Identification and Control of Critical Process Points Using Complementary Risk Assessments (corrected)

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RISK is a four letter word

- Over-encouraged
- Over-exposed
- Misunderstood
- Misapplied
- The process is subject to unfounded assumptions and opinion to influence the result

Pre-emptive Risk

- When is the best time to assess risk?
  - Before a failure occurs!
    - Objective
    - Unemotional
- When is the worst time to assess risk?
  - Before a bad decision is made
  - After a bad decision is made
    - Pressure to come to a certain conclusion

GMP and Standards References

- Guidance for Industry: Q9 Quality Risk Management

  http://www.fda.gov/cder/guidance/7153fnl.htm
- Pharmaceutical cGMPs for the 21st Century: A Risk Based Approach
- ISO 14971:2007, “Medical devices - application of risk management to medical devices”

Getting Started

- Identify and assemble a cross functional team
- Describe/understand the product, its formulation and its distribution
- Identify and understand the intended use and quality attributes of the product
- Develop a flow diagram that describes the process
- Understand processing methods

Risk Assessment 1: HACCP

- Hazard Analysis and Critical Control Point
- Pillsbury created HACCP in the 1960s as a process control mechanism for food for NASA
- FDA adopted HACCP as a requirement for process control in the food industry
  - Hazard Analysis and Critical Control Point Principles and Application Guidelines, August 1997, http://www.cfsan.fda.gov/~comm/nacmcfp.html
- HACCP identified as a risk assessment tool in FDA, ISO, ICH and WHO documents

HACCP: 7 Steps

1. Conduct a Hazard Analysis
2. Determine the critical control points (CCP)
3. Establish critical limits
4. Establish monitoring procedures
5. Establish corrective actions
6. Establish verification procedures
7. Establish record-keeping and documentation procedures

