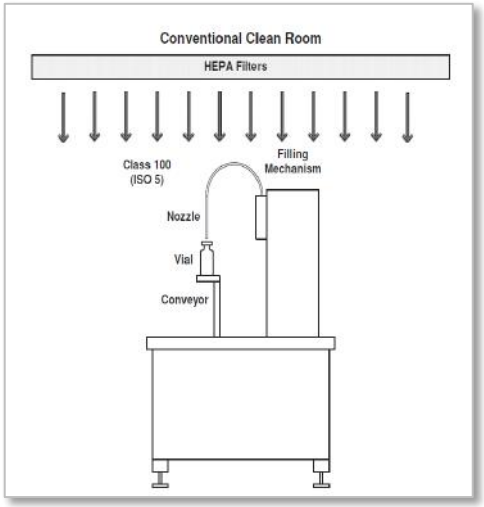
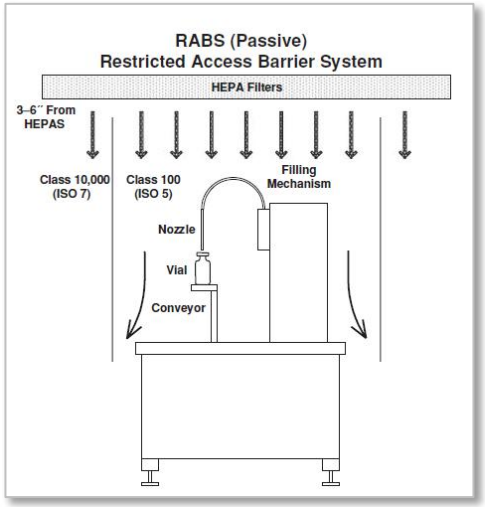
Transforming Injectable Operations

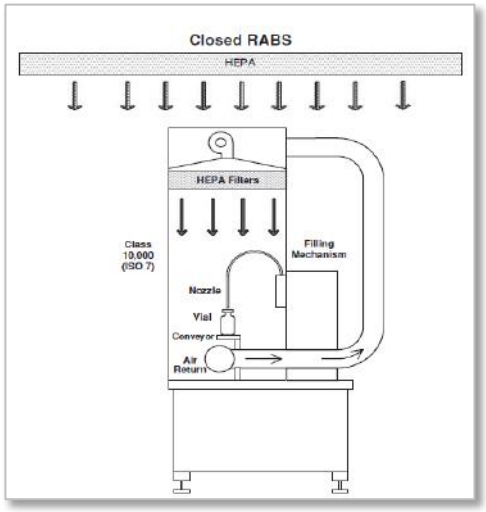
Overview of Injectable Manufacturing

Comparison

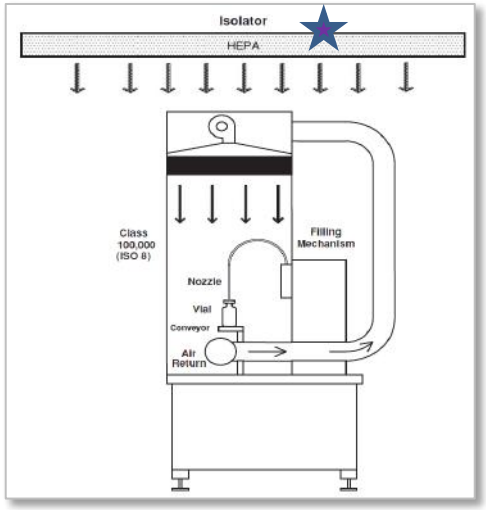




- A barrier to prevent human intervention
- Air flow provided by ceiling HEPAs to critical zone
- Bottom of enclosure is open for air outlet
- Glove ports and transfer ports for manipulations/ commodity additions
- Manual high-level disinfection



- Similar to an isolator without vapour bio-decontamination
- Manual high-level disinfection
- Can be used for\ containment applications



- Vapour bio-decontamination
- High level disinfection

Technology used at Dr. Reddy's

Overview of Injectable Manufacturing

Comparison

Scrutiny of Aseptic Processing:

- Sterile products are considered relatively high risk as there is a potential for patient injury, and in a worst-case situation, even death due to microbial contamination
- Aseptic processing is subject to intense scrutiny in every application to assure that the product has no patient risk

Manufacturing of Aseptic Sterile Products:

- Manual/semi-automated assembly by gowned personnel in clean, but unclassified environments (the concept of room classification had not yet fully emerged)
- Manual assembly by personnel using a glovebox (a non-ventilated sealed unit accessed via gloves)

Advent of the HEPA filter:

- The HEPA filter allowed entire rooms to reach new levels of particle and microbial cleanliness resulting in wholesale changes in facility designs and operating practices
- Now, human borne contamination (greatest source of risk) could be diluted/ removed from the environment by using equipment inside a cleanroom to for aseptic processes
- More automation in bottling and assembly equipment, resulted in higher volumes at lower costs, while reducing human activity; thereby minimising risk

Current Operations:

- This operational concept evolved into the manned cleanroom that remains today; the commonly used environment for aseptic processing operations

Reacting to Issues!

Situation – FY22:

- Delivery Inconsistency – 78% vs the requirement
- Backorder value - $12M

Main Issues:

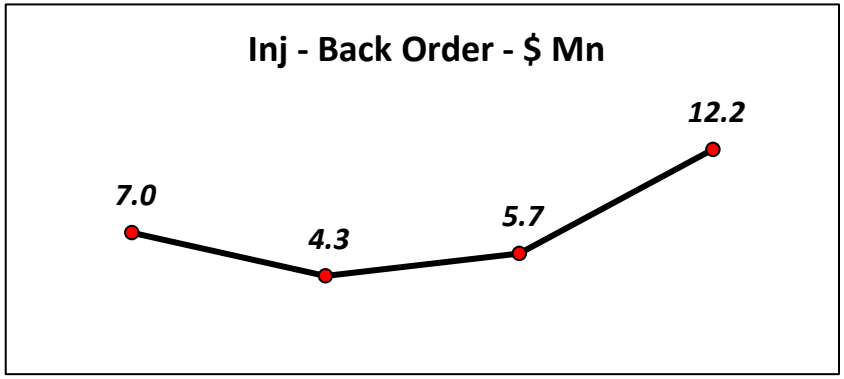
Breakdown time loss - 14% (Frequent Stoppages of Lines)

a. Chronic/Sporadic equipment and change part issues

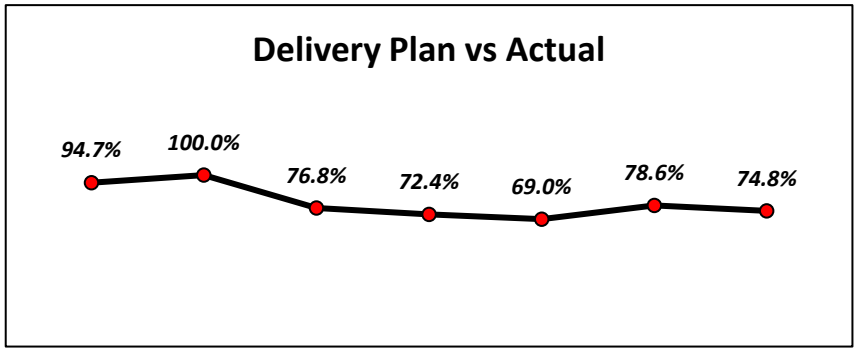
b. Inadequate PM prog & Spare part Management

c. Higher resolution time - more dependency on OEM

d. High Interventions & Minor stoppages



Higher Batch to Batch Changeover times – 27 hours (average)



Frequent quality Incidents & OOS

a. Inadequate Processes – 20% CQA's <1.67 PpK

b. High Human errors - 18%

c. More corrective, Less preventive CAPAs

d. Ineffective LDM process

While incremental changes adds short term value, a full-fledged transformation of our Operational Strategy addressed the root cause and provided a long-term solution

Levers for Transformation

*"**Re-ignite**" is a systemic transformation initiative to move from **a reactive to a preventive approach and then to a predictive way of working which will result in "Sustained deliveries from manufacturing lines"***

Asset Robustness – Functionality and performance improvement towards zero loss

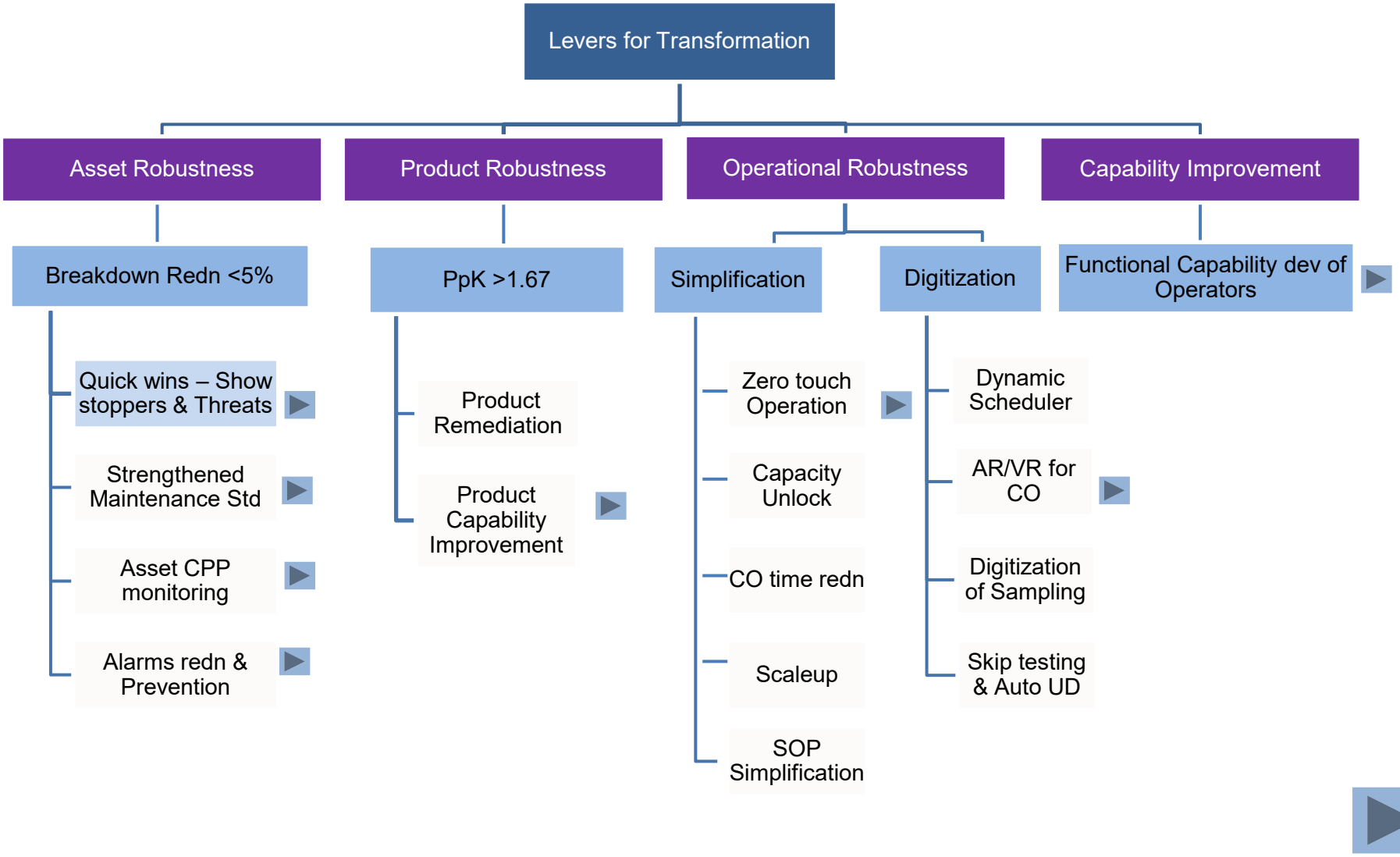
Operational Robustness – Reduce the losses in the process & NVA activities

