THE USE OF STATISTICAL PROCESS CONTROL IN PHARMACEUTICALS INDUSTRY

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Abstract

The use of statistical process control has gained a major importance in the last years due to very good results that is provides and due the ease interpretation of the results, even by the people who are not specialists in the field. An essential quality, that differs the statistical process control to the other quality analysis statistical methods is that it examines the process in all stages, not only in the final stage. The increase of the competitiveness in all areas of industry made that the methods used in quality control to be more performant. No organization can maintain a high standard without a performant quality control. The pharmaceutical industry is one of the most important industries, holding an essential role in human's health in particular and in welfare of the whole society in general. This application is meant to illustrate, by using some of statistical indices, control diagrams and capability process indices, how it is used the statistical process control in the pharmaceutical industry and highlights both advantages and disadvantages of using it.

Key words: statistical process control, pharmaceutical industry, capability process indices, control diagrams

The main goal of most organizations, no matter of their nature, object or size, is to be competitive as possible on the market, a crucial factor in ensuring a long operating duration. All organizations follow three very important ways: quality, delivery and price.

A process is the transformation of a set of inputs, which may include materials, actions, methods and operations in desired output results, results which take the form of products, information or services. In each area of an organization could be many processes that take place. Any process must be analyzed by a careful examination of the inputs and outputs. This thing will determine the necessary actions for improve the quality of the process (Oakland, 2003). The output value of a process is "something" that is transferred to someone or something – namely the customer. Clearly, to produce an output that meet customer requirements, it is necessary to define, monitor and control the system inputs, process which in turn may have provided an output of the previous process.

To start a monitoring and analysis of any process, it is necessary to first identify what kind of process it is and then what are the inputs and the outputs. Many processes are easy to understand and related to known procedures, e.g: polymerization of a chemical product, filling boxes with paint, labeling or encapsulation of tablets (Montgomery D.C., Keats J.B., 1996). Some processes are more difficult to identify, for example, a customer service, providing lectures or selling a product. In some situations can be difficult to define a process. Defining the scope of a process is vital, because it will determine the necessary inputs and the output. In this paper, I present, based on a practical application, the statistical process control in pharmaceutical industry, based on some data received from a big national pharmaceutical company.

Statistical process control is not only a tool, but a whole strategy to reduce variability, the cause of most problems of achieving the quality standards. The variation can occur anytime and anywhere: in production, in delivery process, in people's attitude, in equipment and in it's use and in maintenance practices. The Total Quality Management (TQM), as well as the statistical process control requires the process to be continuously improved by reducing variability (Ciobanu R.C., Schreiner C., 2002).

MATERIAL AND METHOD

As I said, the data used in the presentation of the application have been received from a local pharmaceutical company, very strong at national and international level.

In this application I have analyzed the process of ampicillin bottles, of 1000 mg, 500 mg and 250 mg, within an hour of production. The quality control is made at the end of each day, and wasted is accounted and destroyed at the end of each working day. The tolerance permitted is $\pm 5\%$, i.e. the dose from the bottle is contained in

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the interval [950; 1050] mg, if the machine is set to 1000 mg. If, the machine should be set to 950 mg, then could be an even an efficiency higher than 100% ! The adaptation of product amount is made according to the content of the active substance that varies between 95% and 100%. Per hour is made an average of 8000 1000 mg ampicillin bottles, which means that in one day of 10 effective working hours are made 80000 bottles. It is obvious that for the quality control of production process it is not take into account the whole quantity of bottles, but only some representative samples. After consulting with experts on the field, I learned that to verify the quality of 1000 mg bottles it must be considered samples of 1000 bottles, from each working hour, so that daily is checked an average of 8000 produced bottles. In this application I don't take into account 10 samples of 1000 bottles, because this thing would required a long time for data introduction, but 10 samples of 10 bottles each, i.e. a sample for each working hour.

Similarly I proceeded in the case of 500 mg bottles and 250 mg bottles, the permitted tolerances being also $\pm 5\%$, i.e. the dose from the 500 mg bottle is contain in the interval [475; 525] mg, and the dose from the 250 mg bottle is contain in the interval [237.5; 262.5] mg. Regarding the number of ampicilin bottles of 500 mg and 250 mg, this is more lower than the number of bottles of 1000 mg. Per hour is produced an average of 1000 bottles of 500 mg, and only 500 bottles of 250 mg. For each of these two cases I considered the same number of samples as in the case of 1000 mg bottles. But, it is clearly that, because the total number of bottles of 500 mg and 250 mg daily produced is much lower that the number of 1000 mg bottles, the accuracy in these two cases is much higher.

Regarding the method used, these are presented in (Spiridonica, Doloca, Ciobanu, 2010), so that I don't went into details.