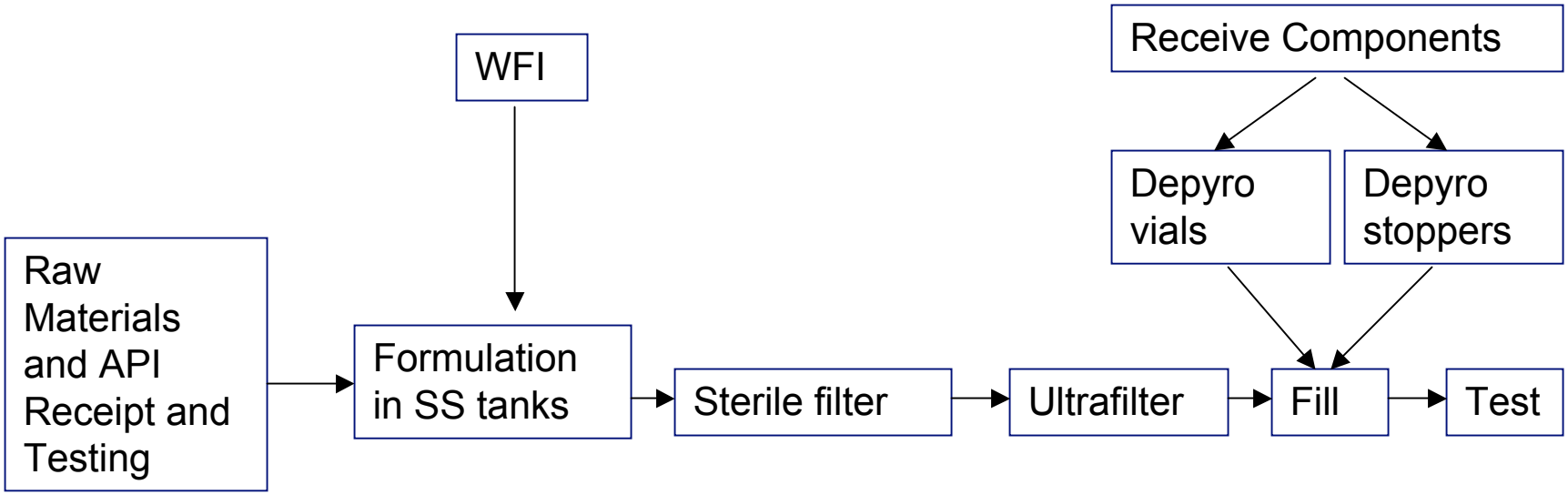
1. Hazard Analysis

- Identify all of the potential hazards
- “Hazard” is defined as any condition that results in an adverse consequence detrimental to the patient or product.
- Common hazards for all parenterals are
  - Non sterility
  - Endotoxin (pyrogen) in excess of the limit
- For our discussion, the Hazard is endotoxin in excess of the limit, and the adverse consequence (harm to the patient) is fever or maybe even death.

