Quality by design (QbD) in process development

DCVMN 10 March 2017

Product quality cannot be ensured by inspections, it has to be designed into the product by a robust production process

What is QbD?

Four key steps defining process design space

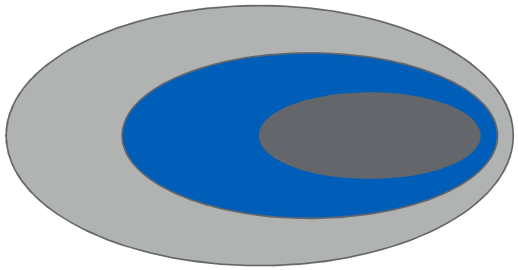
- Process mapping
  - Process flow, fishbone diagrams
  - Which factors could potentially affect our process?
- Risk analysis
  - Failure Mode and Effects Analysis (FMEA)
  - Which parameters should be investigated in detail?
- Design of experiments (DoE)
  - Screening extended space in many parameters
  - Detailed quantification of cause and effect relationships
- Execution and analysis, definition of design space

Why QbD?

Screening
- Which factors are important?
- What are the appropriate ranges?

Optimization
- Detailed quantification of the vital factors. What are the optimal ranges for these factors?

Robustness
- Verify that process is robust to small variations in the vital factors.



Characterized space

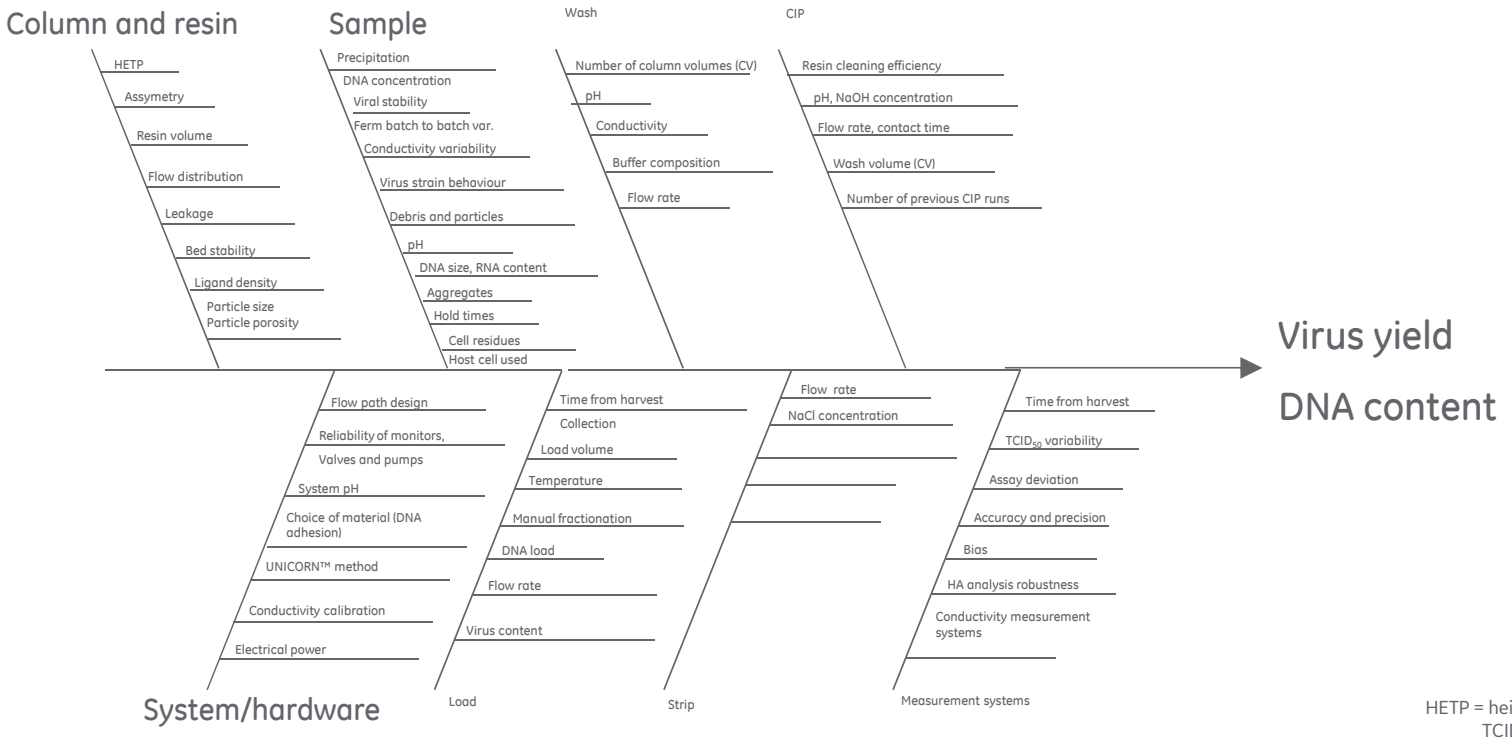
Design space
(quality adequate)

Operating space
(production)

Risk analysis

Example of fishbone analysis

DNA removal using an anion-exchange chromatography column for cell-based influenza purification



CIP = cleaning in place
HA = hemagglutinin
HETP = height equivalent to the theoretical plate
$TCID_{50}$ = 50% tissue culture infective dose

FMEA: failure modes and effects analysis

Risk analysis and mitigation

1. What might go wrong?
2. How severe are the consequences?
3. What is the likelihood the failure will occur?
4. Can we detect the failure?

S	=	Severity of each failure (1–10)
O	=	Likelihood of occurrence (1–10)
D	=	Likelihood of detection (1–10)
RPN	=	Risk priority number = S × O × D

Define what each level represent

To be performed in cross-functional teams (operators, R&D, QA/QC, management, etc.)

DoE essentials

What is DoE?

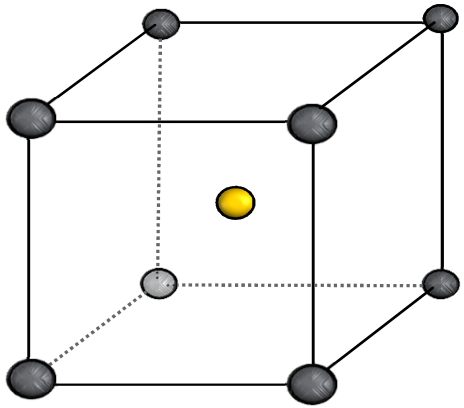
DoE is a systematic way of changing process inputs and analyzing the resulting process outputs in order to quantify the cause and effect relationship between them while using a minimum number of runs.

Keywords for DoE

Factors

A parameter (variable) that is thought to affect the result

Can usually be controlled

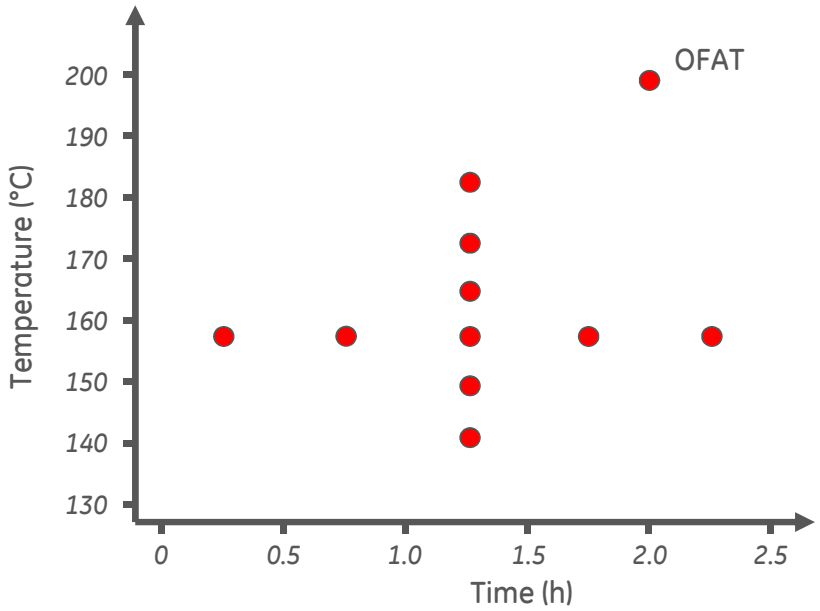


Responses

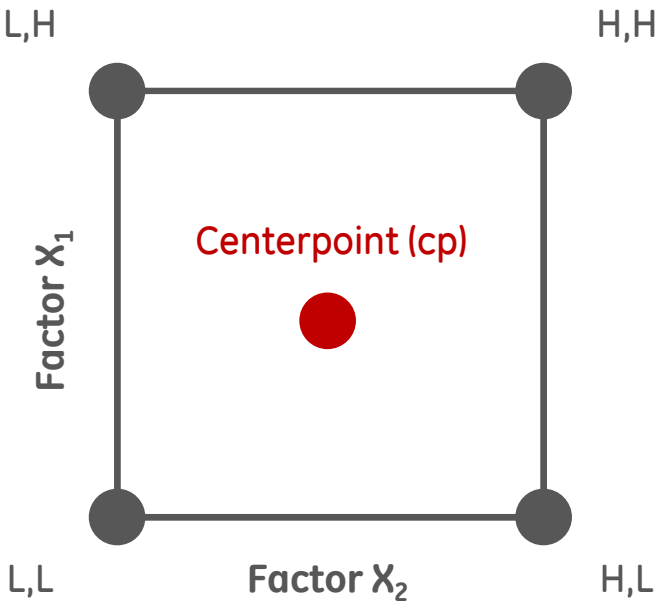
One or more measured variables describing the outcome of the experiment

