Case Studies with Fishbone Analysis

Abstract

Root cause analysis is an important part for identifying failures during investigation. This article will provide you a number of examples of fish bone diagram, which will be useful for all Pharmaceutical professional.

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FROM THE AUTHOR'S DESK

Dear Readers,

Through PRES we are trying to connect with the Global Pharma community. Where we discussed, share and explore lots of pharmaceutical hot topics. Being a Pharma professional it is very difficult to get time for own to do something different from the routine responsibilities. Hope you all professionals are agreed with my views. That's you, the readers and followers of my blog, who always encouraged me a lot to do something different than my routine assignment.

We know most of the information's are easily available in web media; I am just trying to collate all those information in a single article.

I have collated the information's broadly from the major regulatory guidance document including FDA, PIC,s, MHRA and other pharmaceutical knowledge resources like ISPE, PDA & other websites.

Once again I would like to thanks to my readers, followers and seniors, who has encourage me a lot.

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Mr. Palash Chandra Das is recognized as an expert in the field of aseptic manufacturing of parenteral products, and is a frequent presenter at several web conferences and technical training for Sterile Drug Manufacturing.

He earned his Master's for Pharmaceutical chemistry from the University of West Bengal University of technology in India.

Since 2011 Palash has associated with installation, qualification and operation of several production-lines in standard Clean room Technology as well as in Isolator Technology at major regulatory facility across India.

Contents

1. Introduction :

Fishbone diagram may also be referred to as "Cause and Effect" diagram, or Ishikawa diagrams, after their founder Kaoru Ishikawa. Whatever your preferred term, the fishbone diagram is a great tool for delving into a problem when we need to determine the root cause, and you are surrounded by the opinions of those around you. It provides a process to clearly define the "Effect" and then puts you to thinking about the possible causes, based on the categories of common problems in manufacturing.

In manufacturing, it it accepted that there are 6 main branches that need investigation. These are often describes as the "6M's" but feel free to use the terms that best suit your company.

- People / Manpower: Everyone involved with the process across the value stream, including support functions
- Processes / Methods: This defines how the process is performed and the all requirements needed for doing it, including quality procedures, work orders / travelers / work instructions, drawings
- Machines / Equipment: All machines and equipment, needed to accomplish the job, including tools
- Materials: Raw materials purchased parts and sub assemblies that feed into the end product
- Measurements: defines how have we determined that the outcome is wrong
- Environment: The conditions that influence the process including time, temperature, humidity or cleanliness

Reference link: https://txm.com/fishbone-diagrams/

2. Manual Visual Inspection processs :

Figure 1: Elaborated fish bone analysis for idntifying the root cause for failur of **manual visual inspection process** for Lyophilized and liquid formulation:

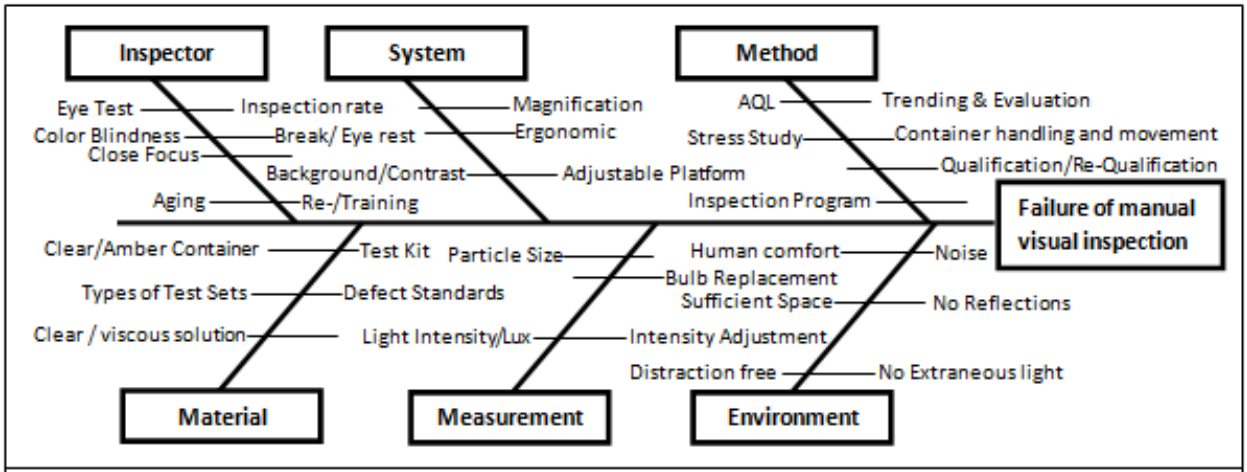
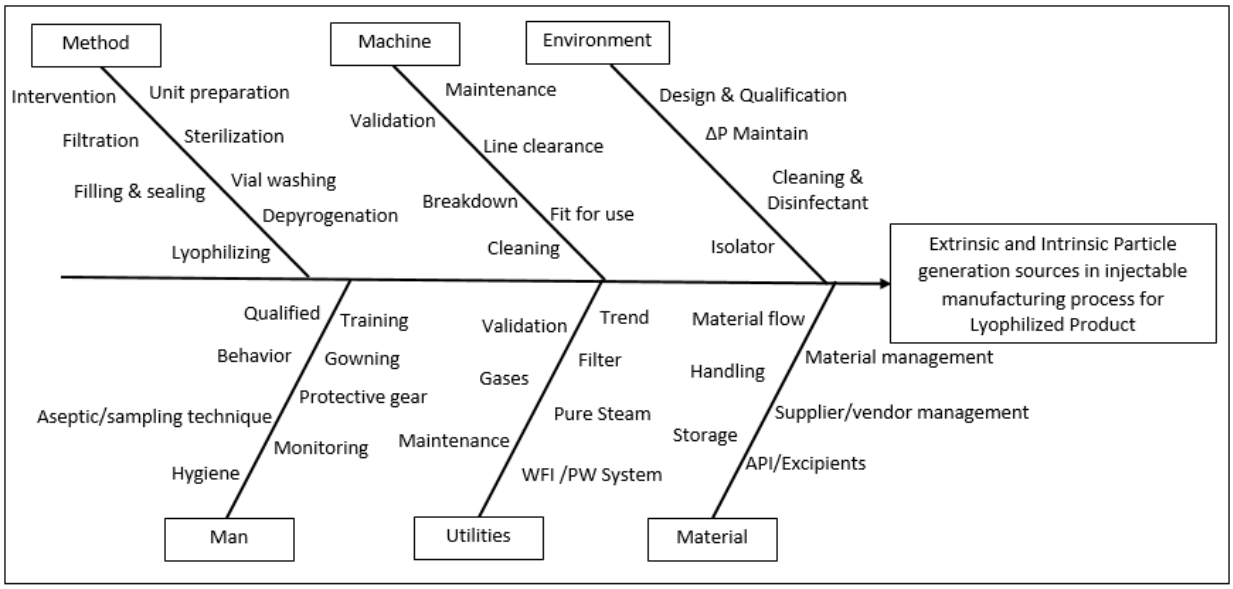