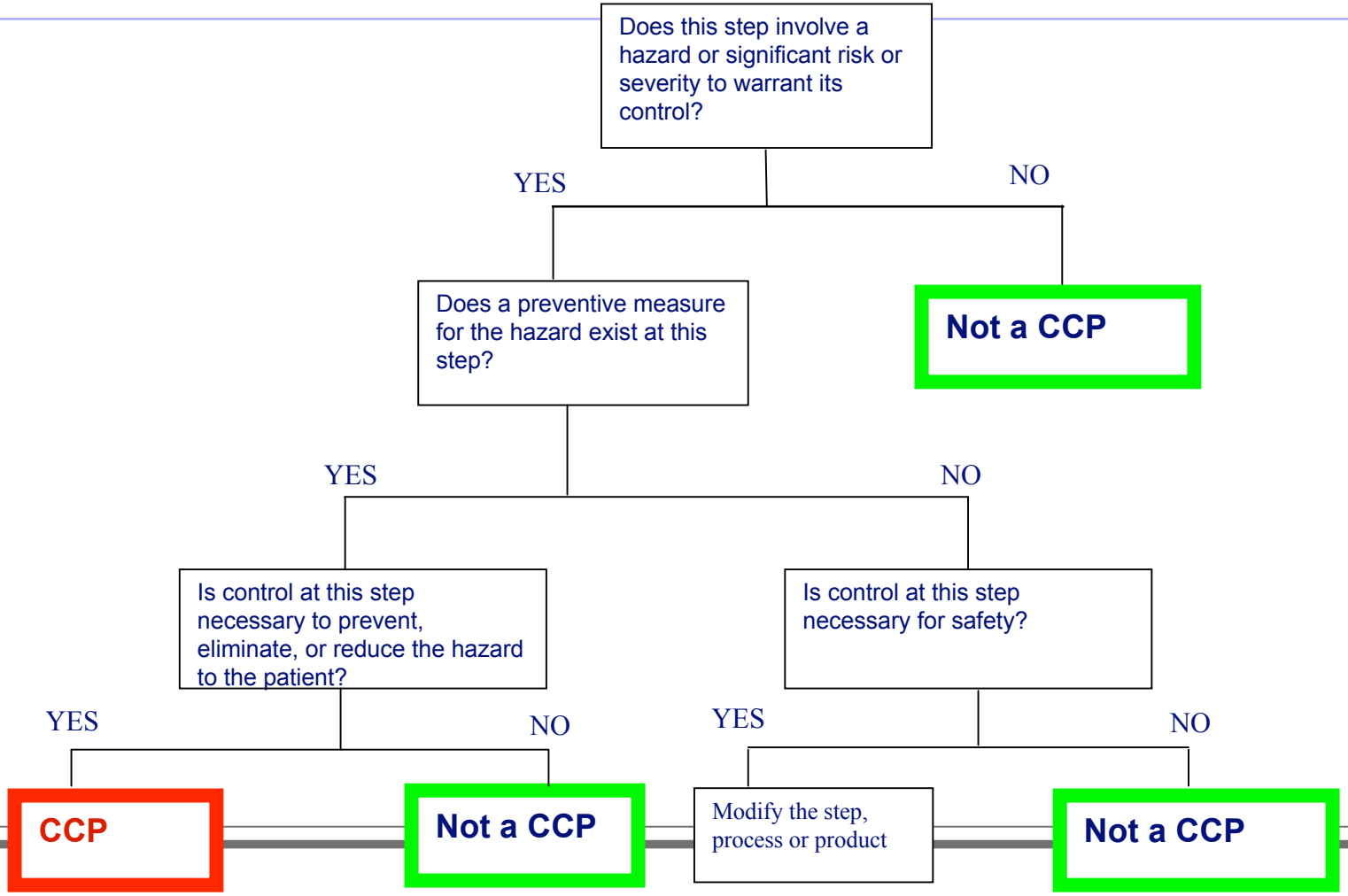
2. Determine the CCP

- Critical Control Point = step at which control can be applied and is essential to prevent or eliminate an identified hazard or reduce it to an acceptable level
- CCPs are hazard-specific. Not all hazards have the same critical control points
  - Example: 0.2μm filters remove microorganisms, but do not eliminate free endotoxin. So, a product can be sterile but still contain a high level of endotoxin
- Decision Trees provide a consistent and unbiased way of identifying CCP

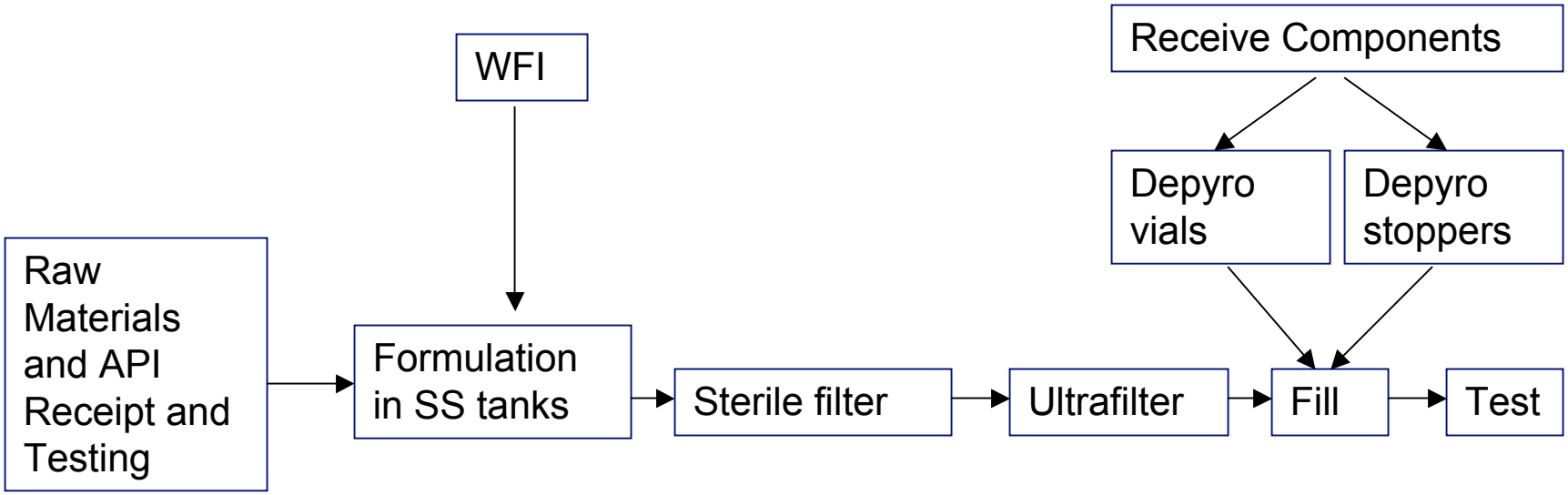
Process Map


Receive Components
WFI
Depyro vials
Depyro stoppers
Raw Materials and API Receipt and Testing
Formulation in SS tanks
Sterile filter
Ultrafilter
Fill
Test