RESULTS AND DISCUSSIONS

Following the introduction of values for the bottles of 1000 mg, I obtained the following results, presented in the Figure 1:

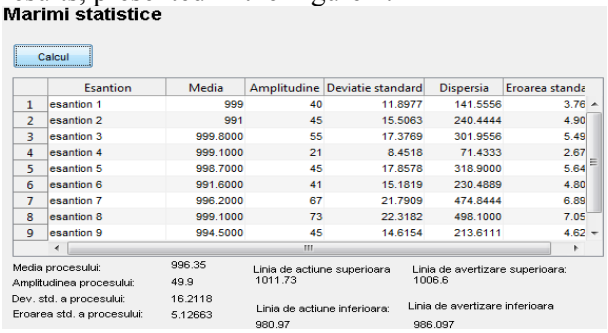

Figure 1 **Statistical indices and the process values in the case of 1000 mg bottles**

So, in this figure I note the average, the amplitude, the standard deviation, the variance and the standard error for every sample considered. Below, note the process' mean, the process' amplitude, the process' standard deviation, the process' variance and the process' standard error and also the warning and action lines of the process. The process' standard deviation was calculated by using the *Hartley constant*, a very used measure in statistical process control. For use the Hartley constant, I implemented two functions with the name "hartleymean.m" (that determines the Hartley constant for the average based on sample volume) and "hartleyamplit.m" (that determines the Hartley constant for the amplitude based on sample volume). In this application the process' standard deviation was calculated as a fraction between the process' average amplitude and Hartley constant for the amplitude based on sample volume. All considered samples have the volume of 10, so that the Hartley constant in this case is 3.078. In the Figure 2 is presented the diagram of the values mean, calculated above:

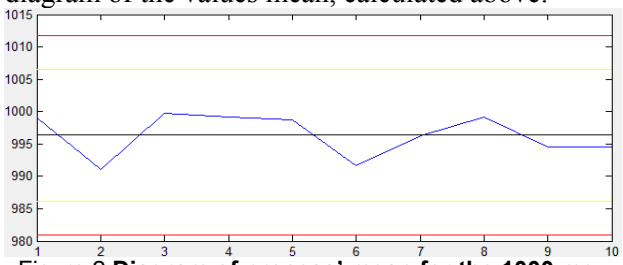

Figure 2 **Diagram of process' mean for the 1000 mg bottles**

The black line represents the process' mean, the yellow lines are the warning lines, red lines are the action lines. It is easy to observe that the process is in statistic control throughout the period of 10 hours. There is a slight downward trend in the samples with number 2 and number 6, but there is no need for any review of the process, because the mean value of the samples don't lie in the outside of lower warning line. Even if the process' mean value would be left outside of the lower warning line, the process could be found throughout the statistical control, because it is only one value, and the mean of the previous sample lie between the two warning lines. So, it can say with confidence that the process is in statistical control.

The next step is represented by the calculation of process capability indices. For this thing I realized the "indici.fig" window, where, based on the example from this application, I calculated the values of four capability indices:

Figure 3 **Process capability indices for the bottles of 1000 mg**

So, the first analyzed index was *relative precise index*. In our example the process amplitude was 57.3 mg. In the case where tolerance is ± 50 around the target value then the relative precise index will be: IPR = 2*50/49.9 = 2.00401. It is very important to calculate, also, the minimum value of IPR. So, IPRm = $6/d_n$ = 6/3.078 = 1.94932 (the value 3.078 representing the Hartley constant for the amplitude in the case of a sample of 10). The conclusion is that IPR > IPRm and everything is alright, there is no scrap material.

The second analyzed index was *Cp* index. In this application, the lower specification limit (LSL) was fixed 950 mg, and the higher specification limit (USL) was fixed 1050 mg. So, *Cp* = 1.02806, which means that *Cp* > 1 so that it can say that the process is in statistical control because the tolerance band is higher that the process variation.

The third and last calculated index is *Cpk* index. The *Cpk* value represents the minimum value between Cpk_l and Cpk_u. The value for Cpk_l is 0.9530, and the value for Cpk_u is 1.1031. So, the resulted *Cpk* value is the minimum between these two, i.e. 0.9530. Conforming to this value, the situation is far from the acceptable because the non-conformity still can not be detected by the process control charts. Although this index provides a value that cannot be satisfactory, it can say that the process is in statistical control, they are no scrap material, and the only problem is related to the tolerance setting, which should be closer or farther away from the mean value. The tolerance setting of a manufacturing process is a difficult problem and the decision to establish a tolerance value is taken after a long series of tests. In this application I presented only the way where this application, developed in MATLAB, rules. The data used in this application was only the data related to measurements of bottles of ampicilin. In the final part of the application I calculated the value σ_{max} in order to observe what is the maximum standard deviation at which the customer accepts the products. The window is the following:

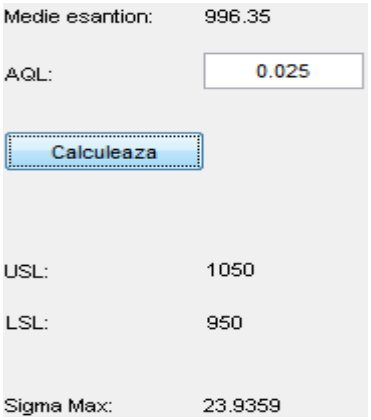

Figure 4 **Acceptable quality level for the bottles of 1000 mg**

Conforming to the Figure 4, I considered a tolerance of 50 mg. I chose an AQL of 2.5%, i.e. the value of AQL represents 0.025. The *Z* corresponding value for a value of AQL of 0.025 is 2.24 (value taken from the tables). So, the relation of σ_{max} is: $\sigma_{max} = (USL - \overline{X})/Z$ = 23.9359. In order to meet the specified tolerance band of 50 mg and a quality acceptable level of 2.5%, it allows that the maximum acceptable standard deviation of the process to be 23.9359.

Following the introduction of the values for the bottles of 500 mg, resulted the following results, presented in the Figure 5:

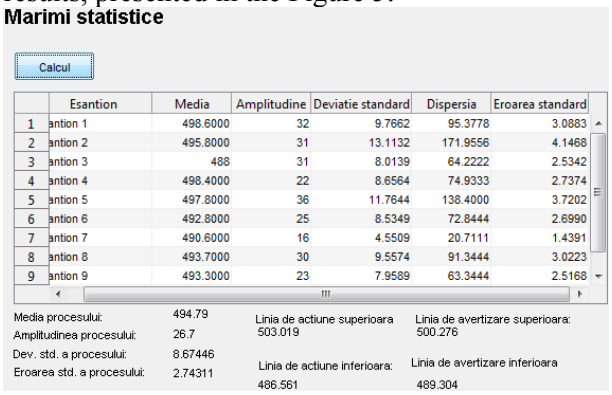

Figure 5 **Statistical indices and the process' values in the case of the 500 mg bottles**

All considered samples have the volume of 10, so that the Hartley constant in this case is also 3.078. In the Figure 6 is presented the average values diagram calculated above:

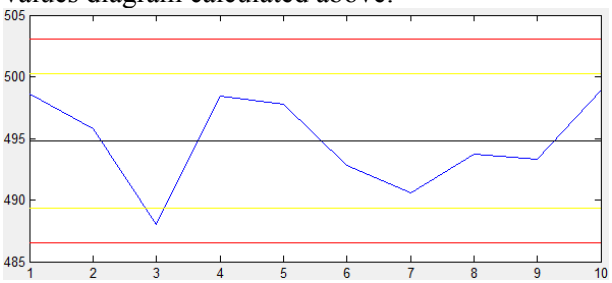

Figure 6 **Diagram of process' mean for the 500 mg bottles**

It can observe that the sample mean number 3 falls outside the lower warning line, but this thing should not be thought as a bad thing, because the previous sample means are fall between the two warning lines. The other sample averages are included between the two warning lines. So, it can be say with confidence that the process is in statistical control.

The capability indices reveal some problems related to the setting of process' tolerance, conforming to the Figure 7:

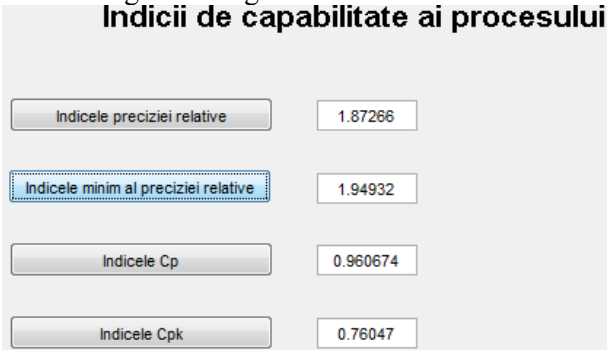

Figure 7 **Process capability indices for the 500 mg bottles**

The minimum relative precision index has a value greater than the relative precision index and I can affirm that there are scrap material between 500 mg bottles! The *Cp* index has a value slightly below to 1, so that it can be say that the process is in statistical control. The *Cpk* index has a low value, so that it can be say that the manufacturer is not able and they are obviously unsatisfactory process results.

