Manufacturing Processes Yield Improvement

Edgar de Paiva Bártolo
edgarbartolo@tecnico.ulisboa.pt

Instituto Superior Técnico, Lisboa, Portugal

October 2019

Abstract

The generic drug sector is extremely competitive. A market leader like Generis needs to streamline its processes and get the most out of its equipment and employees to stay competitive. Improving the yield of your manufacturing plant is a way to increase your income. If this yield improvement is done without the need for monetary investment, the increase in income will all be converted into profit for the company. The yield of the 2018/2019 production cycle was 96.1% and the target for the 2019/2020 cycle was set as an increase of 0.5% to 96.6%. It was necessary to understand which unit operations contributed the most to product loss and yield decrease, this was achieved by analyzing the production reports and OEE platform data. It was concluded that the tablett compression and capsule filling steps were the ones that most contributed to the yield reduction. The main sources of losses and their causes were identified and quantified. Some improvement proposals have been made to reduce losses in the initial tuning processes of the compressing and capsule filling machines. In the end the results obtained were positive, the objective was exceeded and the average yield during the study was 96.9%

Keywords: Yield Improvement, Tablett pressing, Capsule Filling, Optimizing, Losses,

1. Introduction

Generis Farmaceutica's main objective is to develop, manufacture and sell generic drugs and was the first Portuguese pharmaceutical company exclusively dedicated to this purpose. Generis is the company in Portugal with the largest number of active substances marketed (over 200 INNs) and since 2011 is the leader in this market in Portugal. It also has a significant presence in some foreign markets in Europe, Africa and East Asia.[1]

In 2017 it was acquired by the Aurobindo group and now has the only drug production unit of this group in Europe. This has led to an increase in products to be manufactured at Venda Nova's plant and an increasing need to streamline all company processes.[2]

The generic medicines sector is extremely competitive. A market leader like Generis needs to streamline its processes and get the most out of its equipment and employees. It is no coincidence that it has in its structure a department dedicated solely to the theme of continual improvement.

Generis Pharmaceuticals started a partnership with the kaizen institute in 2014 that is still in effect today. Improvement projects, referred to as A3 projects, are usually carried out on a quarterly basis and are proposed by the various departments, taking into account possible improvement opportunities. These are projects with clear objectives, which are not very large, and allow the causes of problems and proposals for improvement to be studied quickly and without diverting many resources from the main objective of each department.[3]

An opportunity has been identified for improvement in plant productivity and yield. Although the processes are already well optimized, with regard to the use of the various Work Centers and their setup times, the global yield of the manufacturing unit is still below the standard for the pharmaceutical industry, which for a production unit of oral solid dosage forms is in the order of 97.5% This project is based on monitoring the processes of the plant, identifying the causes of losses and decreased yields and developing solutions to problems encountered.

2. Background

Kaizen and Lean methodologies are aimed at reducing waste of various types: waste of time, material, movement and occupation of employees. The Kaizen methodology is largely based on a visual organization system in which all the information and material necessary for the proper functioning of the company is properly organized and identified in order to facilitate its use.

To achieve its objectives, Generis has invested in a culture of continuous improvement, acting in four aspects: - Daily Kaizen - Development of transversal projects for process improvement - Kaizen in

Top Management and various intermediate levels of leadership - Support activities such as training, workshops and incentive programs.

3. Implementation

3.1. Diagnosis and Planning

The yield of the 2018/2019 production cycle was 96.1%. The target set by the Industrial Unit Director for the new production cycle was 96.6%. This 0.5 % increase in yield corresponds to an increase in production of about 4.2 million units for the 2019/2020 cycle.

