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RISK MANAGEMENT AND STERILIZATION PROCESS IN MEDICAL DEVICE INDUSTRY

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ABSTRACT

FMEA is a structured method to study a design or process that anticipates and minimizes unwanted performance or unexpected failures. FMEA is primarily a qualitative technique and is considered a "bottom-up" technique, as individual aspects of risk are analyzed separately and combined. Reusable devices are contaminated with microorganisms after the use of medical devices. To overcome these risks, "reprocessing" is carried out. As per the manufacturer's instructions, all medical devices must be reprocessed before use. In this paper, we will describe the FMEA, Risk management process, and different types of sterilization and cleaning steps. It will give an overview of medical device remediation of risk management and sterilization process.

KEYWORDS: FMEA, PFMEA, RPN, PMSR, Implant, Sterilization, Contaminants, Reprocessing, Cleaning, Disinfection.

Nomenclature

FMEA	Failure mode effect analysis
PFMEA	Process failure mode effect analysis
RPN	Risk Priority Number
Lay Person	Patient/Caregiver
PMSR	Post market surveillance report
SAL	Sterility Assurance Level
ETO	Ethylene Oxide
PQ	Process Qualification
IFU	Instruction of Use

Definition of terms:

Terms	Definition
Sterilization	the validated process used to render a product free from viable microorganisms [14]
Reprocessing	activities such as cleaning, disinfection, and sterilization at a health care facility for re-usable devices

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Cleaning	removal of contaminants to the extent necessary for further processing or for intended use [14]
Contaminant/Residue	biological, chemical, or physical substance on the device that can impair the safety or the performance of the implant [15]
Re-usable Medical Device	medical device designated or intended by the manufacturer as suitable for processing and reuse [14]
Sterile	free from viable microorganisms [14]
Equivalence	Product is compared to master products in terms of different challenge features
Disinfection	the process to reduce the number of viable microorganisms to a level previously specified as being appropriate for a defined purpose [18]
Single-Use Device	Provide sterile and use on a patient for a single time and then disposed
Product Family	group or subgroup of the product characterized by similar attributes determined to be equivalent for evaluation and processing purposes [14]
Sterility Assurance Level	probability of a single viable microorganism occurring on an item after sterilization [14]
Process Qualification	process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification [16]
Instruction of Use	information provided by the legal manufacturer for the reprocessing of the device.

INTRODUCTION

A FMEA provides the design engineer, reliability engineer and others with a Systematic process to analyze systems, subsystems, products with all possible hazards and harms. After that, it will places a probability that the failure mode/hazard will occur and what causes &effect this failure has on the rest of the systems. There are four types of FMEAs in general:

- Design FMEA
- Process FMEA
- System FMEA
- Functional FMEA

Design FMEAs are performed on the product at the design level. Design FMEAs are used to analyze a design and to identify and assess the risk of failures and their impact on the next level of assembly. There are nemourids benefit of developing design DFMEA:

a. Preventive measures can be planned
b. Product Traceability
c. Easy going audit Perform

Process FMEAs are performed on the manufacturing process. Process FMEAs are used to analyze a process and identify all possible risk of failures. Process FMEAs permit preventive measures, can be planned maintenance procedure effectively, and helpful to identify nonconformity product. Developing PFMEA has some merits:

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a. Less scrap in Production
b. Less rework in production
c. Optimal Production Cost
d. Product traceability
f. Strong inventory control

System FMEAs are composed of part level FMEAs such as design FMEAs for individual components. It is considered a detail observation in each components level and all possible causes; effects are being listed.

Functional FMEAs focus on the performance of the component or device being analyzed. This type of FMEA is also known as a "Black Box" FMEA. FMEA focuses on the performance of the intend part or devices.

FMEA is a detailed analysis of a system down to the component level. Once all the items are classified as to the hazard/failure, causes of failure, effect of failure and the probability that the failure will occur then it will be converted to quantitative value called RPN. It is a risk priority number and goal are to reduce this RPN value lower by taking extra effort from design, engineering, manufacturing, and testing point of view. Some sort of cleaning or field test result, additional testing may use to reduce RPN value and mitigate overall risk.

