Sterilizing and Bioburden Filter Risk Assessment in Vaccine Processes as part of QRM

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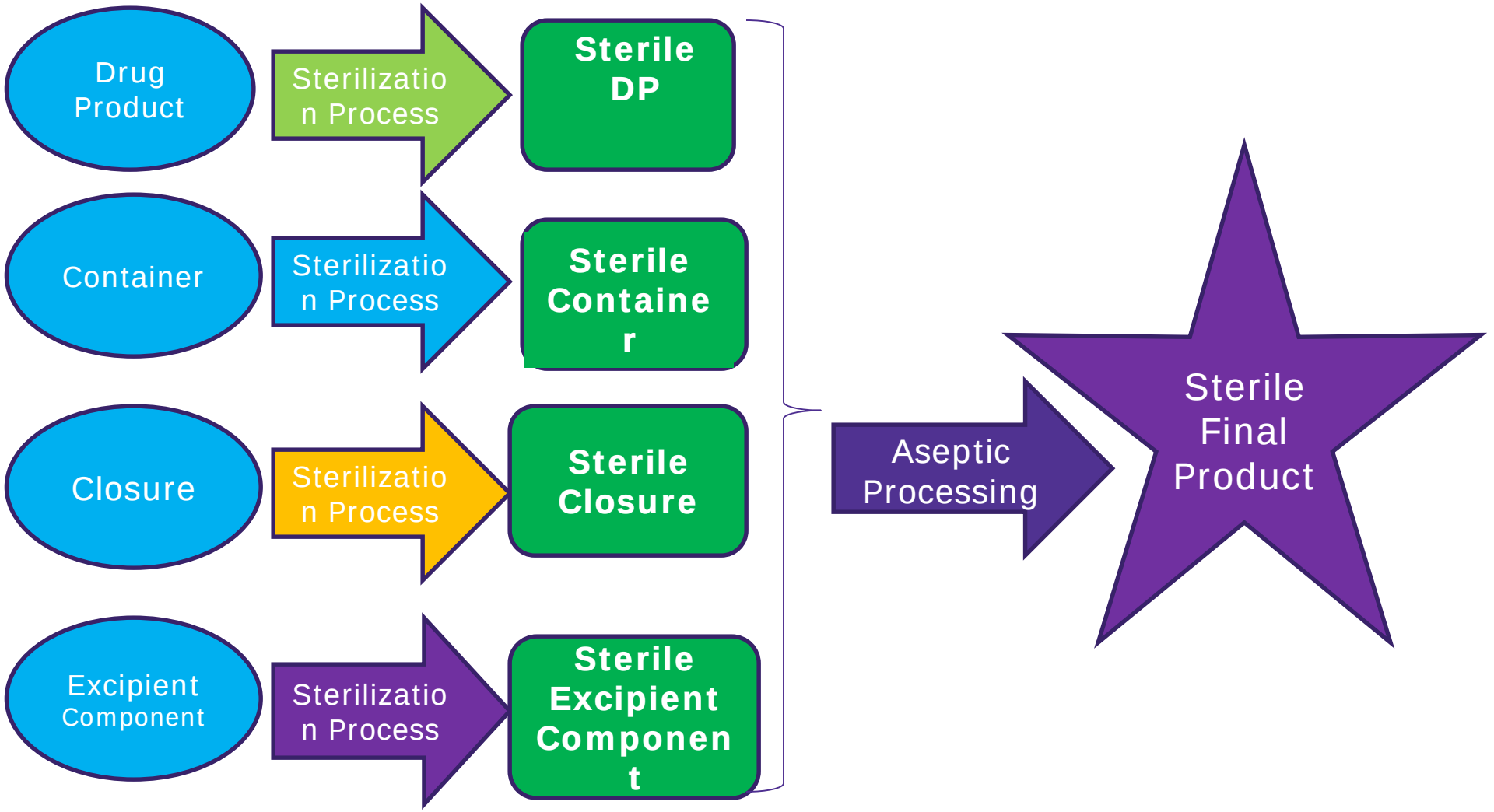
Overview

- Key Regulatory Concerns
- Aseptic Processing Risks
- Some Risk Assessment Tools
- Examples of 3 Typical Schematics
- Risk Sources in Sterile Filtration
- Filter Categories
- Definitions
- References

Key Regulatory Concerns

Efficacy / Strength	Does the validated production process result in a material / residues that interfere with product efficacy or strength?
Identity & Purity	Does the validated production process result in a material / residues that interfere with product purity?
Safety	Does the validated production process result in a material / residues that are toxic to the patient?

Challenges of Aseptic Processing



Multiple sterilization processes optimized for the individual materials

Higher potential risk of non-sterile product

Overall picture of Quality by design

Product & process design and development

Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Understand impact of material attributes and process parameters on product CQAs

Identify and control sources of variability in material and process

Continually monitor and update process to assure consistent quality

Risk assessment and risk control

Implementing Quality by Design - Helen N. Winkle, FDA, Sept 2007

cGMP - Risk-Based Approach

"...the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk"
Chapter 1, EU GMP guide
"With the revision of the chapters on quality management in GMP Parts I and II quality risk management becomes an integral part of a manufacturer's quality system.
PICS Annex 20
"All manufacturing authorisation holders . . must have a system for QRM. Inspectors will review the QRM system as part of the Quality Systems section of the inspection"
GMP Frequently Asked Questions (MHRA)
Article 12: The manufacturers should establish the management system of quality risk . . . . The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient.
Pharmaceutical Products GMP
(Draft for Comment) China SFDA, Version 1, 12-Oct-2009

Example of Traditional vs. Science / Risk-based Approach to Validation

Traditional	Science and risk-based lifecycle
• Arbitrarily selecting three batches for initial validation (e.g., qualification batches) and typically for process changes	• Uses scientific rationale to determine number of batches / amount of data required • Determines scope of validation by analyzing data and significance of change • Uses statistical tools during development, initial validation, and process monitoring • Considers all potential risk factors in designing process validation studies and so helps prioritize critical aspects and reduces effort on aspects that are not important

Based on objective evaluation, we need to move from left to right.