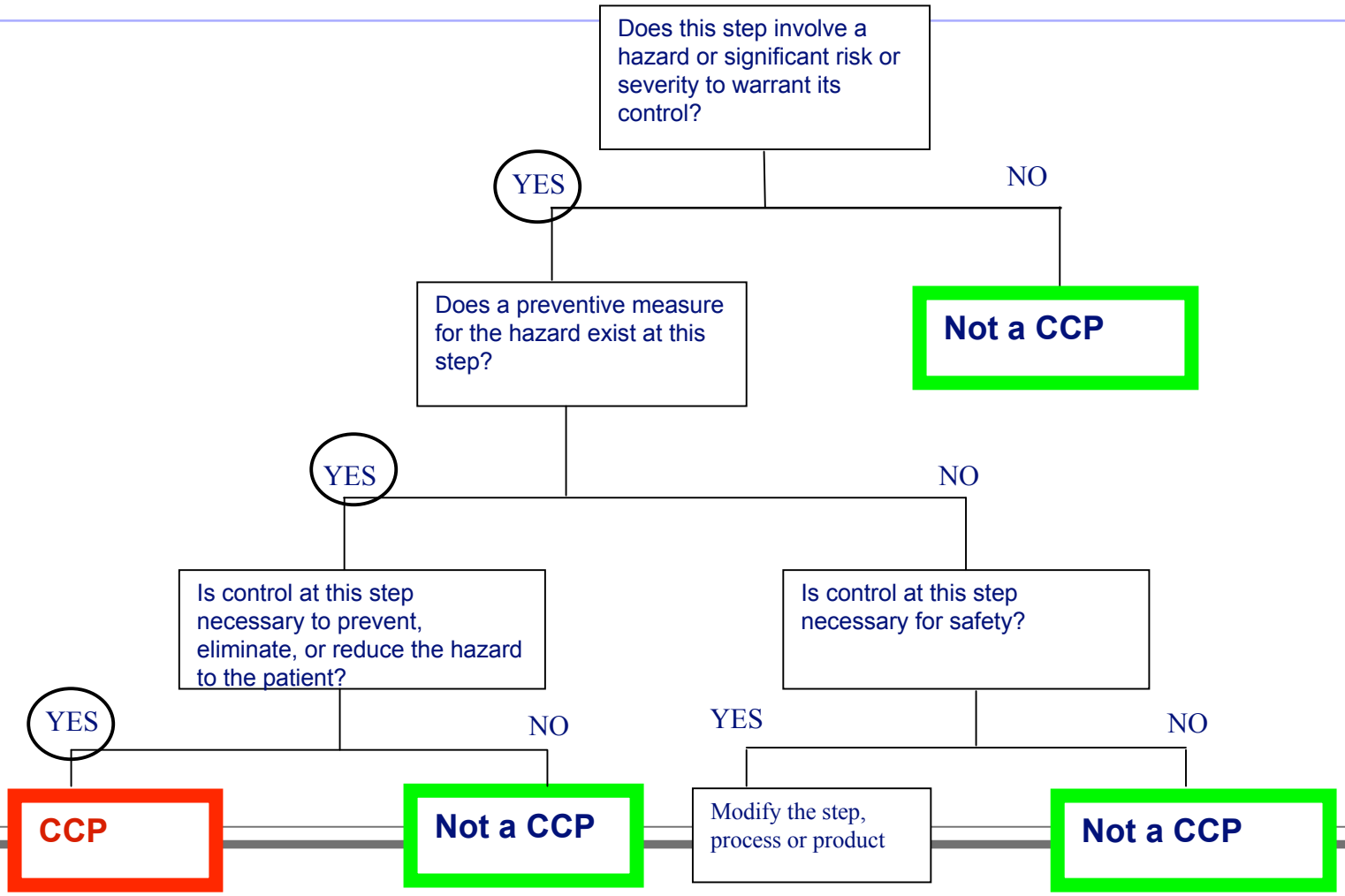
Decision Tree for HACCP