FMEA PROCESS STEPS

Design FMEA process:
Design FMEA consist following sections:
Function, Failure mode, Severity, Potential cause, effect Occurrence, Occurrence number, RPN, Preliminary outcome, Corrective actions & Outcome.

Table 1: Typical sample Design DFMEA [1]

Function	Failure mode	Potential Effect	Severity class	Cause	SEV	OCC	RPN	Outcome	Responsibility and target	Action taken	SEV	OCC	RPN	Final Outcome
Implant must sustain in load.	Implant broken	Patient Serious ill.	Infection	Poor Design	8	2	16	Accepted	N/a	N/a	8	2	16	Accepted

Function: Need to provide a summary of the intended use and function of the device, component, or sub-system. For an example, screw is considering an implant and screw must adequately secure to bone and maintain integrity to withstand the forces. It must withstand all kind of shocks and anatomic fatigue loads. This is the intended use of screw in medical device term.

Cause of failure: It is basically potential failure modes. We must list how the part, assembly, sub-assembly, or components/device could potentially fail. Identify known or foreseeable hazard arising from design and end user point of view. For an example, Bone screw or rod are used to make correction scoliosis issue on spine side. Screw or rod can fail during surgical time due to poor design, materials defect, or mating issues. These are the failure modes and need to be addressed on DFMEA.

Severity: severity is to link with harm. Each harm in the harms list has a severity score as well as detail explanation as to why it was scored as such. Different organization has different benchmark and must follow company own protocol. It can be ranged from 1-9. Higher number consider higher risk.

Occurrence: Occurrence rate calculation includes harm link to all intended user profile. It includes surgeon, doctor, patients, nurse, technician, and all end users. Occurrence calculation can be determined by using below table.

Sometime post market data, Engineers comments and review note play vital roles to determine occurrence calculation [1,2,4].

Table 2: occurrence calculation [2]

Category	Occurrence	Probability	Rating
Very High	1 in 10 1 in 50	≥10% 2%≤Occurrence<10%	10 9
High level	1 in 100	≥1%	8
	1 in 500	0.2%≤Occurrence<1%	7
Moderate	1 in 1000	≥0.1%	6
	1 in 2000	0.05%≤Occurrence<0.1%	5
	1 in 5000	0.02%	4
Low	1 in 100,000	≥0.001%	3
	1 in 1,00,0000	0.0001%≤Occurrence<0.001%	2
Very low	No defect	--------	1

(Table source: Bill Wortman (Eleventh Edition, 2018) CQE Primer, Quality Council of Indiana)

RPN: It is product of the (S) and occurrence(O) ratings. Sometime detection(D) term is being used. Then RPN is simple of product of severity, occurrence, and detection. Since each scale (S, O, D) ranges from 1 to 10. Min(RPN)=1and max(RPN)=1000.The RPN is used to rank order the concerns in the design[1].

Outcome: Different organization has different approach to represent outcome. In medical device industry, outcome represent "acceptable" risk is one category. Means, risk have been reduced to the lowest possible and no further action is required. Some risks are high and need to do further investigation and detail risk mitigation plan is required. Organization's management need to be involved to determine, establish, and maintain risk protocol and procedures to mitigate risks.

Recommended actions: All risk, regardless of the level, need to be reduced as far as possible. For RPNS that are unacceptable, high, and identified by the cross functional team, recommend action need to be developed. The intent of any action is to reduce the severity and or occurrence ratings by some type of risk mitigation plan. For an example- Screw and rod to be secured and locked by each other to prevent any failure. Failure mode found the screw broken and further investigation reveal that- the alignment and detail procedures of the closure mechanism of screws and provided a solution to minimize cross threading and breaking. Detail analysis, complaint study and data from the single counterpart indicates that it was difficult to cross thread and break. It could be happened due to the lack of knowledge of using implants and instruments by the experts. Workshops, in-house instructions are excellent materials to keep expert knowledge update.

Area responsibility: Identify & list individual responsibility for completing the recommended action. In medical device, typically Quality, Mechanical, R&D are responsible for design DFMEA Purpose. Manufacturing Engineers are responsible for any kind of change & improvement occurs in Process FMEA.

