Thinking about Risk and Endotoxin Control

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Risk Analysis and Management

- Risk Management = The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk (ICH Q9, PDA TR 54)
- Risk Assessment = A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (ICH Q9, PDA TR 54)
- Risk Analysis = The estimation of the risk associated with the identified hazards (ICH Q9, PDA TR 54)

HACCP

- HACCP - **H**azard **A**nd **C**ritical **C**ontrol **P**oint analysis is one method of applying Quality System concepts to individual processes
  - Identify hazards
  - Assess risk of those hazards
  - Identify critical control points relative to those hazards
  - Manage critical control points

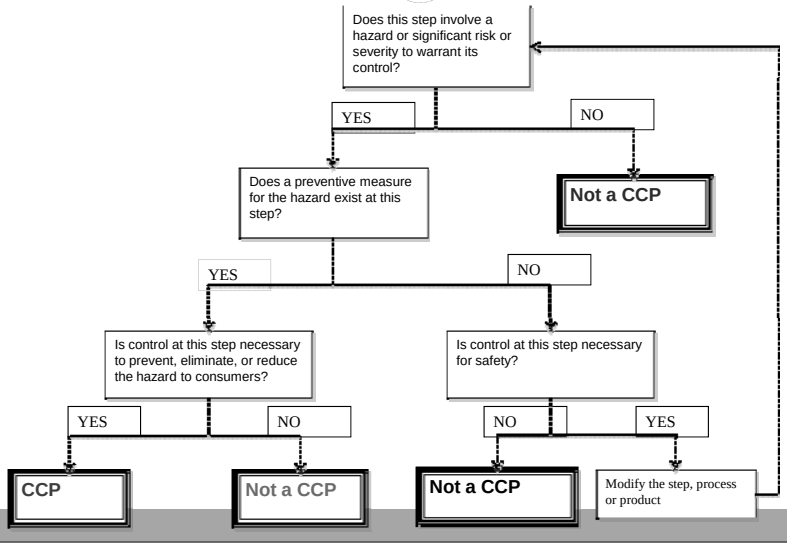
HACCP Step 1

- Conduct a hazard analysis
  - A *hazard* is defined as any condition that results in an adverse consequence detrimental (harm) to the product or patient. In HACCP, each step of a manufacturing process is be evaluated to determine whether any hazards will result if the step is not controlled. Hazards include physical, biological, chemical, electrical, and environmental.
  - For our purposes, the hazard is endotoxin in excess of the calculated limit

HACCP Step 2

- Identify all Critical Control Points (CCP)
  - Critical Control Points are hazard-specific. Not every action or step within a process is critical to a given hazard.
  - The application of HACCP facilitates the identification of the minimum number of CCPs required to successfully control the process and prevent a hazard from occurring.

Example: CCP Decision Tree



HACCP Step 3

- Assign Limits for each CCP
  - Each CCP must have an assigned limit that is accurate, attainable, and verifiable.

HACCP Step 4

- Verify monitoring and testing of limits
  - Once CCPs are identified and limits are set, verify that the measurement instrumentation – manual or automatic – is in place, calibrated and operational. Verify that all analytical methods used to obtain the results are validated. Results must be documented in a manner that is usable and understandable.

HACCP Step 5

- Verify corrective actions
  - What are the appropriate corrective actions if critical limits are exceeded? How are these documented? Has a CAPA (**C**orrective **A**ction/**P**reventive **A**ction) program been established?
  - Proactive, not reactive
    - Reduce bias

HACCP Step 6

- Verify operational procedures for CCPs
  - This stage must be complete and verified. Training must be complete and documented for all tasks and SOPs.

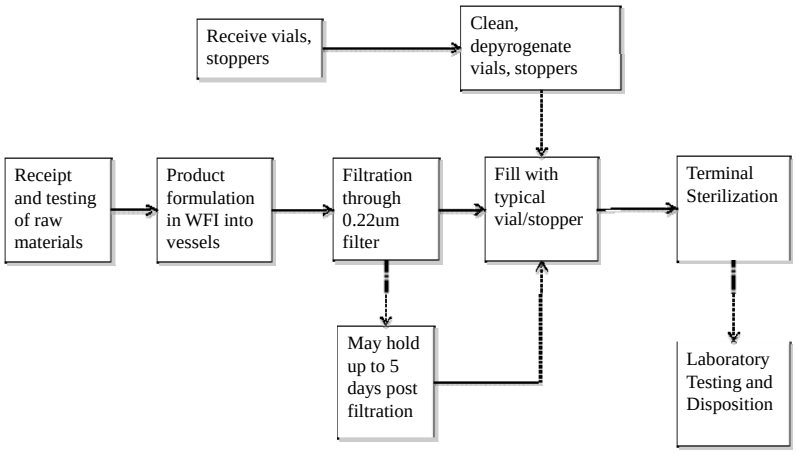
HACCP Step 7

- Verify that records of each CCP are documented
  - Record keeping is the foundation of all regulatory requirements. The batch record, calibration and maintenance records, environmental monitoring results, are all examples of documentation needed for identified CCPs.