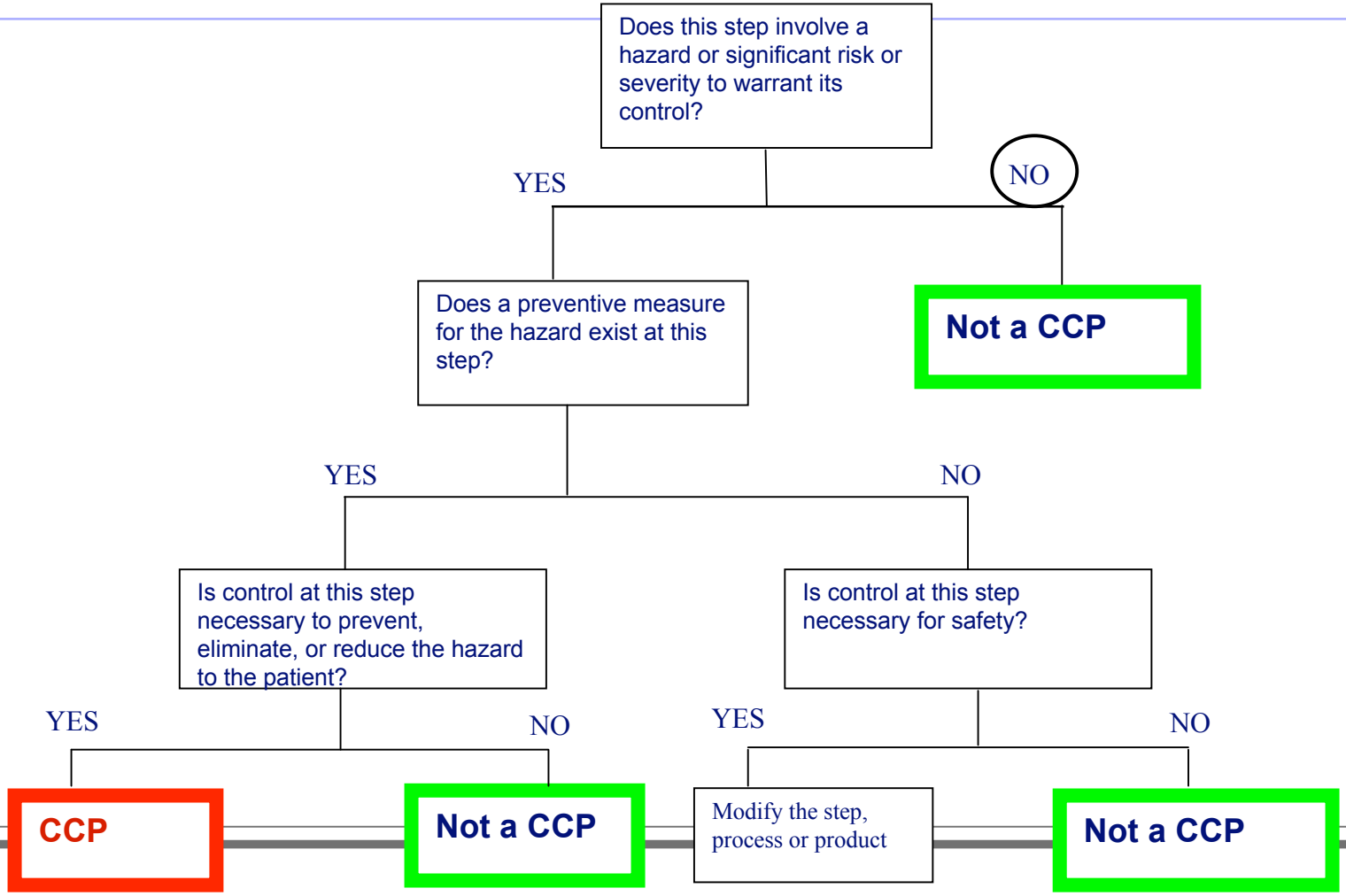
Which Steps or Components are CCP?