Action taken: Need to provide a brief justification of actual action taken and referring to supporting documentation. For broken off the screw implant an example of detail action can be expressed like below rationale:
"Screw materials found to be appropriate. Fatigue test has been performed to see any kind of internal failure and satisfied by the outcome."

Final outcome- We need to update these categories and plug the new RPN after providing enough design verification, validation activities have been completed to ensure an acceptable level of risk. Before entering final RPN, all potential risk to ensure as low as possible. Decision of all risks are low base on providing enough evidence of design verification, validation, testing protocol and management approval [1,2,3,5].

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Process FMEA

Process PFMEA occurrence calculation and severity are the same as described above. Process PFMEA describe process related failure, hazard, cause, and effect of failures. In medical device industry we can take one example for driver manufacturing steps where below flow diagram has been developed. We will describe getting Raw materials hazard, cause& effect as an example of process PFMEA.

Process Flow:

Raw material-----Cleaning method-----Machining Process---De-bulk process---Heat treatment-----Passivation----Laser etch------Inspection per ASL guideline-----Final inspection----Packaging----Shipping.

We can consider getting raw material is a first process.

Possible Potential Failure Mode**:**

1. Incorrect batch of raw material
2. Incorrect material specifications

Potential Effect of Failure**:**

1. Return materials
2. Production delay

Potential Cause of Failure:

1. Supplier error
2. Poor communication

Severity and occurrence calculation: Severity conssits1-9 ranges from Harm table. Higher severity considers higher risk. Each company follow their own harm table. If there is a Raw materials scarcity for example then it could end up delay production, means-Patient life matter. It can be considering in higher risk and mark as"9". Detection can be calculated by using table 3[1].

Table 3: process fmea detection criteria: [1]

Some organization use detection table to represent total RPN value. Detection sample table is given below.

Category	**Criteria**	**Probability**	**Rating**
Failure is certain to be happened	No know control that detect failure	50%-60%	10
		30%-49%	9
High, failure occurs periodically	Control detects failure mode	10%-20%	8
		5%-9%	7
Moderate	Moderate control failure mode	2%-4%	6
		1%	5
		0.5%	4

Relatively low	Low control failure mode	0.05%	3
		0.005%	2
No failure	Failure almost impossible	0.0005%	1

(Table Source: Sarah E. Burke, Rachel T. Silvestrini, The Certified Quality Engineer Handbook, Fourth edition)
RPN calculation: RPN is the product of Severity, Detection, and occurrence. Need to determine whether fall under accepted range or do need to do further investigation.

Table 4: sample pfmea [1]

Customer	Medical device Manufacturing Company					PFMEA date	01/01/20		Supplier name: XXXXX						
Part#	Driver					PFMEA rev	A								
Drawing#	2					Rev date	XXXX		Perform by: Process Quality Engineer						
SL#	Function	Failure Mode	Potential Effect	SEV	Potential Cause	OCC	DET	RPN	Re-commanded action	Action taken	SEV	OCC	DET	RPN	Outcome
1	Getting Raw material	Wrong Material	Process delay	9	Wrong supplier	2	3	54	See material spec	N/A	9	2	3	54	Accept
2	Clean	Part not clean	Rework	8	Inadequate machine	2	3	48	See Procedure	N/A	8	2	3	48	Accept
3	Heat Treat	Inadequate finish	Production delay	9	Furnace issue	1	4	36	Heat treat# XYZ	N/A	9	1	4	36	Accept

As we discussed of two FMEA, we found outcome “accepted”. Some failure and occurrence could force to move further investigation and need to reduce risk as much as possible. Some sorts of mechanical testing, fatigue test or improvement of materials lead to reduce failure. Manufacturing process improvement, improvement of inspection methods, applying lean, six sigma, Kaizen tools could lead up improvement of Process FMEA steps [13].

DFMEA/PFMEA LOGIC

Basic decision flow chart for DFMEA/PFMEA structure has been shown in below.