Case Study:

- You've been provided a flow chart for the manufacture of the product, SilverBullet
- Your identified hazard is endotoxin in the drug product that is in excess of the calculated limit. Potential consequence of the hazard (harm): patient death

SilverBullet Process Flow



Product Formula

(With apologies to formulation scientists)

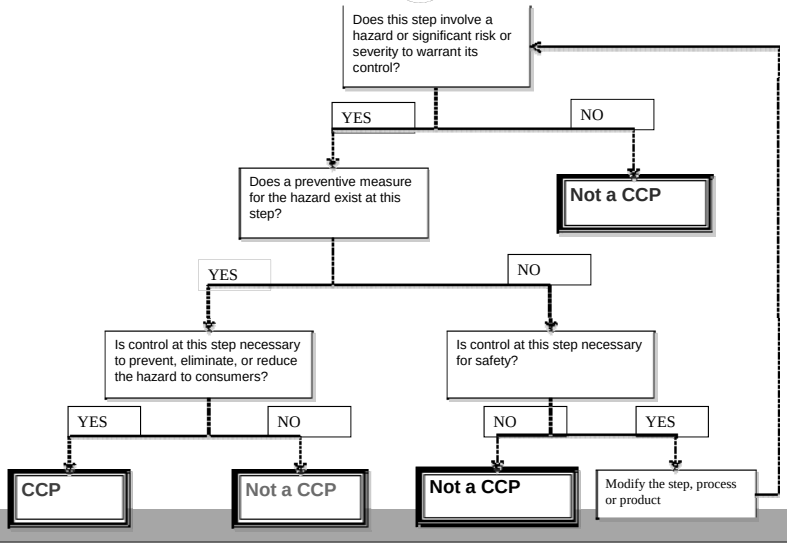
The following is the formula for our new product, SilverBullet

Active (small molecule)	9 mg
Mannitol	30 mg
NaCl	10 mg
Propyl paraben	1 mg
WFI	1 mL

The Challenge:

- Using the principles of HACCP and common sense, determine and justify
  - CCP for the hazard, endotoxin
  - Limits, where appropriate
  - Monitoring scheme
  - Thoughts for dealing with CAPA
  - Documentation

Example: CCP Decision Tree



Example 1: Vial Depyrogenation

Question	Answer
Does this step involve a hazard or significant risk or severity to warrant its control?	Yes. Lack of depyrogenation could result in endotoxin on vials/stoppers that could harm the patient
Does a preventive measure for the hazard exist at this step?	Yes. Depyrogenation processes are validated.
Is control at this step necessary to prevent, eliminate, or reduce the hazard to consumers?	Yes. We must continuously monitor the process to assure that the container/closure system does not introduce endotoxin

Complete the HACCP for Depyrogenation

HACCP Step	Answer
1. Identify the hazard	Endotoxin
2. Identify the CCP	Depyrogenation of vials
3. Assign Limits	Limits for time and temperature determined during validation
4. Verify monitoring and testing of limits	Timer, temperature controller, chart recorder are calibrated. All instrumentation on calibration and PM schedules
5. Verify Corrective Actions	Use FMEA or other tools to identify what can go wrong, and the proper mitigations
6. Verify operational procedures	SOPs in place for operation of ovens. Training of personnel has taken place (Operations and QA)
7. Documentation	All validation documentation and completed batch records are filed in the QA document room

Raw Materials

Question	Answer
Does this step involve a hazard or significant risk or severity to warrant its control?	Yes. There is no step in the SilverBullet process to eliminate endotoxin
Does a preventive measure for the hazard exist at this step?	No. There are no endotoxin limits for incoming raw materials. We accept the Certificate of Analysis
Is control at this step necessary for safety?	Modify this step. Add endotoxin limits where appropriate for raw materials.

