Evaluating SIP and Sterilization Methods

Investigating Microbial ~~Contaminations~~

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Agenda

- Overview
- “Bioburden” – what is it? Regulatory References
- Investigation Details
- Prevention of microbial ingress
- Sterilization Review
- Case Studies

"Bioburden" – what is it?

PIC/S Glossary:

Bioburden

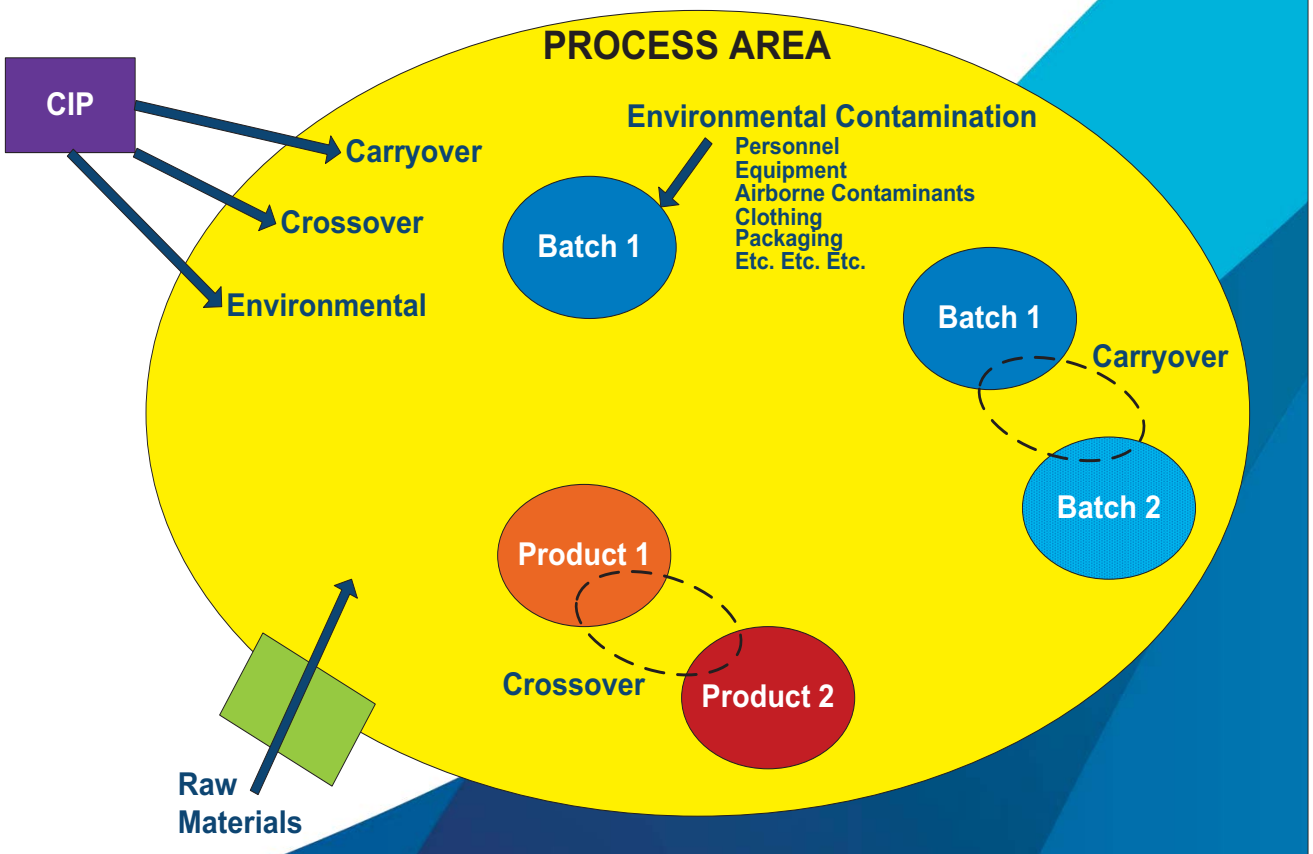
The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bioburden happens……