General design constructions with two factors

One factor at the time (OFAT)

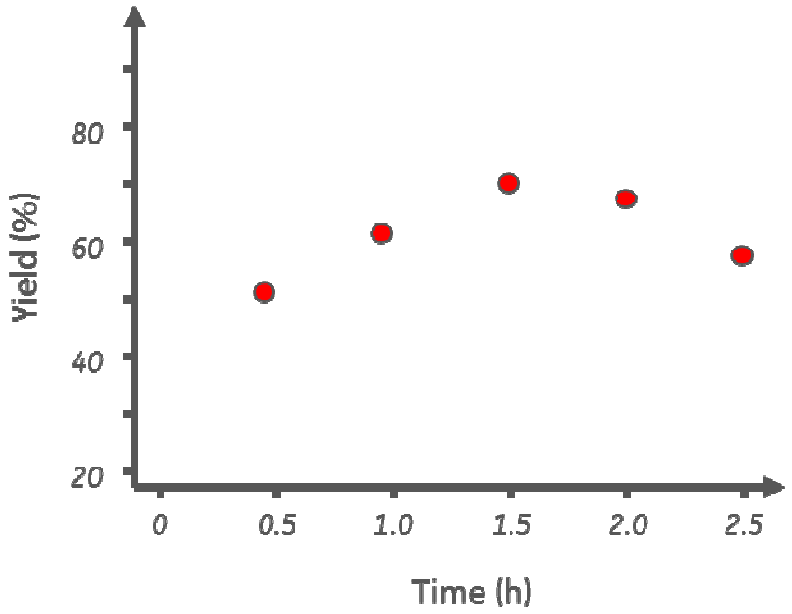


DoE

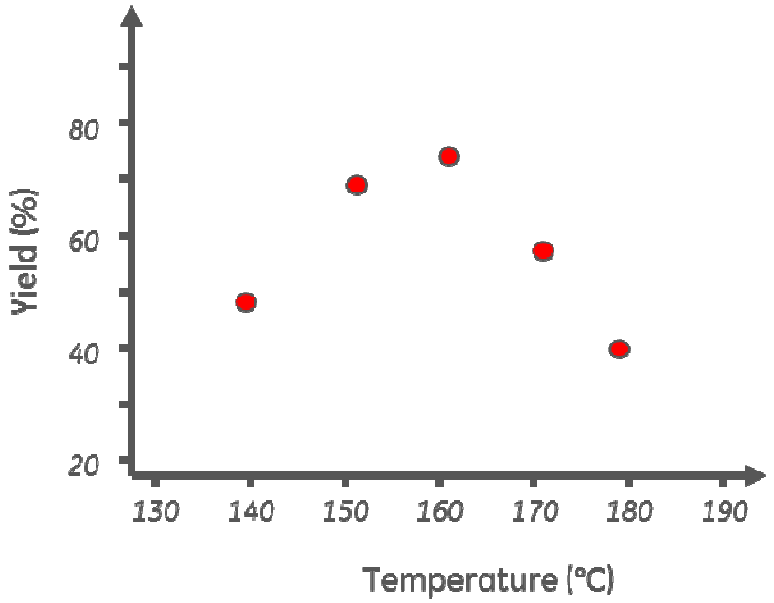


OFAT: the classical/intuitive approach

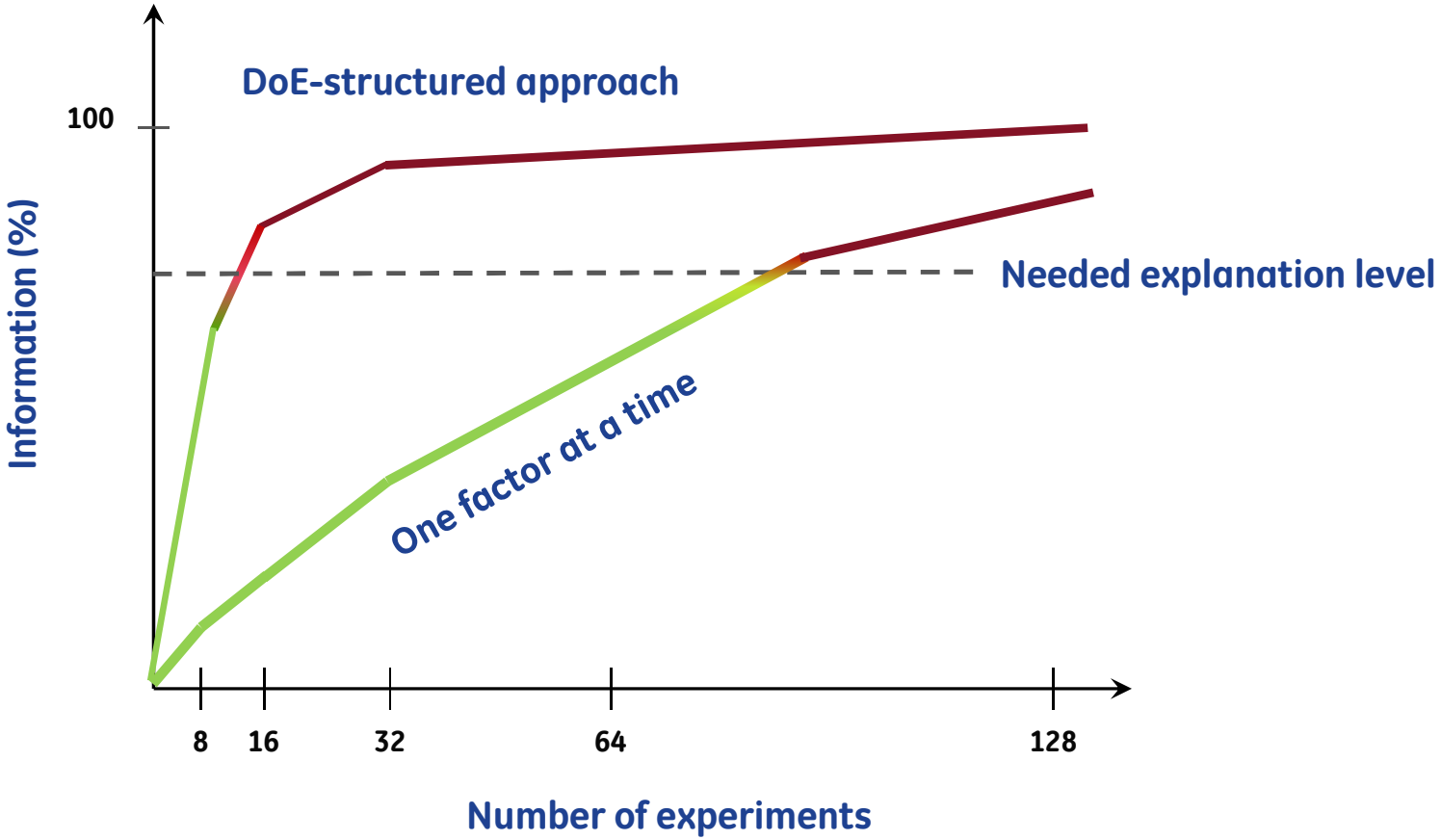
Time (h)



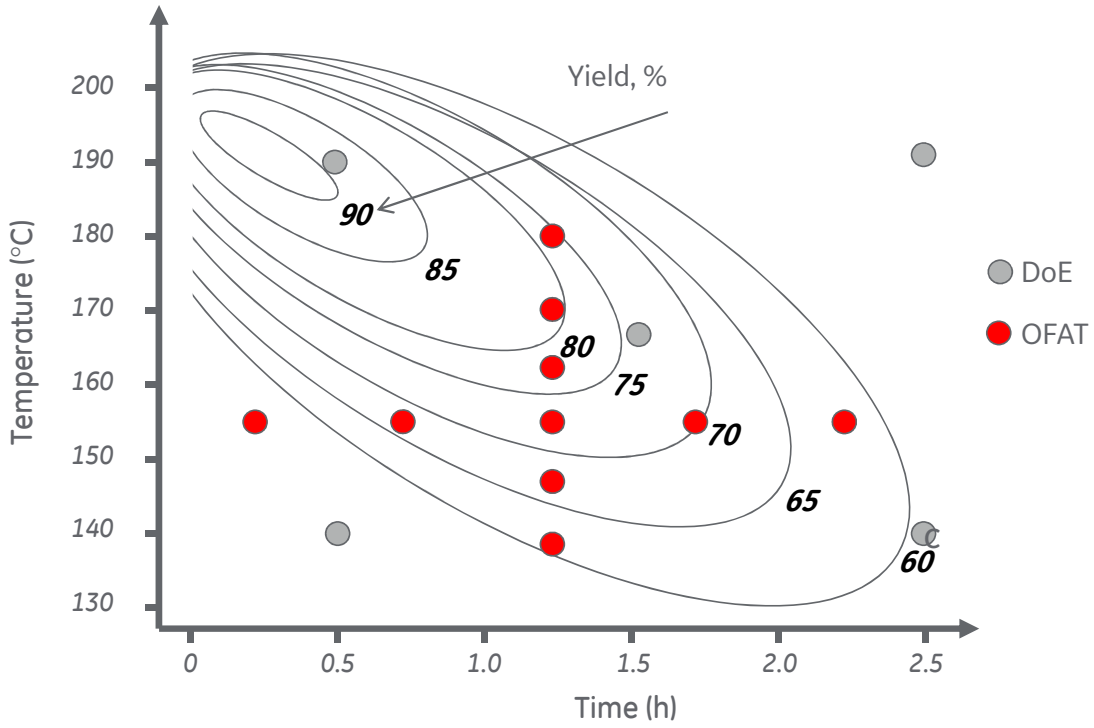
Temperature (°C)