Table 1: Manufacturing plant yield; cycle off 2018/2019

Month	Expected prod.	Real prod.	Yield
04/2018	56.625.178	53.894.437	95,2%
05/2018	75.010.206	71.985.815	96,0%
06/2018	73.654.333	70.810.228	96,1%
07/2018	91.237.540	87.491.421	95,9%
08/2018	39.177.506	37.888.508	96,7%
09/2018	70.753.404	68.020.146	96,1%
10/2018	67.082.738	64.376.512	96,0%
11/2018	65.799.984	63.538.054	96,6%
12/2018	53.017.050	50.765.061	95,8%
01/2019	74.301.580	71.090.249	95,7%
02/2019	89.308.531	85.515.037	95,8%
03/2019	92.197.243	89.550.373	97,1%

3.1.1 Unit operations and work centers with the greatest negative impact on manufacturing yields

In addition to analyzing the monthly yields of the 2018/2019 cycle, the data from the production reports, where the yield values of each production step are recorded, were analyzed to verify which unit operations had the greatest impact on manufacturing yields.

Table 2: Yield per unit operation; data collected from production reports; 2018/2019 cycle

Unit Operation	Yield
Mixing	99,7%
Granulation	98,6%
Tablett pressing	96,2%
Capsule filling	91,2%
Coating	99,2%

The data collected led to the conclusion that,in terms of unit operations, those with the highest impact in the final yield are the Tablett pressing and capsule filling steps. Both have average yield values below the target yield of 96.6%. These were then defined as the unit operations to be studied in order to improve their yield.

With the data previously collected in the production reports and also in the Overall Equipment Effectivness (OEE) platform the average yields per Work Center were calculated.

The tabblet pressing work centers defined as target for the study were Killian BB Killian D and Unipress B. The Zanasi capsule filling work centre was also defined as a target for the study. These work centers had average yields bellow the established objective of 96.6%.

Table 3: Yields per Work Center; 2018/2019 cycle

Work Centre	Yield (Prod. Report)	Yield (OEE)
Killian BB	96,8%	96,3%
Killian D	96,4%	95,9%
Unipress B	94,20%	94,6%
Fette	97,2%	96,5%
Xpress	97,2%	97,3%
Zanasi	91,0%	89,0%

3.1.2 Identification of loss sources in the different processes

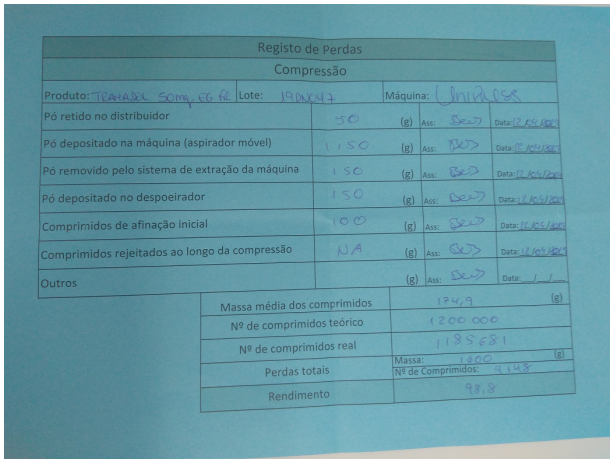
In the case of tablett pressing work centers, the following sources of loss were identified as significant: - Product retained in the dispensing mechanism after the batch has ended; - Product used for initial tuning of equipment, which is out of specification; - Pressing machine extraction system; - Product accumulated in the deduster; - Product collected by the mobile vacuum cleaner, resulting from losses of normal pressing operation and accumulated inside the press;

In the case of the capsule filling work center the causes of losses identified were: - Product that was retained in the dispenser tank after the batch ended; - Product used for initial tuning of equipment, which is out of specification; - Extraction system of capsule filling machine; - Product collected by the mobile vacuum cleaner, resulting from losses of normal machine operation and accumulated inside the capsule filling machine;

As important as identifying the sources of losses it was necessary to quantify them. The waste collection method implemented did not allow quantification of losses from different sources as all of the waste was collected in the same bag and then wighted . It was necessary to introduce a loss registration form and change the way waste was collected. Each line of the form would correspond to a distinct source of losses and stored in a separate bag, each weigted separately. This way of quantifying the residues allowed to assign a relative importance to each of the sources of loss and thus to understand which had the greatest impact on the final yield of the batch.