~~Contamination~~

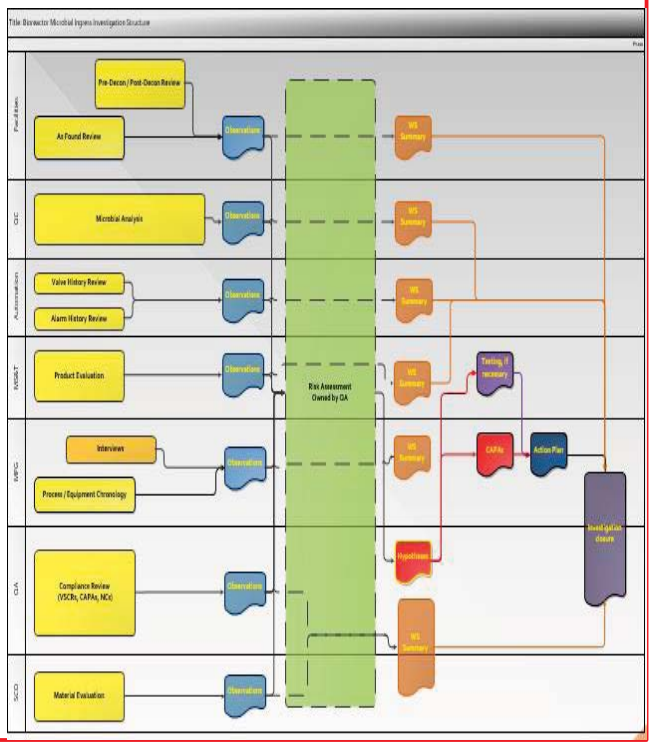
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

SOURCES OF POTENTIAL PRODUCT ADULTERATION



Contamination – Let the "fun" begin

- Root Cause Analysis
  - **Which tool to use?**
- Define the Road Map
- Structure the Process
- Define the Team / RACI
- Communication Plan



Investigation – Team Structure

Operations
- Chronological order
- MBR / Logbook Review
- Interviews

Automation
- Alarm History
- Valve Sequencing
- CIP / SIP report

MSAT / Val
- Batch data review
- Hold time Review
- Testing Protocol Dev.

QC
- Sampling Plan
- Organism ID
- IPT results

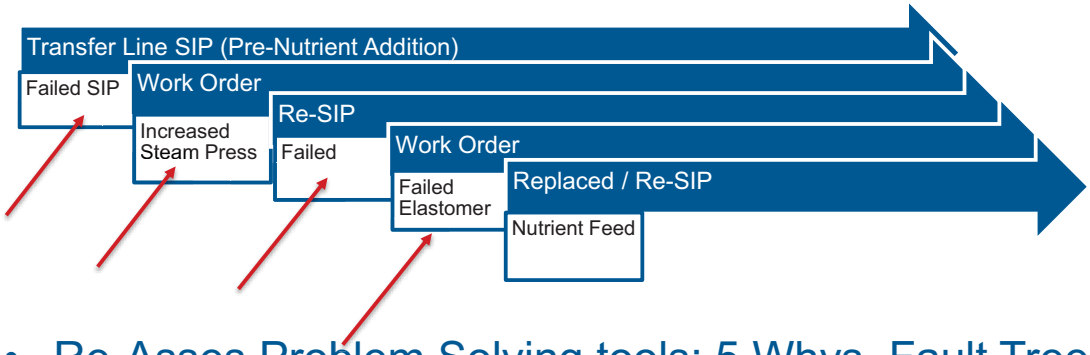
Maintenance
- Work order history
- Process maintenance interviews

QA
- Compliance review
- Change Controls

Investigation – Let the "fun" begin

We have a contamination……relax?

- Isolate the situation, As Found State Review
- Prevent the easy / common RCA. Trust the Process



- Re-Asses Problem Solving tools; 5 Whys, Fault Tree Analysis, PEMME, Ishikawa (Fishbone), etc etc

Investigation Data

Raw Material review – Everything PASSES

Alarm History – Nothing of interest

Review of CIP and SIP cycles

- Vessel – PASS
- Media sterilization filter(s) – PASS
- Inoculation Line – PASS
- Nutrient Vessel – PASS
- Filter Integrity Tests - PASS

- But…….. Lets take a closer look

Investigation Data – SIP Review

Vessel SIP PASS?