- Capacity Unlock – CO time redn, Scaleup
- SOP simplification
- Investigation Robustness & Incident reduction
- Digitization and digital interlocks

Product Robustness – Product issues, OOS/OOT, improvement of process capability

Culture and Capability – Fostering a culture of Quality that goes beyond compliance and developing capabilities that support this culture

Levers for Transformation



Asset Robustness – Effectiveness (Use Case 1)

Problem:

Good vials mix-up with Rejected vials – Frequent stops & Incidents

Gap Identified:

Star wheel timing mismatch due to position locking Pin and pin hole diameter mismatch. Thread damage in shaft head.

Systemic Gap:

No Preventive maintenance standard to detect the failure

Actions taken:

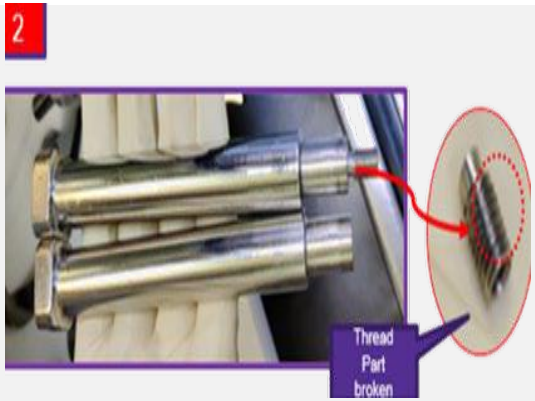
1. Star wheel shaft replaced, and star wheel realignment done in existing Capper
2. Set-up demo video training given to operators on star wheel shaft tightening

Preventive Measures:

Change over standard established & AM / PM std updated for TBR of the shaft

Effectiveness:

After shaft replacement and training to operators on how to assemble star wheel “No timing issues observed from Dec-21



Asset Robustness – Effectiveness (Use Case 2)

Problem:

Frequent line stoppages of LYO due to Pizza door not open/close during Lyo loading / unloading

Gap Identified:

Teflon bushes in the Slot door opening are worn out

The door movement is not free causing load on motor and stopping.

Systemic Gap:

No Preventive maintenance standard to detect the failure

Actions taken:

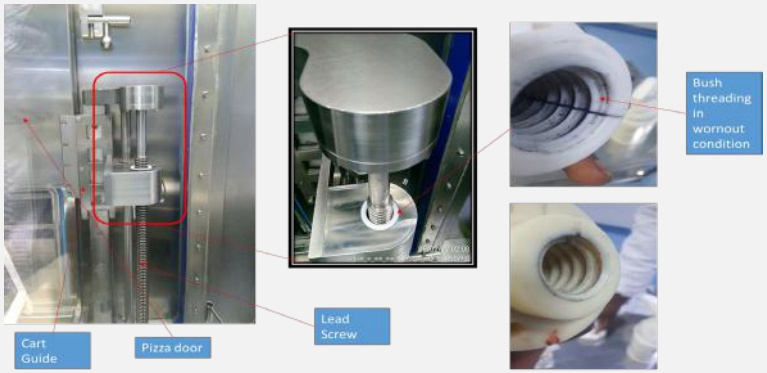
Replaced the Teflon bushes with new ones

Preventive Measures:

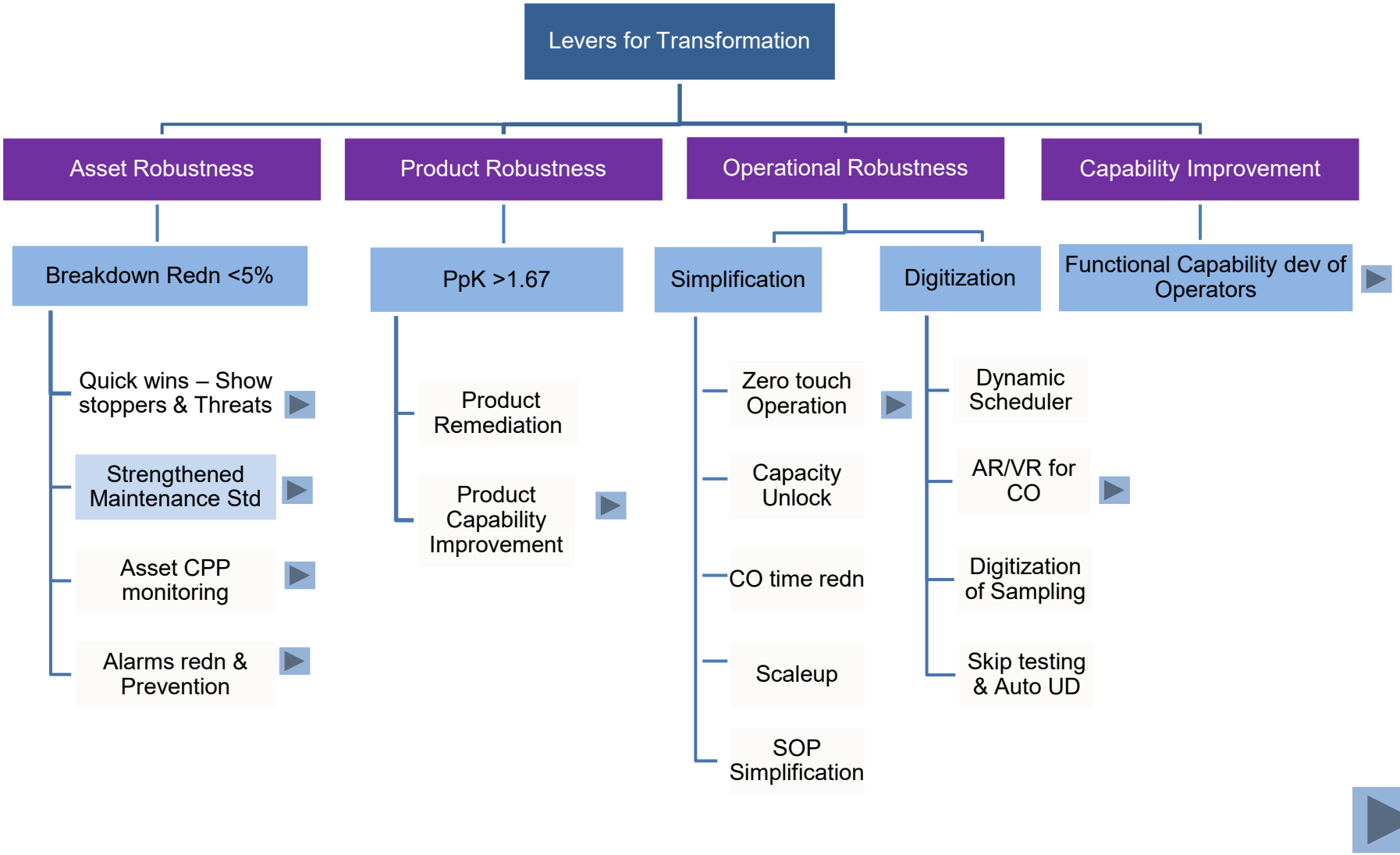
PMP incorporated with Replacement of the Teflon bushes once a year part of PM

Effectiveness:

>30 batches executed & No Pizza door movement related issues noticed post Corrections



Levers for Transformation



Re-Defining PM Standards

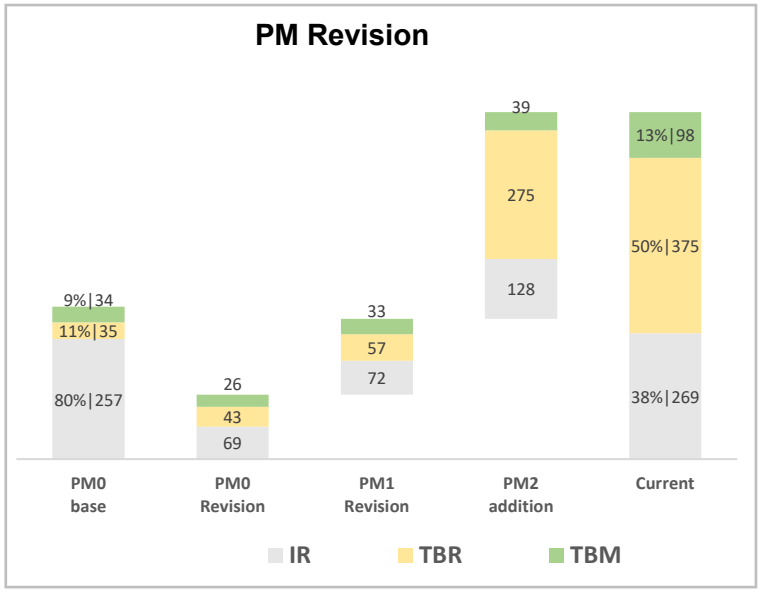
Before (Oct 2021)	Revision – AM/PM Phase 1	Revision – AM/PM Phase 2
Task: Prepared based on inputs from the manual **Actions:** ▪ PM/AM prog is based on check lists, not covering the full details – What & How ▪ It is more generic – does not cover every component of the equipment	**Task:** ▪ Detailed “What and How” for all critical components ▪ Activities strategized as TBM & CBM ▪ Tasks with < 6 months frequency moved from PM to AM **Actions:** ▪ Listed down actions from historical RCAs to AM & PM ▪ Referred OEM manuals and took inputs from SME & Operators **Status:** Standards revised & uploaded in SAP for all lines	**Task:** ▪ Building above AM1 & PM 1 **Actions:** ▪ Detailed FMEA covering all the components and sub systems ▪ All the abnormalities/alarms getting analyzed. ▪ Considering failure modes from the manual **Status:** PM Standards revised & uploaded in SAP; AM standards are incorporated in SOP