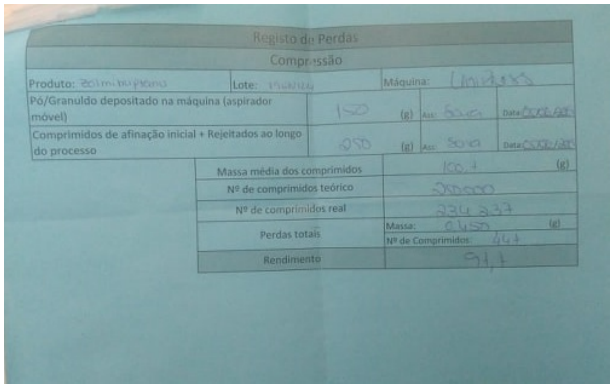
After an initial phase of about one month of data collection at the target work centers, a tendency for the sources of losses to have the greatest and most frequent impact on batch yields was observed. This made it possible to design a new form template with fewer fields to fill out. These forms were better received than the initial forms by the operators, as it represented a decrease in the

Figure 1: Loss registration form



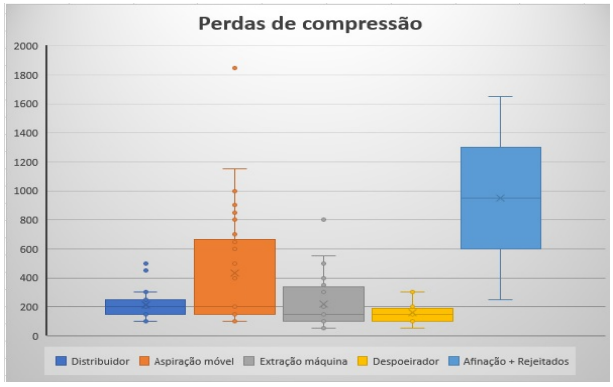
time spent with the closing tasks of each batch.

Figure 2: Loss registration form version 2



In the case of tablet pressing work centers it was observed that the losses due to the normal operation of the machine (product collected by the mobile vacuum cleaner) and the initial tuning and rejections during the pressing process were clearly the ones that had most impoact in the final yield. In the case of losses in the dispensing mechanism, machine extraction and dusting losses were always relatively constant and in much lower quantities.

Figure 3: Losses(g) Tablett pressing work centers



In the Killian D and Killian BB work centers the main source of losses is the initial tuning and the product loss during normal pressing operation comes in second plan, as we can observe in the graphics

Figure 4: Losses(g) Killian D work center

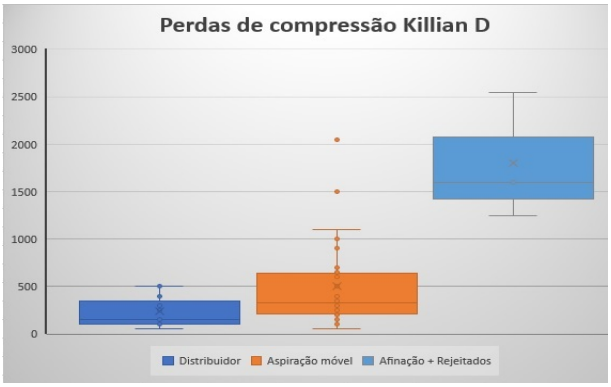
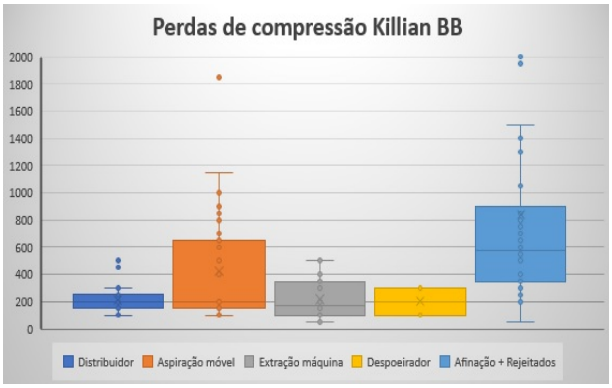
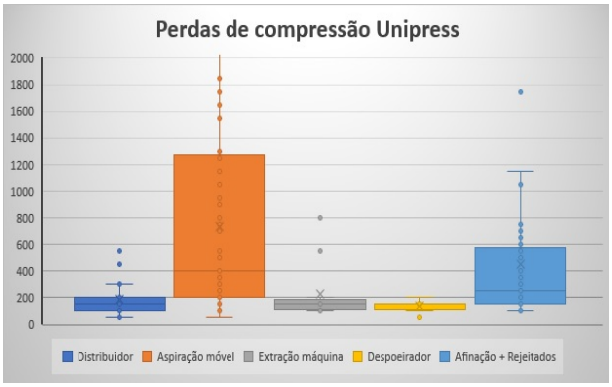