TC Serial Number	Exposure Min	Exposure Max	Exposure Avg	Fo
101A-T01	123.71	132.93	129.36	72.45
102A-T02	123.71	132.92	129.35	72.29
103A-T03	123.02	132.94	129.26	71.54
104A-T04	123.32	132.89	129.26	71.32
105A-T05	123.47	132.98	129.35	72.77
106A-T06	123.38	132.95	129.32	72.34
107A-T07	123.46	132.95	129.32	72.19
108A-T08	68.44	99.7	88.84	0.02
109A-T09	122.95	132.54	128.33	59.54
112A-T12	122.36	132	128.34	57.78
201A-T13	122.45	132.11	128.48	59.58
202A-T14	123.21	132.66	129.09	67.8
203A-T15	117.58	132.5	126.09	34
204A-T16	120.17	132.94	129.2	71.36
205A-T17	114.42	132.11	127.32	52.98
206A-T18	123.53	132.92	129.31	71.89
207A-T19	123.89	132.75	129.21	69.52
208A-T20	123.8	132.94	129.38	72.7

Investigation Data – SIP Review

Transfer Line SIP

PASS

- F_0 – the more the better?
- Look deeper
  - **Temp variation between TC's**
  - **Excessive temperature**

TC Serial Number	Exposure Min	Exposure Max	Exposure Avg	Fo
101A-T01	135.2	142.03	139.46	553.96
102A-T02	135.09	141.86	139.34	537.8
103A-T03	134.85	141.78	139.18	520.36
104A-T04	124.54	134.95	130.76	84.23
105A-T05	128.05	141.18	137.01	381.55
106A-T06	134.86	141.8	139.2	522.67
108A-T07	134.93	141.85	139.25	825.99
109A-T08	134.95	141.77	139.21	522.42
111A-T09	124.38	132.07	128.79	48.49
201A-T10	134.61	141.65	139.04	504.51
202A-T11	135.01	141.91	139.32	536.9
203A-T12	134.79	141.58	139.03	501.64
204A-T13	128.61	141.51	137.78	420.52
205A-T14	34.21	70.47	57.08	0

Design Standards

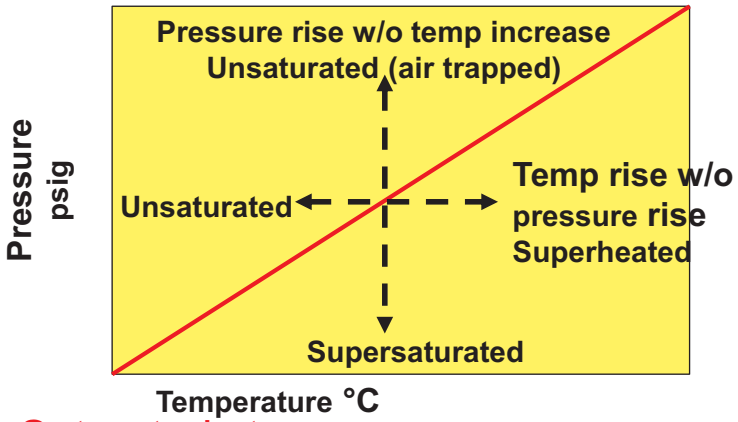
ASME BPE-2016

Equipment Longevity – Soft Parts

- ≤ 130°C

SD-2.3.1.1 Steam-in-Place. Equipment parts and components subjected to SIP should be designed and constructed to withstand continuous exposure to saturated steam at a minimum temperature of 266°F (130°C; representing 24 psig/1.65 bar under saturated steam conditions) for a duration of at least 100 hr under continuous steady-state conditions. All process contact surfaces subjected to SIP shall reach the required temperatures, under the required saturated steam pressure conditions, during the SIP cycle. Executing SIP operations at temperatures exceeding 266°F (130°C) may cause degradation of elastomers and/or damage to other components, resulting in reduction of overall equipment life. SIP conditions that are more stringent **(16)**

SIP Details



Saturated steam curve

- Monitor temperature and pressure
- Effective draining
- No vacuum
- Maintain integrity/closure

Saturated Steam Table

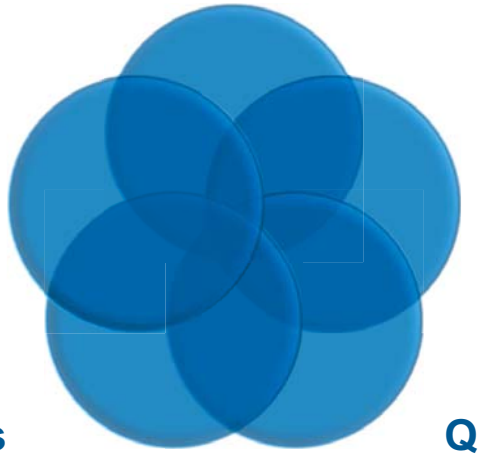
Pressure (PSIG)	Temperature (°F)	Temperature (°C)
0	212	100
1	216	102
2	219	104
3	222	106
4	224	107
5	227	108
6	230	110
7	232	111
8	235	113
9	237	114
10	240	116
15	250	121
20	259	126
24	266	130
25	267	131
30	274	134
35	281	138
40	287	142
45	292	144
50	298	148

