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Validation Tools in the Pharmaceutical & Biotech Industries

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Objective

- The objective of validation in the food, pharmaceutical and biotech industries is the same….

- Confirm that the equipment or process performs as designed now and over time.

Getting Started

- What is the equipment or process?
- What is the scope?
- What is the validation strategy?

Critical to Quality Tree Definitions

- CTQ – Critical to Quality Tree
- KPOV- Key Process Output Variables
- KPIV – Key Process Input Variables
- VOC – Voice of the Customer

Critical to Quality Tree (CTQ)

VOC	CTQ	KPOV	KPIV
Good quality product **Commercially sterile product**	**Recipe executes as specified (time, temperature, pressure)**	**Recipe executes as specified (time, temperature, pressure)** **Calibration Performed as specified** **PM performed as required**	**Right Recipe (time, temperature, pressure)** **Calibration of temperature sensors** **Preventive Maintenance (PM) performed**
	No retort bypass	**Other KPOV's: Water chlorination documented; temperature sensitive tape changes color**	**Other possible KPIV's: Chlorinated cooling water, temperature sensitive tape**

Risk Assessment

Process/Product Failure Modes and Effects Analysis (FMEA)

Food products with low water activity and low pH are considered lower risk than foods with high pH or high water activity

RISK

Food products with low water activity and high pH were thought to be lower risk than foods with low pH or high water activity, but …..

without good GMP compliance, low risk can become high risk.

RISK - BSE

- ***Bovine Spongiform Encephalopathy*** *(**BSE**), commonly known as **Mad-Cow Disease** (MCD), is a fatal, neurodegenerative **disease** in cattle, that causes a spongy degeneration in the brain and spinal cord and also causes red eyes. **BSE** has a long incubation period, about 4 years, usually affecting adult cattle at a peak age onset of four to five years, all breeds being equally susceptible. In the United Kingdom, the country worst affected, more than 179,000 cattle have been infected and 4.4 million slaughtered during the eradication ...*

  For Biotech industry using animal products, the risk of BSE getting into one of their products is very low, but the severity, if it does, is unacceptably high.

Process/Product Failure Modes and Effects Analysis (FMEA)

Process Step	Key Process Input	Potential Failure Mode	Potential Failure Effects	S E V	Potential Causes	O C C	Current Controls	D E T	R P N
What is the process step	What is the Key Process Input?	In what ways does the Key Input go wrong?	What is the impact on the Key Output Variables (Customer Requirements) or internal requirements?	How Severe is the effect to the customer?	What causes the Key Input to go wrong?	How often does cause or FM occur?	What are the existing controls and procedures (inspection and test) that prevent either the cause or the Failure Mode?	How well can you detect cause or FM?	
Cook	Time	Time too short	Under cooking product		Wrong recipe, Operator error, wrong product		Training, record review, QC		
Cool	Time	Time too short	Under cooling product		Cooling water too warm, operator error, wrong cool time				

Severity Evaluation

Effect of Failure	Customer Effect	Manufacturing/ Assembly Effect	Environmental Effect	Ranking
Hazardous without warning	Very high severity ranking when a potential failure mode effects safe operation and/or involves non compliance with government regulation without warning.	Or may endanger operator (machine or assembly) without warning.	Ecosystem structure and function are adversely affected. Impact is long lasting. Possible severe injuries or death to individuals, population is at risk.	**10**
Hazardous with warning	Very high severity ranking when a potential failure mode effects safe operation and/or involves non compliance with government regulation with warning.	Or may endanger operator (machine or assembly) with warning.	Ecosystem structure and function are adversely affected. Impact is long lasting. Possible severe injuries to individuals, population is not at risk.	**9**
Very high	Item inoperable (loss of primary function)	Or 100% of product may have to be scrapped, or item reworked off-line with rework time greater than one hour.	Ecosystem structure and function/environment are exposed but impact is intermittent. Ecosystem structural and functional integrity are intact. Possible injuries to individuals, population is not at risk.	**8**
High	Item operable but at a reduced level of performance. Customer very dissatisfied.	Or product may have to be sorted and a portion (less than 100%) scrapped or item reworked off-line with rework time between half an hour and an hour.		**7**
Moderate	Item operable but Comfort/Convenience item(s) inoperable. Customer dissatisfied.	Or a portion (less than 100%) of the product may have to be scrapped with no sorting, or item reworked off-line with rework time less than half an hour.	Ecosystem and function/environment are exposed but impact is temporary. Ecosystem structural and functional integrity are intact possible minor injuries to individuals, population is at risk.	**6**
Low	Item operable but Comfort/Convenience item(s) operable at a reduced level of performance. Customer somewhat dissatisfied.	Or 100% of product may have to be sorted and reworked or repaired off-line.		**5**
Very minor	Fit & Finish/Squeak & Rattle item does not conform. Defect noticed by discriminating customers (less than 25%)	Or a portion (less than 100%) of the product may have to be reworked with no scrap, on-line but in-station.	Ecosystem structure and function are not exposed to stress, or expression of stress is not measurable or adverse.	**2**
None	No discernible effect.	Or slight inconvenience to operation or operator, or no effect.	Ecosystem structure and function are not exposed. Individuals and populations are not at risk.	**1**

