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A case study at stallion laboratories: identifying and fixing risk events by application of QRM in tablet manufacturing

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Abstract
It is, in the management science, well known and prominently accepted that "QRM" (Quality Risk Management) is an important component which helps identify risk factors (known and unknown – both) and once identified employs sound efforts either to mitigate or to nullify their devastating effects on operations to be carried out at any stage during the entire execution of a business cycle. In this article, we attempt to show the achievements in the direction through a case study at Stallion Laboratories Pvt. Ltd. which is involved in tablet manufacturing.

Keywords: Risk factors, QRM, paired 't' -test

1. Introduction
It is known and thoroughly accepted fact that the role of pharmaceutical industry is the most important since it directly relates to health aspect of human life. Due to stringent regulatory requirement, manufacturers of pharmaceuticals strive to find new strategies that helps improving the efficacy and efficiency of the drug product. With steadily increasing of economic pressures, for the manufactures it is also necessary to improve the business outcomes by achieving high productivity for its manufacturing and business operations along with maintaining quality of the product. GMP rules which is considered to be the heart of pharmaceutical quality management just talks about the quality but does not provide any specific guidance or approaches towards pharmaceutical manufacturing that helps increase the process productivity. Hence, it is critical to understand the real manufacturing outcomes and associated product quality and process productivity implications. The main purpose of this paper to make some suggestions in the daily operations of tablet manufacturing that may help to achieve higher production output without compromising product quality. Here, we will discuss a case study conducted at one of the leading pharmaceutical manufacturing company "Stallion Laboratories Pvt. Ltd.". Stallion Labs is a leading WHO, GLP and ISO 9001-2015 certified pharmaceutical company having own State-of-Art manufacturing facility situated at Kerala GIDC Bavla, Ahmedabad. It is into business of manufacturing large scale Oral Solid Dosage (OSD) forms since last 25 years. It has established strong presence in major Pharma markets viz. South East Asia, South Latin America, CIS region, Africa and Francophone countries. Stallion is also coming up with second unit for manufacturing of OSD with aim to enter in the regulated markets. Stallion firmly believes to provide quality products and faces many challenges in its day to day manufacturing operations. Only Scientific approaches and We Grow Together' policy helps find better solutions.

1.1. Understanding Tablet Manufacturing Process
The manufacturing of tablets which is considered to be oral solid dosage form involves a multi-stage, complex process by ensuring correct amount of drug is delivered at desired location with a well-defined time and rate. Along with the complex manufacturing process, the manufacturing facility should be in stringent compliance with Good Manufacturing Practice (GMP) guidelines. Figure 1.1 gives a brief overview of the steps or processes involved in any traditional tablet manufacturin.