Key Factors

Design

Maintenance

Installation

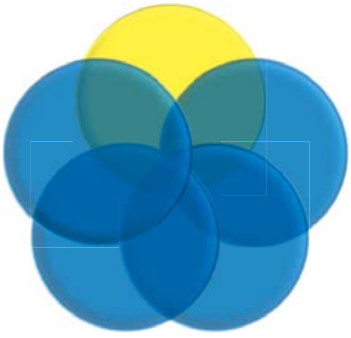


Operations

Qualification

Key Factors

Design



Process / User Requirements

Single Use? Stainless?

Sterile Boundary definition

Utility requirements / sizing

HAZOP / Risk Assessments

Automation vs Manual controls

ASME / BPE Standards – 2016

Design

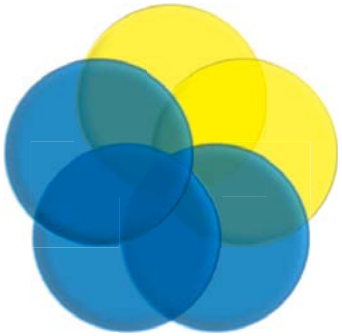
16. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

17. Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilisation. The use of "clean in place" and "sterilise in place" systems should be encouraged. Valves on fermentation vessels should be completely steam sterilisable. Air vent filters should be hydrophobic and validated for their scheduled life span.

ANNEX II: PREMISES AND EQUIPMENT

Key Factors

Installation



Dead legs

Properly sloped piping

Weld inspection

Piping runs / Flexible hose

Connection alignment

Walk Downs

Design and Installation

5. PROCESS EQUIPMENT

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

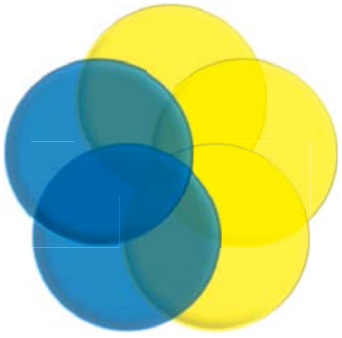
5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Key Factors

Qualification

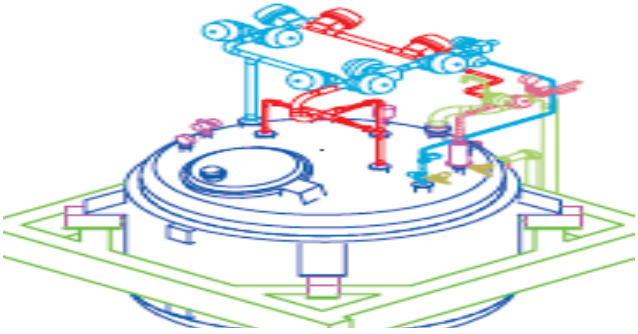


SIP Recipe Development

Temperature Mapping

Biologic Reduction Challenge

Post Validation Monitoring



Qualification

Process Contact: a surface under design operating conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g., WFI, CIP, pure steam, process gases), or components and where there is a potential for the surface to affect product safety, quality, identity, strength, or purity

Product Contact: a process contact surface that is in contact with, or has the potential to be in contact with, a product where product is defined by the owner.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

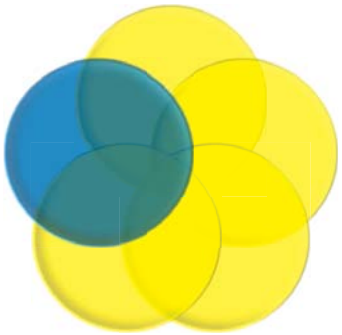
18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

Qualification- Define Closed

- Select Subject Matter Experts (SMEs): Quality, Manufacturing, R&D
- The Program. Define "Closed". Set the Risk Assessment Parameters
  - **Develop Impact (Severity) & Likelihood Criteria**
  - **Pre-Establish Risk Matrix**
  - **Use Tools for systematic evaluations**
  - **Develop Closure Philosophy and Strategy**
- Understand your process & systems, PFDs, Protocols, Batch Records
  - **Evaluate and Confirm "Closed"**
  - **Assess & Develop Sound Risk Mitigation Plan Based on Science & Engineering NOT on Perception of Regulatory Requirements or Legacy**