Figure 5: Losses(g) Killian BB work center



In the Unipress B work center we have the opposite situation, where the main source of losses is the normal operation of the pressing machine and the losses in the tuning phase have a minor impact on the final output.

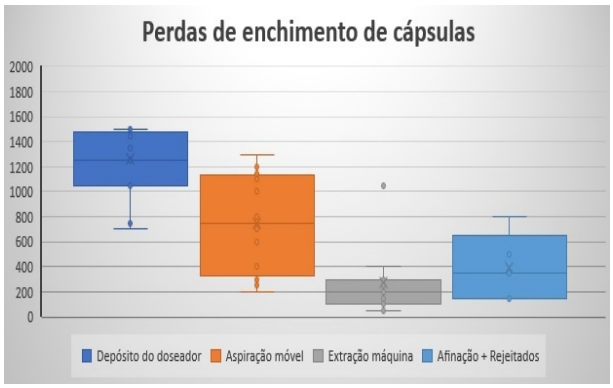
Figure 6: Losses(g) Unipress B work center



In the Zanasi work center the main cause of loss is the amount of product that is retained in the dispenser tank. Product losses during normal machine operation and the amount of capsules spent

tuning also represent a significant amount of product lost.

Figure 7: Losses(g) Zanasi work center



3.2. Product loss source causes

After identifying the main sources of losses in the tablett pressing and capsule filling processes it was necessary to study the causes of those losses. During the process of accompaniment to the various work centers while they were in labor, some theories for the causes of losses have emerged.

3.2.1 Tablett Pressing

3.2.2 Losses during normal pressing operation and accumulated inside the press

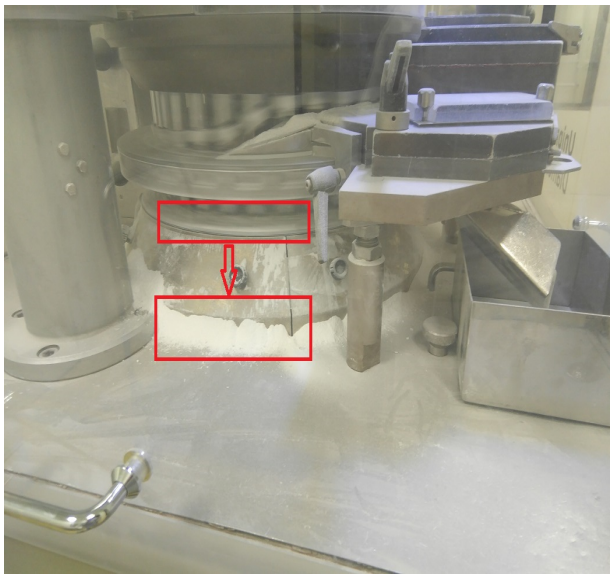
One theory was that the particle size profile of the product would be directly related to the amount of losses. Some batches of products with different particle sizes were analyzed. It would be expected that a product with a larger proportion of smaller particles would have greater losses because they escape more easily with the centrifugal forces derived from the rotation of the turret. However, the data collected comparing the loss values with the particle size profiles did not allow us to reach this conclusion. Products with particle size profiles with finer particle percentages had equal or lower loss values than products with higher percentages of larger particless, as shown in Table 4.