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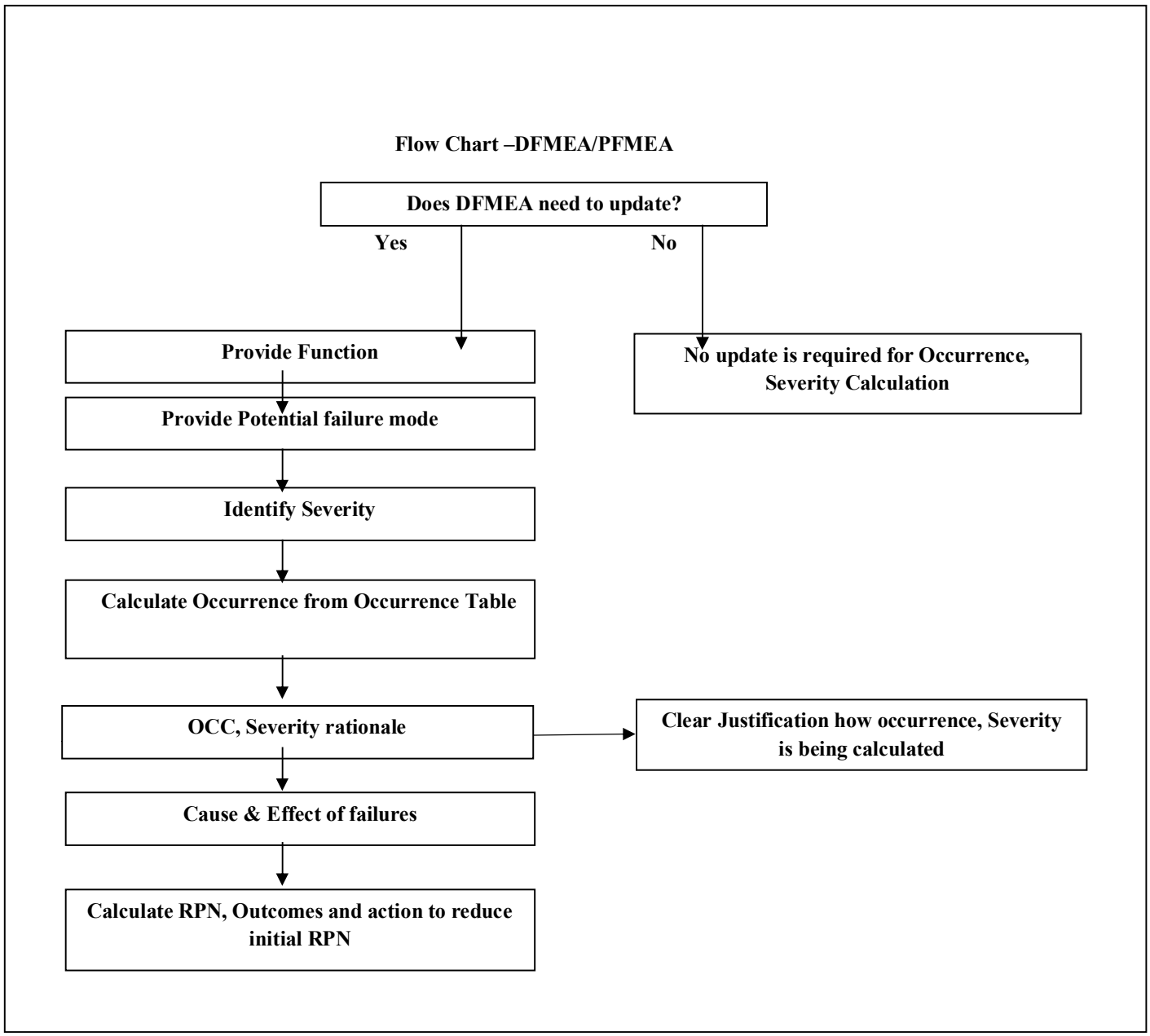

Fig 1: DFMEA/PFMEA Flow Chart

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RISK MANAGEMENT TOOL

Many Quality professionals have been trained in the regular use of risk management tools, The FDA guidance document provides a list of risk management tools to assess and manage risks. Some of the tools are listed below [2]:

a) Flow chart/Block Diagram
b) Check sheets or list
c) Failure mode Effects and criticality analysis (FMECA)
d) Fault Tree/decision Tree analysis (FTA)
e) Hazard Analysis and critical control Points (HACCP)

Risk Management Continuous Process

Plan: Need to transfer risk information into decisions and actions. Each single activity needs to be recorded. Action's plan should be realistic and achievable.