Key Factors

Operations



Procedural Controls (SOPs)

Process Training – Levels

Operational Controls

In Process Testing / Monitoring

Operations / Maintenance

Operations is ***not*** a 1-Department activity

- Design/ Start-up
- Shut-Down
- Return to Service (RTS) execution
- Data Review via Dashboards, KPI's

Maintenance Involvement

- Supe / Operator Involvement
- Building collective expertise & competency
- Training: Competency-based / future SME's
- Co-Ownership / Shared R&R : FE, Metrology, QA, Eng, Ops
- OEM

Operations

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

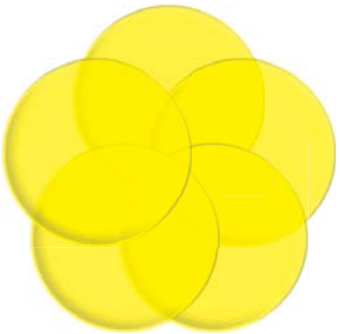
PIC/S

Operations

Design & Qualification	Implementation Fixes	Operation & Maintenance
• Sterile Boundary & Visibility	• Exhaust Filter Condensation Removal	• Maintenance Program
• SIP Strategy and Validation	• Standard Torque Valve Installation	• General Housekeeping
• Bio-Waste Venting	• Correct Line Slopes To Remove System Low Points	• Training & Awareness
• Sanitary Connections	• Align Pipework & Filter Connections	• Maintenance Program Enhancements
• Diaphragm Valve Maintenance	• Sanitary Connection Evaluation	• Return to Service Protocol
• J-Tube (2k) direction into the overlay	• Bioreactor design (Complex)	• Major Change Management Plan
• Exhaust Heat Exchanger	• Gasket Replacement	• Training Enhancements
	• Implement SIP/CIP Automation Changes	• Training – Manufacturing
		• Training – Facilities
		• Equipment Reliability