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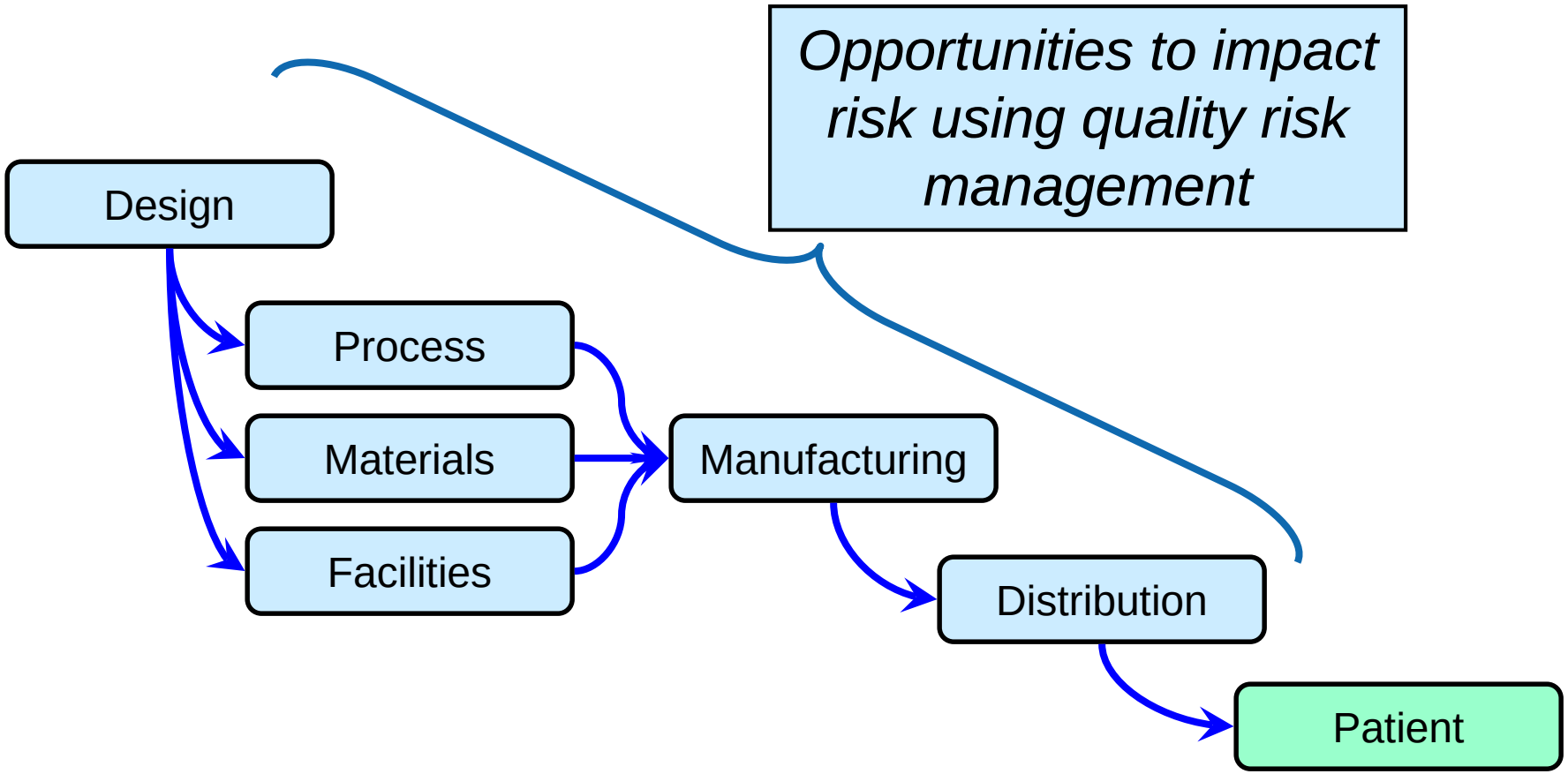
ICH Q9 Links Risk of Process to Patient



G.- Claycamp, FDA, June 2006

Examples of Tools to Assess and Manage Risk

Failure Mode Effects Analysis (FMEA)

Failure Mode, Effects and Criticality Analysis (FMECA)