Figure: Fish Bone on failure of manual visual inspection process for Injectables formulation (Liquid & Lyophilized)

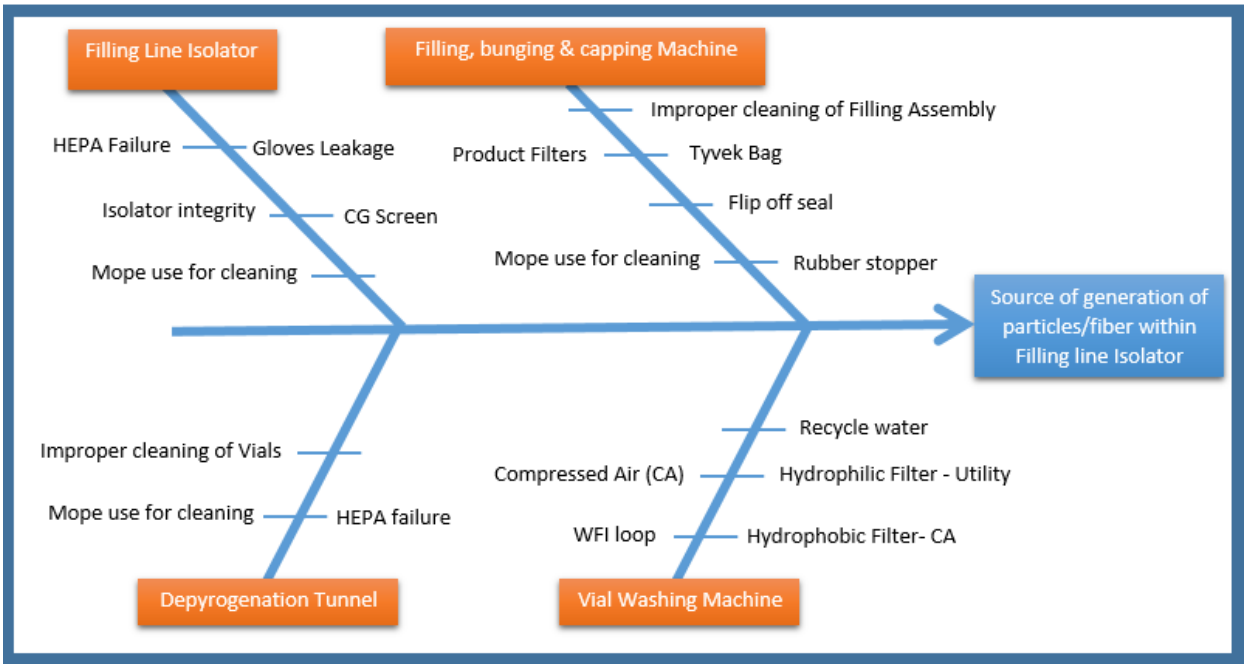
3. Particle generation source in sterile injectable process :

Figure 2: Detailed fish bone analysis for identifying probable root cause for generating **extrinsic and intrinsic** Particle in liquid and lyophilized injectable manufacturing process



4. Particle generation source with in filling line Isolator :

Figure 3: Elaborated fish bone analysis for idntifying the root cause for **generating particles/fiber** with in aseptic filling line Isolator :



5. NVPC/CPMS excurtion in filling line:

Figure 4: Elaborated fish bone analysis for identifying the root cause for NVPC /CPMS excursion in aseptic filling line/ Isolator:

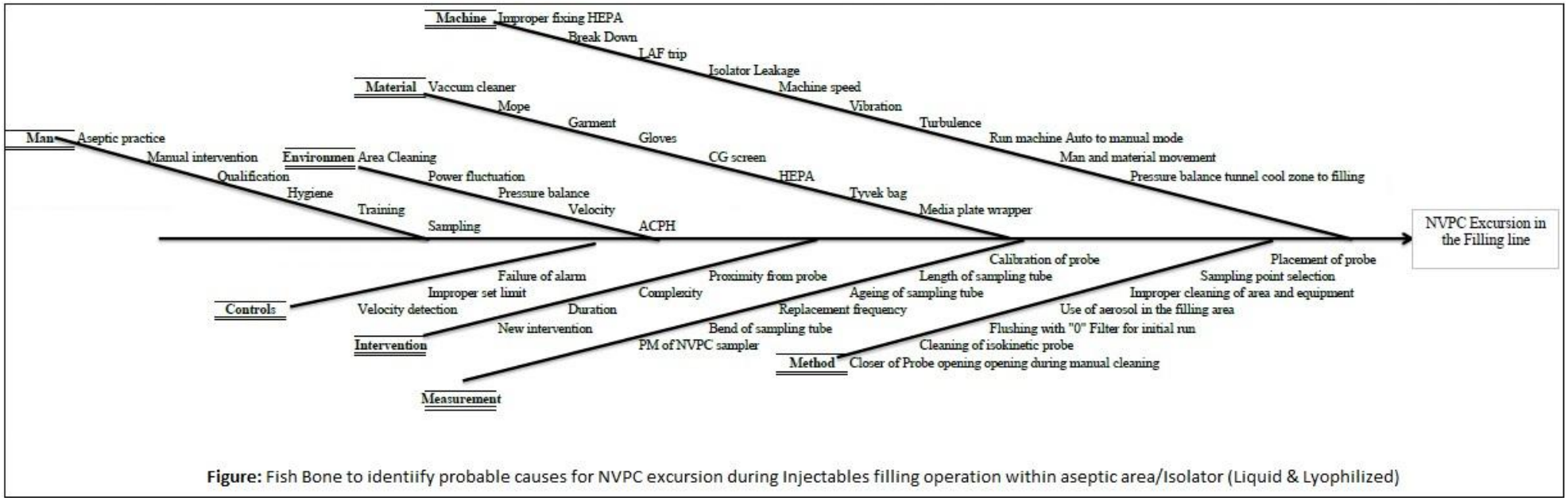


Figure: Fish Bone to identiify probable causes for NVPC excursion during Injectables filling operation within aseptic area/Isolator (Liquid & Lyophilized)

Note: Apart from the above mentioned fishbone *(figure 4)*, additional root causes is derived and incorporated in the below mentioned Table 1.

Table 1: Root cause analysis for NVPC failure in clean room/filling room:

Sr. No.	Category	Root Cause
1	Man	Training
2	Man	Hygiene
3	Man	Qualification
4	Man	Intervention
5	Man	Aseptic practice
6	Man	Sampling
7	Man	Stress/ Work load
8	Man	Cross contamination
9	Man	Sampling/EM activity
10	Man	Improper Tyvek bag tear off
11	Machine	AHU
12	Machine	Improper fixing HEPA to ceiling
13	Machine	HEPA filter damage/leakage/Age
14	Machine	Door Interlock
15	Machine	Vial Washing
16	Machine	Improper cleaning of vials due to,
17	Machine	Low pressure in utility
18	Machine	Filter quality used for utility
19	Machine	improper handling of vials
20	Machine	Dismantled machine guard
21	Machine	Depyrogenation tunnel
22	Machine	Final washer to tunnel in feed GAP
23	Machine	HEPA filter damage/leakage/Age
24	Machine	Dirt chaired in 350 temperature
25	Machine	Mope lint in tunnel track
26	Machine	DP disturbed
27	Machine	Entry and exit flap setting
28	Machine	Gloves integrity Tester
29	Machine	Calibration
30	Machine	Gloves integrity Failed
31	Machine	Online particle counter
32	Machine	Amplitude of the sensor output function
33	Machine	Effect of flow on sizing in counter/Pulse Height
34	Machine	Isokinetic sample heads shall be used in unidirectional airflow systems
35	Machine	VHP tolerant flow path and optics
36	Machine	Illumination Uniformity Affects Resolution
37	Machine	Isolator
38	Machine	Improper fixing HEPA/integrity
39	Machine	LAF trip/Interruption in power supply

Sr. No.	Category	Root Cause
40	Machine	Isolator Leakage
41	Machine	Leakage from Glove/sleeve system
42	Machine	Turbulence
43	Machine	Pressure balance tunnel cool zone to filling
44	Machine	Turbulence as return riser obstruct with material
45	Machine	Sharp ages of machine
46	Machine	Concealed base of Isolator
47	Machine	Isokinatic probe near isolator exhaust create turbulence in air flow
48	Machine	Filling and bunging machine
49	Machine	Machine speed variation
50	Machine	Vibration
51	Machine	Run machine Auto to manual mode
52	Machine	Post PM, improper assembling
53	Machine	Sharp ages of machine
54	Machine	Other
55	Machine	Use of sharp item within filling activity
56	Machine	Vacuum Cleaner efficiency
57	Machine	vacuum cleaner filter bag damage
58	Material	Mope quality
59	Material	Garment quality
60	Material	Gloves quality
61	Material	CG screen aging
62	Material	Tyvek bag
63	Material	Media plate wrapper
64	Material	Non GMP tooling used
65	Material	Damage bag of Vacuum Cleaner
66	Material	CA/Nitrogen purging
67	Material	Integrity Air Filters use for CA/Nitrogen
68	Material	Drug product crystal formation from spillage
69	Material	Media spillage
70	Method	Placement of isokinetic probe
71	Method	Sampling point selection
72	Method	Flushing with "0" Filter for initial run
73	Method	Cleaning of isokinetic probe
74	Method	Tube length and distance
75	Method	Lid of Probe opening during manual cleaning
76	Method	Setting of warning level
77	Method	Alert/Action level and Trending
78	Method	Cleaning of area and equipment
79	Method	Use/ generation aerosol/powder in the filling area
80	Method	Man and material movement

Sr. No.	Category	Root Cause
81	Method	Machine stoppage reporting procedure
82	Method	Post brake start up procedure
83	Method	Qualification of area and equipment
84	Method	Break Down maintenance
85	Method	HEPA replacement frequency
86	Measurement	Online particle counter
87	Measurement	Calibration of probe
88	Measurement	Air velocity or flow rate of the particle counter
89	Measurement	Tubing length
90	Measurement	Number of tubing bends
91	Measurement	The radius of these bends
92	Measurement	Tubing diameter
93	Measurement	Tubing material.
94	Measurement	Ageing of sampling tube
95	Measurement	Distance of installed probe
96	Measurement	Replacement frequency
97	Measurement	Bend in sampling tube
98	Measurement	PM of NVPC sampler
99	Environment	ACPH
100	Environment	Velocity
101	Environment	Pressure balance/drop
102	Environment	Power fluctuation
103	Environment	Inadequate cleaning
104	Environment	Laminar air flow
105	Environment	Unidirectional Air flow
106	Controls	Failure of alarm
107	Controls	Improper set limit
108	Controls	Velocity detection sensor
109	Controls	Pressure low alarm
110	Controls	Door position sensor
111	Controls	Disable machine controls & sensor
112	Intervention	Proximity from probe
113	Intervention	Complexity
114	Intervention	Duration
115	Intervention	New intervention
116	Intervention	Unidentified intervention
117	Intervention	Corrective
118	Intervention	Inherent