Another theory was related to the wear level of the fast wear parts, namely the scrapers located before and after the dispensing mechanism and the bronze part that interfaces between the dispensing mechanism and the plate where the dies are placed. These parts are essential so as not to allow product to be lost at the dispenser exit, and at the end of each cycle ensuring that excess product left in the plate is recovered back to the dispenser. These parts, when worn let more product escape. It was therefore attempted to understand to what extent the wear of these parts interferes with the yield of each batch.

The theory was tested by exchanging the worn parts in use for new parts and compare results betwen batches. For this test were chosen products in which several batches were produced consecutively (at least two batches, ideally 3 batches), and which presented an history of below the standard yields. In the first batch the parts in use would be those in the machine. In the second batch new parts would be placed without any wear. In the case of products with 3 consecutive batches, in the third batch the parts used in the first batch would be placed again in order to try to validate the results. The results obtained did not indicate a clear improvement in the exchange of parts in use for new parts as shown in table 5.

In the case of the Unipress work center it was necessary to analyze and identify the causes of loss of product by the inferior punctures.

Figure 8: Loss of product by the inferior puncures, Unipress work center



In conversation with the technicians of the company Lurga (one of the suppliers of die and punch sets), who were at the factory to calibrate one of the tablett pressing machines, I was given a possible explanation for this phenomenon. The cause would be the wear of the punch and die sets due to repeated use. This wear led to an increase in the distance between punch and die which would allow product to escape whenever the lower punch drops to the die filling phase.

3.2.3 Losses during the initial tuning of equipment

Losses associated with the tuning process, as noted earlier, had a greater impact on Killian work centers. In the case of the Unipress work center

Table 4: Losses vs Particle size profile

work center	Product	unit mass(mg)	losses per unit(mg)	losses per unit(%)	particle size profile
Killian BB	Indapamida 1,5mg	200	0,5	0,3	89,64% $\leq 0,25mm$
Killian BB	Alprazolam 1mg	350	1,0	0,3	72,76% $\leq 0,25mm$
Killian D	Domperidona 10mg	100	0,5	0,5	0.1mm$\leq 75,03\% \leq 0,85mm$
Unipress	Venlafaxina 37,5mg	150	0,8	0,5	76,0% $\leq 0,25mm$
Unipress	Tramadol 50mg	175	1,2	0,9	89,90% $\leq 0,425mm$
Unipress	Clopidogrel 75mg	250	2,4	0,9	0.063mm$\leq 73,05\% \leq 0,25mm$
Killian BB	Gliclazia 80mg	160	1,6	1,0	79,4% $\leq 0,425mm$
Unipress	ADT 10mg	100	1,4	1,4	87,07% $\leq 0,25mm$
Killian D	Lorazepam 1mg	100	2,0	2,0	79,27% $\leq 0,1mm$

Table 5: Fast wear parts test

Work center	Product	batch	parts	losses per tablett(mg)
Killian BB	ADT 10mg	19EN097	In use	0,5
Killian BB	ADT 10mg	19EN098	New	0,7
Killian D	Amlodipina 5mg	19EN080	In use	1,3
Killian D	Amlodipina 5mg	19EN082	New	0,5
Killian D	Amlodipina 5mg 100	19EN083	New	1,4
Killian D	Claritromicina 500mg	19EN095	In use	2,4
Killian D	Claritromicina 500mg	19EN096	New	2,0

the machine software recorded the tuning parameters used in previous batches of the same product. This was not the case in the killian work centers, where the software kept only the final manufacturing values for each batch. These final values may differ greatly from the tuning parameters. In order to reduce the amount of product left in the dispenser, operators changed filling volumes, feeder speed, machine operating speed and precompression and compression forces. These changes were necessary as with less powder in the dispenser (end of batch) the die filling was changed and required these adjustments to keep the tablets within specifications. Only by making these adjustments can you make the most of the product, otherwise the machine will stop early because it detects to out-of-specification tablets in two consecutive punctures and the amount of product lost would be much higher. Since the values recorded in the software are those of the end of the batch, each time a new batch of the same product is started it is necessary to adjust the compression parameters again.