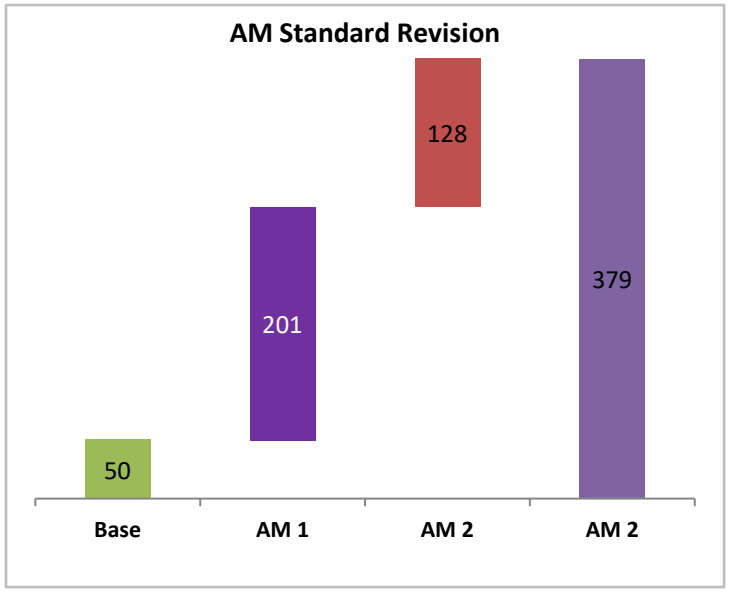
Re-Defining PM Standards

Maintenance Stds :

	Base	Phase 1	Phase 2
PM	138	162	442
AM	251		379

- ***AM Checks Frequency –*** *Before batch, Daily, Weekly, Fortnightly, Monthly, Quarterly*
- ***PM Checks Frequency*** *–Half yearly, Annual, 2 Years, 3 Years, 4 years, 5 years, 8 years, 10 years*





Autonomous Maintenance

Autonomous Way of Working:

- Target - **I Operate – I Maintain – I Manage & I OWN**
- To bring the ownership to the operator, concepts of Autonomous Maintenance are deployed
  - **CLIT** - CLIT (Clean, Lubricate, Inspect & Tighten) is basic maintenance activities which are performed by operators on the equipment, to maintain the equipment in OEM condition
  - **Abnormality identification & mitigation** – Identification & mitigation of deviations from the desired state reduces unplanned failures/breakdowns
  - **Capability Building** – For operators to maintain the equipment, trainings are given to provide asset engineering knowledge & skill of handling maintenance activities

Activities Performed:

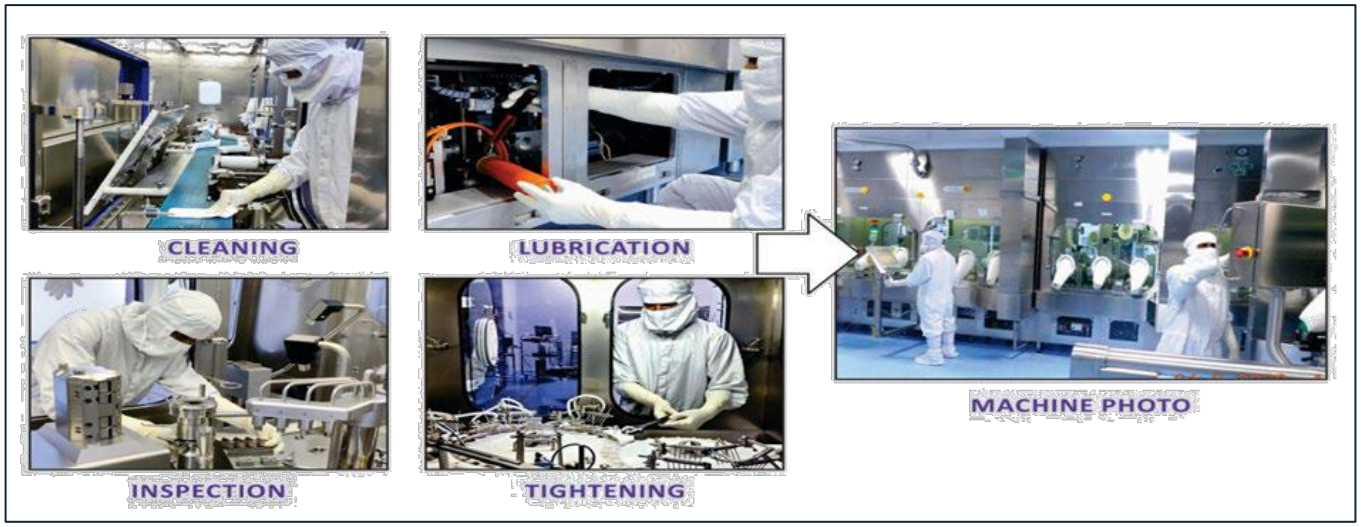
- Maintenance standards derived through Component level analysis of the equipment through FMEA
- Performed Capability assessment of individuals & trained the operators to enhance their knowledge on asset maintenance
- 34% of Maintenance activities transferred from Engineering to Operators with periodical skill assessment in place for continuous improvement

Maintenance activities done by Engineers vs Operators	Before	After
Engineers	541	742
Operators	251	630
No of Maintenance tasks transferred	-	186
Ratio (Engg : Opr)	68% : 32%	54% : 46%

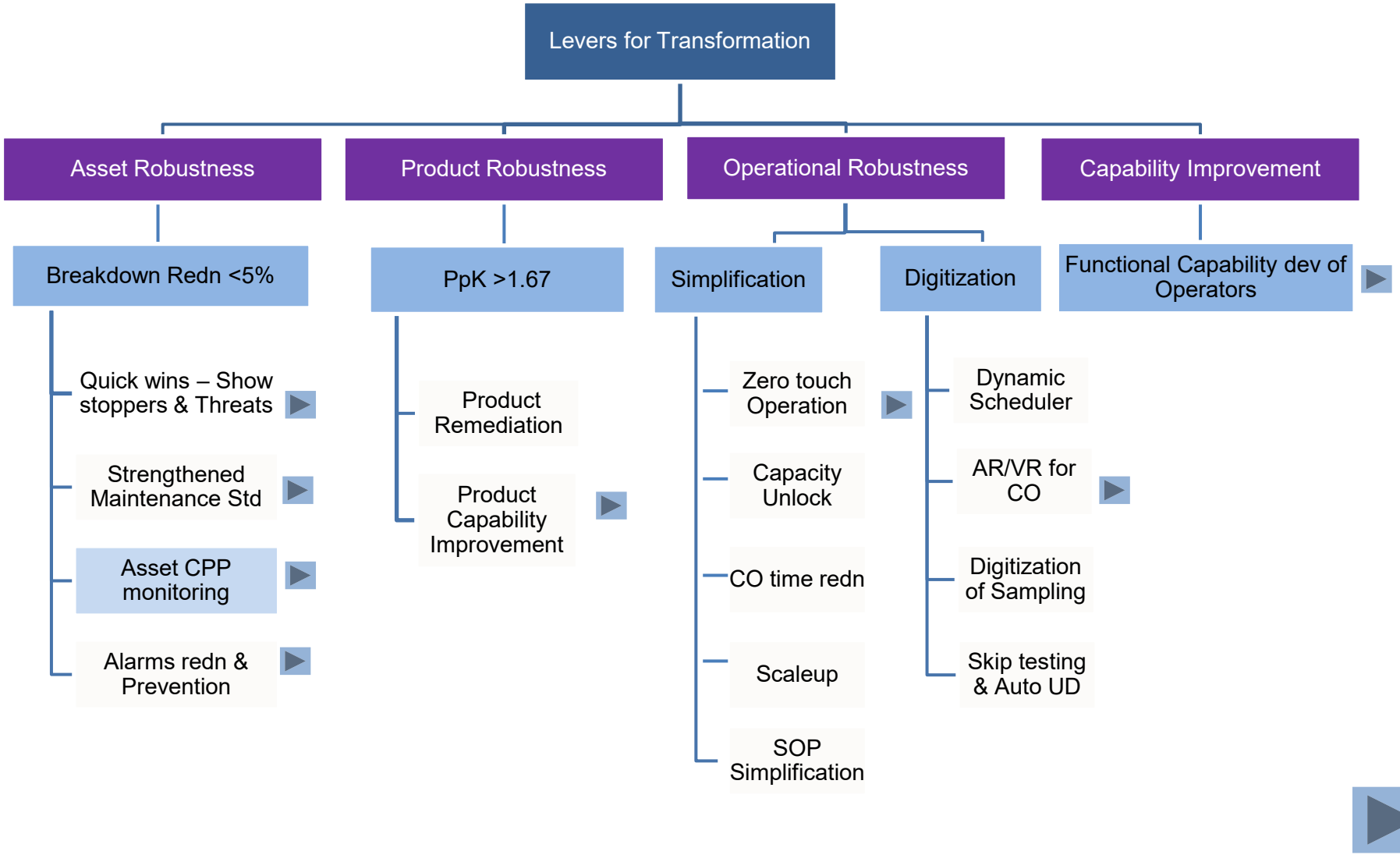
Autonomous Maintenance

Benefits:

- Ensures that equipment are maintained in optimum condition
- Reduces forced deterioration of the equipment resulting in extended service life of component
- Abnormalities are detected proactively at early stage and corrected before it fails
- Increased reliability and availability of the machine, hence increased OEE
- Being documented through quality system adherence becomes culture



Levers for Transformation



Asset Predictive Analysis (Use Case 1)

Problem:

Air velocity is operating at a set point of 0.4m/s across the isolator. But in IS2, the air velocity sensor (VT03) is recorded at <0.4m/s

Gap Identified:

Sensor measured value is wrong compared to the external anemometer that is used part of requalification

Systemic Gap:

Sensor calibration is currently standalone, calibrated at FS of the instrument. And is not compared with any of the external device that is used during RQ

Actions taken:

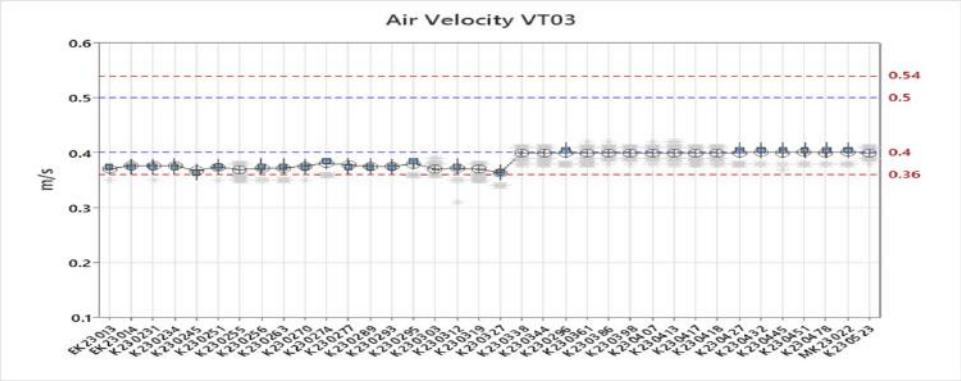
Sensor is calibrated in accordance with the Anemometer used for RQ