Key Factors

Maintenance

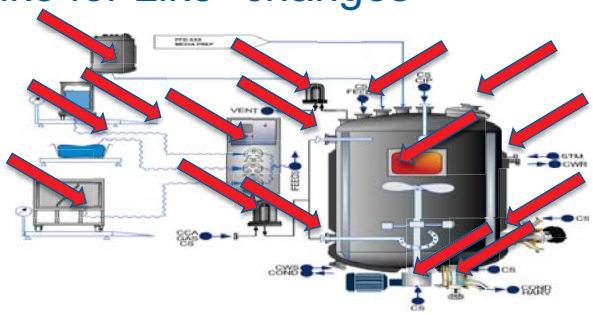


Preventative vs Predictive

Training

SOP's / PM / Checklists

"Like for Like" changes



Maintenance

5.2 Equipment Maintenance and Cleaning

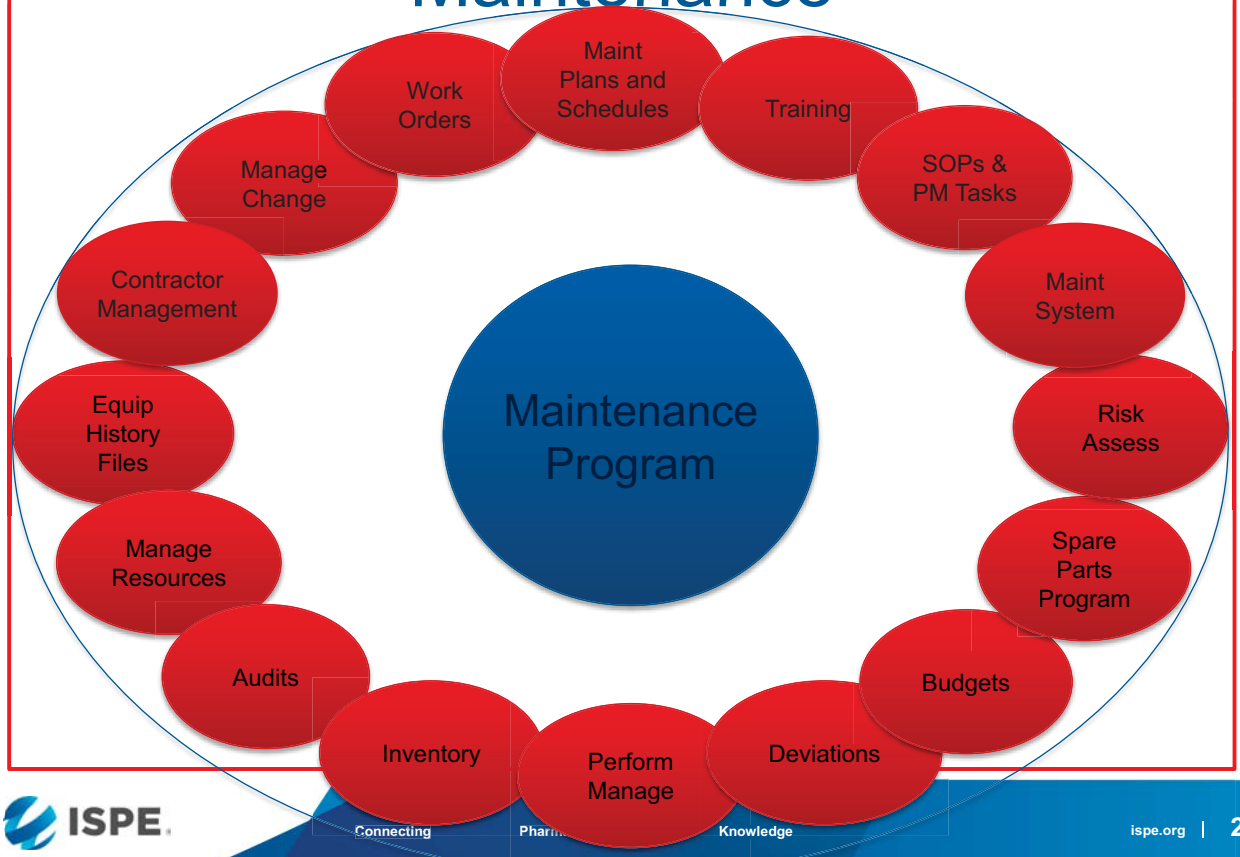
5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs.

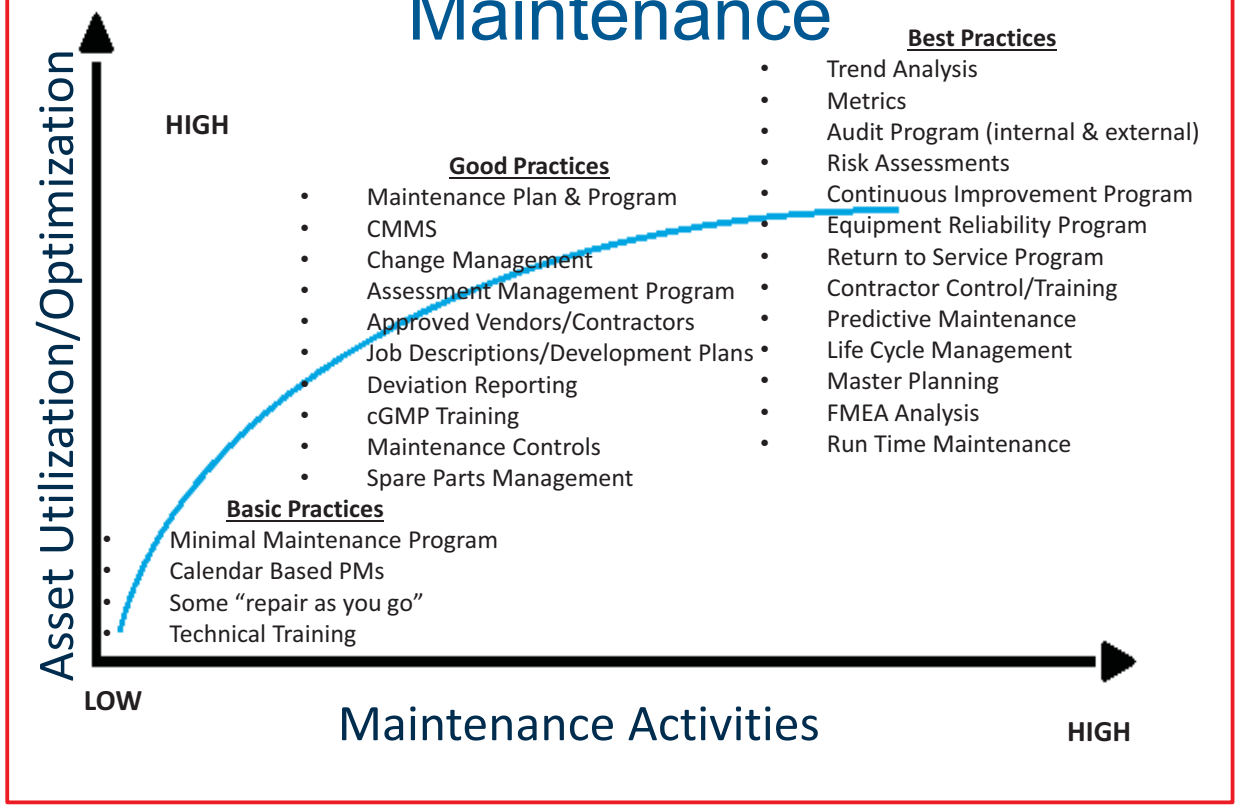
5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Maintenance