Track: Monitor the risk indicators and action taken throughout the activity. If anything, risk identified during design review time, designer and all stakeholders should agree and need to provide farm timeline to track the risk till mitigate.
Control: Adjust for deviations from planned action.
Mitigate: Reduce the impact of any unforeseen event. In medical device industry, risk mitigation is quite challenging. If it is concern of strength and stability then tensile, fatigue test needs to be conducted. Further communications are required to involve of cross functional team until risk has been fully mitigated.

Primary goal of risk control is to maintain the level of risk at or below an acceptable level and reduce risk low as much as possible. This determination should be made by stake holders and should involve the risk management team. Documentation is an important part of the risk management process. Risk plan should be in details & realistic. Plan should review in periodically and close all actions within the time frame. If new risk identify, should identify its origin and proper documentation is required. In medical device industry more frequently risk assessment and update are required. Sometime audit flag forced to do update risk documents in an unplan situation. Control and monitoring risk could be determined whether current risk plan and process are enough or not. Additionally, it is important to determine whether risk treatments, hazards, harm etc. are effective or not and can be determine by additional testing, auditing phase [1,2]

STERILIZATION STRATEGY

The sterilization strategy includes requirements for device sterilization, reprocessing evaluation which includes cleaning, disinfection, and sterilization at a health facility, and cleaning validation for removal of manufacturing residues which are listed in the Sterilization Section of the Design Requirements Matrix (DRM). The strategy is based on the requirements from the applicable harmonized ISO standards for sterilization of medical devices.
Based on the device category sterilization strategy needs to be established as mentioned in Figure 2:

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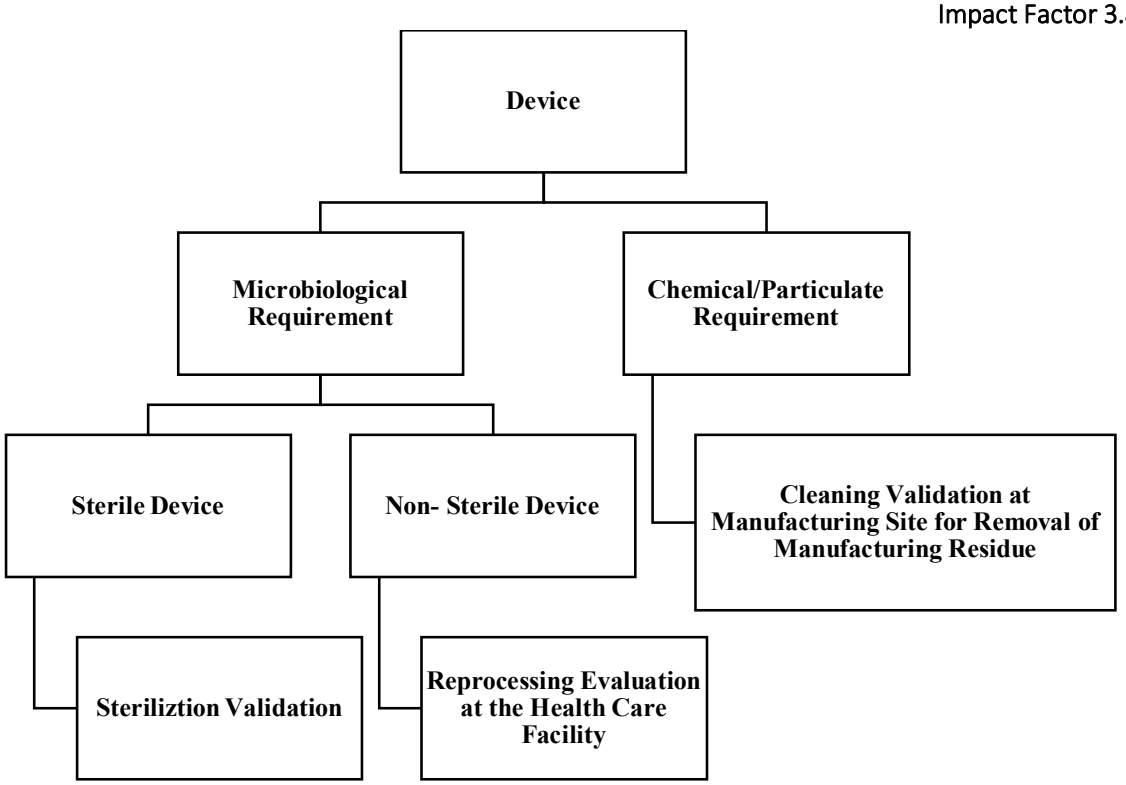