DoE results in more information with less experiments



Interactions between factors can be discovered with DoE



Analysis for vaccines

Examples of analytical methods for vaccines

Single radial immunodiffusion (SRID)

Hemagglutinin (HA) agglutination assay

Enzyme-linked immunosorbent assay (ELISA)

SDS-PAGE/Western blot

qPCR

Plaque assays

$TCID_{50}$

Challenges with analytical methods for QbD and DoE

Sensitivity, detection range

Method variation (precision, accuracy)

Hands on time

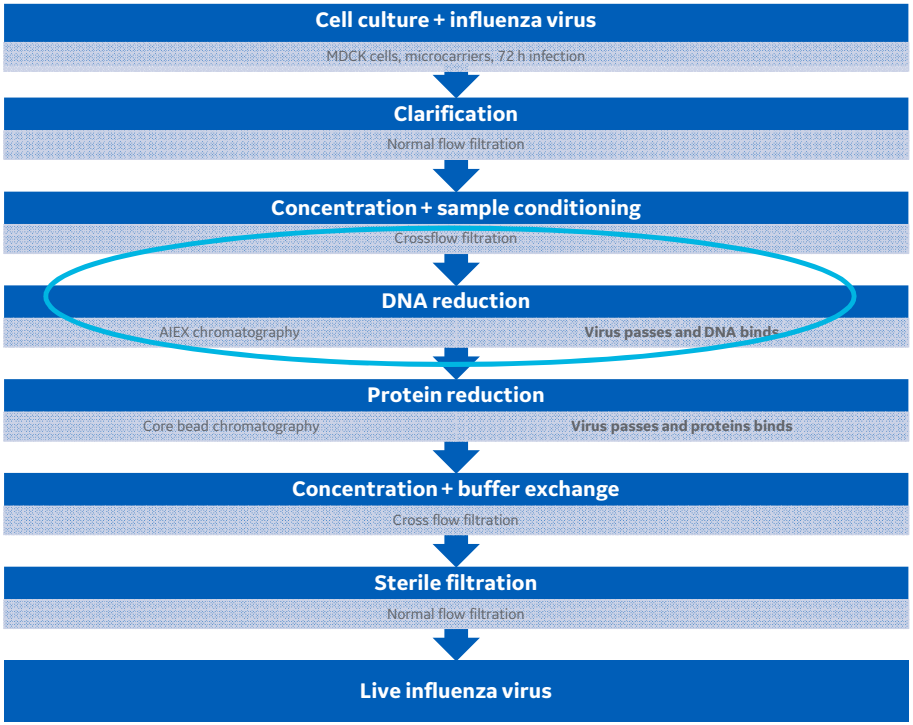
Cost

Robustness

$TCID_{50}$ = 50% tissue culture infective dose

DoE case study: DNA reduction in vaccine processing

DNA removal in vaccine process



- Process mapping and FMEA showed that loss of product and inefficient DNA removal have highest impact on product quality.
- Host cell DNA is a critical impurity.
- DoE setup with pH and conductivity as factors, and antigen yield and DNA removal as responses.

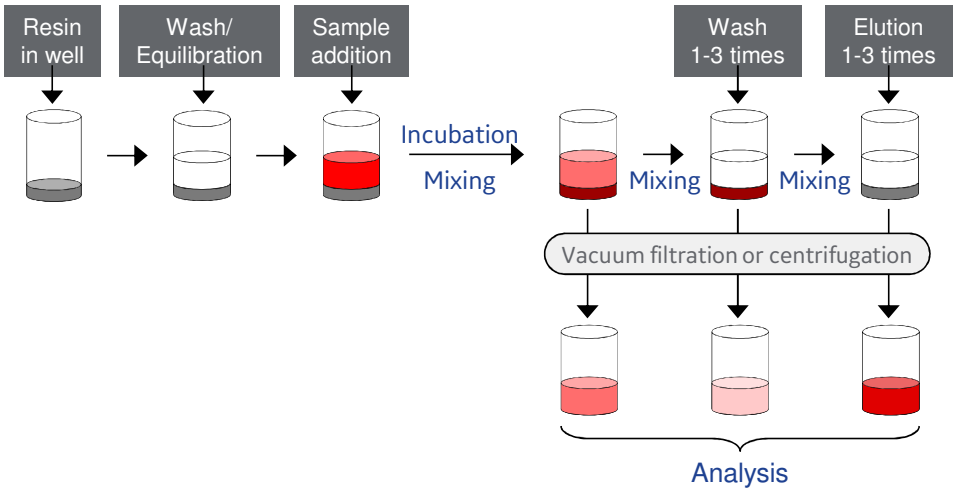
AIEX = anion exchange chromatography

DoE: experimental parameters

Factors	DoE range
pH (equil., load, wash)	7.0–9.0
NaCl (equil., load, wash)	300–800 mM

Responses (supernatant)
MDCK cell DNA (qPCR)
Influenza HA analysis

DoE: experimental set-up

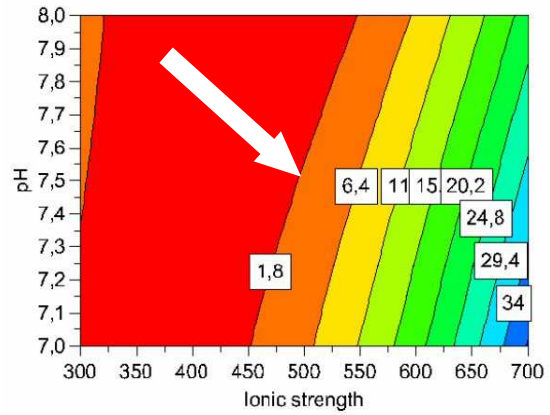


Material

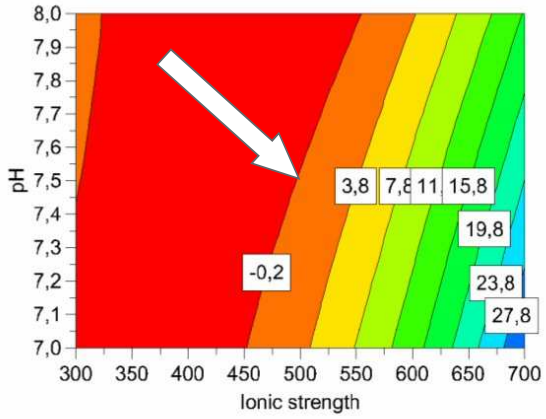
Sample	A/Solomon Island/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 (B)
Sample conditioning	PD-10 Desalting columns
Format	Prepacked 96-well plates
Capto™ Q resin	50 µL/well
Sample load	400 µL/well
Incubation	10 min/shaker
Supernatant collection (flowthrough)	Centrifugation, 500 × g

DoE reveals optimal DNA reduction

A/Solomon Islands/3/2006 (H1N1)

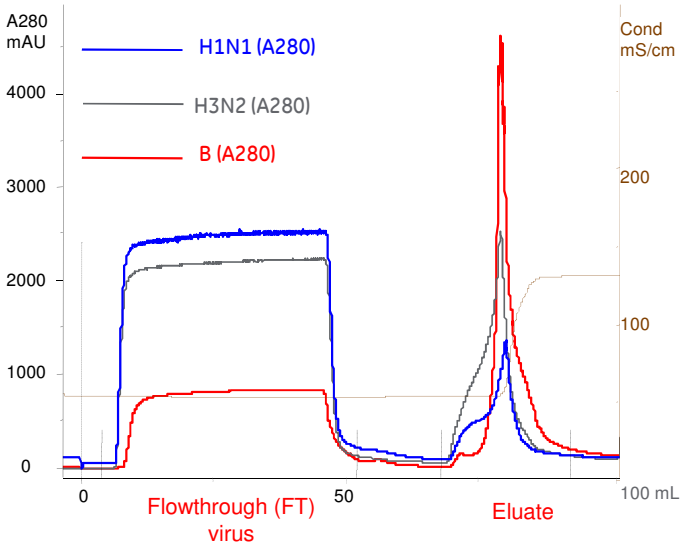


A/Wisconsin/67/2005 (H3N2)



- The level of gDNA (%) in the flowthrough is shown in the boxes.
- Conditions were chosen to achieve efficient DNA reduction (red region) and keep the influenza virus in a non-binding mode.

Chromatography—confirmation of DoE



Column: XK16/20
Volume: 20 mL Capto™ Q resin
Flow rate: 2.0 mL/min (60 cm/h)

Equil. buffer: 20 mM Tris, 0.5 M NaCl, pH 7.5
Elution buffer: 20 mM Tris, 1.5 M NaCl, pH 7.5
CIP: 1 M NaOH

Sample load: 40 mL (2 CV)
FT volume: 1.12-fold sample volume

Sample	HA yield (%)	gDNA (ng/mL) before	gDNA (ng/mL) after	DNA log reduction
A/Solomon Island/3/2006 (H1N1)	> 85	2010	17	2.1
A/Wisconsin/67/2005 (H3N2)	> 85	11 300	16	2.9
B/Malaysia/2506/2004 (B)	> 85	96 800	16	3.8

CIP = cleaning in place

Summary: benefits of QbD and DoE

QbD

Systematic approach to identify potential sources of process variability and parameters likely to have greatest impact on product quality.