Maintenance



“Maintenance” – Routine Monitoring

In-Process Testing (Process vs Product)

Alert Level vs Action Level – when to ID?

Develop a library of local flora – know your enemy!!!

- Gram (+), Gram (-), Facultative Anaerobe, Spore forming?

EXAMPLE VALUES	Upstream		Downstream	
Sample No	Area	Levels	Area	Levels
1	Scale Up	> 0 CFU / mL	Chrom	100 CFU / 10mL
2	Harvest	1 CFU / 10 mL	Formulation	10 CFU / 10 mL
3	Sterility – Harvest	10 CFU / 1 mL	BDS	1 – 4 CFU / 10 mL

Is Maintenance Important?

Is Maintenance Important?

Is Maintenance Important?

Summary

- Cannot over come design deficiencies with increased steam pressure
- Air and water hold up are SIP enemies
- Design using ASME BPE – that's why it's there
- Utilize Risk Based Maintenance NOT Calendar
- Evaluate process closure / Monitor routinely / Prepare & React accordingly

Questions?

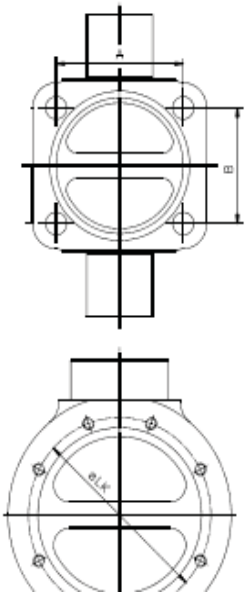
Please use the microphone indicated so our recording includes audio of your question

Back-up slides

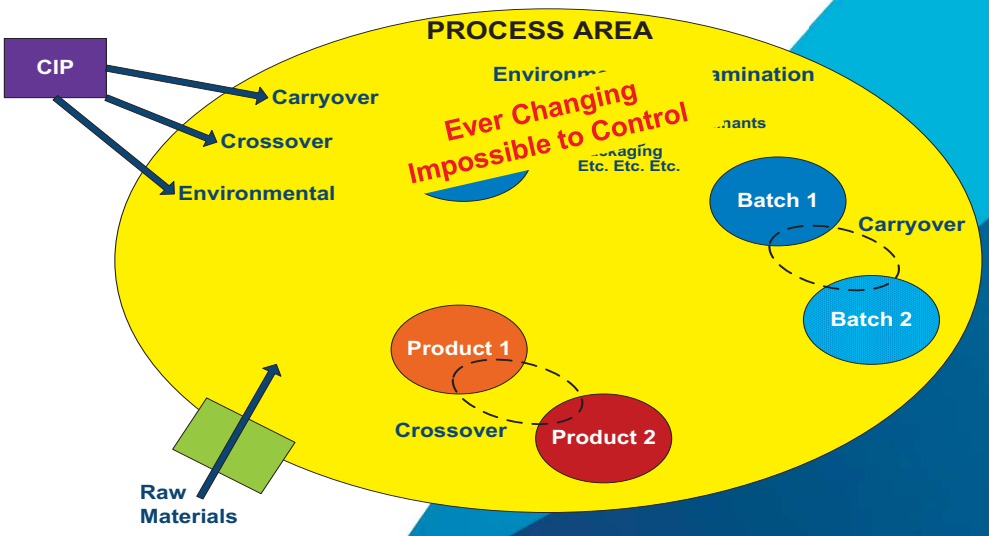
Valve Handling

elastomers.