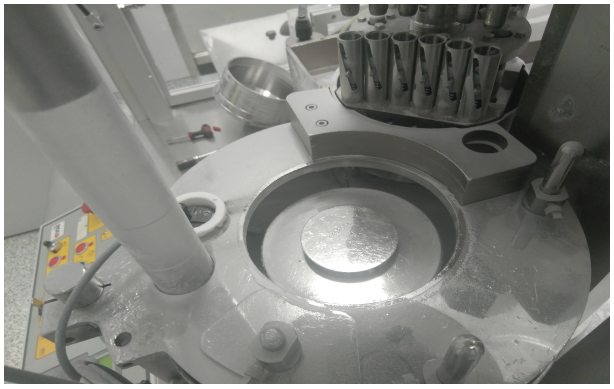
In addition to this difference at software level, the variation between operators were studied. This was done to try to understand the influence of operators' experience on the tuning process and to assess the need for more operator training. (table 6)

The difference in experience between operators is also a factor that may contribute product loss. the differences observed in the average number of tablets per tuning are quite significant, amounting to about 3000 more tablets per tuning within the same work center. These results are indicative of the need for reinforcement in the specific training for the tuning step by some operators.

3.3. Capsule Filling

In the accompanied bathces, the minimum value of product left in the doser deposit was 750g, which in a 65kg batch (average size of the accompanied batches) corresponds to a loss of about 1.15% and in the case of the maximum value 2300g corresponds to about 3.5%, which would immediately place the lot below the target value even before taking into account the remaining sources of losses. the idea of reducing the volume of the doser deposit was discussed with the maintenance department but this idea was promptly discarded as it would not be possible to make this reduction without compromising the proper functioning of the equipment.

Figure 9: Doser deposit Zanais work center



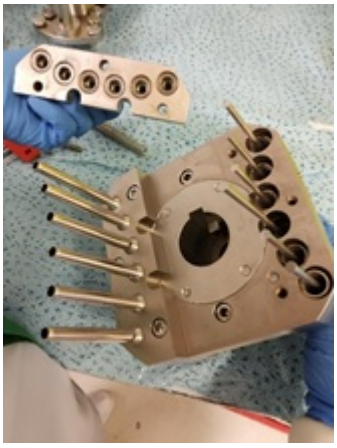
In the capsule filling work center the main cause of loss due to initial tuning is that every time the capsule filling machine needs to be cleaned more thoroughly it is necessary to completely disassemble the dosing group. After the dosing group is reassembled it needs to be tuned to match up with the dies. This tuning is a thorough process involving millimeter tolerances and it is necessary to

Table 6: Tuning data per work center and operator

Operator	Work center	Total Losses(un)	Mean(un)	Number o tunings)
Brito	Killian BB	34575	4322	8
David	Killian BB	49869	3325	15
Paulo O.	Killian BB	56876	6320	9
Genário	Killian D	19866	4976	4
Inês	Killian D	25643	3205	8
Maximiano	Killian D	13331	6666	2
Sandro	Killian D	15278	4097	8
Bruno	Unipress	15278	2197	7
Joaquim	Unipress	20465	1860	11
Sónia	Unipress	36345	2796	13

align two sets of 6 punctures with the respective dies. In addition to adjusting the dispenser with the dies, it is also necessary to further adjust the height of the dispenser which controls the filling volume of the capsules. These two tuning steps need to be performed with the product already in the machine and during this process all the capsules produced are considered out of specification.

Figure 10: Zanasi dosing unit disassembled



Normal machine operation derived losses in the capsule filling work center were considered as one of the main causes of yield reduction. These losses are also associated with the process of tuning the doser with the dies. As this was a very complex process that required disassembling the dosing group, operators often made the decision to operate the machine even though it was losing small amounts of product per cycle, as this adjustment was independent of product quantity filled in each capsule thus not rendering the capsules out of specification. This small amount of product that is lost per cycle, after several thousand cycles the ammount of product lost can reach about 1% of the total batch.