DoE

Systematically vary several experimental parameters simultaneously to obtain sufficient information with minimum number of experiments.

Analytical methods are crucial for a successful DoE

Introduction to QbD exercice

What is QbD?

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Process mapping

- Which factors could potentially affect our process?
- Tools: High level process maps
  Fishbone diagrams

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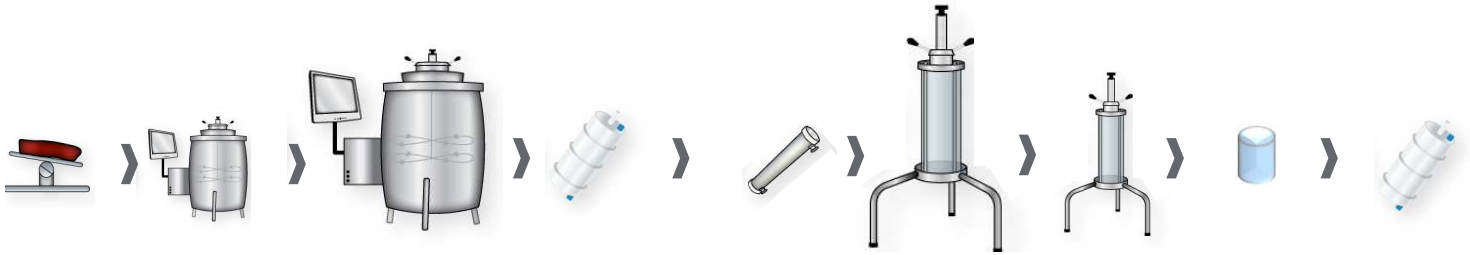
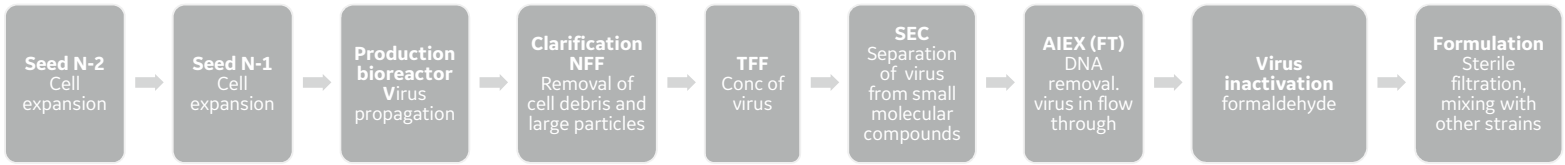




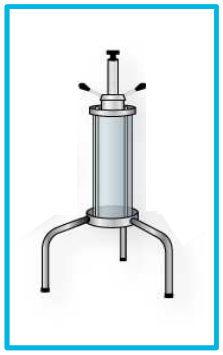
Process mapping

- Which factors could potentially affect our process?
- Tools: High level process maps
  Fishbone diagrams

Seed N-2 Cell expansion → **Seed N-1** Cell expansion → **Production bioreactor** Virus propagation → **Clarification NFF** Removal of cell debris and large particles → **TFF** Conc of virus → **SEC** Separation of virus from small molecular compounds → **AIEX (FT)** DNA removal. virus in flow through → **Virus inactivation** formaldehyde → **Formulation** Sterile filtration, mixing with other strains

Process mapping

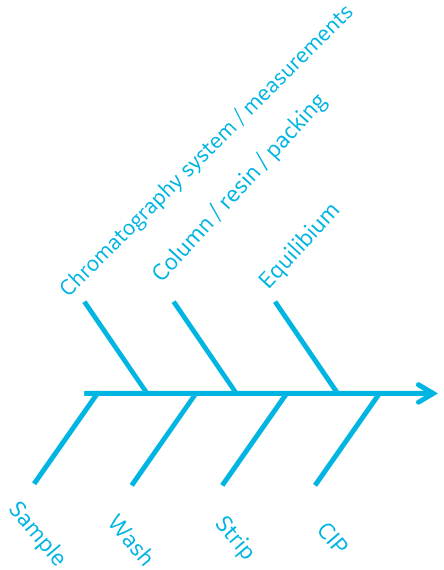
- Which factors could potentially affect our process?
- Tools: High level process maps
  Fishbone diagrams



Break down →

- Chromatography system / measurements
- Column / resin / packing
- Running conditions:
  - Equilibrium
  - Sample
  - Wash
  - Strip
  - CIP

Fishbone analysis →



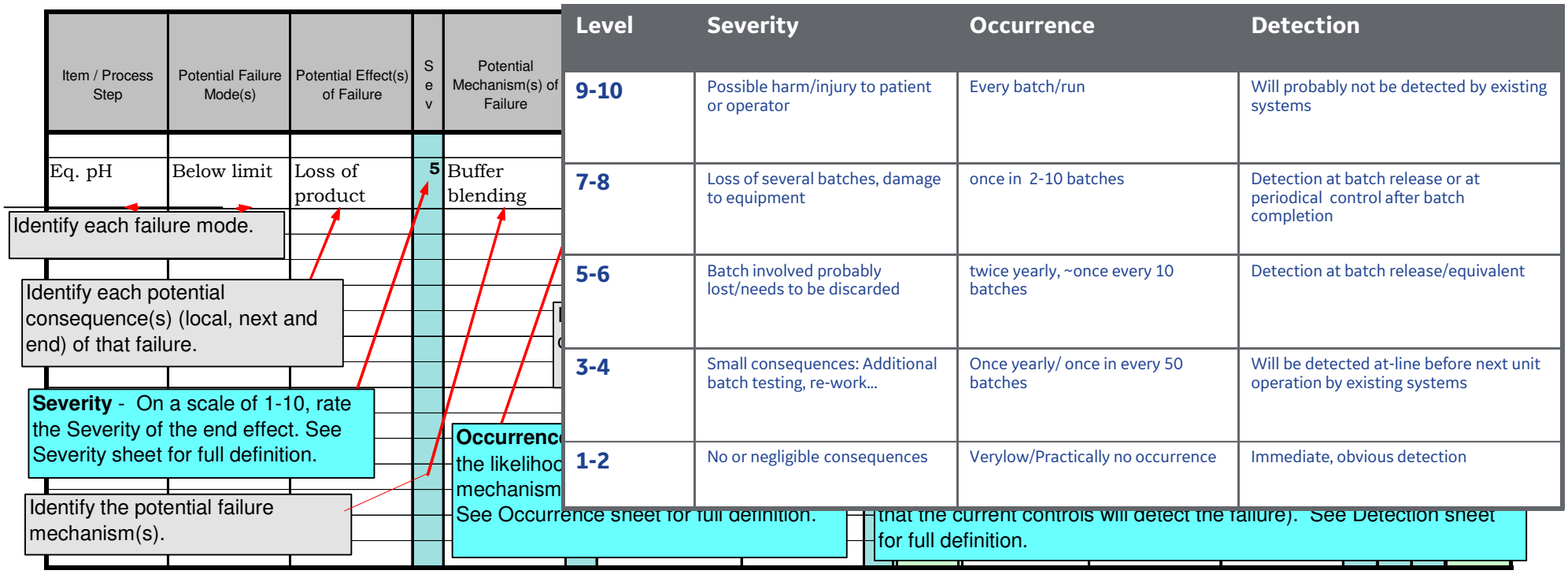
FMEA – Failure Modes and Effects Analysis

Risk analysis and mitigation – To be performed in cross-functional teams

1. What might go wrong?
2. How severe are the consequences?
3. What is the likelihood the failure will occur?
4. Can we detect the failure?

S - Severity of each failure (1-10)
O - Likelihood of occurrence (1-10)
D - Likelihood of detection (1-10)
RPN - Risk Priority Number = S x O x D
Define what each level represent