6. Sterile poduct quality assesment:

Figure 5: Fishbone analysis for identifying risk for Product Quality (sterile injectable formulation):

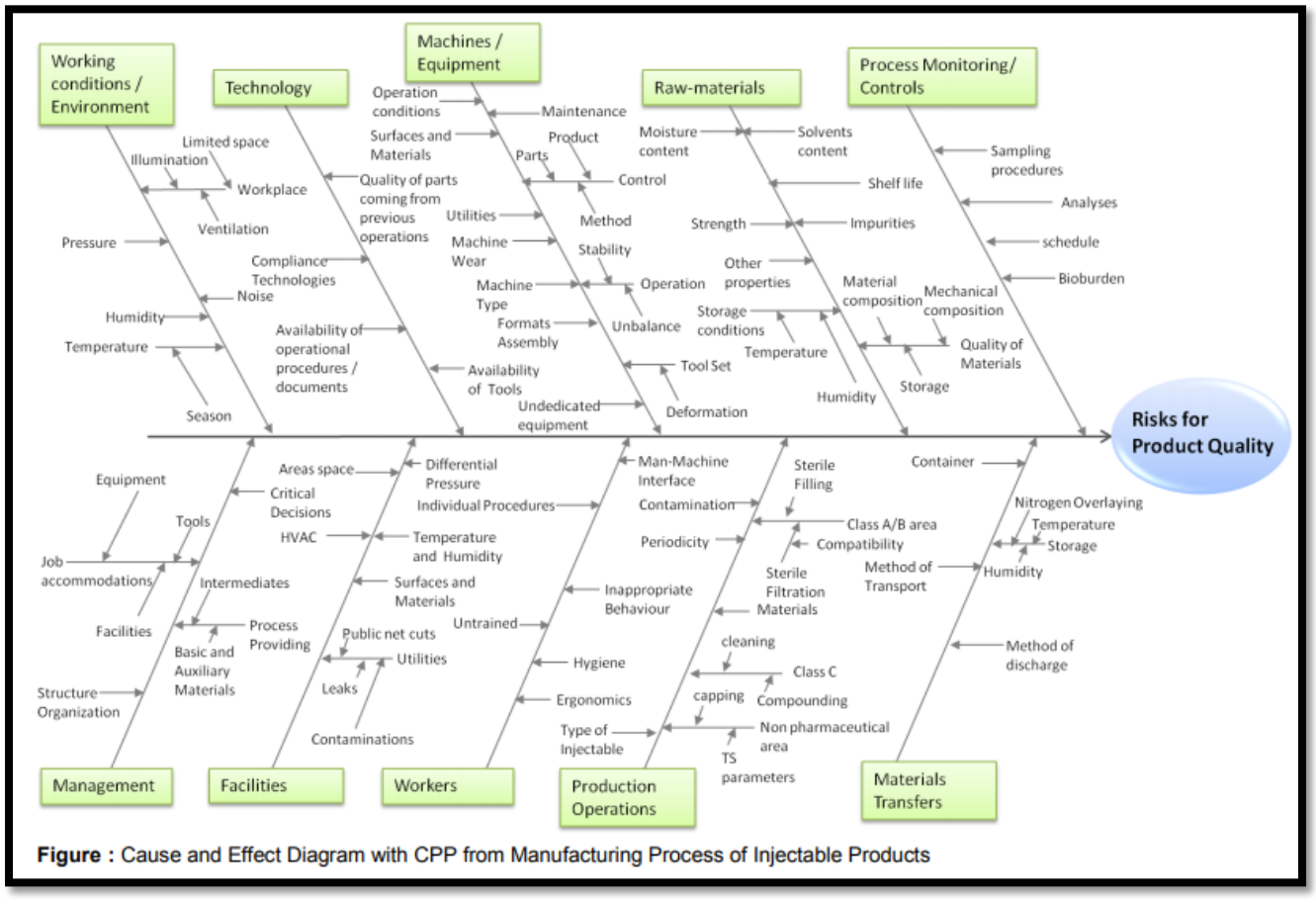
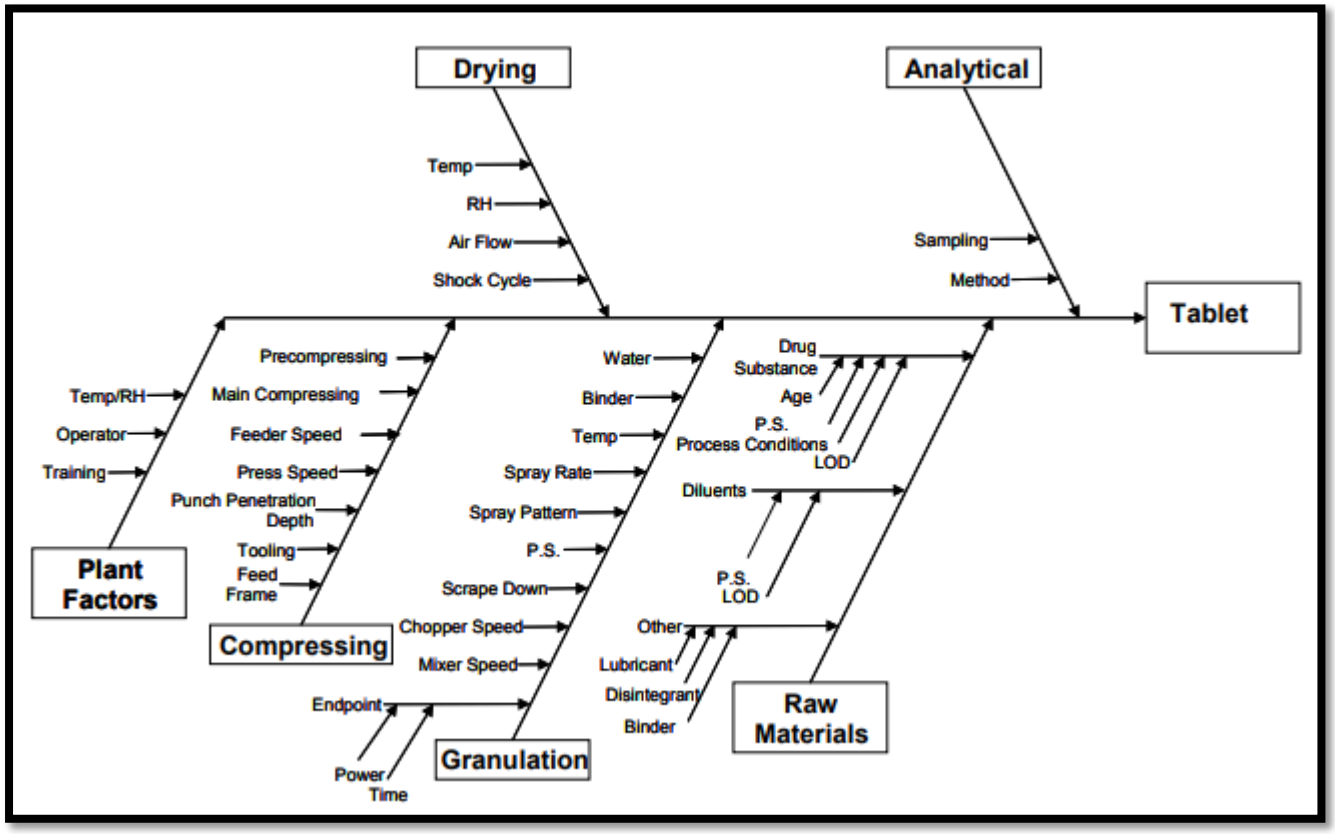