The Figure 8 shows the AQL, in which I remark that the maximum standard deviation for products to be within acceptable quality limits is 13.4782 mg:

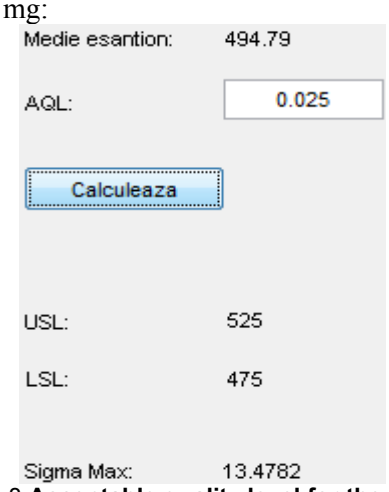

Figure 8 **Acceptable quality level for the 500 mg bottles**

Following the introduction of the values for the 250 mg bottles, resulted the following results, presented in the Figure 9:

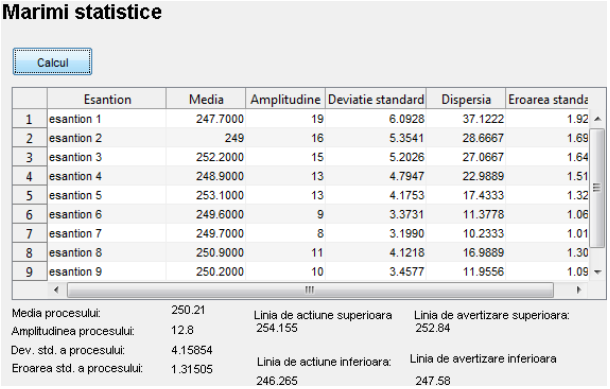

Figure 9 **Statistical indicators and the process' values for 250 mg bottles**

As in the case of 1000 mg and 500 mg bottles, all considered samples have the volume of 10, so that the Hartley constant is also 3.078. In the Figure 10 is presented the diagram of mean values calculated above:

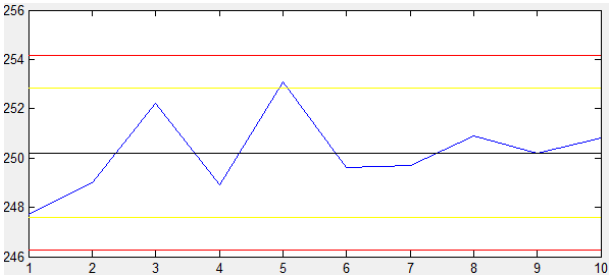

Figure 10 **Diagram of process' mean for the 250 mg bottles**

It can show that the sample mean number 5 falls outside the upper warning line, but this thing should not be thought as a bad thing, because the previous sample means are fall between the two warning lines. So, it can be say with confidence that the process is in statistical control.

The capability indices are presented in the Figure 11:

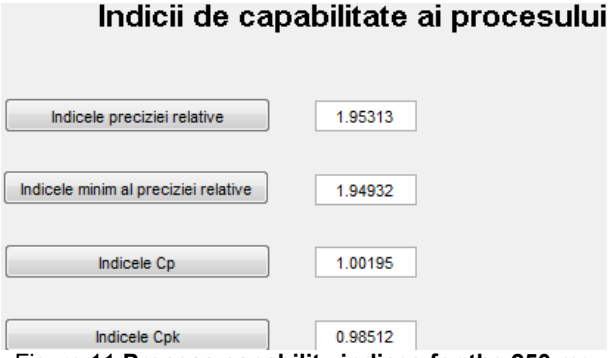

Figure 11 **Process capability indices for the 250 mg bottles**

There is no scrap material because the relative precision index has a higher value than minimum relative precision index. The *Cp* index has a value of 1, so that the process is also in this case in statistical control. *Cpk* index has a value lower than 1, so that the manufacturer is not able and exists obviously unsatisfactory process results.

Figure 12 shows also the AQL and is noted that the maximum standard deviation for products to be within acceptable quality is about 5.5 mg:

Figure 12 **Acceptable quality level for the 250 mg bottles**

As a conclusion at the rows above, it can say that the process is in statistical control in all three cases (1000 mg, 500 mg and respectively 250 mg), but the problem appears regarding the process' tolerance imposed by the manufacturer, that is $\pm 5\%$. It is possible that the tolerance imposed by the manufacturer to be much higher, so that may lose some process' accuracy. Only few registered values were closed from the maximum and minimum value in all of three cases, so that a solution could be the decrease of the tolerance.

CONCLUSIONS

As a conclusion I can say that this application is very useful and easy to apply for all specialists working in industrial quality assurance. This application is suitable for many types of industries and in this paper I used this application for pharmaceutical industry. Acceptable quality level (AQL) is a measure very used in the last years in quality assurance field and is critical for many types of industries. Based on this application it can possible to analyze a lot of processes types through many industries, from the design operation to the final product.

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