Preventive Measures:

Calibration procedure to integrate with RQ (both frequency is 6 monthly)

Effectiveness:

>50 batches executed & no deviations found



Asset Predictive Analysis (Use Case 2)

Problem:

Clear time difference noticed in time taken to achieve less than 1ppm in Aeration phase of VHP b/w IS2 & IS3

Gap Identified:

Sensor – Measuring the PPM at IS3 though having frequency of calibration at 6months, the low concentration sensing ability was deteriorated as the response time is high

Systemic Gap:

Response time could not be monitored during calibration

Actions taken:

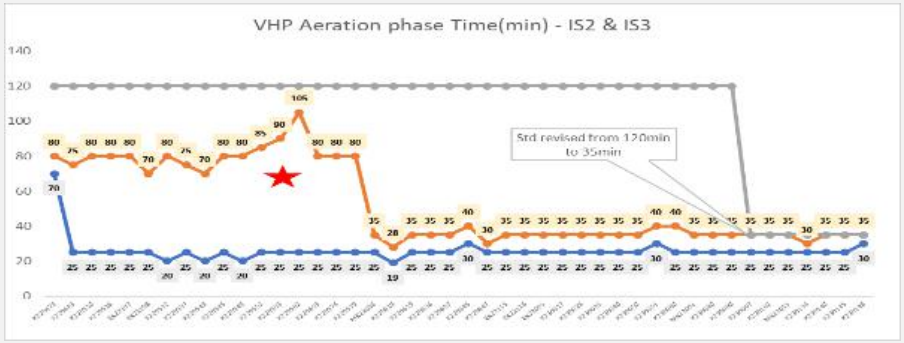
Replaced the IS3 Dragger sensor

Preventive Measures:

CPP monitoring in place to detect the special cause variation. Replication u/p in B+S vial line to convert existing high concentration sensor to low concentration sensor

Effectiveness:

Converted time-based monitoring to PPM based monitoring, Std time of Aeration phase revised from 120min to 35min. No abnormal scenario noticed in last 50B



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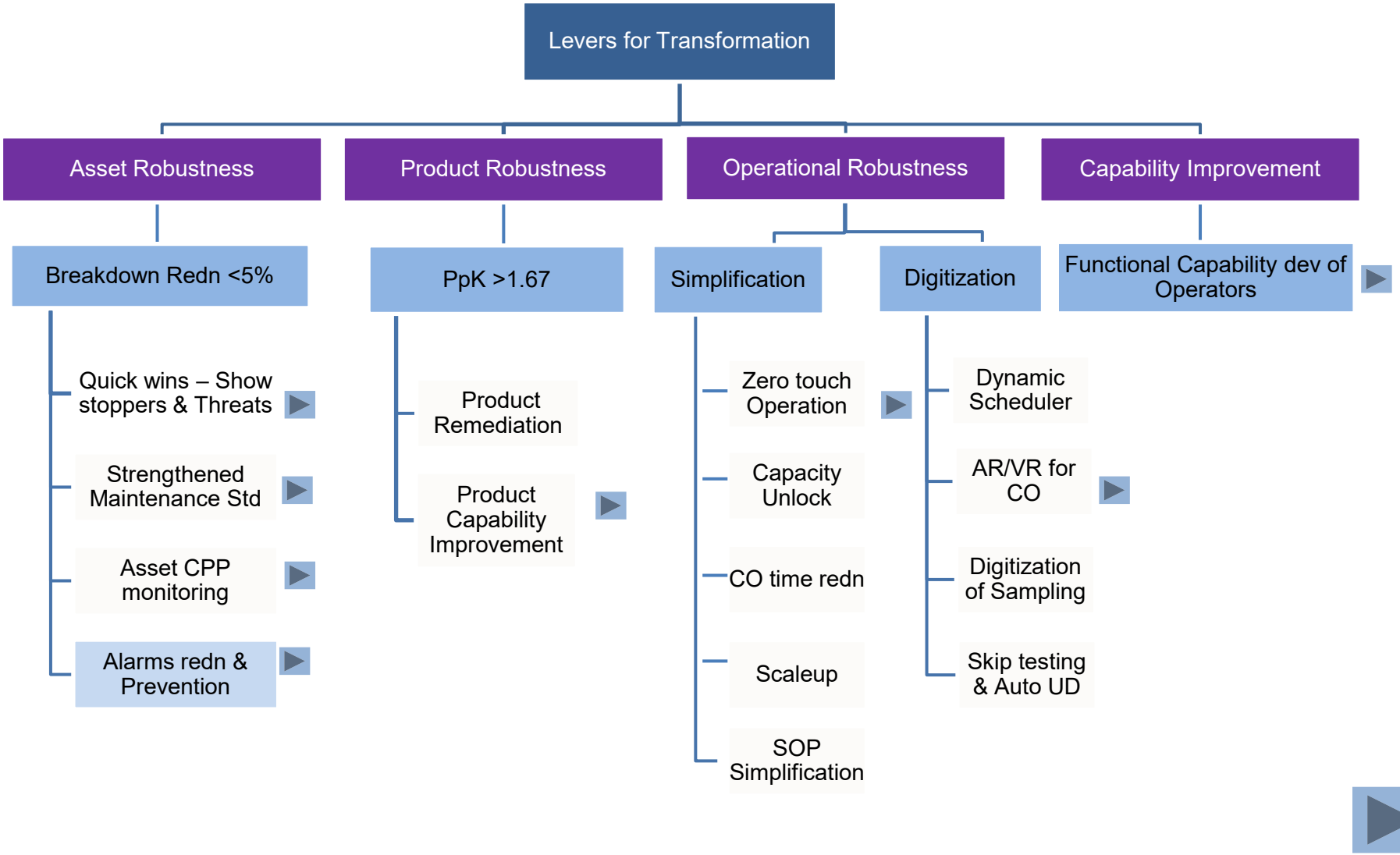
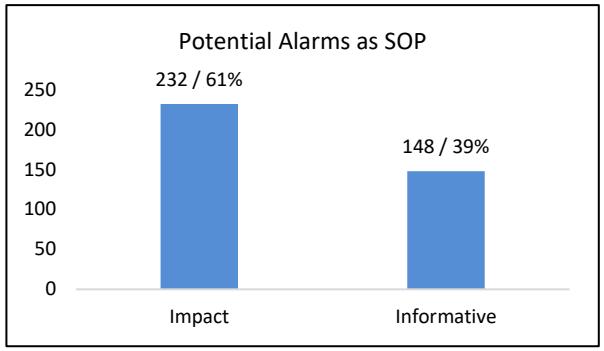
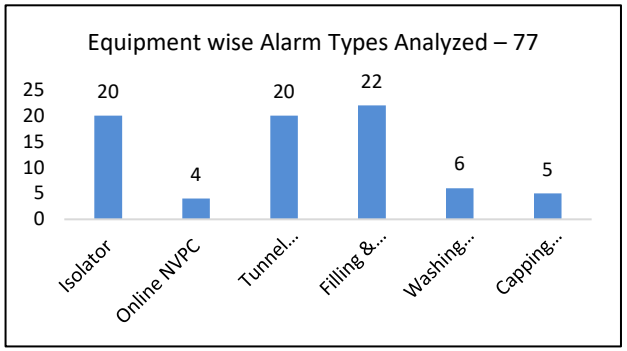


Alarm Management

Actions Performed:

- Categorization of Alarms based on impact.- **Completed**
  - Informative alarms
  - Alarms impacting Machine/process.
- Identify hot spots based on category and Occurrence – **Completed**
- Cause mapping of alarms - **Completed for historic alarms Occ > 1 (77 types) 496 occurrences**
- Solution finalization & implementation - **Completed for all 77**
- Work instructions with action & reaction plan – **Completed**
- Monitor Effectiveness – Under Progress
- Process extended to other lines & sites