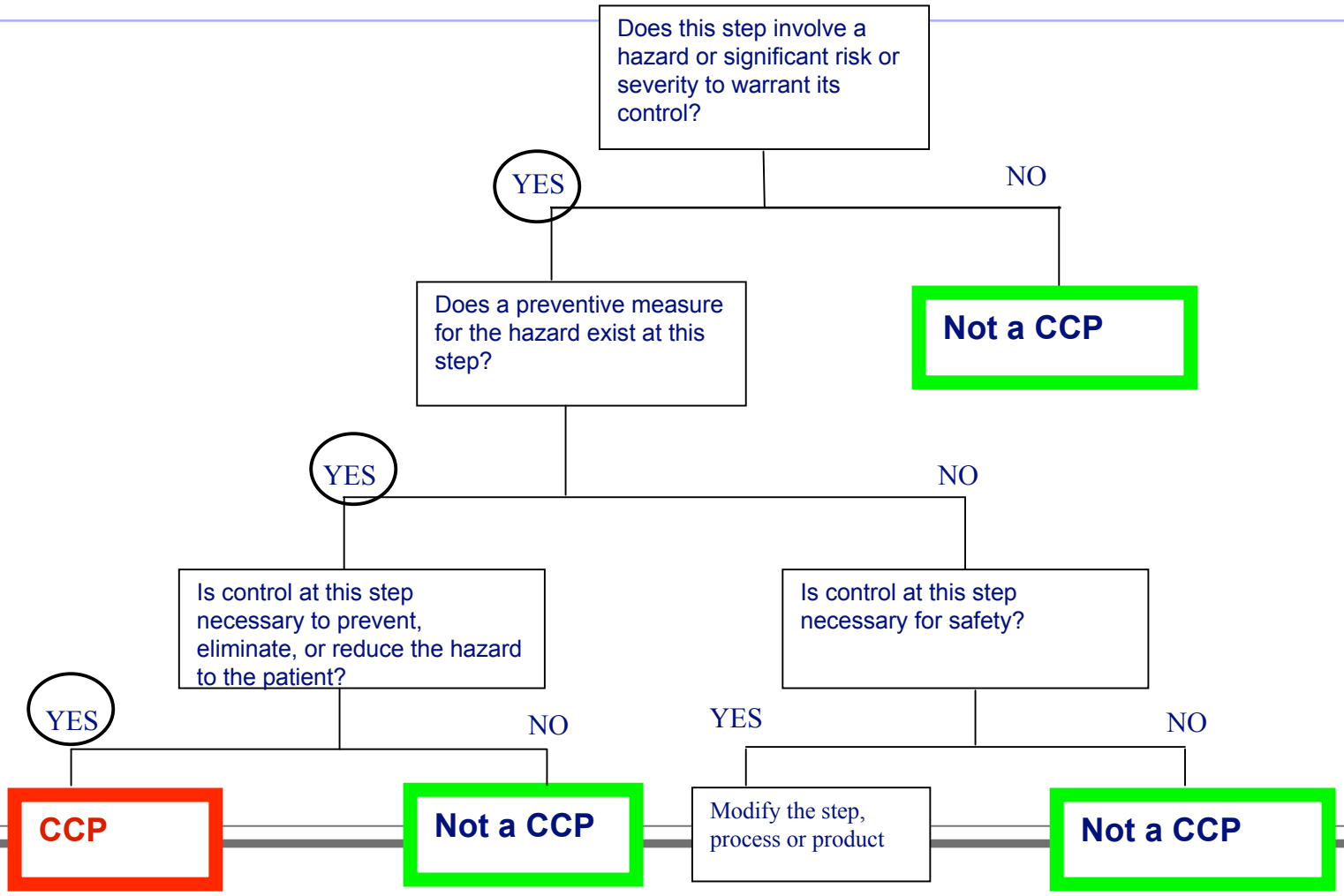
Depyrogenation Example



Sterilization Filter Example



Testing Example



Laboratory Testing

- False Negatives might release a lot that is harmful to patients
  - Patient risk
  - Compliance risk
  - Business risk
- False Positives might destroy a lot that is perfectly fine
  - Business risk