Fig 2: Sterilization Strategy Establishment

For new devices introduction, equivalence can be set by comparing with the master product or validated by performance qualification. If the devices create a new worst-case when compared to the master product family or change in the process flow, then revalidation needs to be performed.

MICROBIOLOGICAL REQUIREMENTS

The microbiological requirements are dependent on the intended use of the device. The product could be a sterile/single-use device or a re-usable device.

Sterile Devices

This device is sterilized before reaching the health care facility for use. The commonly used sterilization method is EO Sterilization and Radiation Sterilization. The sterilization process is performed as per the below ISO standards along with the defined requirements.

Table 5: Sterilization Validation Requirements [16] [17][22]

Sterilization Method	Standards	Requirements
Radiation Sterilization	• ISO 11137-1:2013, Sterilization of health care products – Radiation- Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices.	• ISO 11137-1 specifies requirements for the development, validation, and routine control of a radiation sterilization process for medical devices. • ISO 11137-2 specifies methods for determining the

	• ISO 11137-2:2013, Sterilization of health care products – Radiation- Part 2: Establishing the sterilization dose.	minimum dose needed to achieve a specified requirement for sterility and methods to substantiate the use of 25 kGy or 15 kGy as the sterilization dose to achieve a sterility assurance level, SAL, of 10−6. This part of ISO 11137 also specifies methods of sterilization dose audit used to demonstrate the continued effectiveness of the sterilization dose. Also, this part of ISO 11137 defines product families for sterilization dose establishment and sterilization dose audit.
Ethylene-Oxide (ETO) Sterilization	• EN ISO 11135-1 Sterilization of health-care products - Ethylene oxide – Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices	• ISO 11135-1 specifies requirements for the development, validation, and routine control of an ethylene oxide sterilization process for medical devices.

Non- Sterile Devices

These devices are re-usable and provided in non-sterile conditions with the validated reprocessing instructions (including cleaning, disinfection, and/or sterilization) to be carried out before patient use.

ISO 17664 specifies requirements for the information to be provided by the medical device manufacturer for the processing of a medical device that requires cleaning followed by disinfection and/or sterilization to ensure that the device is safe and effective for its intended use. This includes information for processing prior to use or reuse of the medical device. Rather, this document specifies requirements to assist manufacturers of medical devices in providing detailed processing instructions that consist of the following activities, where applicable: [18]

a) Initial treatment at the point of use
b) Preparation before cleaning
c) Cleaning
d) Disinfection
e) Drying
f) Inspection and maintenance
g) Packaging
h) Sterilization
i) Storage
j) Transportation

CHEMICAL/PARTICULATE REQUIREMENTS

The requirements for the cleaning validation for the removal of manufacturing residues were derived from the following.

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- CFR Title 21, Part 820, subpart G, Production and Process controls section 820.70, Clause h Manufacturing Material defines the requirements. A manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented [19].
- ISO10993-1 requires an assessment of risk for manufacturing processes and materials [20].
- EU MDR Regulation 2017/745 Section 10.1 and 10.2 [21].
    - Devices shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements
    - Devices shall be designed, manufactured, and packaged in such a way as to minimize the risk posed by contaminants and residues to patients

Cleaning process validation and the test methods which are based on a risk management process are performed as per BS ISO 19227:2018[15].

CONCLUSION

The above content gives an overview of the risk assessment process and the sterilization strategy based on the device category as per the requirements defined in the FMEA document. Reading this paper, one's can get idea how to develop a DFMEA/PFMEA and factors that need to be considered. However, we tried to provide some overview of sterilization process that used in medical device industry for understanding of process, EU MDR requirements and ISO standards.

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