3.4. Improvement oportunities

One thing that was done since the beginning of the project was raising operators awareness for the importance and impact that improving yields could have on company results. It was emphasized that improving yields would correspond to an increase in revenue without the need for extra investment. From the first moment the commitment on the part of the operators was noticed and this can be seen in the results.

3.4.1 Tablet pressing

To try to decrease the amount of losses associated with the tuning step, especially on Killian work centers, a form has been created to record the machine operating values for each product. In this form were recorded the values of the precompression and compression forces, the dispenser speed and machine operating speed. There should be one form for each product manufactured. In these new forms were also recorded additional data to facilitate the work of operators. Information suchg as the hardness, appearance after stability testing (wich are important in the case of coated tablets) and storing instructions. There was also a field to record problems during pressing and how they were resolved.

The results obtained in the fast wear parts replacement test did not indicate that they contributed significantly to the losses. However, the message has been given to operators that more attention needs to be paid to the inspection of these parts whenever the machine is set up, and if necessary to replace parts that are deformed or worn. Very worn part may cause performance issues or even damage the machine.

3.4.2 Capsule filling

Since it is impossible to change the volume of the doser tank, the main cause of losses in this work center, we focused our attention on seeking a way to reduce losses in the tuning fase. A new methor for cleanin the dosing was tested. This new method was based on washing the dosing group without disassembling it. It was done in a 45C ultrasound bath with detergent for 30 minutes, then washed with purified water, sprayed with 70ethanol and dried with compressed air. The next step was to dry the dosing group in an oven at 45C for two

hours. This new washing method would not increase the setup time as this whole process would be done at the same tima as the capsule filling room was cleaned. In addition to the advantages associated with decreasing the tuning losses another advantage would be to reduce wear of parts by reducing the handling of the part in the assembly and disassembly steps.

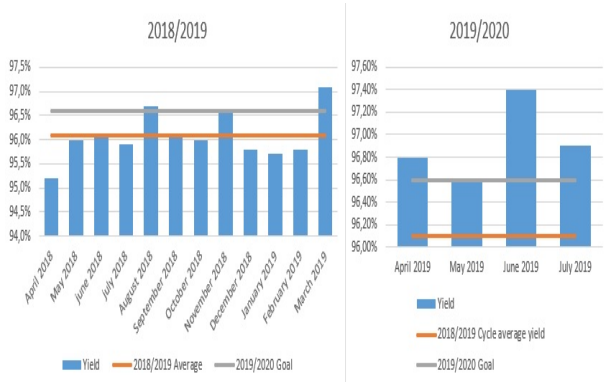
However, it was not possible to implement this improvement proposal because this new washing method did not yield consistent results. Some of the tests performed were successful in washing the doser but not in drying. Others succeeded in both. There were trials where the dispenser contained residues after washing in the ultrasound bath with the detergent.Trials with longer duration and higher temperatures were made but no consistent results were obtained. Being the dispenser a part that is in direct contact with the product to be filled in the capsules the presence of residues is synonymous with cross contamination and rejection of the batch by quality control. Incomplete drying of the part, even if it contains no trace of the previous product, is also an impediment to use of the part as the interaction of water and powders within the dosers can lead to equipment damage. Thus, this idea has been discarded.

4. Results & discussion

O objectivo de melhoria do rendimento do departamento de fabrico em relação ao ciclo de 2018/2019 em 0,5% (de 96,1% para 96,6%) foi conseguido e superado nos meses em que decorreu o estágio. O Rendimento médio durante estes meses foi de 96,9%.

The goal of improving the manufacturing processes yild by 0.5% (from 96.1% to 96.6%) was achieved and exceeded in the months of the internship. The average yield during these months was 96.9%.