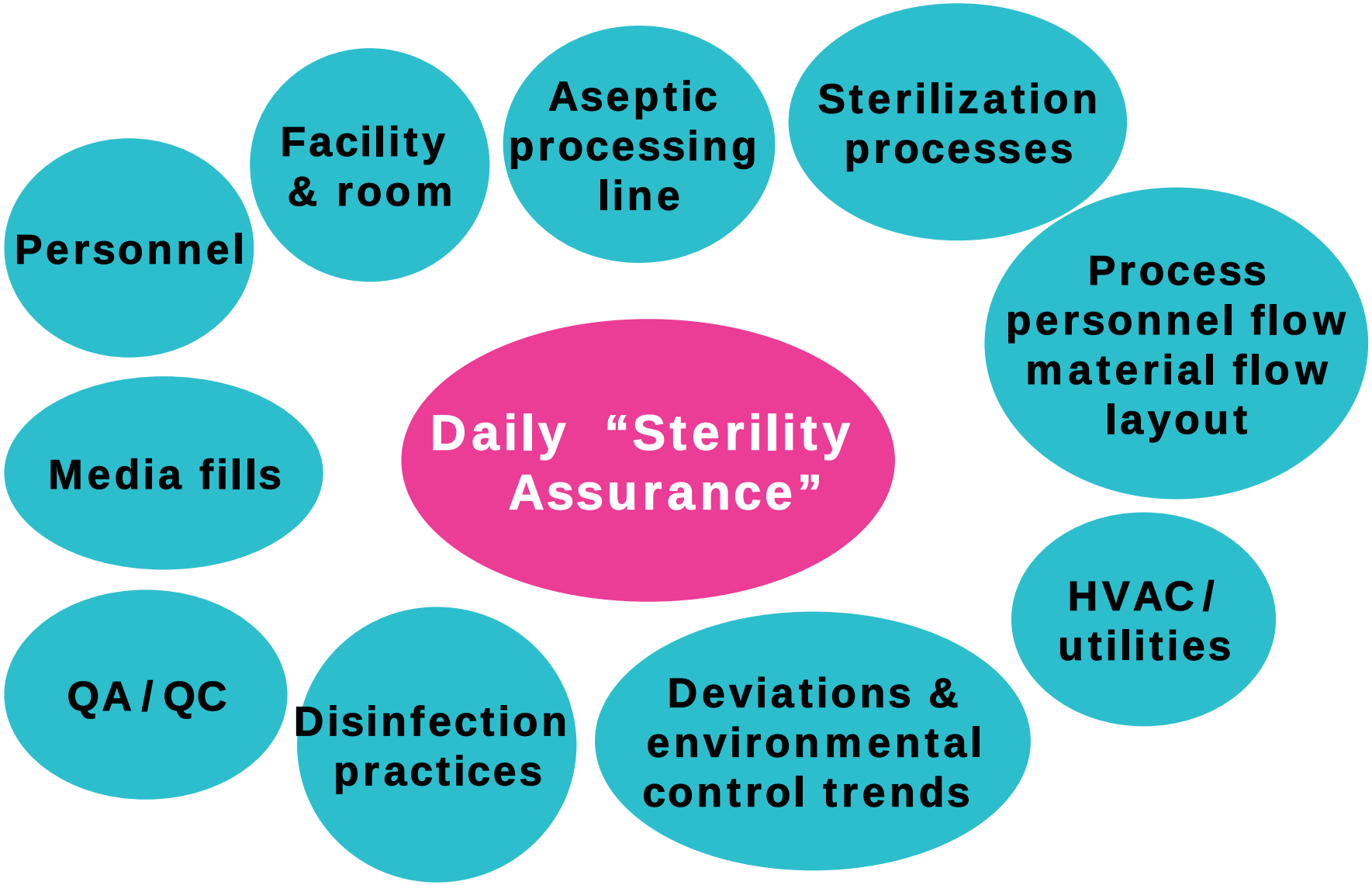
Risk Probability Number (RPN)

Fault Tree Analysis (FTA)

Hazard Analysis and Critical Control Points (HACCP)

Hazard Operability Analysis (HAZOP)

Highest risk – the sterile core



From presentation by Richard L. Friedman, Center for Drug Evaluation & Research

Key Step in Risk-Based Approach
- Critical Control Point Identification

Causes of Contamination

Where are the potential routes of contamination in a sterile or an aseptic process?

Detection of Contamination Problem

What measurements are most valuable in indicating sterility assurance?