What can go wrong at each CCP? Risk Assessment 2: FMEA

- Failure Mode and Effect Analysis
- Analysis of each identified CCP
  - Failure Mode - What can go wrong?
  - Potential effect of failure - What is the consequence of the failure?
  - Potential causes of the failure - Why would the failure happen?
- Assign numerical ratings for:
  - Severity
  - Occurrence
  - Detection

Note Added:

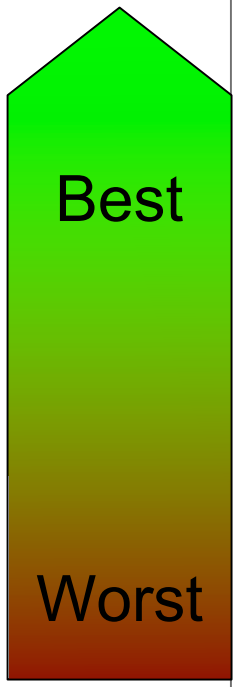
The question was asked at the Chapter Day Meeting regarding FMEA as my choice for Assessment #2. Any risk method can be used (HACCP, fault tree, fish bone, etc). I chose FMEA because the RPN number allows me to rank the failure modes and concentrate on those that pose a real threat to the integrity of the testing lab and the resulting data.

Risk Ratings

Severity	
1	Failure would likely not be noticeable in the final product
2	Failure could increase trendline for final product endotoxin
3	Failure could cause patient injury

Occurrence	
1	Failures are rare
2	Failures are occasional
3	Failure is likely to occur

Detection	
1	Detection of a failure is certain
2	Step is monitored intermittently
3	Step is not tested or monitored



FMEA

- Cross-functional team must consider each potential failure mode for severity, occurrence, detection, and assign
- Calculate RPN (Risk Priority Number) by multiplying ratings for severity, occurrence and detection
- Consider mitigations
- Re-assign ratings
- Re-calculate RPN

Sample FMEA Template

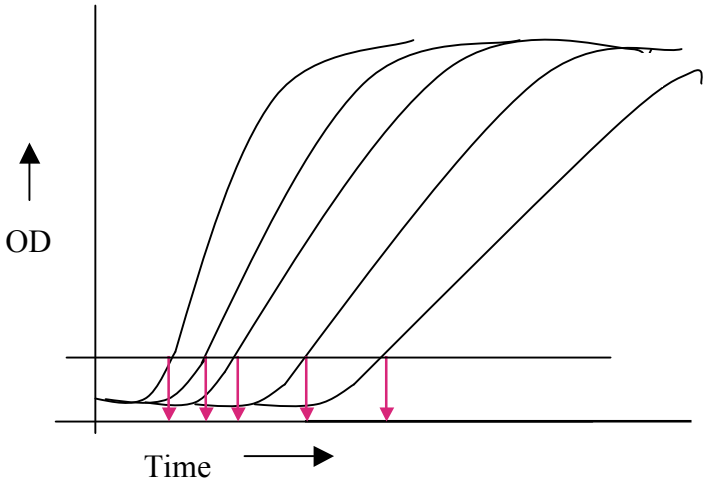
FMEA Process										Action Results				
Item and Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) of Failure	Occurrence	Current Controls	Detection	RPN	Recommended Action	Action Taken	Severity	Occurrence	Detection	RPN