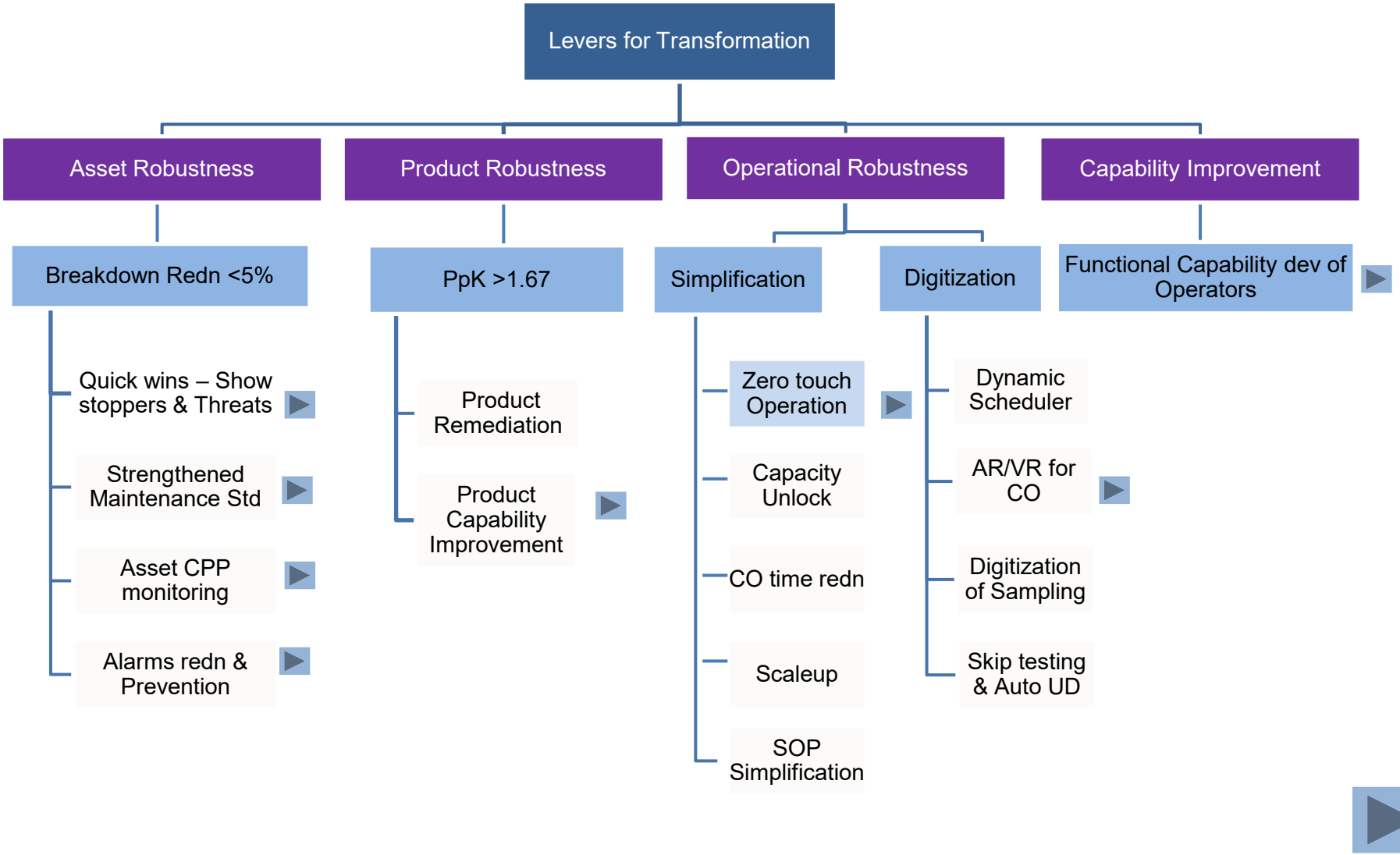




Equipment	Kaizen Opp.	OPL/Work Instr.	AM/PM Std (AM2/PM2)	Setup Std
Isolator	2	2	36	-
Vial Washing	5	3	41	-
Tunnel	7	10	42	-
Filling	11	34	107	7
Capping	6	12	67	2
Online NVPC	-	3	26	6

Equipment	# Alarms Priority 1	Occ/Batch Before	Occ/Batch After
Isolator	20	10	0.2
Online NVPC	4	37.4	4.8
Tunnel Sterilizer	20	5.4	3.6
Filling & Stoppering	22	31.4	20.2
Washing Machine	6	70.8	40.6
Capping Machine	5	2.3	1.9
Total	77	157.3*	71.2

Levers for Transformation



Journey towards Zero Interventions (#/batch)

Problem Statement:

- # of interventions ~ 7.2 Occ./Batch
- Legend: *Int./Batch(No of Int./ No of Batches)*

Asset Issues:

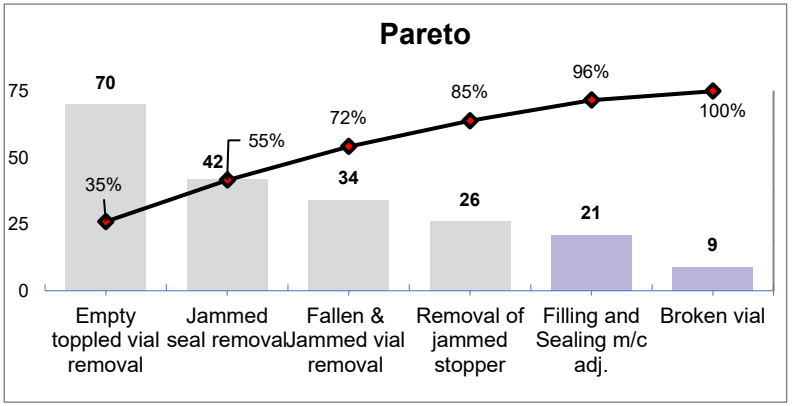
- Alignment issues - Transfer plate and Bridge plate rectified
- Change parts procured and AM/PM Stds. strengthened
- Matchmarking done for fixing of supply sensor in Sorting bowl

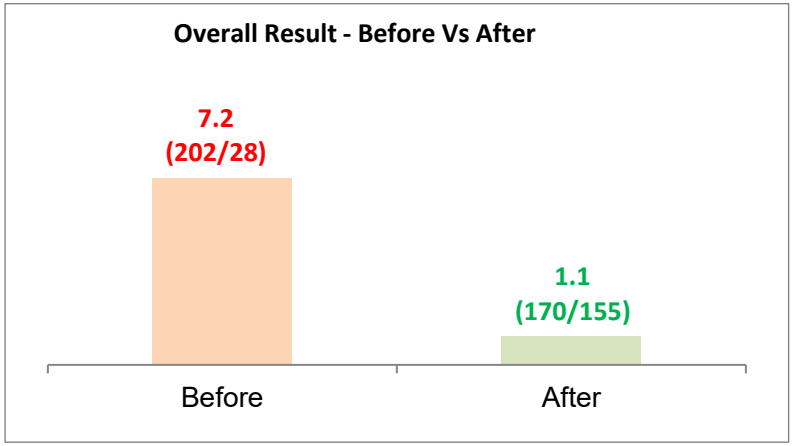
Operational Issues:

- Seals handling method – Changed to hanging storage
- Lyo loading recipe modified to load in honeycomb way

Material issues:

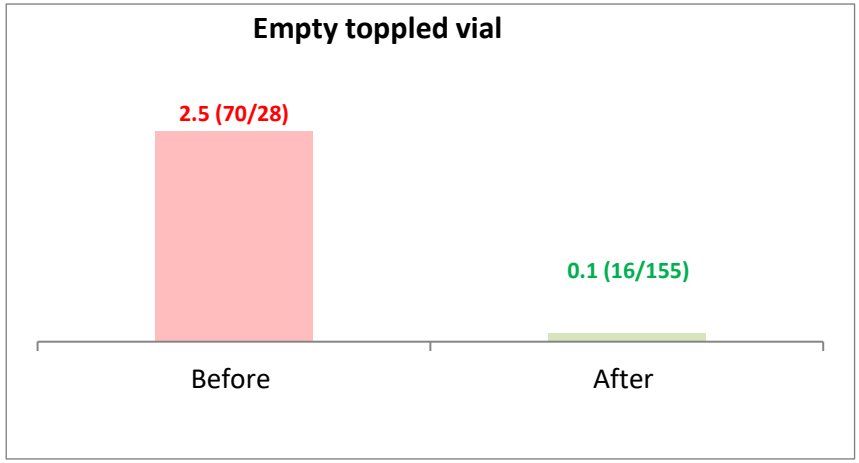
- Rubber stopper jamming – RFS to RTU stopper

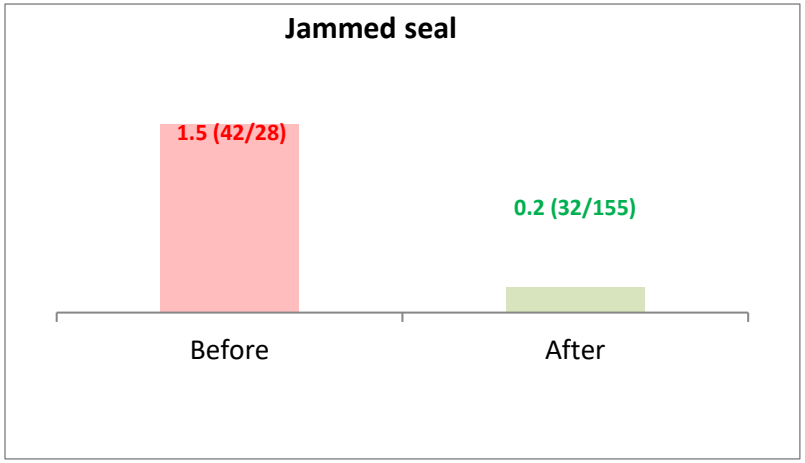


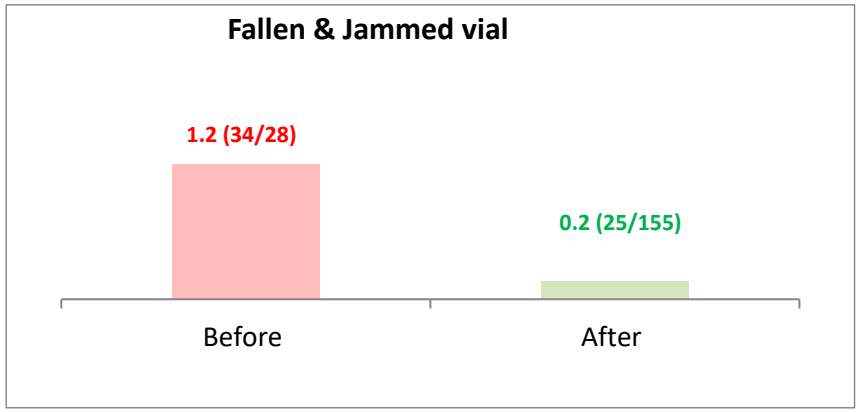


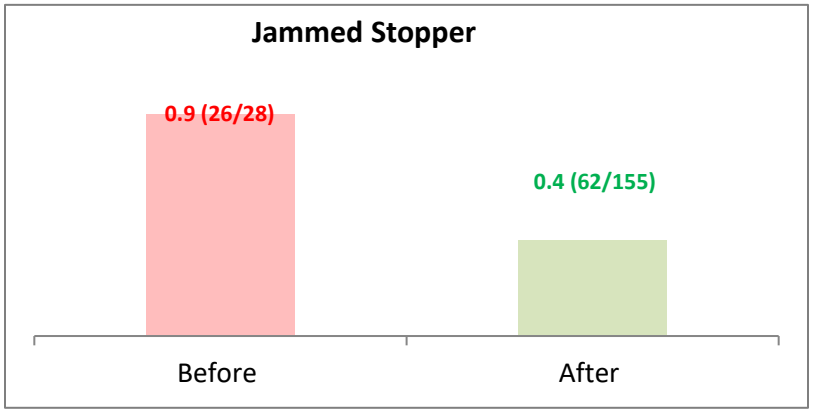
Journey towards Zero Interventions
(Occ/batch)

Results





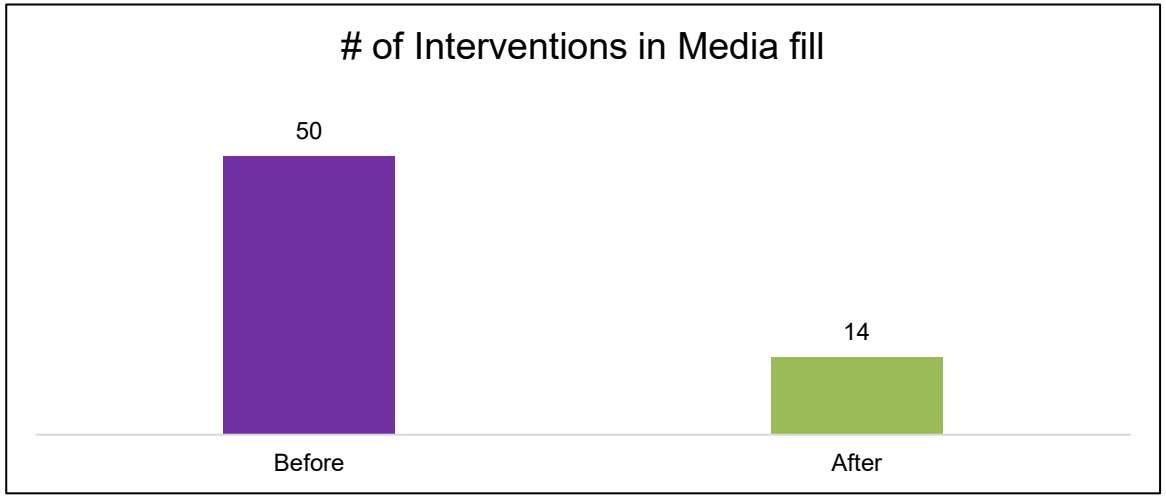




Simplification of Media fills (Elimination of Interventions)