Focus on issues of concern

Influential factors that determine control of the facility and process

Failure to meet cGMP can impact safety or efficacy

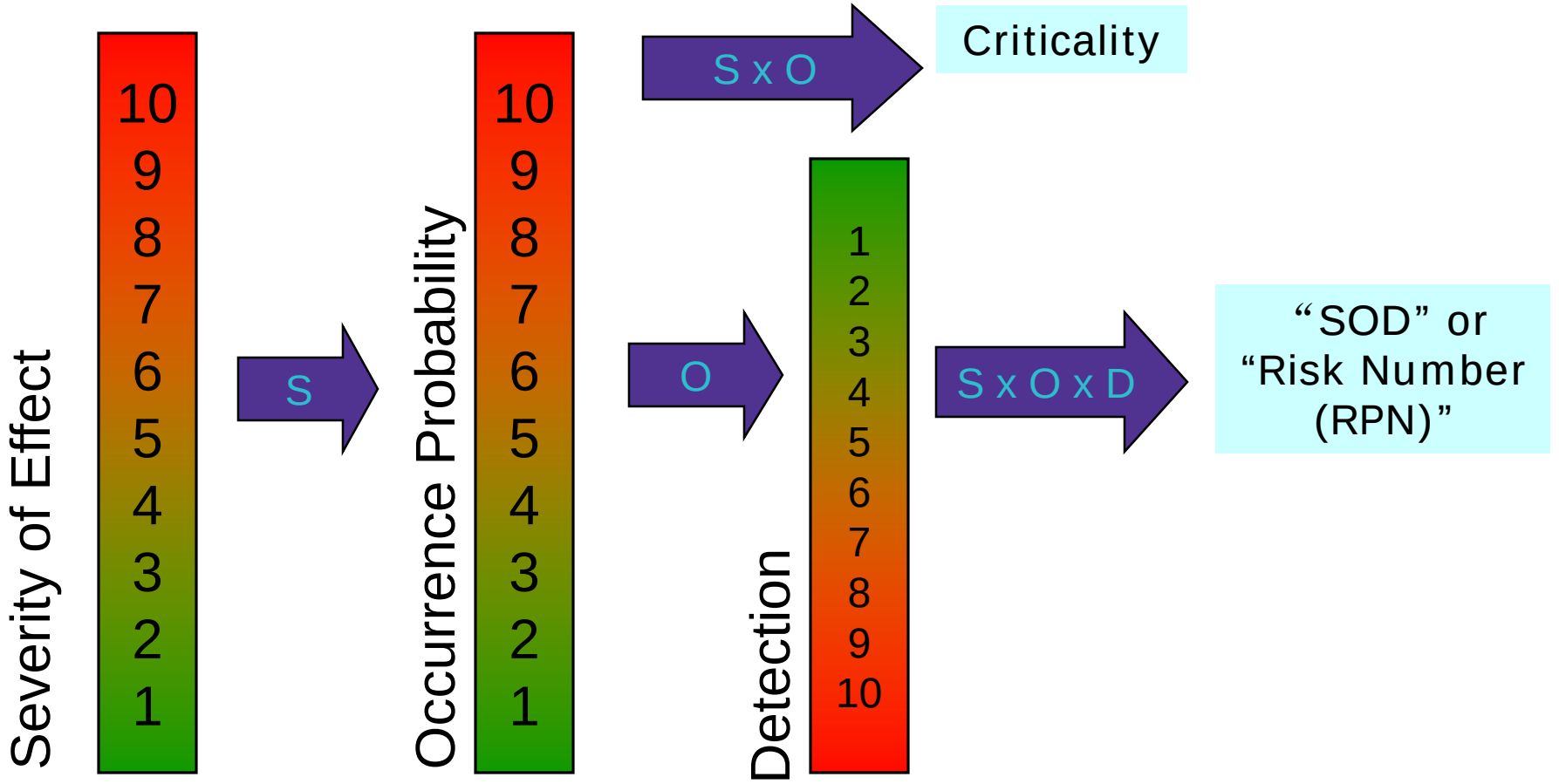
FMEA Risk Assessment Tool

Aligns risks of failure with source of failure
Helps determine risk
Root causes
Likelihood
Impact
Detection
Output of FMEA is a risk priority number (RPN)
RPNs input in a simple matrix to help prioritize tasks

System Function	Failure Mode	Severity of Failure (1 – 5)	Probability of Failure (1 – 5)	Level of Detection (1 – 5)	RPN = (Severity x Probability/Detection)	Actions or Comments

Overview of RPN Calculation

Slide courtesy of Dr. H. Gregg Claycamp (FDA)



Scoring does not have to be linear. Scoring does not have to be 1-5 or 1-10

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Risk Values & Risk Matrix
- Calculates Criticality, Allows Prioritization

Risk values (Probability x Impact) are the same as Criticality (Severity x Probability) in an FMEA analysis Risk matrix allows task prioritization

Score	Probability	Example
1	Rare	• Seen every 10-30 years
2	Unlikely	• Seen every 5-10 years
3	Possible	• Seen every 1-5 years
4	Likely	• Seen to occur more than once a year
5	Almost certain	• Seen several times a year

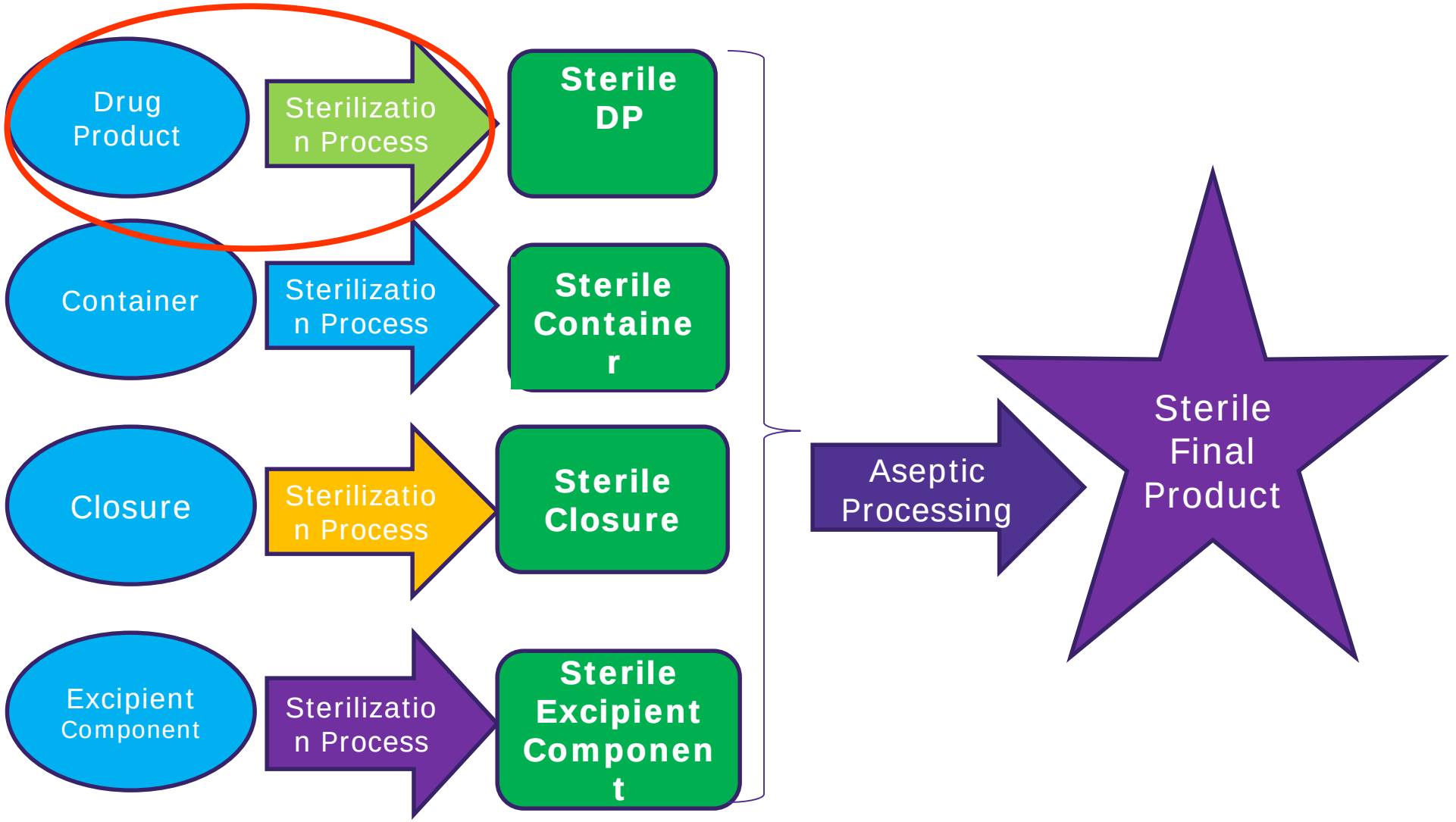
Score	Impact	Consequence
1	Negligible	• No regulatory issue • No effect on and not noticeable by patient
2	Marginal	• May require MRA notification • Decision to release product not compromised
3	Moderate	• MRA inspection may identify a major concern but deficiency quite easily resolved • Limited product recall possible
4	Critical	• MRA inspection may conclude serious non-compliance • Likely product recall from one or more markets
5	Catastrophic	• Enforcement action by MRA such as consent decree, product seizure • Global product recall