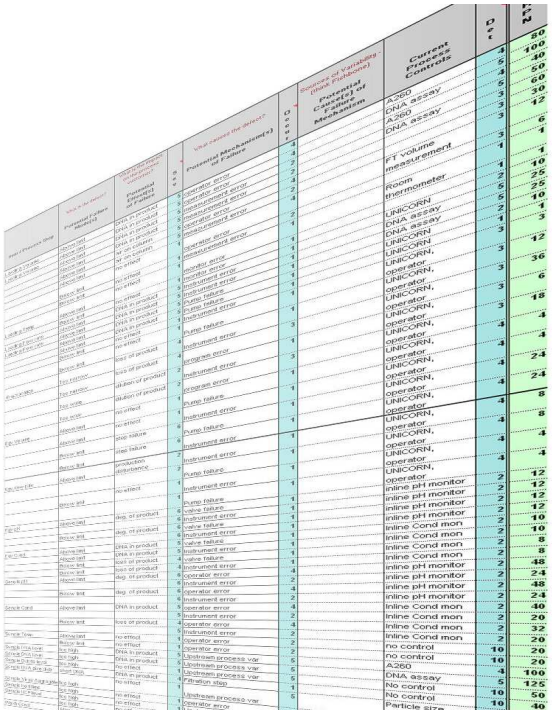
The components of an FMEA



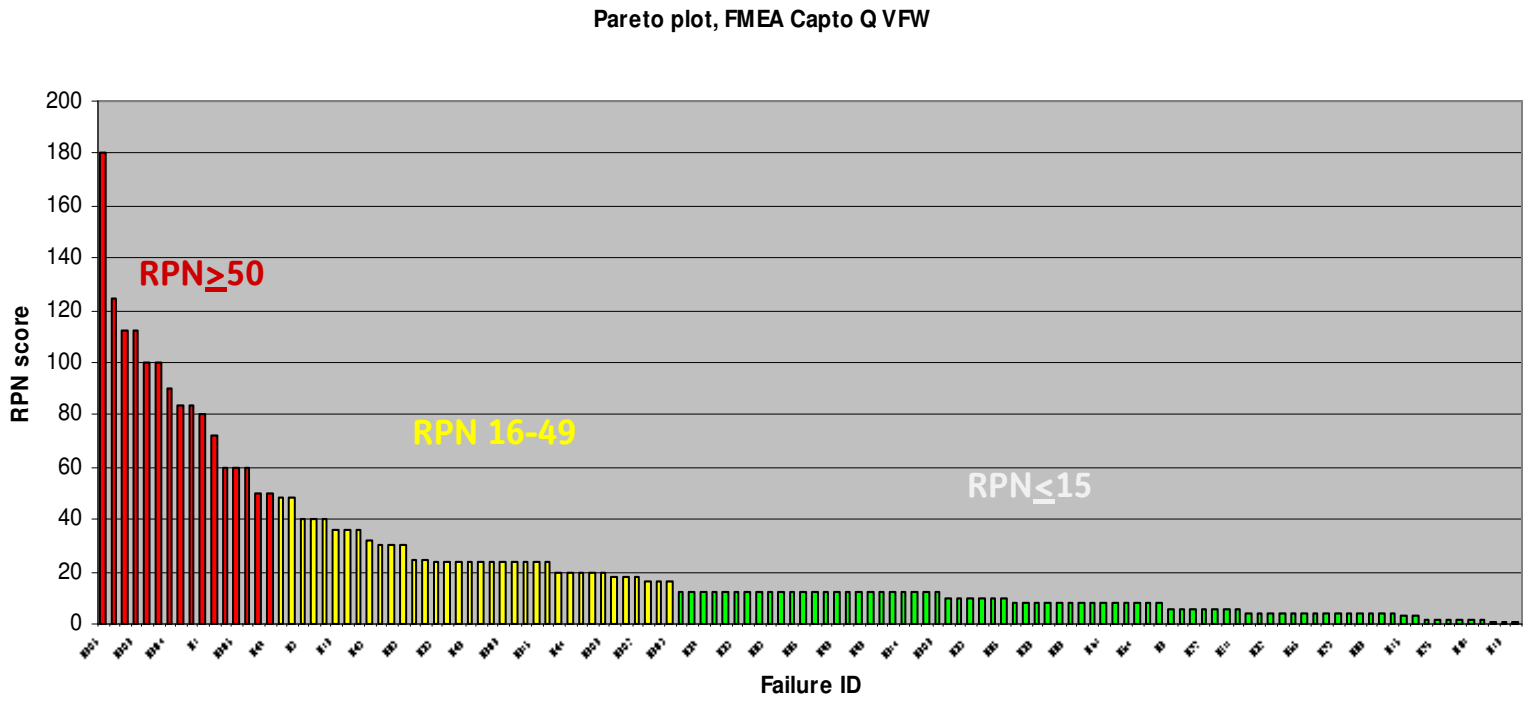
Level	Severity	Occurrence	Detection
9-10	Possible harm/injury to patient or operator	Every batch/run	Will probably not be detected by existing systems
7-8	Loss of several batches, damage to equipment	once in 2-10 batches	Detection at batch release or at periodical control after batch completion
5-6	Batch involved probably lost/needs to be discarded	twice yearly, ~once every 10 batches	Detection at batch release/equivalent
3-4	Small consequences: Additional batch testing, re-work…	Once yearly/ once in every 50 batches	Will be detected at-line before next unit operation by existing systems
1-2	No or negligible consequences	Verylow/Practically no occurrence	Immediate, obvious detection

FMEA-Flow through DNA removal on AIEX

- 128 failure modes identified
- RPN scores 1-180

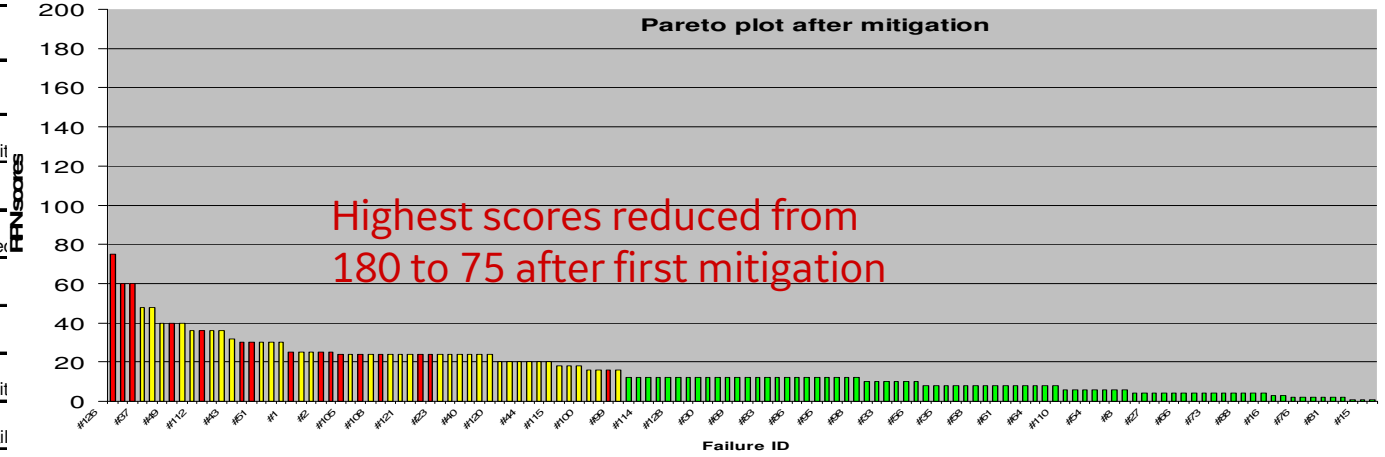


Pareto plot of RPN scores



FMEA score card for top 10 RPN's

Item / Process Step	Potential Failure Mode(s)	Potential Effect(s) of Failure	S	Potential Mechanism(s) of Failure	O	Current Process Controls	D	RPN	Recommended Action(s)	Action Results				
										Actions Taken	New S	New O	New D	New RPN
Analysis assay	failure	loss of batch	6	operator error	5	internal std run, operator	6	180	Consistent re-analysis for OOS results	Yes	3	5	5	75
Sample DNA level	too high	DNA in product	5	Upstream process var	5	DNA assay	5	125	Picogreen screening of sample pre-run	Yes	4	5	3	60
Bioburden	too high													
Bioburden	too high													
Loading volume	Above limit													
Sample DNA level	too high													
Column/resin HETP/As	Out of spec													
Bioburden	too high													
Bioburden	too high													
Loading Volume	Above limit													
System hardware	Monitor fail													