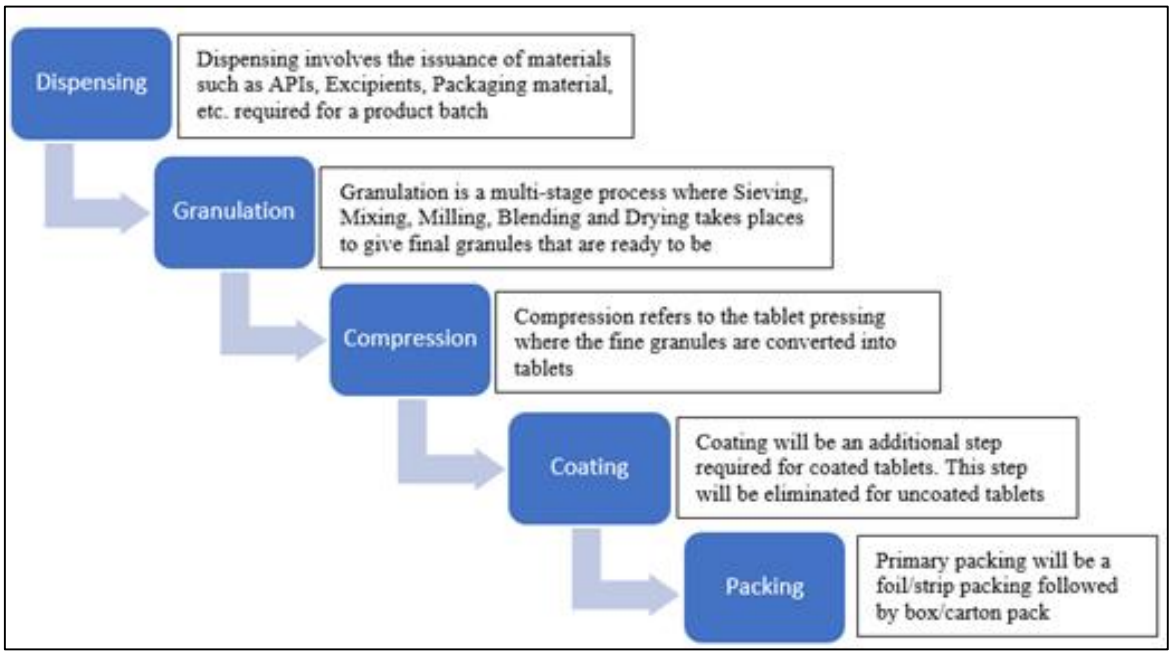


Fig 1.1: Overview of steps involved in tablet manufacturing

2. Planned Output as per Capacity Vs. Actual Output

Pharmaceutical organization faces unwanted and undesirable setback in its day to day manufacturing operations which may be called as Manufacturing Disturbances. Such disturbances cause delay in the production as per the planning or as per the capacity of the organization to give the maximum output. Here in this project, the area of the study is to understand the production output in manufacturing of tablets.

*2.*1 Product Selection

Stallion Labs is in involved in manufacturing of 250 + products in different categories. It is practically impossible to study production output of all products at a time so we have chosen two products i.e. Amlodipine 5mg* and Metformin with Glimepiride 500mg**. We have undertaken Product Selection Criteria as mentioned in Figure 2.1 to short list the product and to study the outcome of actual planning as per machine capacity vs. actual outcome.

- Amlodipine 5mg is anti-hypertensive used in the treatment of high blood pressure
- Metformin with Glimepiride 500mg is antidiabetic drug to stabilize and control blood glucose levels

Fig 2.1: Product Selection Criteria

2.2 Production Planning Outputs

The methodology adopted is to collect the data from Stallion Labs for its 10 days of manufacturing activities for the selected product.

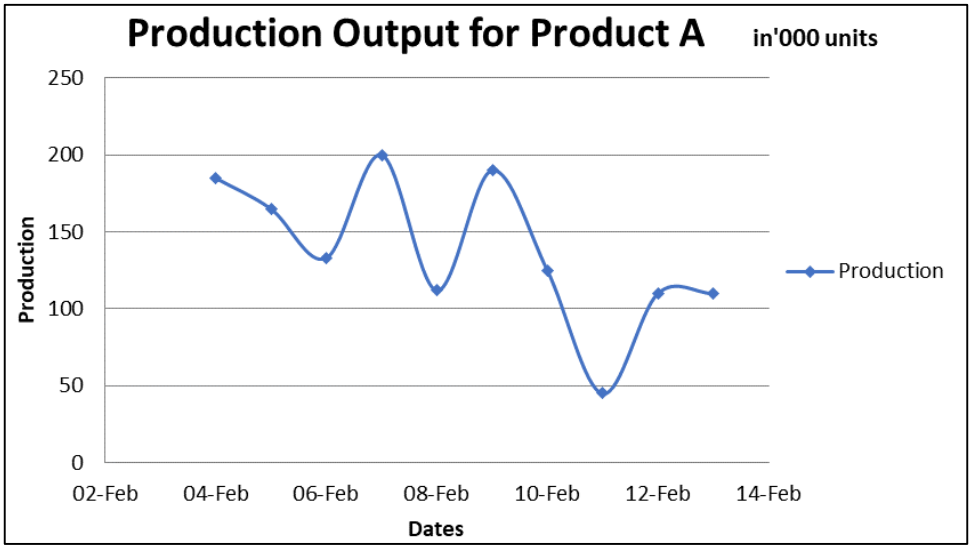
Table 2.2.1 shows the planning done for manufacturing of Product A (Amlodipine 5mg) and the real outputs achieved. In similar way, Table 2.2.2 shows the planning versus achieved output for Product B (Metformin with Glimepiride 500mg)

Production planning has been done calculating the actual capacity of the equipment's that were used for the manufacturing of these two products refer Table 2.2.3

(Product A) and Table 2.2.4 (Product B).
Note: The capacity calculation is as per the optimum capacity validated for particular product and not committed by the machine vendors.