	Impact				
Probability	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

WHO Guideline on QRM. Draft 2010

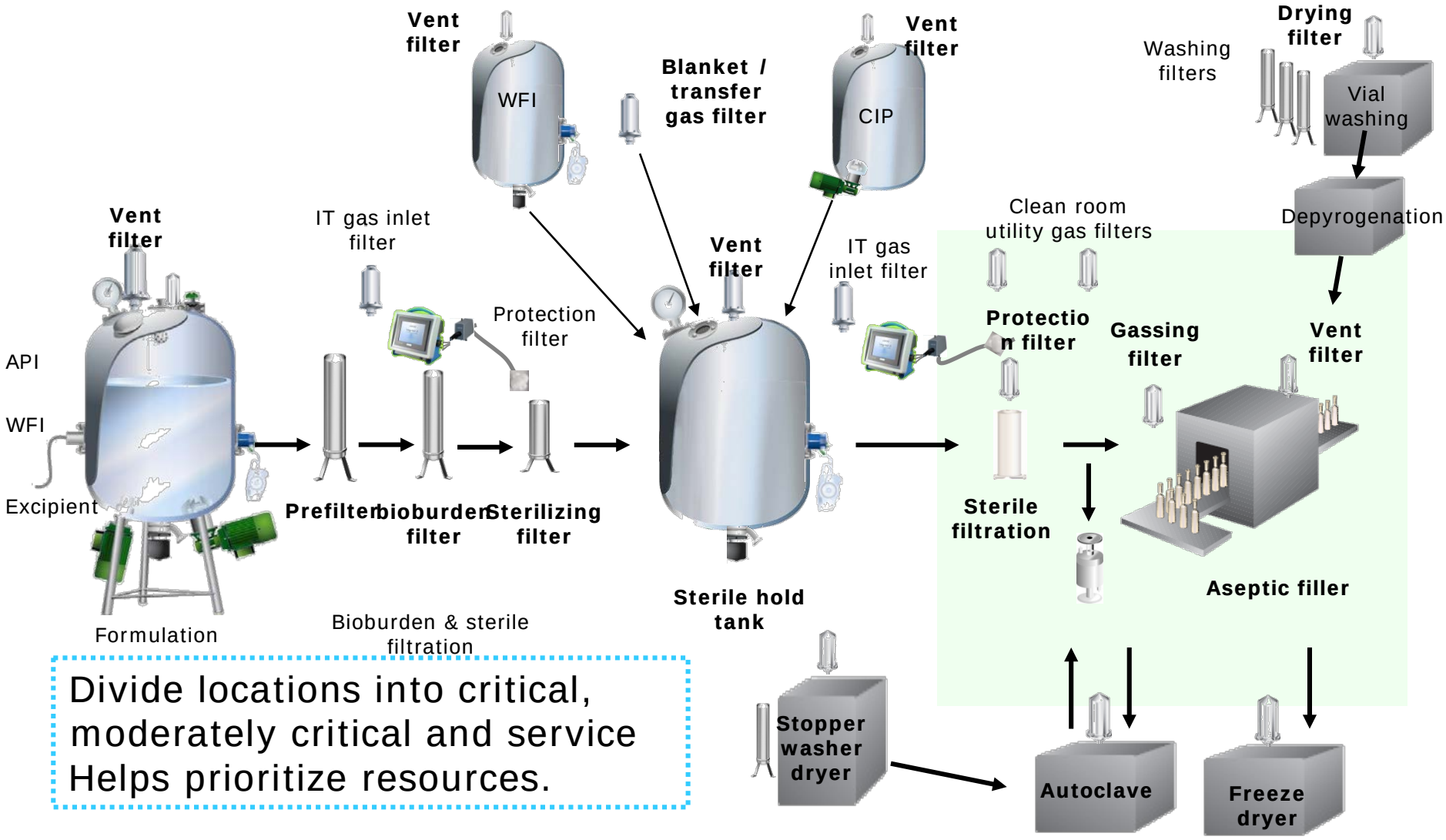
Example of Risk Assessment Applied to Filtration

Challenges of Aseptic Processing



Multiple sterilization processes optimized for the individual materials Higher potential risk of non-sterile product

Filter locations in a generic vaccine formulation / filling suite



Divide locations into critical, moderately critical and service
Helps prioritize resources.