- All planned and corrective interventions need to be simulated during a media fill to ensure product sterility is not impacted
- To minimize and eventually eliminate the number of corrective interventions (which are onerous and time consuming), the impact of any new intervention in a routine batch is assessed prior to simulating media fills
- Through this method, we have drastically reduced the number of interventions we perform; demonstrating our high confidence in our manufacturing process and our commitment to quality excellence

Before intervention list	After intervention list	Difference
Interventions before VHP : 02	Interventions before VHP : 00	# 2
Routine interventions after VHP: 25	Routine interventions after VHP: 05	# 20 ★
Corrective interventions: 20	Corrective interventions: 06	# 23
Worst case interventions: 03	Worst case interventions: 03	-



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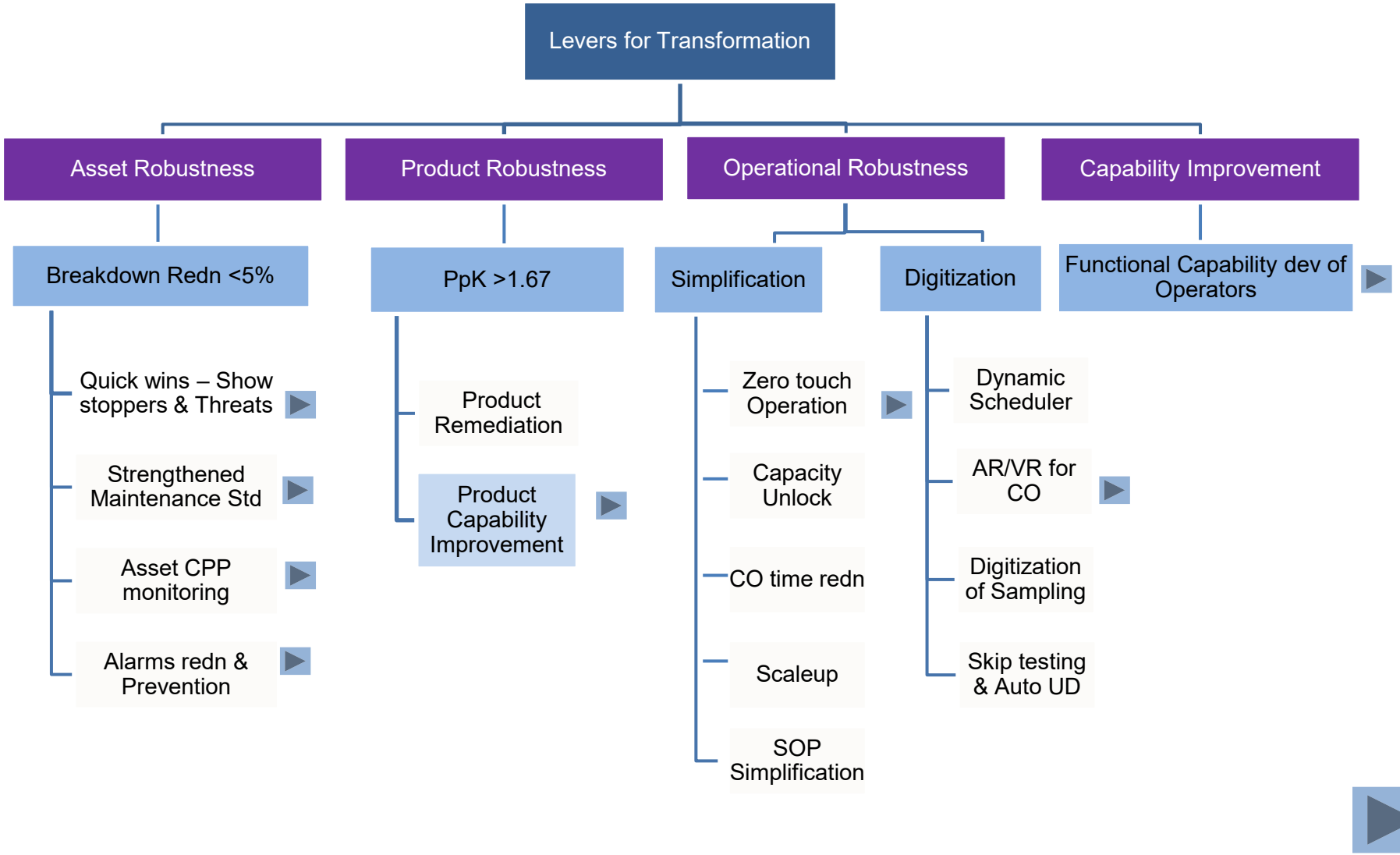
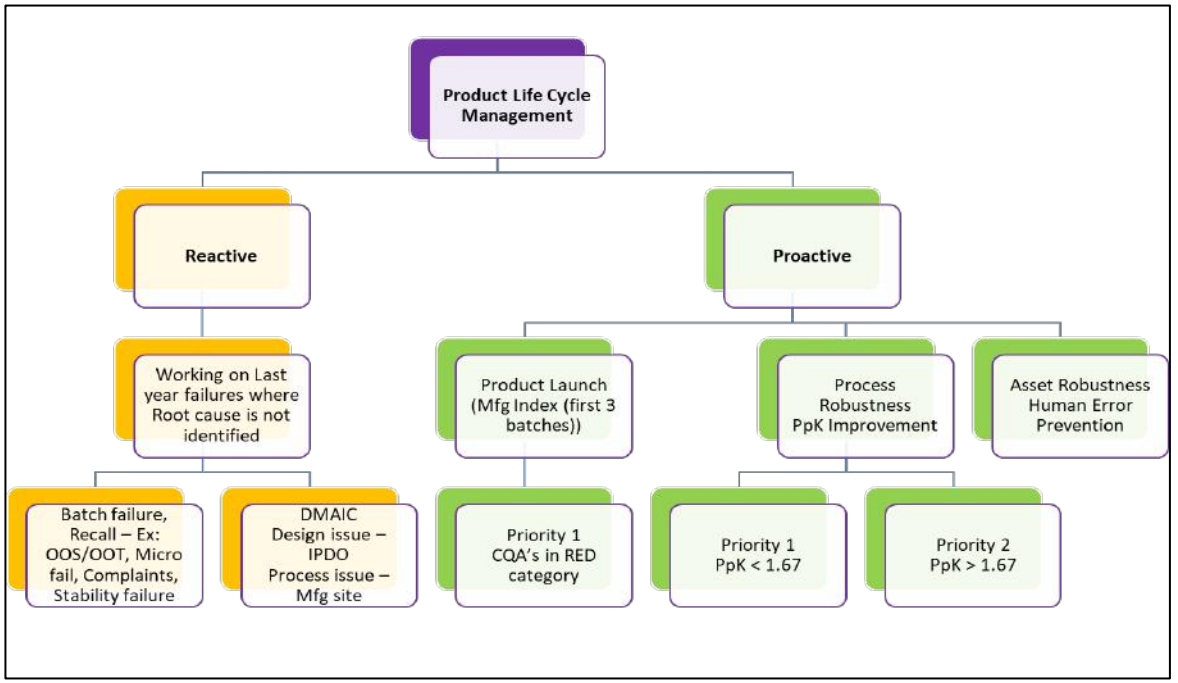


Product Robustness Approach (Proactive Measures)

Proactive Approach	Reactive Approach
Mapped Products Vs CQA's for the molecules mfg > 10 batches	Projects identified based on Past Incidents/OOS/OOT relating to "Asset, Process, People"
Identified Hot spots vs CQA (as per grid – Red indicates Ppk < 1.67)	Thematic projects & actions identified & executed using DMAIC approach
Projects identification is based on Product CQA <1.67 and the thematic issues of the CQA across the products	
Projects execution for the Capability Improvement	



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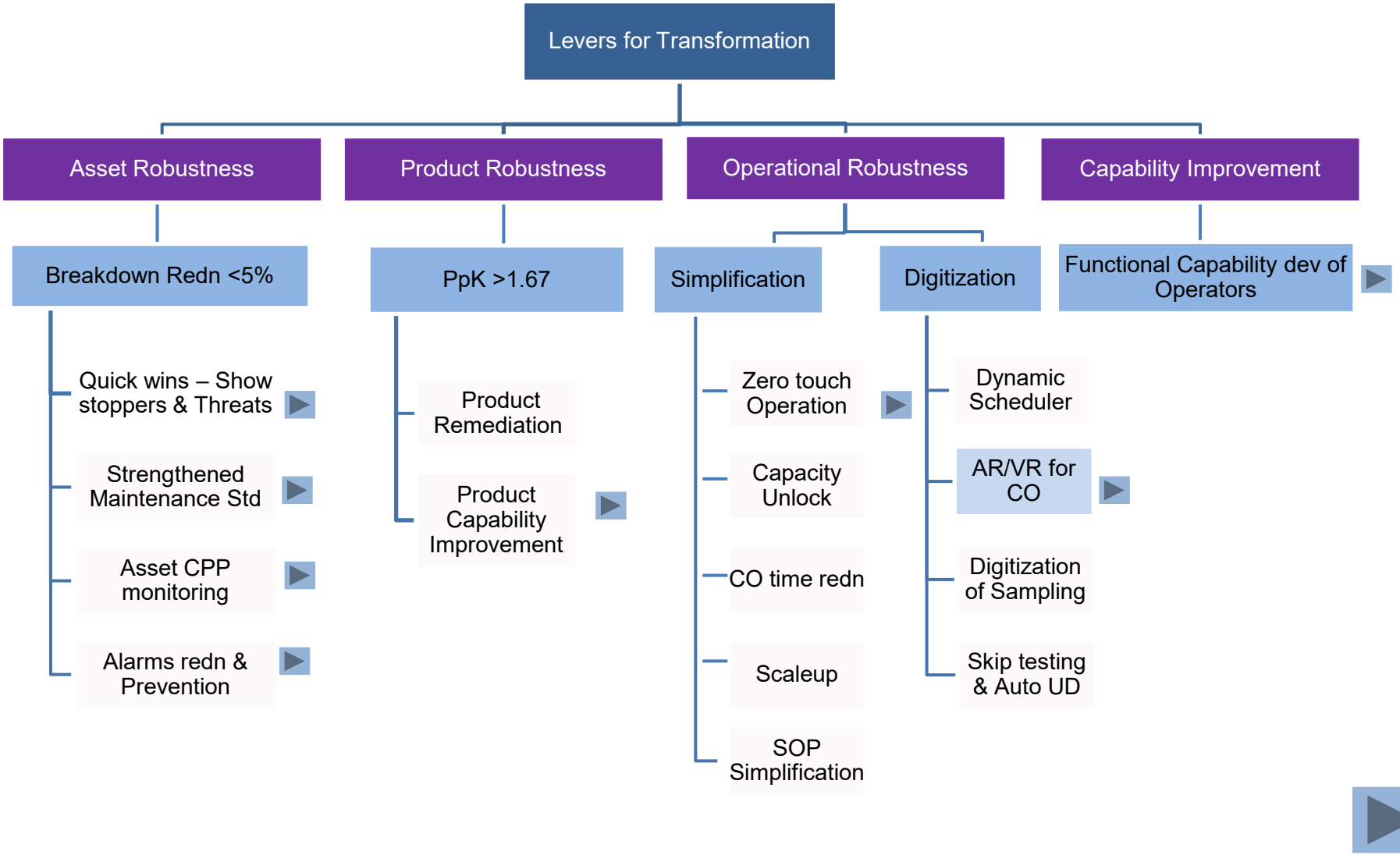