Figure : Cause and Effect Diagram with CPP from Manufacturing Process of Injectable Products

Reference link document for fishbone: https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf

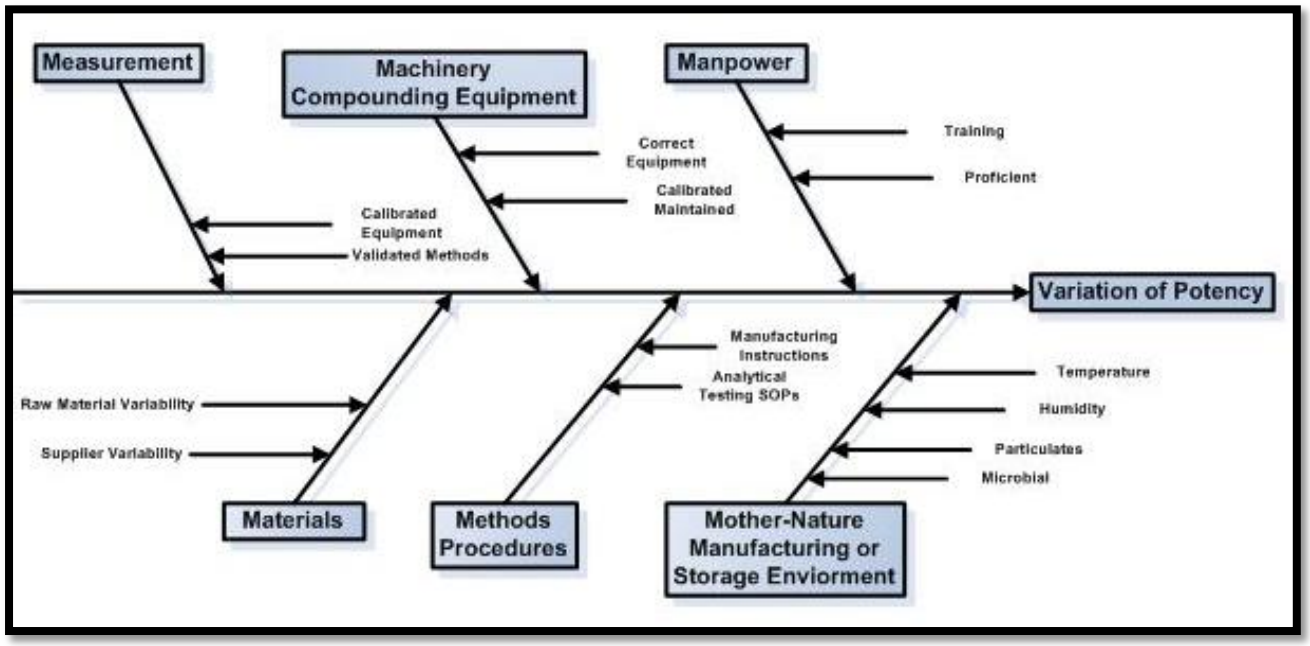
7. Critical procss step of Tablet manufacturing:

Figure 6: Fishbone for identifying critical process steps for Tablet manufacturing:



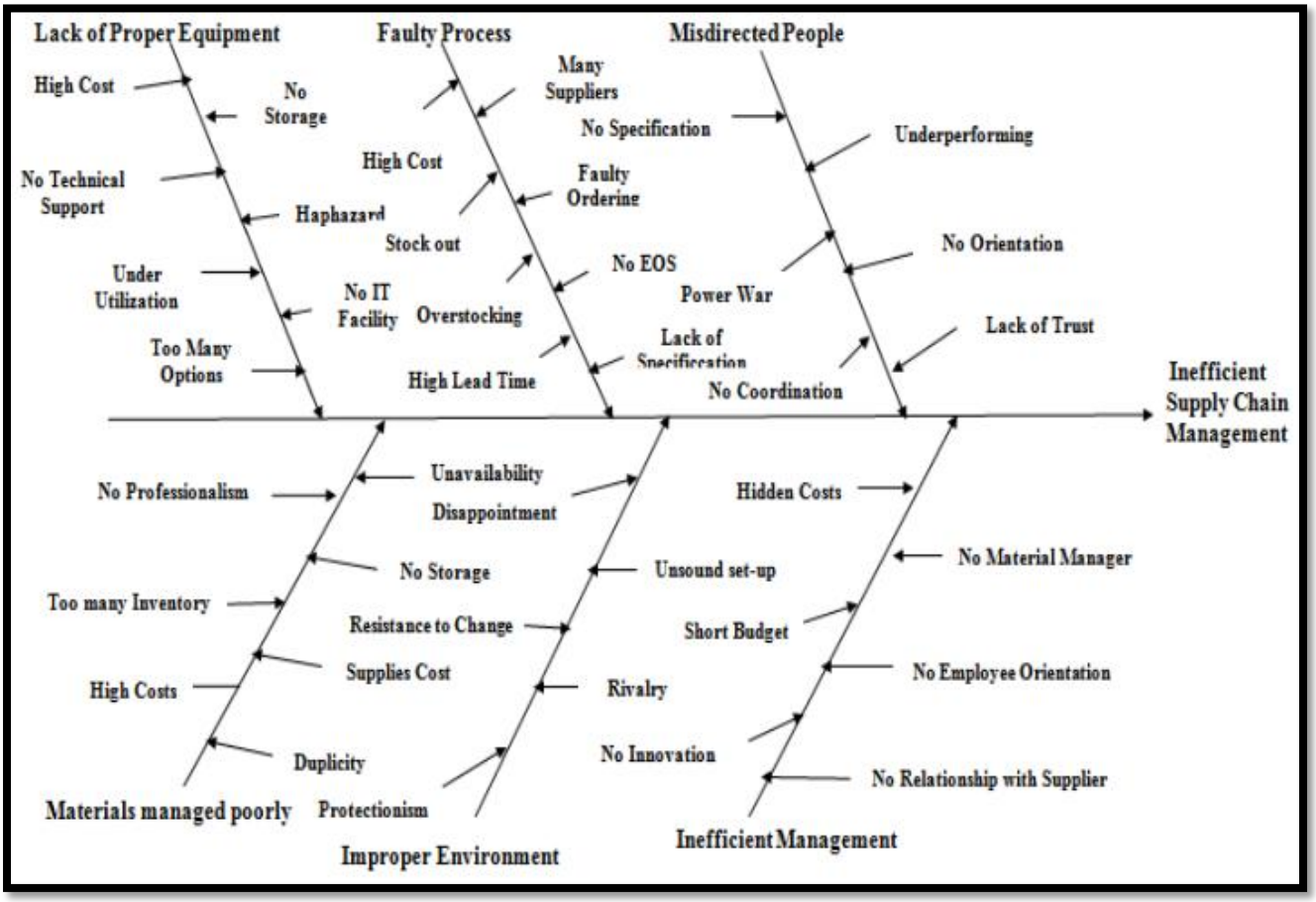
8. Variation of Potency:

Figure 7: Fishbone for identifying critical process steps for identifying the variation of potency:



9. Inefficient Supply Chain management:

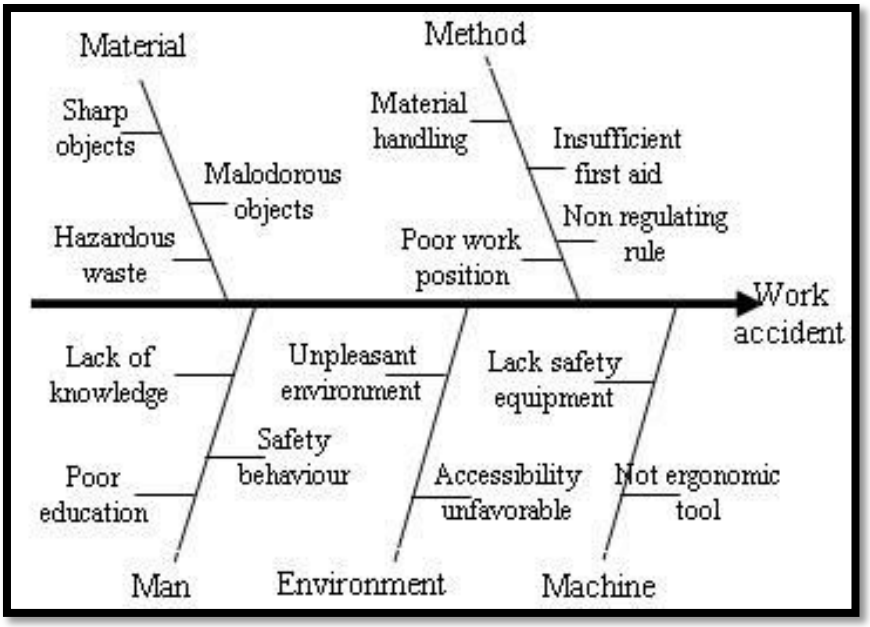
Figure 8: Detailed fishbone for idenfying deficiencies for Supply Chain Management:



Reference link for fishbone http://www.airccse.org/journal/mvsc/papers/3212ijmvsc02.pdf