Review & Categorize Filters Site-wide

Critical

The filter directly affects product quality

Examples: sterile liquid filter, vent filter on a sterile hold vessel,

Moderately critical

The filter indirectly affects product quality

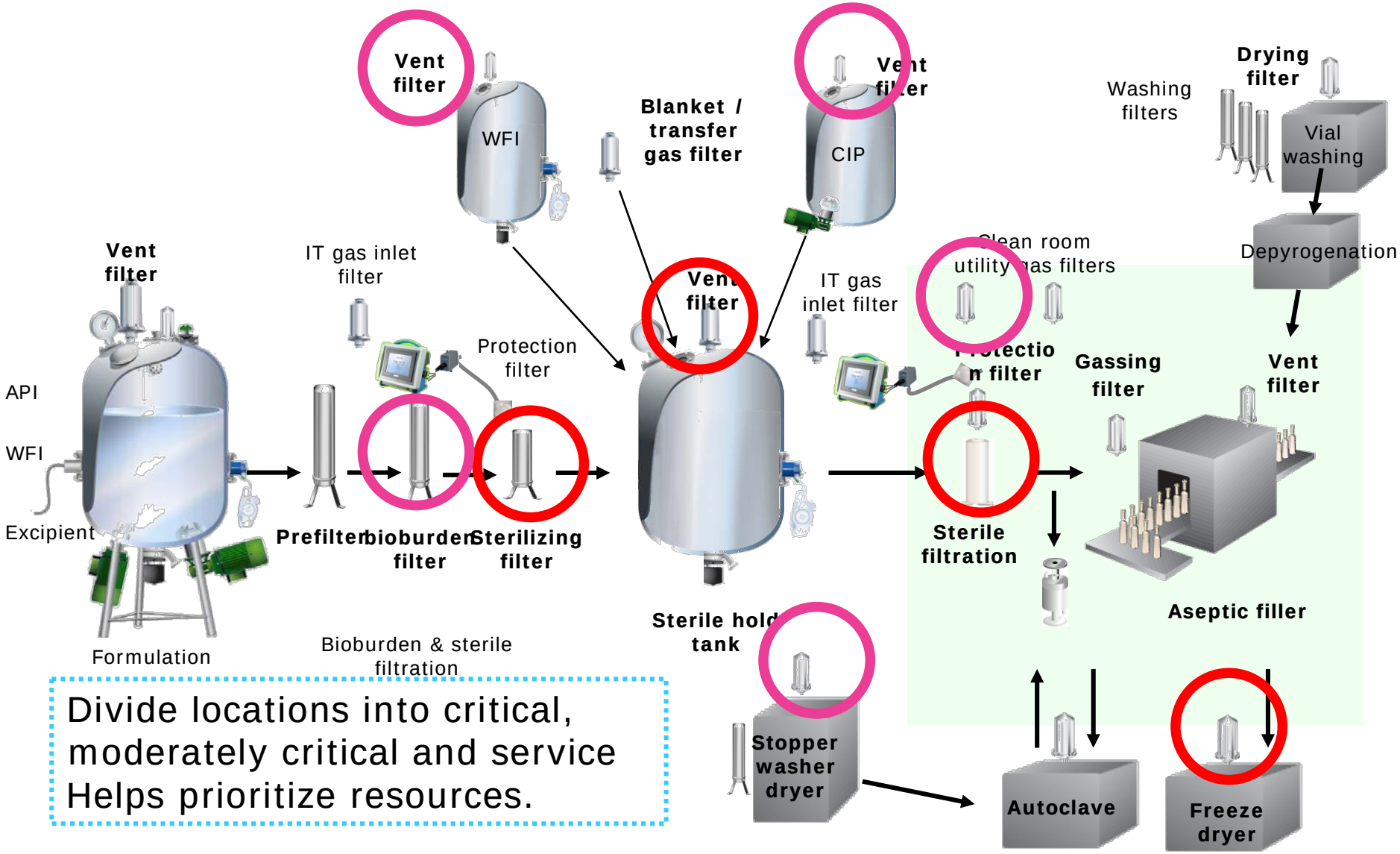
Examples: vent filter in a grade C area, bioburden reduction filter

Service

The filter does not affect product quality

Examples: distribution gas filter, water prefilter

Filter locations in generic vaccine formulation / filling suite



Divide locations into critical, moderately critical and service
Helps prioritize resources.

Filter Risk Assessment Considerations

- Fluid classification
- Dosage form
- Room classification
- Location of filter in the process
- Contact time
- Process conditions
- Fluid pretreatment
- Filter pretreatment
- Prior history

FMEA (RPN) & Detection Rating for Sterile Processes

TABLE 1: FMEA RATINGS FOR STERILITY ASSURANCE

Score	Severity	Occurrence	Detection
10	80-100% probability of affecting multiple batches	More than once per day	Controls cannot or will not detect failure
9	60-80% probability of affecting multiple batches	Once every 3-4 days	Controls will probably not detect failure
8	80-100% probability of affecting one batch	Once per week	Controls not likely to detect failure and must wait for larger volume
7	60-80% probability of affecting one batch	Once per month	Controls may not detect the failure until after the customer is affected
6	40-60% probability of affecting multiple batches	Once every 3 months	Will be detected prior to affecting the customer
5	40-60% probability of affecting one batch	Once every 6 months	Controls may detect the failure before affecting the customer
4	20-40% probability of affecting multiple batches	Once per year	Will be detectable after release but before affecting the customer
3	20-40% probability of affecting one batch	Once every 1-3 years	Controls will have a good chance of detecting failure
2	0-20% probability of affecting multiple batches	Once every 3-6 years	Controls will almost always detect the failure
1	0-20% probability of affecting one batch	Once every 6-100 years	Controls will detect the failure prior to production release

Very useful as starting point for discussion on rankings – especially occurrence

FMEA: A Risk-Based Approach to Sterility Assurance: C. Alexander Pharm Manufacturing 2006

Filter integrity occurrence example:
Score 1 = “out of the box”,
Score 3 = at end of total process

Detection Rating Scale

Detectability = Difficulty of detecting the defect or failure with current process controls.

Rating	Description	Definition
5	Very difficult to detect.	No known controls available to detect failure mode, or defect is not detectable.
4	Somewhat difficult to detect.	Remote likelihood current controls will detect failure.
3	Moderate	Moderate likelihood current controls will detect failure.
2	Somewhat easy to detect.	High likelihood current controls will detect failure.
1	Easy to detect.	Current controls almost certain to detect the failure mode.