Group exercise:
Fishbone analysis and FMEA on buffer preparation

Practical exercise:
Risk analysis for buffer preparations

Contamination

Wrong pH

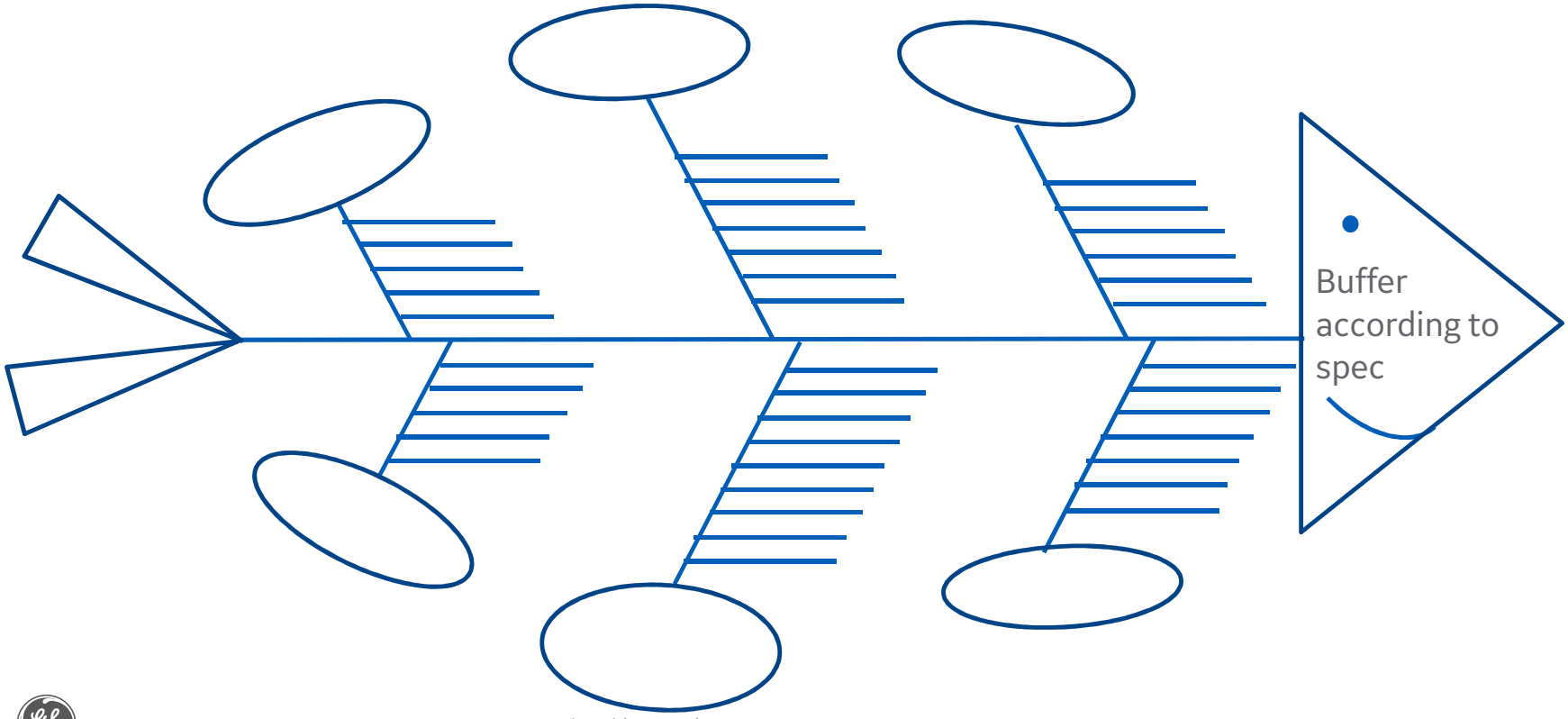
Wrong conductivity

Wrong water quality

Other?

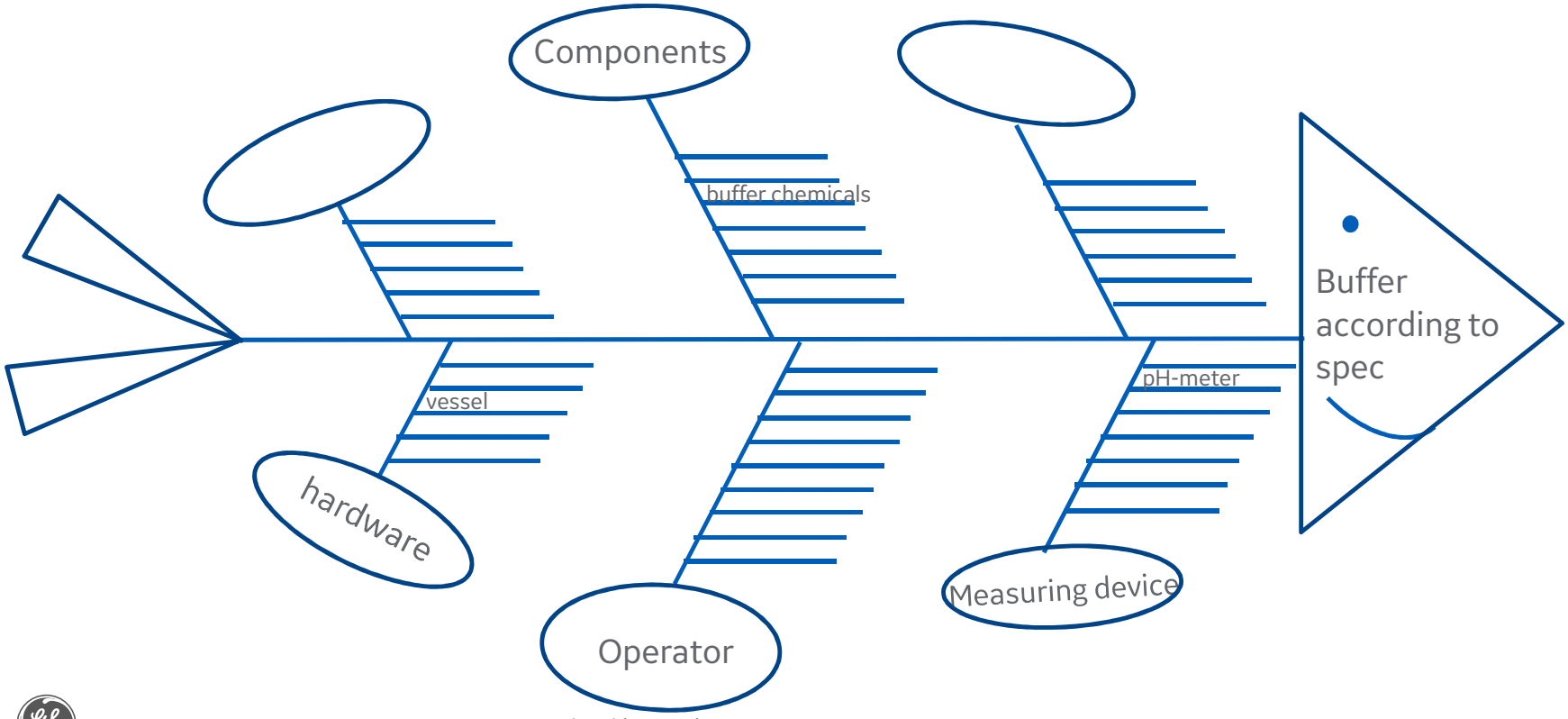
Fishbone analysis: Buffer preparation

What could possibly go wrong?



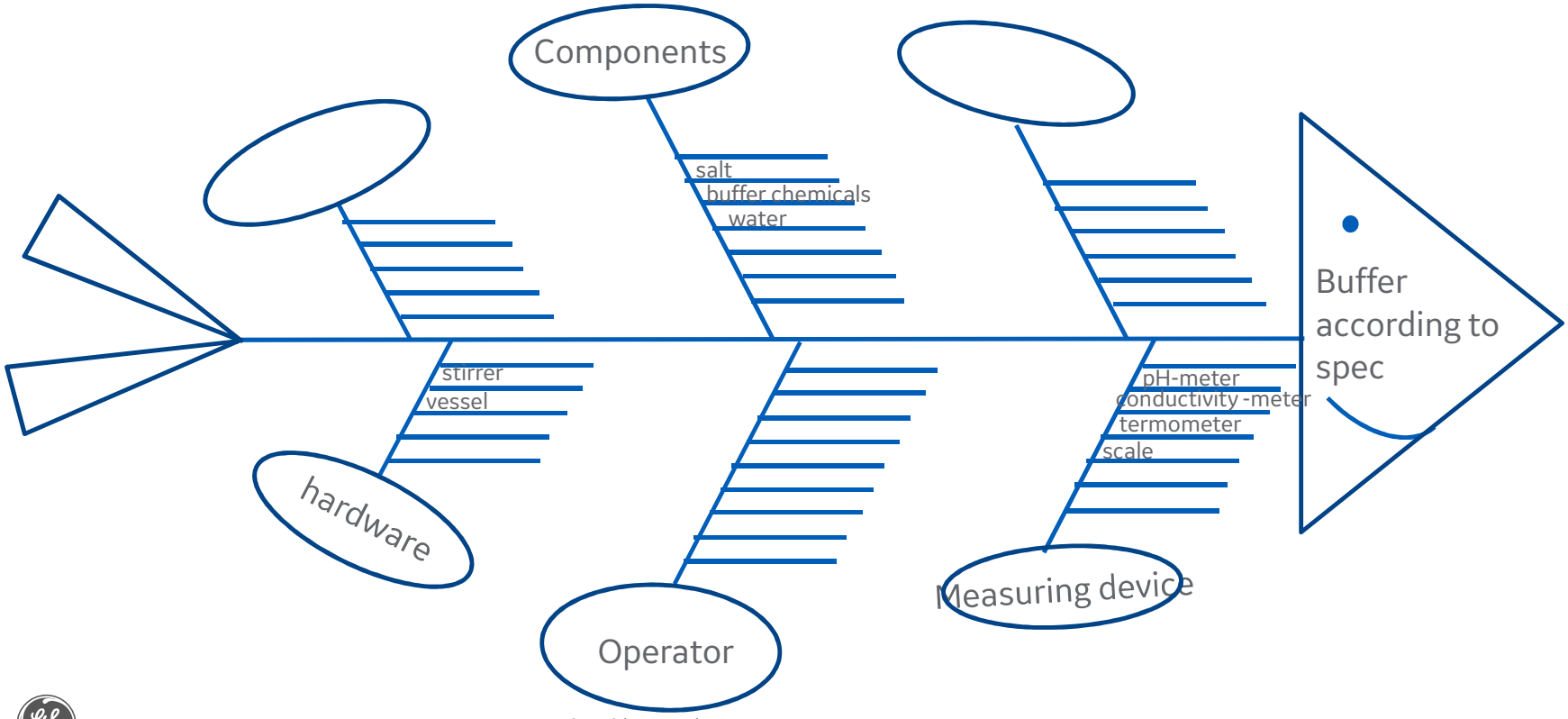
Fishbone analysis: Buffer preparation

What could possibly go wrong?