Occurrence Evaluation Guideline

Probability of Failure	Process	Product	Ranking
Very High: Persistent Failure	> once per day	> 100/1000 pieces	**10**
	once per day	50/1000 pieces	**9**
	once per week	20/1000 pieces	**8**
High: Frequent Failures	once in two weeks	10/1000 pieces	**7**
	once per month	5/1000 pieces	**6**
Moderate: Occasional failures	once in three months	2/1000 pieces	**5**
	once in six months	1/1000 pieces	**4**
	once per year	.5/1000 pieces	**3**
Low: Relatively few Failures	once in five years	0.1/1000 pieces	**2**
Remote: Failure is unlikely	once in ten years	<.01/1000 pieces	**1**

Detection Evaluation

Detection	Criteria	Detection Methods	Ranking
Almost impossible	Absolute Certainty of non-detection	Cannot detect or is not checked	**10**
Very Remote	Controls will probably not detect	Control is achieved with indirect or random checks only	**9**
Remote	Controls have poor chance of detection	Control is achieved with visual inspection only	**8**
Very Low		Control is achieved with double visual inspection only	**7**
Low	Controls may detect	Control is achieved with charting methods, I.e. SPC	**6**
Moderate		Control is based on variable gauging after parts have left the station	**5**
Moderately high	Controls have a good chance of detection	Error detection in subsequent operations or gauging on set-up and FAI	**4**
High		Error detection in station or detection in subsequent operations	**3**
Very High	Absolute almost certain to detect	Error detection in station can not pass bad parts	**2**
Fully Detectable	Controls certain to detect	Discrepant parts can not be made because of error proofing	**1**

FMEA

PROCESS STEP	Potential Failure Mode	Potential Effect(s) of Failure	SEVERITY	Potential Cause of Failure	OCCURRENCE	Current Process Controls		DETECTION	RPN	Recommended Action
						Prevent	Detect			
Cook time	Time too short	Under processing	9	Wrong recipe, program malfunction	2	Recipe, PM, SOP	Record review	3	54	NA. RPN under control
Cooling	Inadequate cooling	Under cooling	7	Cooling water too hot, time too short	3	Recipe, & SOP	Operator, record review, inspection	3	63	NA. RPN under control

Who should be on FMEA team?

- Validation protocol author/leader
- Technology expert
- Technicians that use system (retort operator)
- QA
- Regulatory
- Engineering

Validation Strategy

- What is the process/equipment?
- What is the scope?
- How will we validate the process/equipment?
  - Critical to Quality Tree
  - Acceptance Criteria
- FMEA & Control Plan

What is the process/equipment?

- ABC Batch Water Immersion Retort
- Automatic loading
- Computer control by recipe
- Containers are aluminum and steel cans
- Products are low acid vegetables
- Flow chart of process

What is the scope?

- Retort processing temperature range: 240-260^{o}F
- Overpressure (25-35 psi)
- Containers: Steel 300x400 to 603x700
  - and Aluminum: 300x400
- Cans staggered loaded
- Other restrictions

How will we validate the process/equipment?

- Critical to Quality Tree (CTQ)
- Acceptance Criteria for IQ, OQ and PQ

Critical to Quality Tree (CTQ)

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Acceptance Criteria

- Installation Qualification (IQ)
- Operation Qualification (OQ)
- Performance Qualification (PQ)

Installation Qualification

- Was the equipment installed as the manufacturer specified and the user requires?
- Questions to consider:
  - Are right utilities in place?
  - Does it work when turned on?
  - Do alarms activate as specified?
  - Is system in the calibration program?
  - Has preventive maintenance occurred or is it in place?
  - SOP’s in place?

  (Note: Empty chamber mapping in Pharm industry)

Operation Qualification (OQ)

- Does the equipment operate as expected when tested at the operational extremes?

Heat Sealer

- Setting time and temperature extremes:

  +/-10%.