Use as discussion on detection methods – sterility testing is statistical, filter integrity testing relies on quality filter, good procedure, qualified tester, etc.

Managing Process Risk Line by Line: Greulich & Hardy Pharm Manufacturing 2007

Example for a Sterile Filter Issue - From PQRI Final report

Event

Microorganisms not removed from the product resulting in non-sterile product

Severity score = 4

Major: Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product

Frequency score = 3

Likely: Event may occur and/or has occurred in the past

Detectability score = 1

Readily Detectable: Can be detected using IT and sterility test

Overall Score: 4 * 3 * 1 = 12

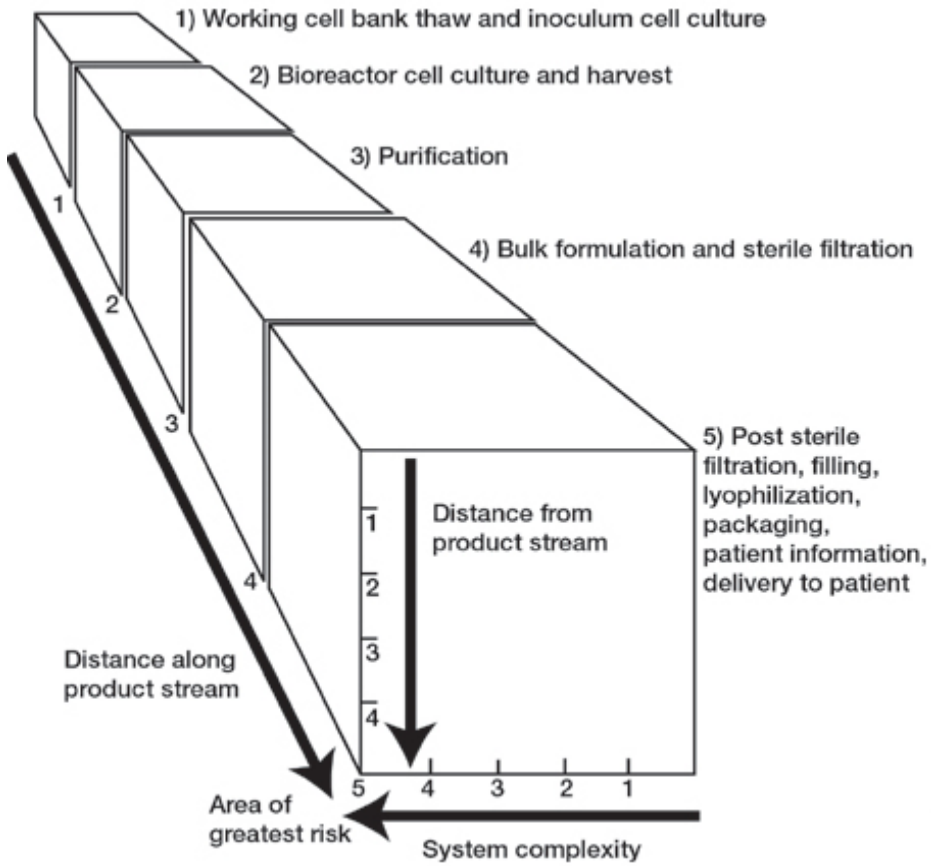
NB max score is 64 in this category (i.e. 4 * 4 * 4)

Example of Sterile Filter Issue in Facility not Practicing cGMP or QRM

Failure Mode	Potential Effects	S	Potential Causes	O	Current Controls	D	RPN
Non-Integral Filter	Non-sterile product	5	Incorrect filter used	1	Operator compares filter catalog number to BMR	2	10
		5	Unqualified filter	5	No filter comparability testing performed	5	125
		5	Pre-use IT test not done	4	No pre-use test required on BMR	5	100
		5	False post-use IT pass value	5	Operator training on IT equipment	4	100
		5	Unqualified integrity tester	3	No tester IOQ & PQ completed	5	75
		5	Out-of-spec. SIP cycle	2	Sterilization cycle details on BMR	3	30
		5	Poorly maintained housing	4	No visual inspection required and noted on equipment log	5	100

3D System Risk Assessment Concept

Considers
a system‘s distance from the process stream
its location along the process stream
the system‘s complexity
Highest score is highest risk
This tool is mainly used to assign a risk level to an overall system
Excellent for complex systems as part of “big picture” analysis



“A 3-D Risk Assessment Model”, *Journal of Validation Technology* [Autumn 2008] pp70 - 76

potential sources of filter-based risk

Potential Risk Source
- Poor Vendor Qualification

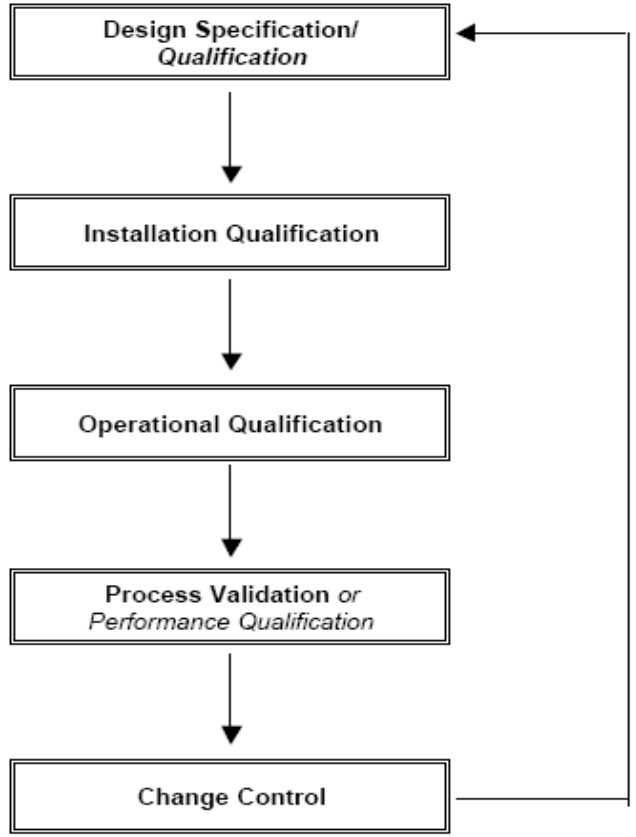
Vendor qualification is a cGMP requirement