Table 2.2.1: Production Planning done versus Actual Outcome for Product A (Amlodipine 5mg)

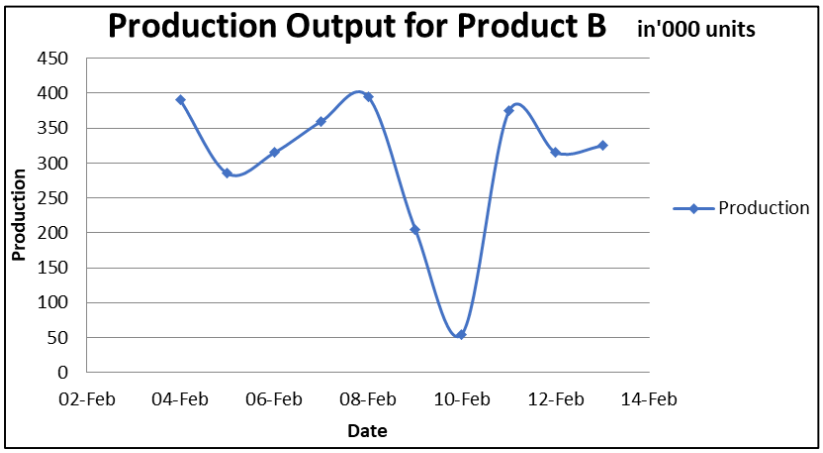
Production Planning of Amlodipine 5 mg				
Date	**Production Planning**		**Actual Output**	
	Product Name	**Plan Qty (In Tabs)**	**Product Name**	**Actual Output (In Tabs)**
04/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,85,000
05/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,65,000
06/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,33,000
07/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	2,00,000
08/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,12,000
09/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,90,000
10/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,25,000
11/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	45,000
12/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,10,000
13/02/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,10,000
	Total Planned Qty	20,00,000	Actual Packed Qty	13,75,000



Graph 2.2.1: Actual Production Output for Product A before application of QRM

Table 2.2.2: Production Planning done versus Actual Outcome for Product B (Metformin and Glimepiride 500mg)

Production Planning of Metformin 500 mg + Glimepiride 2 mg				
Date	**Production Planning**		**Actual Output**	
	Product Name	**Plan Qty (In Tabs)**	**Product Name**	**Actual Output (In Tabs)**
04/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,90,000
05/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	2,85,000
06/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,15,000
07/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,60,000
08/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,95,000
09/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	2,05,000
10/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	55,000
11/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,75,000
12/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,15,000
13/02/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,25,000
	Total Planned Qty	40,00,000	Actual Packed Qty	30,20,000



Graph 2.2.2: Actual Production Output for Product B before application of QRM

Table 2.2.3: Capacity Calculation for Product A (Amlodipine 50mg)

RPM	50 RPM
Strip / stroke	1 STRIP
Mins / hour	60 MINS
Net working hours	7 HOURS
Tablets / strip	10
Total capacity	210000
Working capacity	200000

Capacity Calculation forBlister Machine 1

Table 2.2.4: Capacity Calculation for Product B (Metformin and Glimepiride 500mg)

RPM	50 RPM
Strip / stroke	2 STRIP
Mins / hour	60 MINS
Net working hours	7 HOURS
Tablets / strip	10
Total capacity	420000
Working capacity	400000

Capacity Calculation for Blister Machine 2

3. Application of QRM

From the above data it is clearly identified that the manufacturing activities were not efficiently carried out as the actual output was far less than the desired output. Hence, by application of QRM we have studied the risk factors involved in manufacturing activities, root causes that affects the process productivity as well as affects the quality of the product and its mitigation strategies.

3.1 Team Selection

The key approach to stabilize and make full utilization of production capacity is to form a competent team to identify the causes of delay in production. Team consisted of all relevant subject matter experts and has been selected very critically by taking into consideration Team Selection Criteria as mentioned in Figure 3.1. The goal and responsibilities of all the team members were clearly defined.