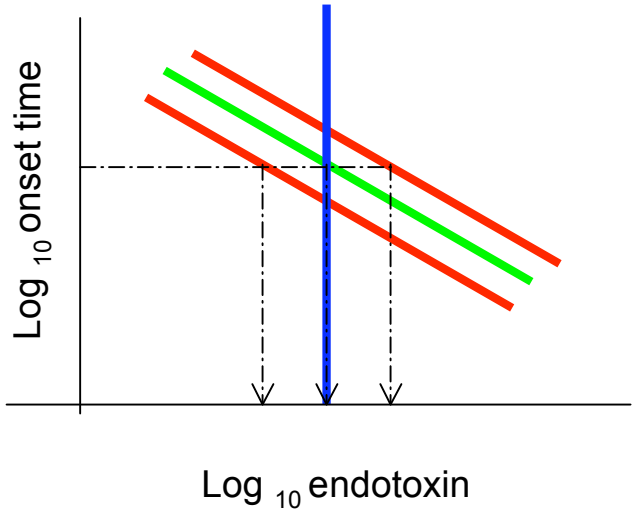
FMEA Process: Testing (Not Exhaustive)										Action Results				
Item and Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) of Failure	Occurrence	Current Controls	Detection	RPN	Recommended Action	Action Taken	Severity	Occurrence	Detection	RPN
Positive Product Control - Inhibition	PPC Does not react	invalid test	1	Inhibitory product	2	Validation	1	2	Receive CC Notifications	Get on list	1	2	1	2
			1	Spike incorrectly prepared	1	Training	2	2	None	NA	NA	NA	NA	NA
			1	Reagent not stored properly	1	Qualified Storage	1	1	None	NA	NA	NA	NA	NA
			1	Pipettors not calibrated	1	Pipettors on schedule	2	2	None	NA	NA	NA	NA	NA
Standard curve - kinetic test	Standard curve is OOT	over-estimation of endotoxin	2	Standard curve impoperly prepared	1	Training	3	6	Trend standard curve parameters	Trend onset times, slope, intercept	2	1	1	2
		Under-estimation of endotoxin	3		2		3	18	Trend standard curve parameters		3	1	1	3
Depyrogenation	Endotoxin in sample	False positive	2	Glassware contributes endotoxin	1	Validated cycle; review of charts	1	2	None	NA	NA	NA	NA	NA
Platicware used in sample prep/standard series	Endotoxin in sample	False positive	2	Plasticware contributes endotoxin	2	None	3	12	Institute screening per USP	Test plastic as device	2	1	1	2
Sampling of test material	Sample contaminated	False positive	2	Human error	2	Training	3	12	Regular observation	Observation schedule	2	1	1	2
			2	Plasticware contributes endotoxin	2	None	3	12	Institute screening per USP	Test plastic as device	2	1	1	2

3. Establish Limits for Each CCP

- What attributes need monitoring?
- What are the limits for or expectations for those attributes?
- For the lab example
  - Standard curves
  - Depyrogenation processes
  - Equipment IOPQ
  - Screening of plasticware

Standard Curve





4. Establish Monitoring Procedures

- Lay out/justify monitoring plans
- Describe analysis of monitoring data - tracking/trending.
- For the testing example:
  - Screen plasticware as medical devices
  - Trend standard curves
  - Monitor depyrogenation processes and refrigerator/freezer temperatures
  - Assure re-validation if required (follow change control)
  - Provide continuing training

5. Establish Corrective Actions

- What could go wrong, and how might we mitigate or correct it?
- Problems may be anticipated and mitigations suggested by the FMEA tool

6. Establish Verification Procedures

- Write SOPs
- Validate methods and processes
- Calibrate/qualify equipment
- Training

7. Establish Documentation

- Is there a provision for the recording of all essential information?
- Where do we go for records?
  - Routine monitoring
  - PM
  - Validation data
  - Calibration
- Are records complete?

Extra Added Bonus!!!!!

- Go through the FMEA and make a list of the potential causes for the failure and the mitigation
- This list is the basis for your checklist if/when you have an OOS that needs investigation!

Summary

- Any analysis, including the various risk analyses are, to some extent, subjective
- Cross functional team makes the “rules” to:
  - Reduce bias
  - Guarantee consistency
- Once the rules are made, the identification of CCP and Failure Modes becomes relative to the process under study and the rules of the team
- Identify and mitigate risk for CCP

Thank you!

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