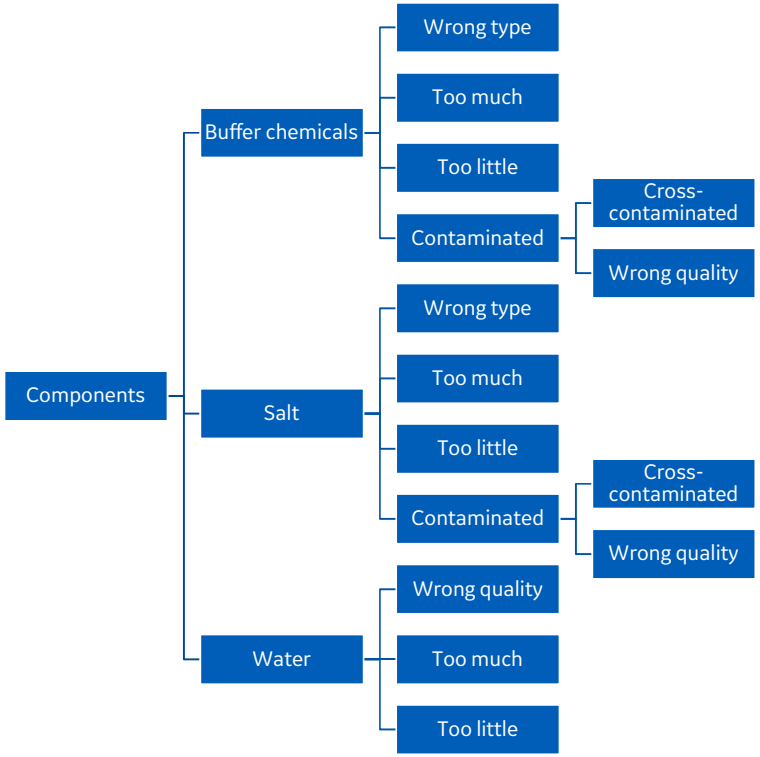
Fishbone analysis: Buffer preparation

What could possibly go wrong?



Breakdown of failure modes for components in buffer preparation

Example



Ranking - Severity

Effect	Severity of Effect	Ranking
Hazardous without warning	Possible harm/injury to patient or operator	**10**
Hazardous with warning	Possible harm/injury to patient or operator	**9**
Very High	Loss of several batches, damage to equipment	**8**
High	Loss of several batches, damage to equipment	**7**
Moderate	Batch involved probably lost/needs to be discarded	**6**
Low	Batch involved probably lost/needs to be discarded	**5**
Very Low	Small consequences: Additional batch testing, re-work…	**4**
Minor	Small consequences: Additional batch testing, re-work…	**3**
Very Minor	No or negligible consequences	**2**
None	No or negligible consequences	**1**

Severity is an assessment of the seriousness of the effects (next, local and end) as felt by the customer.

Ranking - Occurrence

Probability of Process Failure	Failure Rates* (failures per batch)	Ranking
Very High: Failure is almost inevitable	> 1 in 2	**10**
	1 in 5	**9**
High: Repeated failures	1 in 10	**8**
	1 in 10	**7**
Moderate: Occasional failures	1 in 20	**6**
	1 in 20	**5**
	1 in 100	**4**
Low: Relatively few failures	1 in 100	**3**
	1 in 1 000	**2**
Remote: Failure is unlikely	< 1 in 1 000	**1**

Occurrence is the likelihood that the failure mechanism and subsequent failure mode will occur (based on historical data on similar processes or past experience knowledge).

Ranking - Detection

Detection	Likelihood of Detection	Likelihood of Detection	Ranking
Absolute Uncertainty	Will probably not be detected by existing systems	< 1%	**10**
Very Remote	Will probably not be detected by existing systems	1% - 5%	**9**
Remote	Detection at batch release or at periodical control after batch completion	5% - 15%	**8**
Very Low	Detection at batch release or at periodical control after batch completion.	15% - 30%	**7**
Low	Detection at batch release/equivalent	30% - 50%	**6**
Moderate	Detection at batch release/equivalent	50% - 75%	**5**
Moderately High	Will be detected at-line before next unit operation by existing systems	75% - 85%	**4**
High	Will be detected at-line before next unit operation by existing systems	85% - 93%	**3**
Very High	Immediate, obvious detection	93% - 99%	**2**
Almost Certain	Immediate, obvious detection	>99 %	**1**

Detection is the likelihood that the control will detect the failure.

FMEA

Practical example

Item/ process step	Potential Failure Mode(s)	Potential Effect(s) of Failure	Severity	Potential Mechanism (s) of Failure	Occurance	Current process control	Detection	RPN (S x O x D)
Component / Chemical	Contamination	Chemicals	6	Contaminated hardware	3	pH / cond	3	54
Component / Chemical	Contamination	Bioburden	6	Contaminated hardware	3	Bioburden testing	6	108
Component / Chemical	Contamination	Bioburden	6	Contaminated chemical	5	Bioburden testing	6	180

Practical exercise

Fill in the table in groups

Contamination

Wrong pH

Wrong conductivity

Wrong water quality

Other?

FMEA

Practical example

Item/ process step	Potential Failure Mode(s)	Potential Effect(s) of Failure	Severity	Potential Mechanism (s) of Failure	Occurance	Current process control	Detection	RPN (S x O x D)
Component / Chemical	Contamination	Chemicals	6	Contaminated hardware	3	pH / cond	3	54
Component / Chemical	Contamination	Bioburden	6	Contaminated hardware	3	Bioburden testing	6	108
Component / Chemical	Contamination	Bioburden	6	Contaminated chemical	5	Bioburden testing	6	180

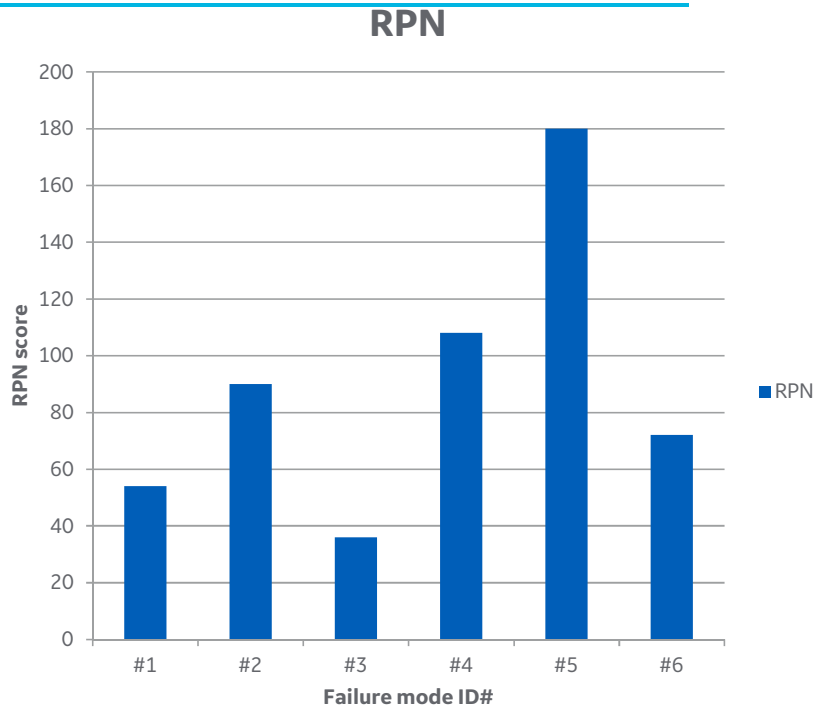
FMEA

Practical example

Failure mode ID #	Item/ process step	Potential Failure Mode(s)	Potential Effect(s) of Failure	Severity	Potential Mechanism (s) of Failure	Occurance	Current process control	Detection	RPN (S x O x D)
1	Component / Chemical	Contamination	chemicals	6	contaminated hardware	3	pH / cond	3	54
2	Component / Chemical	contamination	chemicals	6	contaminated buffer componant	5	pH / cond	3	90
3	Component / Chemical	contamination	chemicals	6	contaminated buffer componant	2	pH / cond	3	36
4	Component / Chemical	contamination	bioburden	6	contaminated hardware	3	bioburden testing	6	108
5	Component / Chemical	contamination	bioburden	6	contaminated buffer componant	5	bioburden testing	6	180
6	Component / Chemical	contamination	bioburden	6	contaminated buffer componant	2	bioburden testing	6	72