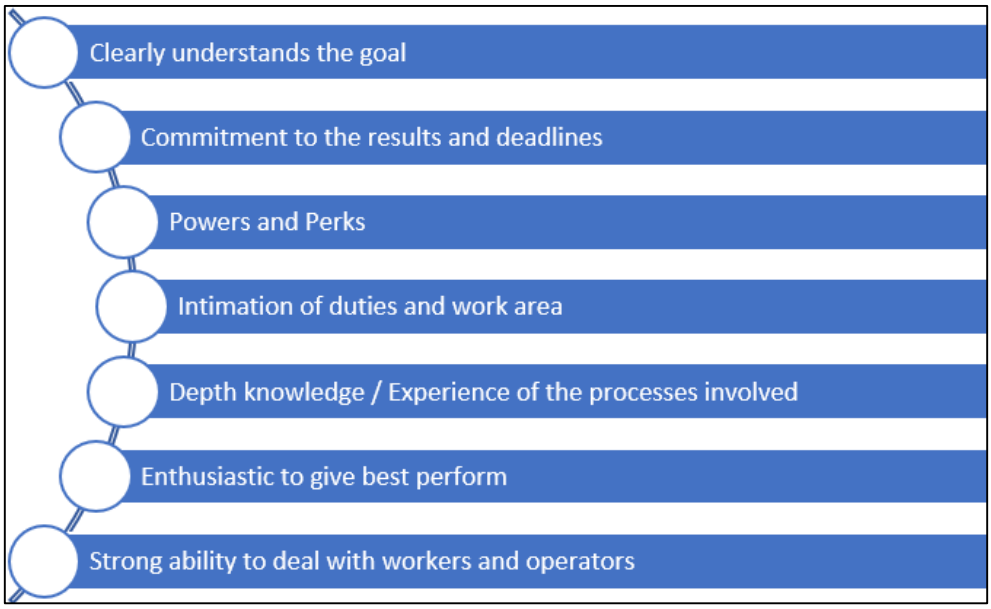


Fig 3.1: Team Selection Criteria

3.2. Identification of Root Cause

In this project, inductive approach adopted is to identify the root causes of risk factors involved in manufacturing activities which are or can be responsible for causing delay in the production activity as per planned scheduled and affects the quality of the product. Based on the responsibility of the team member, production manager, production supervisor and RM store officer investigated the real scenario on basis of their presence as well as their experience and talked to all operators for their views. Through a brain-storming session root cause

identification was done and is well explained by Ishikawa Root Cause Analysis diagram in the Figure 3.2.All causes identified can have different levels of impact meaning not all disturbances can provide similar effect or similar damage.

Different causes referring to particular department or parameters have been identified that produces high impact on productivity and quality loss such as Raw Materials, Packaging, Cross-Contamination, Machine/Equipment, Process Parameters, Cross-Contamination and Manufacturing facility. Root causes of individual risks were identified for instance, improper handling of material can be caused due to material loosely sealed, misplacing of material and storage condition not maintained. Other risk events include, lack of knowledge of personals involved in process, untrained, poor hygiene of workers, poor designing, process parameters issues such as capping, cracking, filling, sticking, improper coating, etc.

