such as SIP and CIP. Assessing the relative risks among various processes will help companies set their validation priorities. An FMEA for each individual process can be used to define the scope and extent of initial validation efforts. Initial validation results may change ratings of occurrence and detection; hence, an initial FMEA should be modified for revalidation purposes.

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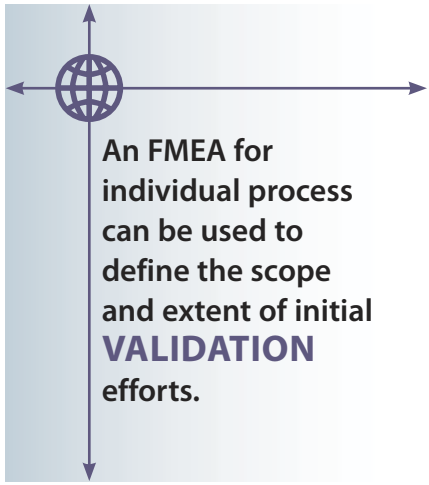

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