Poor / no qualification can result in

Supply issues
Inconsistent quality
Inconsistent performance
Inadequate documentation
Poor technical support

Potential Risk Source
- Poor Equipment Qualification

Equipment unable to achieve required accuracy, reproducibility
Equipment incapable of operating over required range of conditions
Unverifiable data transferred to batch documents and used to release product
Poor reliability
Inconsistent calibration, preventative maintenance
Undocumented or inconsistent change control



E.g. Consider an filter integrity tester

Potential Risk Source
- Poor Sterile Filter Qualification Categories

Flushing
Product instability

Chemical Compatibility
Non-sterile product
Integrity failure
Product instability

Extractables
Product instability
Product degradation

Adsorption
Product instability
Efficacy below spec.
Shelf-life issue

Integrity testing
- Lower filter retention
- Non-sterile product

Sterilization
- Non-sterile product
- Filter damage

Bacterial Retention
- Lower filter retention
- Non-sterile product

Capacity testing
- Filter blocks mid-process

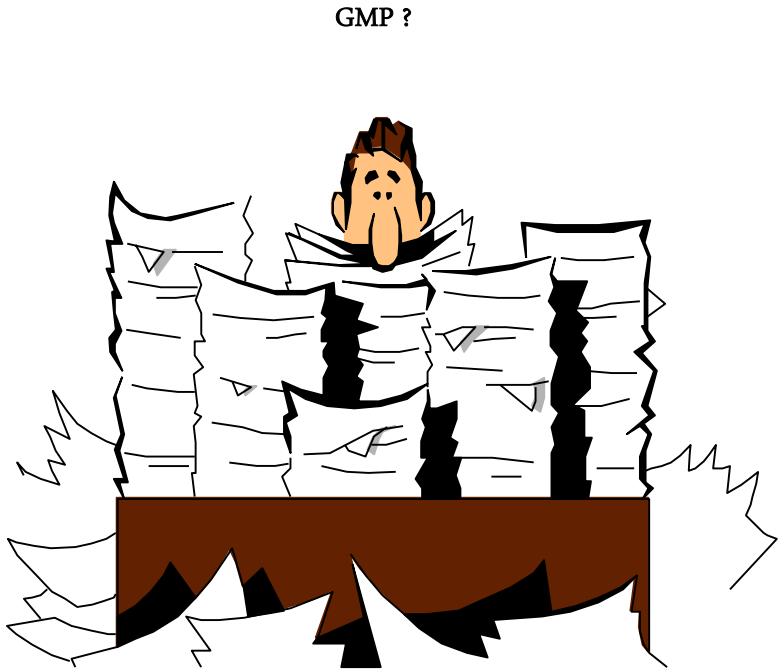
Eight Filter Validation Elements

Validation must represent "worst case" process conditions

- **Feed solution**
- **Time**
- **Pressure**
- **Fluid**
- **volume**
- **Sterilization**
- **environment, etc.**

What Documentation should Support Sterilizing Filtration?

- Risk analysis based approach to processing and product impact
- Quality by design
- Suitability for duty
- Adsorption
- Extractable
- Integrity testing
- Bacterial retention
- Sterilisation process validation
- Product stability testing
- Equipment qualification



Conclusion

- Quality risk management (QRM) is part of cGMP and an expected component of a regulated production process
- Risk is present in all biopharm operations
- Tools are available to assess risk
- FMEA process and output allows risk and activity prioritization
- Sterile and bioburden filtration are integral components in all biopharmaceutical processes
- Vendor, equipment, filter qualification is vital to ensure safe, economic and compliant production
- Sterile filtration qualification is a well-established process
- Filter categorization makes systems simpler and more robust

Some Useful Regulatory References

FDA

Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

PICS

PE 009-7 GMP Guide (especially Annex 1 and Annex 20)

WHO

WHO Guideline on Quality Risk Management (Draft Working copy) (2010)

WHO Technical Report Series 908, Annex 7 (2001)

ICH

Q10 Pharmaceutical Quality System

Q9 Quality Risk Management

PDA

TR44 Quality Risk Management for Aseptic Processing

TR26 Sterilizing Filtration of Liquids

TR40 Sterilising Filtration of Gases

PQRI (Product Quality Research Institute)

Post Approval Changes for Sterile Products Working Group - Final Report April 19, 2007

Useful Definitions

Integrity Test - **Test to determine the functional performance of a filter system**

Validation - **Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.** (PICS PE-009 GMP Guide)

Critical applications - **Where process fluids "are in direct contact with sterile final product or critical surfaces of the associated equipment."** (PDA TR40)

Moderately critical applications - **Are "those where the filtered gas will not be in direct contact with exposed sterile product or surfaces."** (PDA TR40)

Redundant filtration - **A type of serial filtration where a second sterilizing filter is used as a backup in the event of an integrity failure of the primary sterilizing filter.** (PDA TR26)

Serial Filtration - **Filtration through two or more filters of the same or decreasing pore size one after the other** (PDA TR26)

Sterilising Filter - **"a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties" (PICS PE-009 GMP Guide)**
"A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent" (FDA)
"A filter that reproducibly removes all test microorganisms from the process stream, producing a sterile effluent." (PDA TR26)

Thank You for your Attention!

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