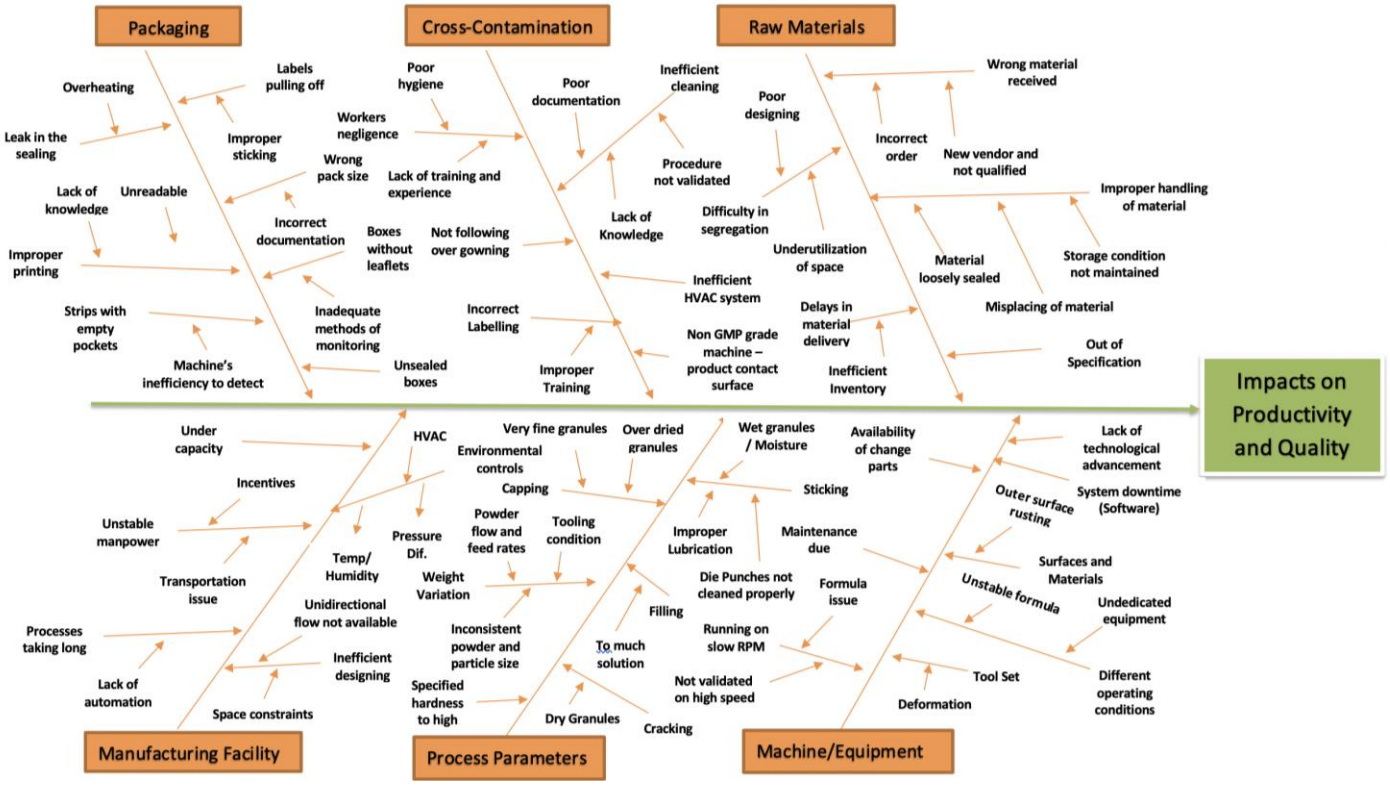


Fig 3.2: Cause and Effect diagram for Impacts on Productivity and Quality

3.3 Mitigation Strategies Applied

Analyses of above risk factors showed that some of the events were pre-known but no action was taken and some of the events were totally unknown and never faced before. The prime focus here is to mitigate the risk factors or to suppress them, if not completely prevented. Some mitigation strategies may be straight forward and easy to impart whereas some other can be highly tactful to impart and prevent in future.

Following line of action were carried out to mitigate or prevent the risk factors which can be known or unknown:

1. Procurement team to ensure to always purchase raw materials from approved vendor list and qualified
2. Ensure proper cleaning by placing strong cross-verification checks and impart periodic training to all personals involved in manufacturing process to make them understand causes and impacts of cross-contamination
3. Efficient designing of the raw materials store for utilizing maximum available space and ordering of new mobile racks
4. Ensure efficient use of ERP system for proper placement and dispensing of materials
5. Optimizing dispensing time by providing training and demonstrations
6. Ensuring the proper cross-verifications of quantity of materials and labels at each stage
7. Periodic audits to be performed for raw material store for efficient inventory management
8. Strongly check that preventive maintenance of all equipment's along with air and water system is done as per schedule
9. Ensure in-process parameters at each stage is as per the batch record provided and authenticated by IPQA person and provide training to operators as and when required
10. Enhance the communication channel for the non-working of equipment
11. Make strong utilization of FND team for proper validation of the formula
12. Provide periodic training to all operators involved in manufacturing process for the usage of the machine
13. Upgradation of machine by adding NFD (no fill detector) to packing lines
14. Making efficient use of packing machines during day shift and total close down of night shift packing which is more prone to error
15. Ensure proper and periodic training for proper printing of foils and labels and to avoid misprinting or mislabeling on finished product during packing stage
16. Provided incentives to all personals responsible for production efficiency and quality of the product

Note: Quality cannot be tested into products; but it should be in-built in design and verified during the on-going process

rather than relying along on the finished product testing

4. Results and Analysis

After successful implementation of QRM by application of mitigation strategies across all the personals involved in the manufacturing process we have checked what impact it gives on quality as well as productivity.