10. Work accident:

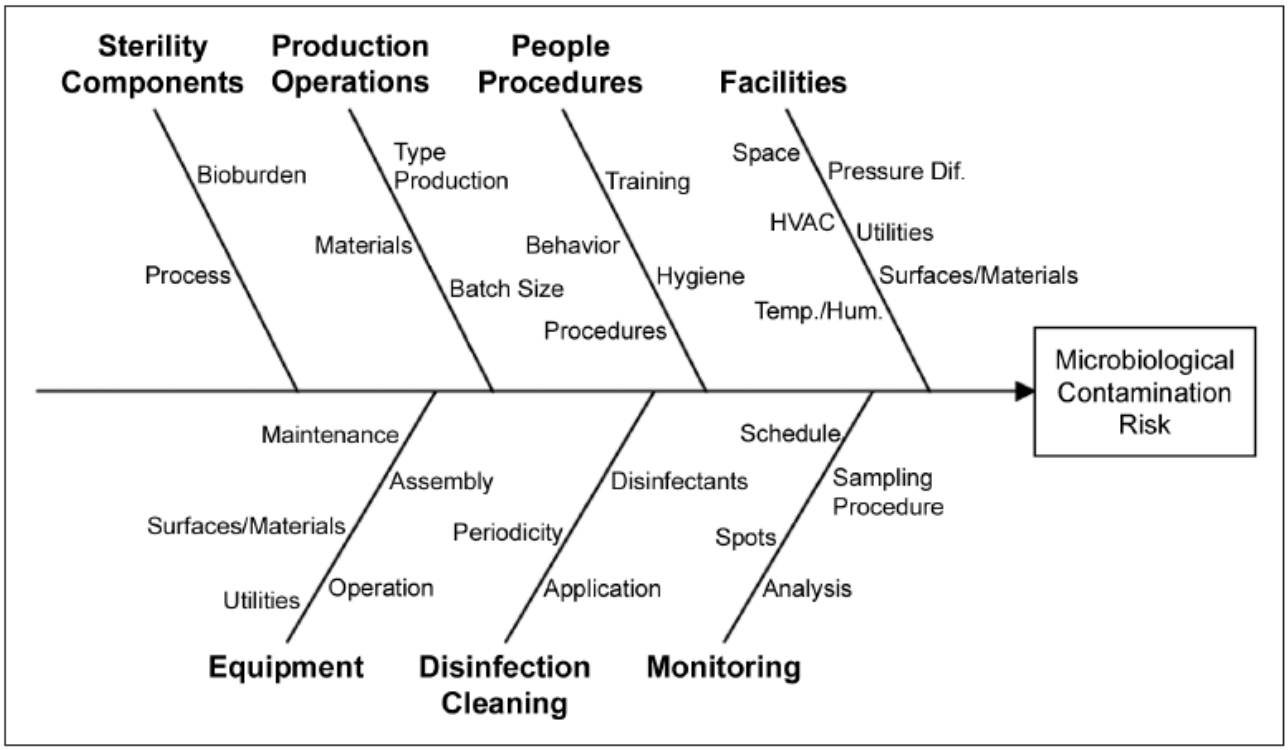
Figure 9: Fishbone for identifying probable root cause for work place accident:



11. Microbiological Contamination Risk:

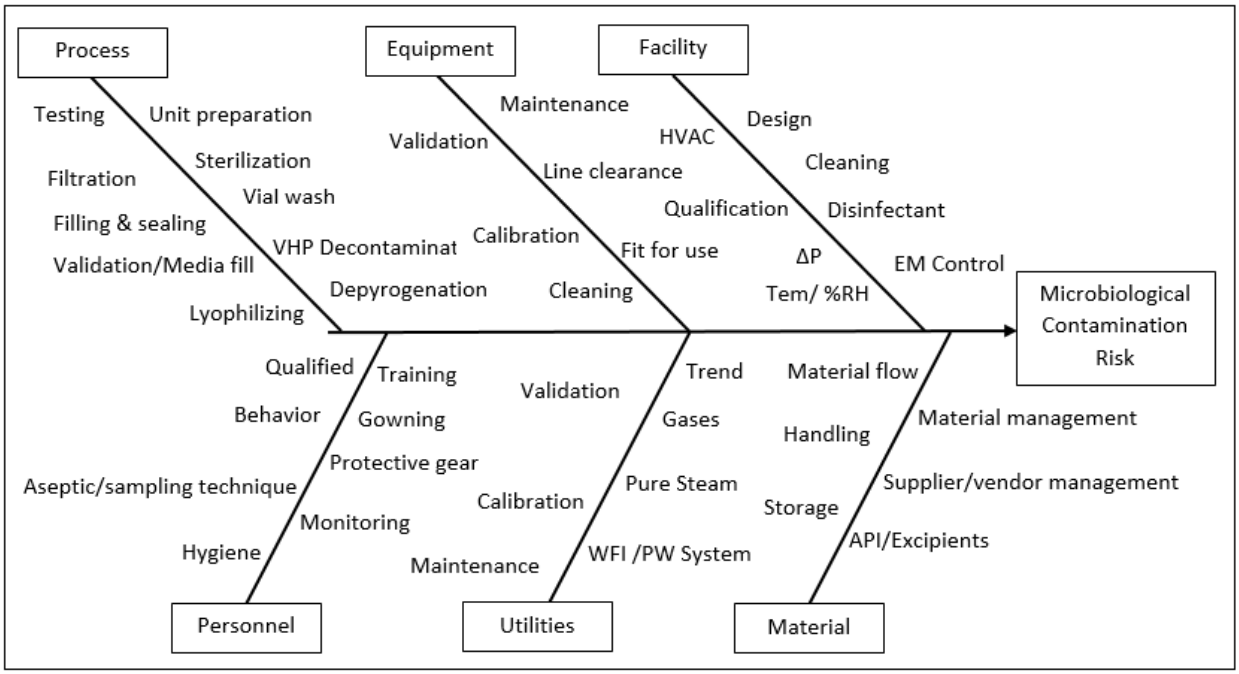
Figure 10: Cause and effect diagram with **microbiological contamination** parameters from aseptic process.