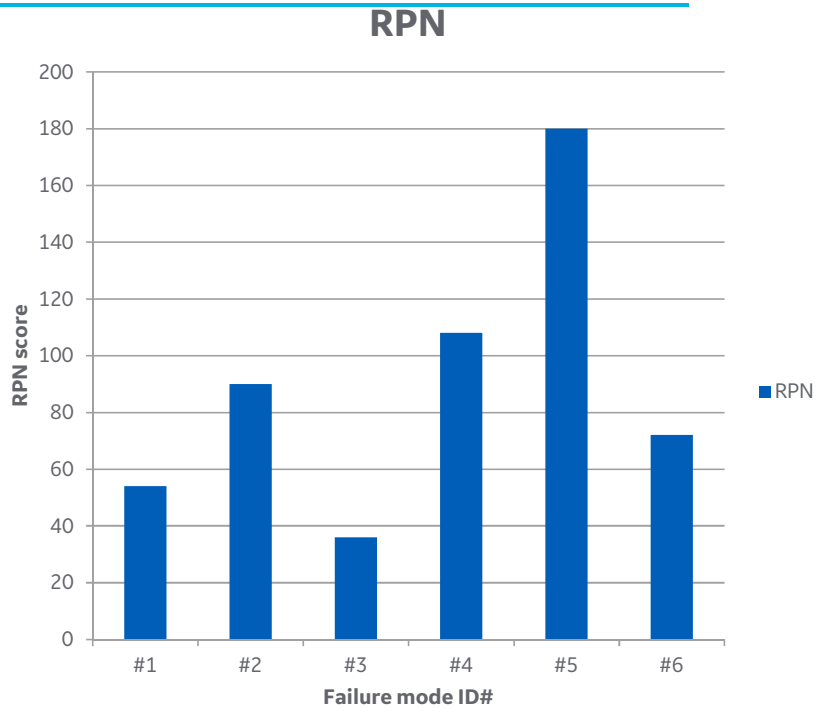
Pareto plot - Failure mode ID vs RPN

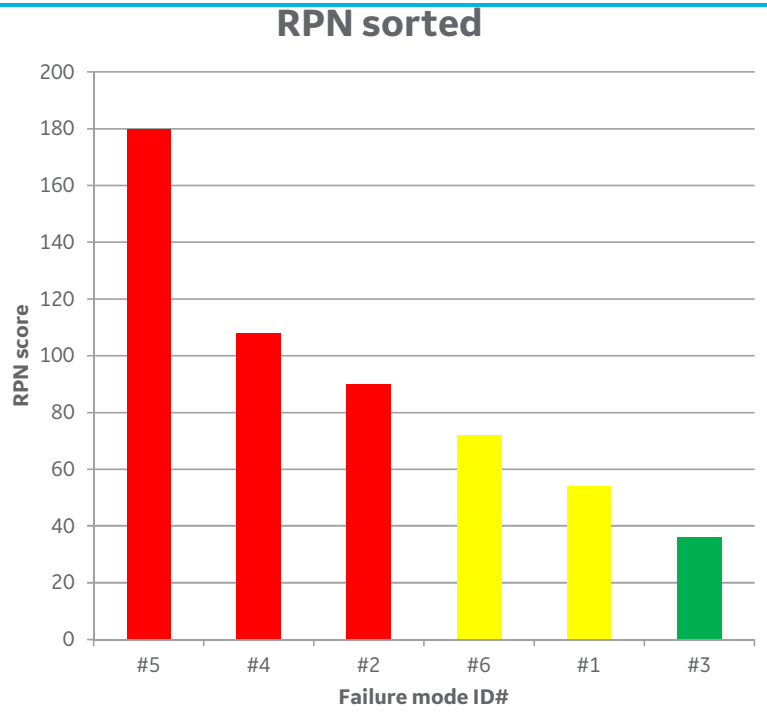
RPN



Pareto plot - Failure mode ID vs RPN

RPN





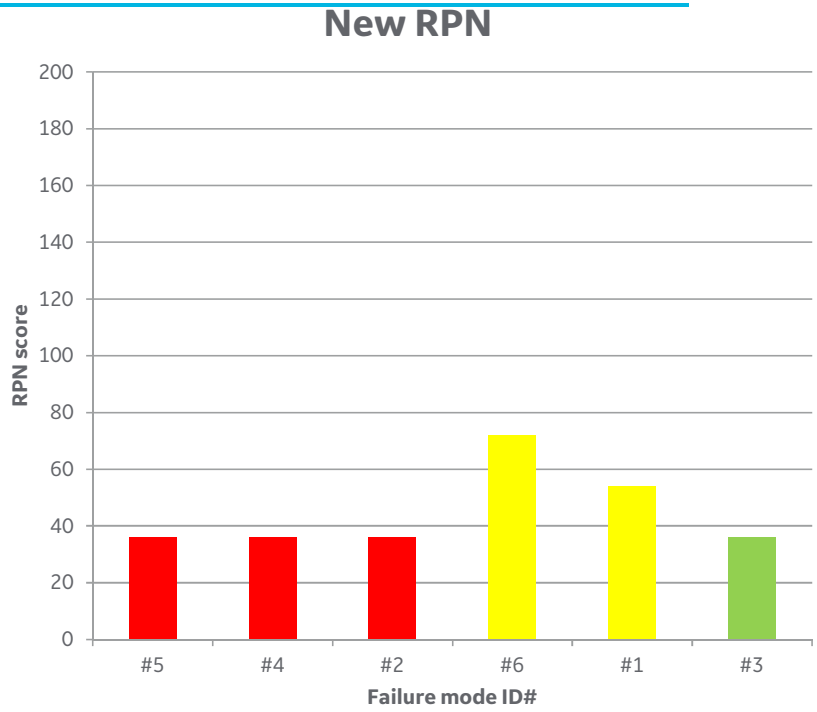
FMEA risk mitigation

RPN > 80

Failure mode ID#	Item/ process step	Potential Failure Mode(s)	Potential Effect(s) of Failure	Severity	Potential Mechanism (s) of Failure	Occurance	Current process control	Detection	RPN (S x O x D)	Action(s)	New Severity	New Occurance	New Detection	New RPN
5	Component / Chemical	contamination	bioburden	6	contaminated buffer componant	5	bioburden testing	6	180	Sterile filtration	6	1	6	36
4	Component / Chemical	contamination	bioburden	6	contaminated hardware	3	bioburden testing	6	108	Sterile filtration	6	1	6	36
2	Component / Chemical	contamination	chemicals	6	contaminated buffer componant	5	pH / cond	3	90	Clear SOP	6	2	6	72

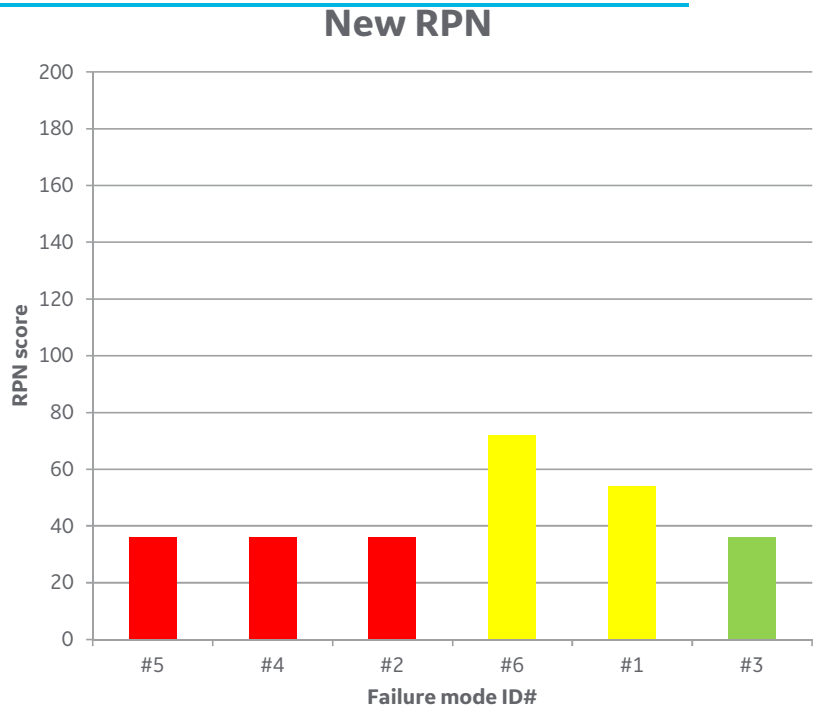
Pareto plot after risk mitigation

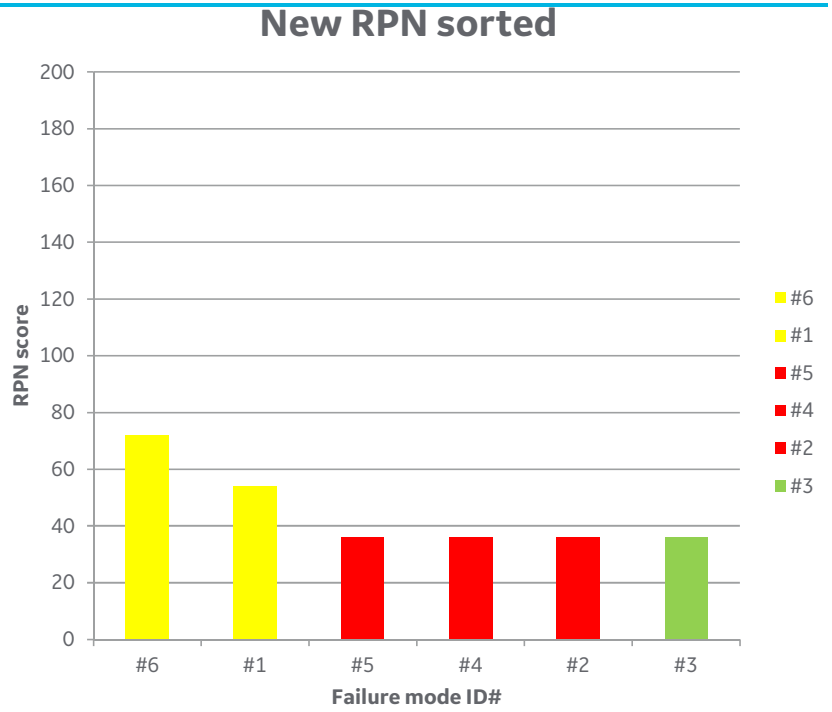
RPN



Pareto plot after risk mitigation

RPN





Investigation on highest risks after mitigation

Examples

Experimental work

Training

New equipment

Facility upgrade

Business management

DoE

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For local office contact information, visit **gelifesciences.com/contact**

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