4.1 Production Planning Outputs after application of QRM

Production data for 10 days for the same product was collected after studying the risk factors involved earlier and by proper application of mitigation strategies this data was studied in reference to previous data collected before application of QRM. Table 4.1.1 and Table 4.1.2 shows the planning done for manufacturing of Product A (Amlodipine 5mg) and Product B (Metformin with Glimepiride 500mg) and the real outputs achieved after applying mitigation strategies.

Table 4.1.1: Production Planning done versus Actual Outcome for Product A (Amlodipine 5mg)

Production planning of Amlodipine 5 mg				
DATE	**Production Planning**		**Actual Output**	
	Product Name	**Plan Qty (In Tabs)**	**Product Name**	**Actual Output (In Tabs)**
04/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	2,00,000
05/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,70,000
06/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,85,000
07/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,99,000
08/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,25,000
09/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,99,000
10/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,35,000
11/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,55,000
12/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,40,000
13/03/19	Amlodipine 5 mg	2,00,000	Amlodipine 5 mg	1,10,000
	Total Planned Qty	20,00,000	Actual Packed Qty	16,18,000

Table 4.1.2: Production Planning done versus Actual Outcome for Product B (Metformin and Glimepiride 500mg)

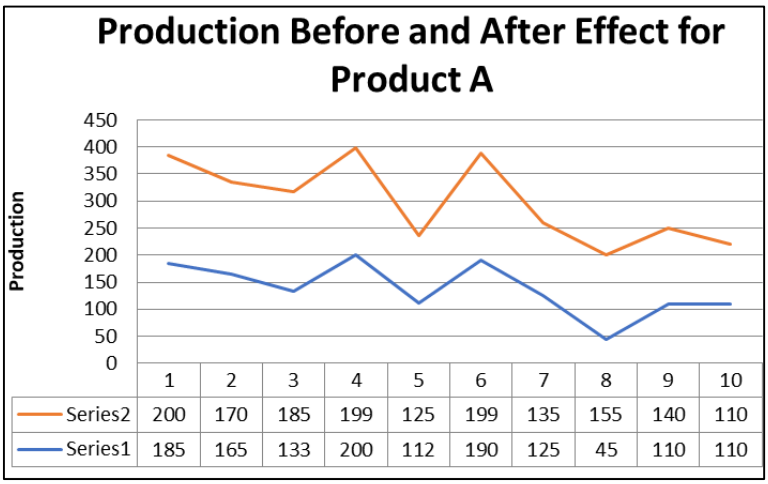
Production Planning of Metformin 500 mg + Glimepiride 2 mg				
Date	**Production Planning**		**Actual Output**	
	Product Name	**Plan Qty (In Tabs)**	**Product Name**	**Actual Output (In Tabs)**
04/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	4,00,000
05/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,70,000
06/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,25,000
07/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,60,000
08/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,80,000
09/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,10,000
10/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	2,35,000
11/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,65,000
12/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,10,000
13/03/19	Metformin 500mg + Glimepiride 2mg	4,00,000	Metformin 500mg + Glimepiride 2mg	3,80,000
	Total Planned Qty	40,00,000	Actual Packed Qty	34,35,000

4.2 To Establish Claimed Effectiveness

In order to justify the direction and the mode of imparting technical education to the operators we designed a 5-days program. The CV (co-efficient of variation) and t-tests were used for analyses to compare the production data achieved by the same operators working on the same machines before and after application of QRM.

4.2.1 Calculation of Mean and Standard Deviation for Product A (Before and After)

Graph 4.2.1 represents the before and after application of QRM effect in the production for product A and Table 4.2.1 shows the calculated mean and standard deviation.