Complete the HACCP for Raw Materials

HACCP Step	Answer
1. Identify the hazard	Endotoxin
2. Identify the CCP	Raw Materials
3. Assign Limits	
4. Verify monitoring and testing of limits	
5. Verify Corrective Actions	
6. Verify operational procedures	
7. Documentation	

Product Formula

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The following is the formula for our new product, SilverBullet

Active (small molecule)	9 mg
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Propyl paraben	1 mg
WFI	1 mL

Raw Materials Review

- NaCl is an inorganic material
  - There is a relatively low risk for endotoxin
- Mannitol is from plants, a natural source.
  - There is a high risk for endotoxin
  - Endotoxin will likely be variable lot-to-lot
- Propyl paraben is a preservative
  - There is a relatively low risk for endotoxin
- Active is a small molecule (not a biological)
  - There is a relatively low risk for endotoxin
- Water for Injection
  - USP limit is 0.25 EU/mL

Setting Endotoxin Limits

- For raw materials, it's a good idea to start with the limit for the final formulation and work backwards to assign limits for formulation components
- The dose for SilverBullet is 1mL/kg/hour
- The endotoxin limit is 5 EU/mL
  - Limit = K/M = (5 EU/kg)/(1mL/kg/hour) = 5 EU/mL

Solution #1: 5 ingredients, each allowed 1 EU

Ingredient	Allowable EU	EU/mg or EU/mL
Active	1 EU/mL 9 mg/mL	0.11 EU/mg

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Ingredient	Allowable EU	EU/mg or EU/mL
Active	1 EU/mL 9 mg/mL	0.11 EU/mg
Mannitol	1 EU/mL 30 mg/mL	0.033 EU/mg

Solution #1: 5 ingredients, each allowed 1 EU

Ingredient	Allowable EU	EU/mg or EU/mL
Active	1 EU/mL 9 mg/mL	0.11 EU/mg
Mannitol	1 EU/mL 30 mg/mL	0.033 EU/mg
NaCl	1 EU/mL 10 mg/mL	0.1 EU/mg

Solution #1: 5 ingredients, each allowed 1 EU

Ingredient	Allowable EU	EU/mg or EU/mL
Active	1 EU/mL 9 mg/mL	0.11 EU/mg
Mannitol	1 EU/mL 30 mg/mL	0.033 EU/mg
NaCl	1 EU/mL 10 mg/mL	0.1 EU/mg
PP	1 EU/mL 1 mg/mL	1.0 EU/mg

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Ingredient	Allowable EU	EU/mg or EU/mL
Active	1 EU/mL 9 mg/mL	0.11 EU/mg
Mannitol	1 EU/mL 30 mg/mL	0.033 EU/mg
NaCl	1 EU/mL 10 mg/mL	0.1 EU/mg
PP	1 EU/mL 1 mg/mL	1.0 EU/mg
WFI	1 EU/mL 1 mL/mL	1.0 EU/mL

What do you think?

Solution #2: Total weight

50 mg total dry weight of the ingredients in the formulation

$$\frac{5\ \text{EU/mL}}{50\ \text{mg/mL}} = 0.1\ \text{EU/mg}$$

What do you think?

Solution #3: By percentage

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.9	0.1

Solution #3: By percentage

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.9	0.1
Mannitol	30 mg/mL	60	3	0.1

Solution #3: By percentage

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.9	0.1
Mannitol	30 mg/mL	60	3	0.1
NaCl	10 mg/mL	20	1	0.1

Solution #3: By percentage

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.9	0.1
Mannitol	30 mg/mL	60	3	0.1
NaCl	10 mg/mL	20	1	0.1
PP	1 mg/mL	2	0.1	0.1

What do you think?

Solution #4: By source

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.5	0.05

Solution #4: By source

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.5	0.05
Mannitol	30 mg/mL	60	4.25	0.14

Solution #4: By source

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.5	0.05
Mannitol	30 mg/mL	60	4.25	0.14
NaCl	10 mg/mL	20	0.1	0.01

Solution #4: By source

Ingredient	Weight	% of total	EU/mL	EU/mg
Active	9 mg/mL	18	0.5	0.05
Mannitol	30 mg/mL	60	4.25	0.14
NaCl	10 mg/mL	20	0.1	0.01
PP	1 mg/mL	2	0.005	0.005

What do you think?

Complete the HACCP for Raw Materials

HACCP Step	Answer
1. Identify the hazard	Endotoxin
2. Identify the CCP	Raw Materials
3. Assign Limits	Limits assigned working backwards from finished product
4. Verify monitoring and testing of limits	Test method suitability has been demonstrated (inhibition/enhancement) for each material. Propose a sampling and testing plan for incoming RM
5. Verify Corrective Actions	Use FMEA or other tools to identify what can go wrong, and the proper mitigations
6. Verify operational procedures	SOPs in place for BET. Training of personnel has taken place.
7. Documentation	Method verification stored in the Micro lab. Results of testing reviewed by the Supervisor and attached to the batch record.

Another Problem

- Q: How do we assign endotoxin limits across products?
- A: Assign limits for each product and choose the most conservative

	Materials, EU/mg							
	NaCl	Propyl Paraben	Active A	Mannitol	Dextrose	Active B	NA_2HPO_4	Active C
Silver Bullet	0.01	0.005		0.14				0.05
New Product	0.06		2.3	0.08	0.23		0.11	
Super Stuff	0.03	0.02			0.57	1.4	0.02	