AR Assisted Changeover

Problem Statement:

To eliminate the machine stoppages which occur due to incorrect installation of change part. Sequential installation of change parts often results in human error during assembly, due to operators' dependency over memory

Objective:

- Zero incidents due to human error
- Upskill personnel performing the changeover and transform on the job training
- Zero machine stoppage due to incorrect change part installation

Execution Strategy Approach:

- Changeover and aseptic assembly steps data collected
- Video captured and 3D models developed for 386 steps
- 3D models of change parts were superimposed on the real machine for easy identification
- Integrated with Hololens using MS Dynamic 365 guides

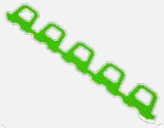
Status:

- Changeover (Washing, Filling, Capping & EDM) - **Completed**
- Aseptic assembly - **Completed**

AR Assisted Changeover

APPROACH & EXECUTION STEPS

1 3D Model Development



Walking Beam

Load Cells

Star Wheel

Crimping Tool

Total 341 3D Models Developed

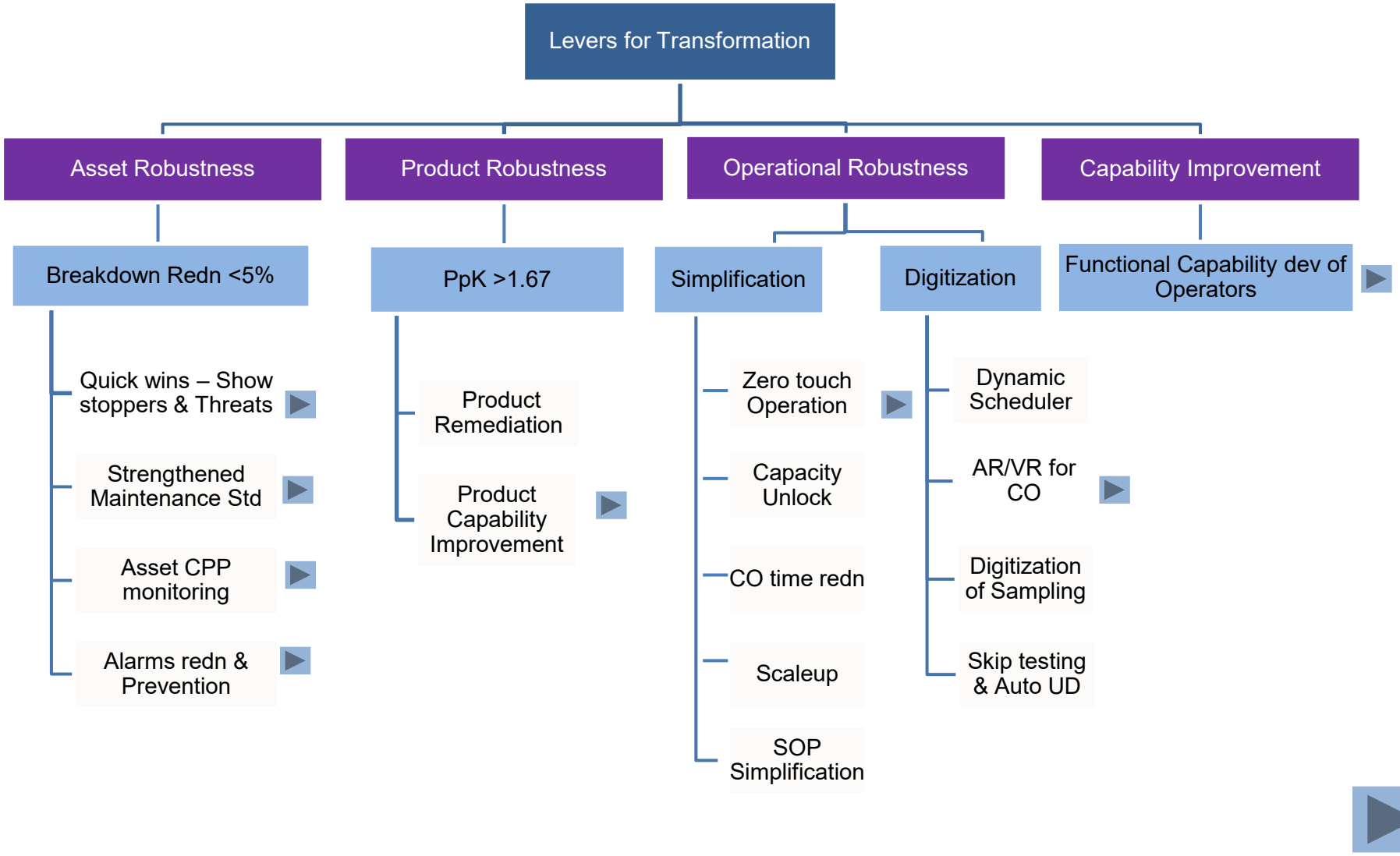
2 Superimposition of 3D models on to machine

3 Voice Over

4 Integration with Hololens

Glimpses of AR assisted C/O with HoloLens

Levers for Transformation



Capability Development Plan

License to Operate

Existing Employees – Front line team to L3 60%, 10% to L4 by Mar-25, 100% by Mar-26

- Develop the Training Modules - Completed
- Training on 84 Equipment component Modules
- Evaluation – Abnormality Identification, Kaizens, PM to AM conversion

New equipment & New product

Target Teams involved in Complex equipment Operations & MW

- Theoretical & design concepts of process equipment & process technology
- MOC of equipment components and P&ID understanding
- Pre start up checks, operation of equipment and good engineering practices
- Preventive maintenance of equipment

Skill Matrix		
Skill	**Description**	**Guidelines**
1	**Basic Know & How**	Is aware of Principles of operation, but needs inputs and hand holding on Meeting expectations
2	**Can Demonstrate**	Meets expectations on his tasks and routines on under supervision/guidance
3	**Autonomous (I Operate, I Maintain)**	Always Meets expectations on his tasks and routines without supervision/guidance
4	**SME**	Takes ownership, Demonstrates the practices, operation,& theory, can Train & Influence others

Operator Technical Proficiency Improvement

Objective:

- Build functional capability – Remove dependency on OEM
- Move PM to AM – AWW (Autonomous Way of Working)

Challenges:

- The method of training was traditional with large volume of content and no practical demonstrations

Actions:

- We implemented a practical “on the floor” training module where systems were explained at a component level
- Further, the duration of training was limited to 20 min/ topic to keep it simple and effective for the trainer as well as trainee

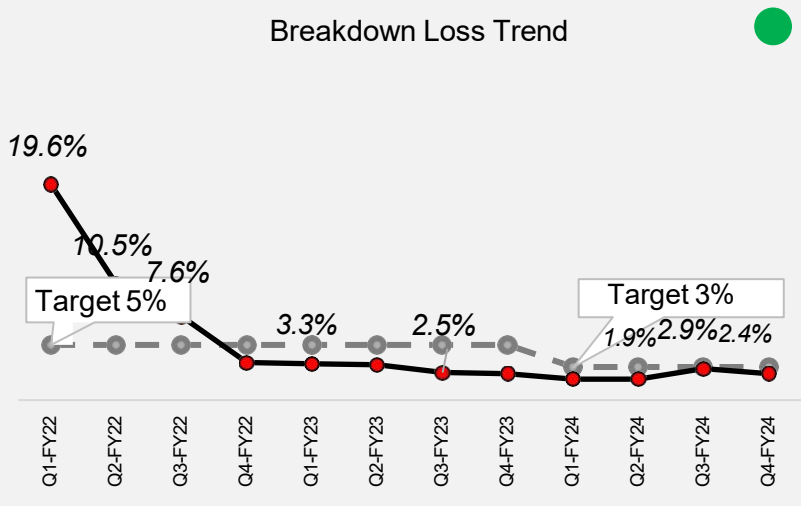
Module	Must	Good	Nice	Total
Pneumatics	4	3	4	11
Lubrication	3			3
Electrical & Electronics	3	6	9	18
Drives	4	6	2	12
Equipment specific	10	12	3	25
General Modules	6	4	7	17
Total	30 – 35%	31 – 35%	25 – 30%	86