A: Basic



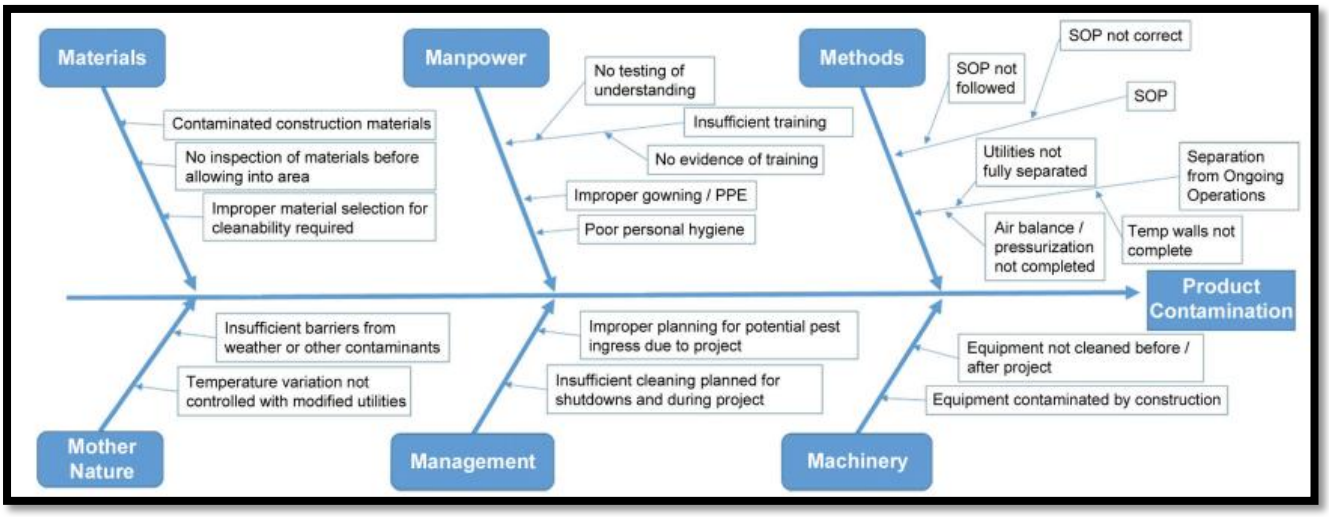
Referance: Design, Validation, and Control of Sterile Manufacturing Facilities: A Brief Overview from the Perspective of Risk Management and Existing Regulations, by Ana Quinto and José C. Menezes

B:Extensive



12. Product Contamination:

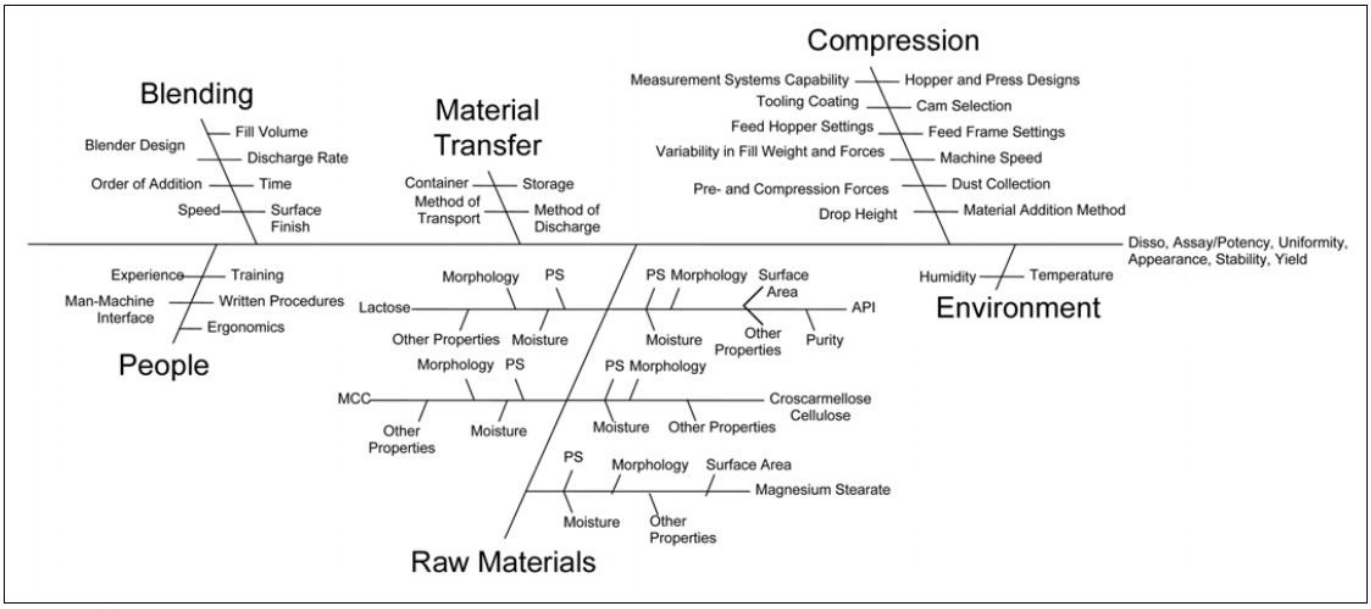
Figure 11: Cause and effect diagram with microbiological product contamination parameters:



http://www.theaustin.com/sites/default/files/files/Contamination%20Risk%20Reduction_Pharma%20Eng%20Mag.pdf

13. Direct compression tablet:

Figure 12: Fish bone for identifying all critical aspect of direct tablet compression:



Case study example: Fishbone diagram for a direct compression tablet.

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