Graph 4.2.1: Production before and after for Product A

Table 4.2.1: Mean and Standard Deviation for Product A

Product A	Before application of QRM	After application of QRM
Mean	137.5	161.8
Standard Deviation	47.81	33.55

4.2.2 Paired 't' Test for Production Data of Product A

Table 4.2.2: Represents production data in "000" units before and after application of QRM for Product A

Before (x)	After (Y)	D = Y—X	D^2
185	200	15	225
165	170	05	25
133	185	52	2704
200	199	--1	1
112	125	13	169
190	199	09	81
125	135	10	100
45	155	110	12100
110	140	30	90
110	110	0	00
		Sum = $\sum D = 243$	Sum= $\sum D^2 = 15495$

T- Test

H_0; That there is no difference between production before and After training (The training is not Effective)

H_1: There is a difference. The production, after training, has improved

Level of Significance = 0.05

One sided Test (As determined from H_1)

n = number of Observations = 10

Test Statistics: Mean =$\widetilde{D}$ = 24.3 Units

$S^2 = (\sum D^2) \ /n - \left(\frac{\sum D}{n}\right)^2 = 959$

$t = \frac{\widetilde{D}}{\sqrt{(\frac{S^2}{n-1}}} = 2{,}344$

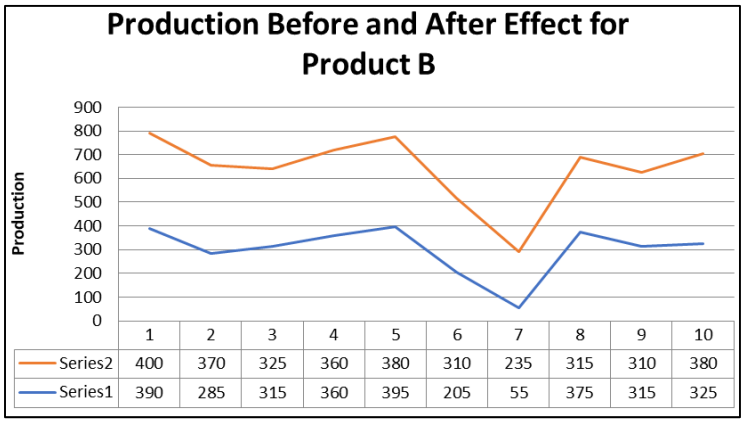
As the calculated value (2.344) is greater than the table value (= 1.833), it falls in rejection region.

We reject the null hypothesis. This means that we accept the alternative hypothesis.

Results for Paired 't' Test of Product A: The specific training has remained effective in increasing the production

4.2.3 Calculation of Mean and Standard Deviation for Product A (Before and After)

Graph 4.2.3 represents the before and after application of QRM effect in the production for product B and Table 4.2.3 shows the calculated mean and standard deviation.



Graph 4.2.3: Production before and after for Product B

Table 4.2.3: Mean and Standard Deviation for Product B

Product A	Before application of QRM	After application of QRM
Mean	302	338.5
Standard Deviation	103.63	49.16

4.2.4 'Paired 't' Test for Production Data of Product B

Table 4.2.4: Represents production data in "000" units before and after application of QRM for Product B

Before (x)	After (Y)	D = Y—X	D^2
390	400	10	100
285	370	85	7225
315	325	10	100
360	360	0	0
395	380	-15	225
205	310	105	11025
55	235	180	32400
375	365	-10	100
315	310	-5	25
325	320	-5	25
		Sum = $\sum D = 355$	Sum= $\sum D^2 = 51225$

T- Test

H_0; That there is no difference between production before and After training.

(The training is not Effective)

H_1: There is a difference. The production, after training, has improved

Level of Significance = 0.05

One sided Test (As determined from H_1)

n = number of Observations = 10

Test Statistics: Mean =$\widetilde{D}$ = 35.5 Units

$S^2 = (\sum D^2) \ /n - \left(\frac{\sum D}{n}\right)^2 = 3862.25$

$t = \frac{\widetilde{D}}{\sqrt{(\frac{S^2}{n-1}}} = 5.1410$

As the calculated value (5.1410) is greater than the table value (= 1.833), it falls in rejection region.

We reject the null hypothesis. This means that we accept the alternative hypothesis.

Results for Paired 't' Test of Product B: The specific training has remained effective in increasing the production

5. Conclusion

Finally from all above analyses, we are led to an enhancing conclusion that though 'Risk Events', in real life situation is unavoidable but at the same time proper analysis and setting up proper frame work of training generates fair chances to improve production productivity and eventually enhances gross profit.

6. Acknowledgements

We are highly thankful to some important suggestions provided by Dr. Pradeep J. Jha.

7. References

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