Pressure Switch

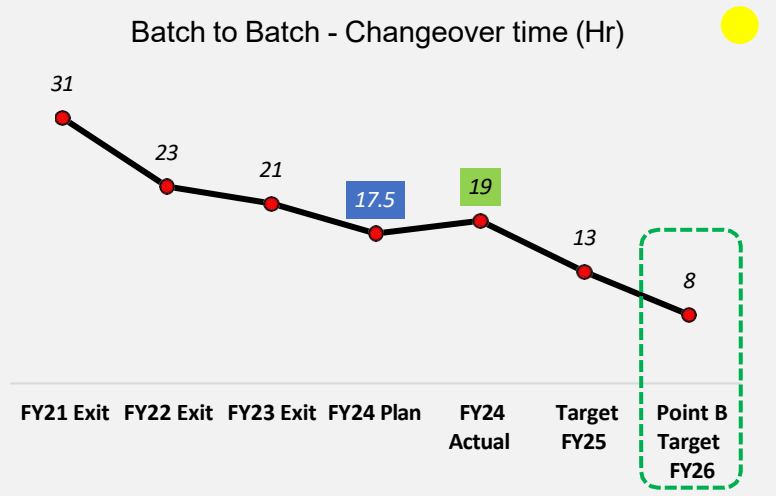

Sensors

Business Outcomes

Asset Robustness



Operational Robustness

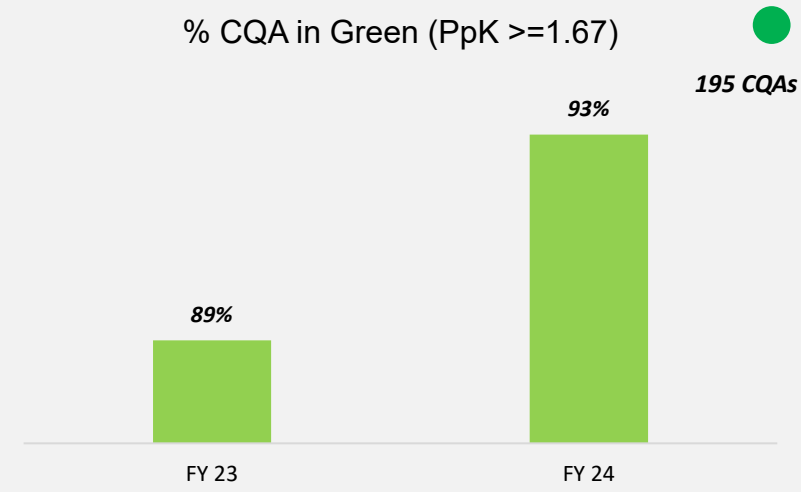


On track

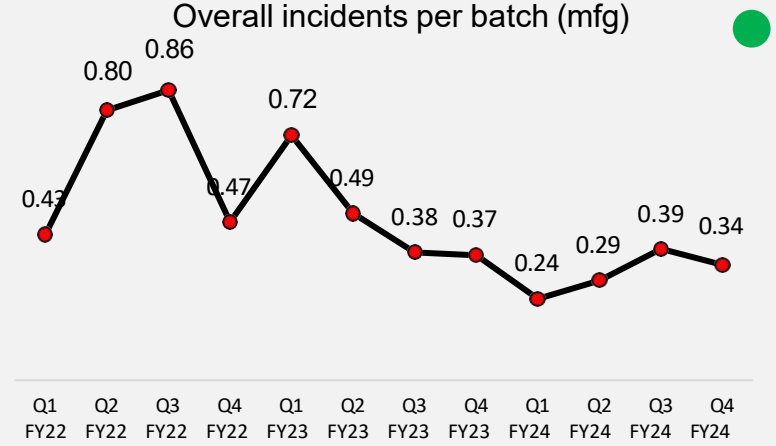
Off Track

Needs Improvement

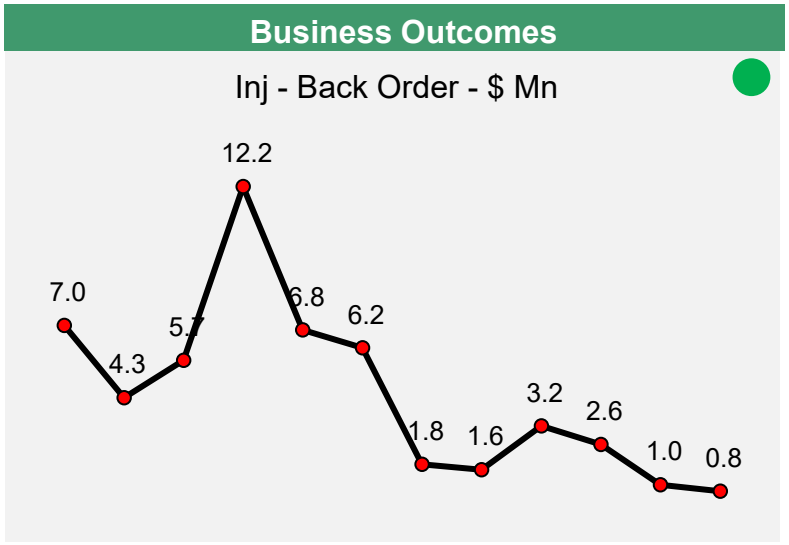
Product Robustness

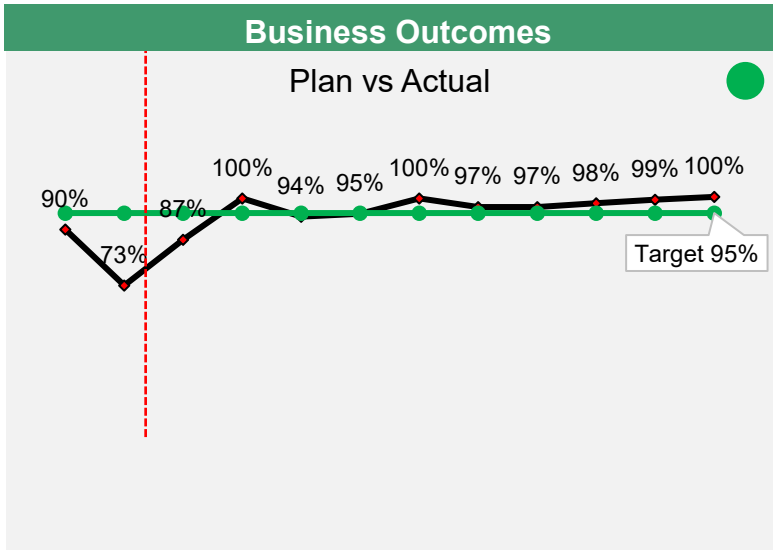


Incidents/ Batch



Business Outcomes





Way Forward

At DRL, the focus is on Service Excellence; to drive business growth by enabling metrics (OTIF, RFT for Zero BO & FTS)

	Transformational	Transactional
Way of Working	▪ Moving from Discrete to Continuous Operations - Integration of Mfg, VI & Packaging ▪ Self Managed team – Asset + Process ▪ One product – One Specification – One Method Globally ▪ QC on floor (In process) – Use of PAT Tools – Cut down waiting ▪ Common laboratory for advanced techniques	▪ Capability Development of Operators – Operational, Maintenance, Analytical ▪ Deploy Changeover crew to externalize few activities ▪ Release of Batches to DRL Warehouse without Sterility Test(UD1 &UD2)
Simplification & Harmonization	▪ Reducing time & effort– Load preparation, Cleaning, Compounding, Documentation ▪ Reduction of Stability Time Point Interval for Sterility & BET ▪ Reduce/Skip Testing ▪ Common PPM Inventory	▪ Reduction of Incidents by 80% ▪ Reduction of asset related issues by 80% ▪ Job Kitting process (Resources-sample, Glass ware, Column etc.)

Way Forward

At DRL, the focus is on Service Excellence; to drive business growth by enabling metrics (OTIF, RFT for Zero BO & FTS)

	Transformational	Transactional
Digitization	▪ Dynamic Scheduler – Integrated Mfg & QC – Real time Monitoring ▪ Review by Exception for IPQA, AQA, MQA Roles ▪ Use of predictive analytics for Asset & Process ▪ AR/VR integrated with MES & LIMS	▪ L2 Integration ▪ Digitization of Trends & all trending's that are part of SOP ▪ Rapid Investigator for Insights & Investigations ▪ Digital Interlocks – Qualification, PMP, Calibration ▪ CPV through OPV, OPVM & APQR, PHR
Automation	▪ 100% Automation of Packing line with Inspection system ▪ Palletizer/Stretch wrapping at Dispatch ▪ Automated colony counter for EM plates ▪ Implementation of Rapid BET for Finished Products ▪ Robotic cleaning machine for Grade C	▪ Auto PR/PO for 100% Spares & Consumables ▪ SCADA & Level controlled Operations in Water system ▪ Conversion of Analog Manual flow meters to Digital ▪ Implementation of Rapid Sterility for Finished Products

Thank You

Backup

Differences Open | Closed RABs | Isolators

Open RABs	Closed RABs	Isolators
✓ RABS means Reduced Access Barrier System, it is a rigid protection made of transparent walls (polycarbonate or glass), equipped with an adequate number of glove flanges and gloves. ✓ It is installed on top of the filling and/or capping machines, separating them from the surrounding area.	✓ It is like an Active RABS (that includes the ventilation system) where the air is not exhausted into the production room but is recycled and/or exhausted via a controlled and well-defined channel.	✓ This is the state-of the-art technology. It is a fully closed enclosure, equipped with a dedicated air circuit, where machines can be segregated. It's normally made of a stainless steel 316L structure, all windows are made of tempered glass, all inner walls are provided with rounded corners and there are no crevices to allow an easy and useful cleaning.
✓ **The RABS can be PASSIVE or ACTIVE type** ✓ **PASSIVE** means that it is NOT equipped with a dedicated air system, in that case the air flow inside the RABS should be generated externally, normally the Laminar Flow required in the filling and capping area is generated by fans and filters embedded in the false ceiling of the production room. ✓ **ACTIVE** means that it is equipped with an independent air ventilation system, in that case the Laminar Flow required in the filling and capping area is generated by fans and filters that are parts of the RABS itself, then the air flow is partially independent by the air flow of the production room.	✓ Normally the classification of the air leak tightness of these systems is not carried out using the ISO 10648-2 standard, which is usually applied for isolators, since different solutions, with very different prices, are available on the market. ✓ Due to the lack of leak tight certification these systems cannot not be used for highly toxic products.	✓ The classification of the air leak tightness of these systems is carried out following ISO 10648-2 standard, these tests give a real value of the system leakage, the achieved value will help to decide if we can use it with highly toxic products or not. ✓ Due to its leak free and easy to clean structure, the isolator can be cleaned with semiautomatic cycles (WIP) very useful to remove traces of contaminating products and can be decontaminated using agents in vapour phase as the Vaporized Hydrogen Peroxide, with fully automatic cycles.
✓ Easy to install, also on existing machines ✓ Inexpensive ✓ Easy to validate (air flow, air classification, doors interlocks) ✓ Possibility to downgrade the production area to class B	✓ Easy to install, also on existing machines ✓ Easy to validate (air flow, air classification, doors interlocks) ✓ Possibility to downgrade the production area to class B ✓ Humidity and temperature inside the Closed-RABS can be controlled adopting a dedicated HVAC ✓ Possibility to recycle the air used inside, saving HVAC energy consumption	✓ **Highest product protection** ✓ Possibility to downgrade the production area to class C ✓ Humidity and temperature inside the Isolator can be controlled adopting a dedicated HVAC ✓ Full operator protection, useful with highly toxic products ✓ Possibility to perform WIP cycles (Wash In Place) ✓ Possibility to perform automatic decontamination cycles ✓ Enhanced automation, fully integration isolator-machine