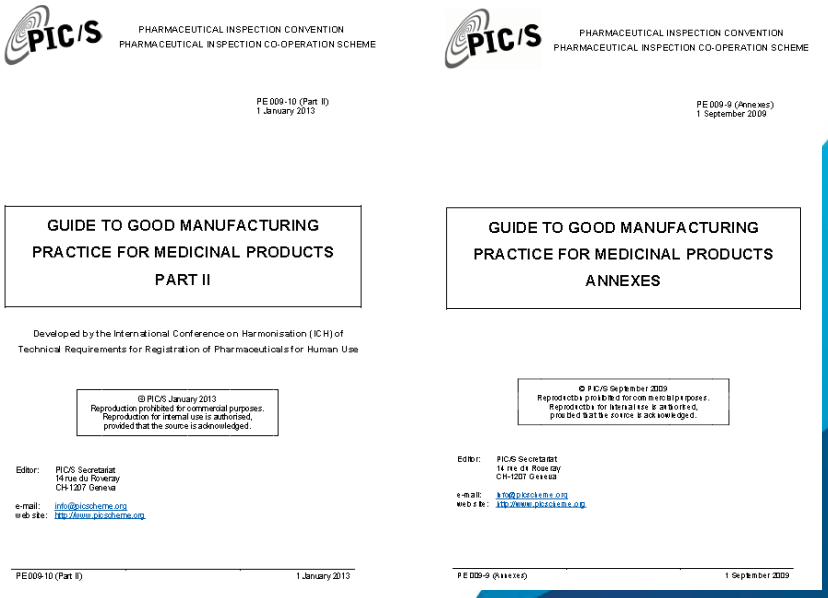
Diaphragm size (MG)		Fastening bolts	Guide values for seal materials			
			EPDM Torque [Nm]		PTFE Torque [Nm]	
MG	A x B / LK [mm]		Min	Max	Min	Max
8	22 x 22	4x M 4	0.6	0.8	0.8	1.2
10	39 x 44	4x M 5	1.2	1.6	1.2	2.0
20	44.5 x 40	4x M 6	2.0	3.0	4.0	5.0
25	54 x 46	4x M 8	5,0	6,5	6,0	8,0
40	70 x 65	4x M10	8.0	10.0	14.0	16.0
50	82 x 78	4x M12	12.0	14.0	20.0	22.0
65	102 x 95	4x M12	18.0	21.0	30.0	33.0
80	127 x 114	4x M16	35.0	40.0	60.0	66.0
100	ø 194	8x M12	40.0	45.0	50.0	60.0
125	ø 222	8x M16	50.0	55.0	60.0	70.0
150	ø 273	10x M16	55.0	60.0	60.0	70.0
200	ø 381	14x M16	55.0	60.0	60.0	70.0
250	ø 438	14x M22	70.0	80.0	90.0	110.0
300	ø 507	14x M22	70.0	80.0	90.0	110.0



WHY ARE CLOSED SYSTEMS IMPORTANT?



PHARMACEUTICAL INSPECTION CONVENTION (PIC/S)



PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-10 (Part II)
1 January 2013

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART II

Developed by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use

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PHARMACEUTICAL INSPECTION CONVENTION
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PE 009-9 (Annexes)
1 September 2009

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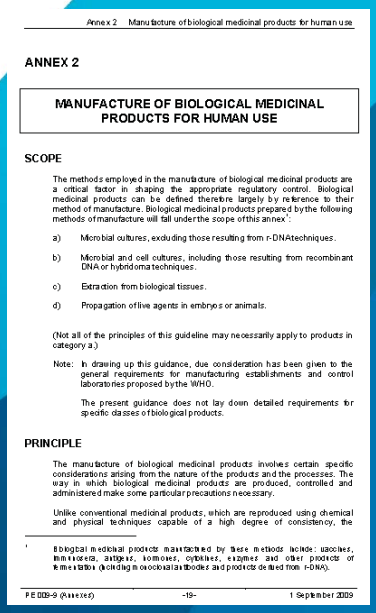

ANNEX 2

MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex[1]:

a) Microbial cultures, excluding those resulting from r-DNA techniques.

b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques.

c) Extraction from biological tissues.

d) Propagation of live agents in embryos or animals.

(Not all of the principles of this guideline may necessarily apply to products in category a.)

Note: In drawing up this guidance, due consideration has been given to the general requirements for manufacturing establishments and control laboratories proposed by the WHO.

The present guidance does not lay down detailed requirements for specific classes of biological products.

PRINCIPLE

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the

[1] Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA).

For further information, please contact
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