Figure 11: Yields of 2018/2019 cycli and 2019/2020 cycle so far



In the graphical representation of the monthly yields of the manufacturing unit in the 2018/2019 and 2019/2020 cycles (figure 11), we can see that from the beginning of the internship, which took place in the last week of February, the monthly yields showed clear improvements. These improvements continued over the following months and so we achieved the proposed objectives.

We can also see in table 7 the yield improvement in the four target work centers, with the tablett pressing work centers averaging above the target value and the capsule filling work center, despite the 3 % yield increase, averaging below the target values 96.6%. The immediate improvement in yields is largely explained by the operators' dedication to meeting the objectives set for this project. It was also noted a change of attitude from the early stage of the internship to the final. As the internship progressed, greater initiative and attention to detail in the prevention and correction of the main causes of losses were perceived.

In terms of improvement introduced it should be noted that the tuning record form was only introduced in the last month of the internship and that its impact on yields will only be visible at medium term. It is necessary to produce again the products for which records have already been made, and in the same work center, to confirm whether or not there have been improvements in the tuning process. It is also necessary to continue to collect loss data in a segregated manner because only with this data can we understand what is possible and necessary to improve.

5. Conclusions

The experience provided by this internship was quite enriching. It has allowed me to be in direct contact with various stages of drug manufacture and many of the processes involved, from equipment maintenance and calibration, manufacturing supervision and hygiene.

With regard to the goals set at the beginning of the stage of performance of the plant, these were met and even exceeded, but the way they were achieved was not what I was expecting. I hoped to achieve the goals by implementing improvements in the manufacturing process, which was not the case. Improvements in yield came primarily from raising operators' awareness of the need to improve manufacturing yields and the benefits this would bring to the business. Operators responded as expected and the change in attitude observed was reflected in the results obtained.

In the case of Generis, the balance between meeting the manufacturing planning schedule and paying attention to yield tends to be on the schedule side, and this is understandable because only by meeting the deadlines set with customers can the company thrive. Even so, during these months

Table 7: Yields of target work centers in the 2019/2020 cicle vs Mean of 2018/2019 cycle

Work center	04/2019	05/2019	06/2019	07/2019	08/2019	Mean 2019/2020	Mean 2018/2019
Killian BB	97,3%	97,0%	98,3%	95,9%	96,8%	97,0%	96,8%
Killian D	98,2%	97,7%	98,1%	97,4%	96,5%	97,7%	96,4%
Unipress	97,8%	96,3%	95,7%	97,4%	97,6%	96,9%	94,6%
Zanasi	95,9%	92,3%	92,4%	94,4%	94,0%	94,1%	91,0%

of internship it was possible to improve yield while maintaining the level of productivity. There is clearly room for improvement. The last measure introduced, which was the tuning history record forms may still have benefits, for the reasons explained in the previous chapter.

6. acknowledgements

I want to thank my parents, my grandparents and my sisters for all the support they gave me during this master's degree, without them it would have been infinitely more complicated.

I also want to thank Dr. Irene Moreira Barros and Dr. Lígia Cardoso, fellow pharmacists, who were the first spark that light the fire that was the desire to do this master's degree.

I want to thank my colleagues in the 2017/2019 Master's Degree in Pharmaceutical Engineering for letting me be their "father" and for making me always feel welcome on this adventure away from my roots.

Finally, a special thank you to Dr. Filipa Guilherme for sharing all her knowledge, dedication and for even in the most difficult days, always having a smile on her face when sparing her precious time to provide guidance in my internship.

Thank you all very much.

References

[1] D. R. Generis, *Manual de Acolhimento*. Generis, 2016.

[2] rtp.pt. (2017, Janeiro) Farmacêutica Aurobindo Pharma compra portuguesa Generis. [Online]. Available: https://www.rtp.pt/noticias/economia/farmaceutica-aurobindo-pharma-compra-portuguesa-generis-por-135-milhoes-de-euros_n974245

[3] Instituto Kaizen Portugal. (2017) Generis - Prémio Kaizen lean 2017. [Online]. Available: https://kim.kaizen.com/kimglobal/userfiles/File/pt/Generis_Ind%C3%BAstriaSMC.pdf