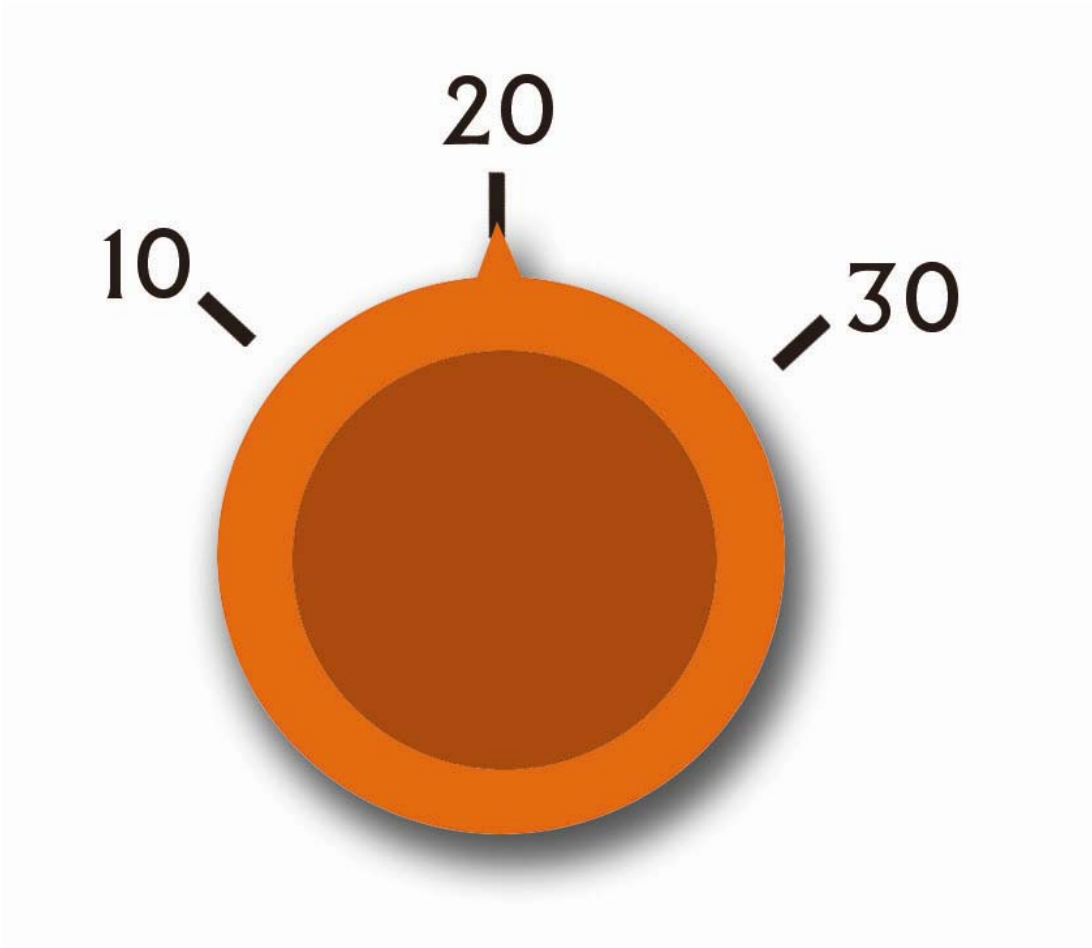
  Temperature was fine … 340, 350, 360^{o}F

  Time: 5.4, 6.0, 6.6 seconds

- But, doing an engineering study, we learned that:

  1/8” makes a 1 second difference in the residence time.

OQ-Heat Sealer



Operation Qualification

- Refrigerators/ Incubators:
  - Open door/recovery test
- Retort:
  - Partial loads

Performance Qualification (PQ)

- Does the equipment operate as designed and specified over time?

For temperature distribution study:

- Most conservative conditions for range of containers and products in duplicate or triplicate.

Acceptance Criterion:

- Reproducible temperature distribution results

Performance Qualification (PQ)

- For Heat Penetration Studies--

Is the process adequate for the most conservative conditions of viscosity, headspace, RPM, fill weight, etc.?

Acceptance criteria:

1) Meet Fo minimum by Ball Method

2) Meet quality guidelines

Performance Qualification (PQ)

- For equipment such as heat sealer:

Is a quality seal delivered over time, e.g., over 2 shifts when operators change?

- Acceptance criteria:

0 critical defects over 13 hours production in 3 production runs

<1cosmetic defect per 200 pouches over same time period.

Control Plan

- The purpose of validation is to confirm that the process or equipment is performing as designed and specified and is properly controlled.
- The Control Plan assures that the process or equipment stays in control.

Control Plan

Process Step	Reference Documents	Process Variable	Variable Classification	Control Method	Setpoints / Limits	Sampling Plan	Responsi-bility	Reaction Plan
Filling bottles	SOP 1234	Headspace	**Major**	Check weigher on line and 1/2 hr checks	0.4 “/ 0.25”, 0.7”	30 min checks	Check weigher tech	Adjust check weigher, Hold product, Call super-viser
Retort cook	SOP 1234	Recipe (time, temperature)	**Major**	Automated time, temperature & pressure control	30 minutes at 250^{o}F/ 29’ at 248^{o}F	Review all process records	Retort operator,QC/ QA	Hold product

Conclusion

- We all want our processes and equipment to operate properly and stay in control all of the time.

- Thorough understanding of the equipment, processes, risks, restrictions and customer requirements will help us determine how best to validate and operate.

- This presentation hopefully added to your validation “Tool kit.”

Things are not always what they seem at first glance