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ORIGINAL ARTICLE

Stage 3: Continued Process Verification of Cefoperazone and Sulbactam Powder for Injection

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ABSTRACT
Stage 3 of the Process Validation Guidance calls for "Continued Process Verification". Process monitoring provides the tools for enabling Continued Process Verification and dealing with variation. Managing and reducing variation is at the heart of the FDA Process Validation Guidance. Clearly stated in the guidance is the need to understand variation, ability to detect variation, understand the impact of variation and ability to control variation. This session addresses the concepts, methods and tools used in continued process verification. It is shown how the tools can be linked and integrated to create a system that enhances the use of the tools and the effectiveness of Continued Process Verification.
Keywords*: Continued process verification, Statistical control tools, process variation*

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INTRODUCTION

It is a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its critical quality attributes (CQAs) and control strategy requirements. In order to enable continuous process verification, companies should perform, as relevant, extensive in-line, on-line or at-line controls and monitor process performance and product quality on each batch. Continuous process verification has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. This approach is based on the knowledge from product and process development studies and / or previous manufacturing experience. Continuous process verification may be applicable to both a traditional and enhanced approach to pharmaceutical development. It may use extensive in-line, on-line or at-line monitoring and / or controls to evaluate process performance.

MATERIAL AND METHODS

In order to review or assess and confirm that the process remains in a state of control (the validated state) during commercial manufacture, following data to be collected for the product supplied to the market.

1. Quality of incoming materials or components shall be assessed or reviewed.

Quality of incoming raw materials of commercial and PV batches of various parameters should be assessed as follows:

- **Potency**
- **pH**
- **Water content**
- **Assay**
- **Particulate matter**
- **Related substances**

- **Bulk density**
- **Bacterial endotoxin**
- **Sterility**

2. Data shall be collected relevant to the product process trends on

Weight Variation during the filling.

Weight variation data at different hopper levels and hopper speed should be collected during the commercial and PV batch manufacturing

In process materials.

In process parameters dummy vials and rubber stopper sterility tests should be monitored

Finished products- Analytical data of PV batches and commercial batches.

Finished product analysis should be checked routinely and the parameters like

ph **Particulate count** **Water content**
BET **Related substances**
Sterility **Assay**

PV batches and commercial batches yield trends.

3. Statistical methods and procedures used should measure and evaluate the process stability and process capability considering:

- **All the CPQ identified parameters shall be considered.**
- **Trending and calculations to be made to know the individual events as well as the failure to detect unintended process variability.**

4. Process variability should be assessed and monitored annually.

- Data gathered in above section need to be reviewed for opportunity to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set- points), process controls, component, or in-process material characteristics.
- Based on CPV outcome the necessity for the planned change if any with well-justified rationale need to be made before implementation plan.

STATISTICAL ANALYSIS OF DATA

A. Control charts for CPV

The control charts are used to: -

- Detect special causes of variation in the process at the time they exist so that they can be easily identified and corrected
- Identify the pattern of variation if product is defective
- Provide statistical limits which define the natural tolerance of the process, and are used to stabilize the process (or get the process in-control).

1. Statistical Trends (for subgroups) to be made for the following parameters:

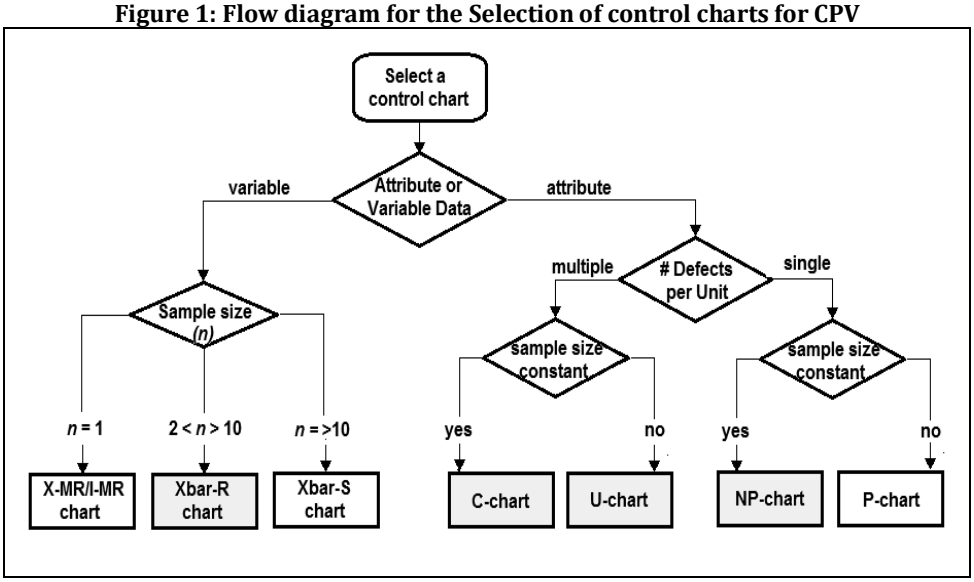
- Weight Variation of sterile powders in filled vials at different hopper level & speed of the filling machine.

2. Statistical Trends (for individual observations) to be made for the following parameters:

- Rubber Stopper LOD
- Assay results of In-Process & Finished product
- Water Content
- pH values
- Impurities
- Bulk density

3. Selection of control charts: The flow diagram for the Selection of control charts for CPV is shown in Figure 1

Figure 1: Flow diagram for the Selection of control charts for CPV



4. Subgrouping

Subgrouping to be made for each filling port in case of injections.

- For Dry powder Injections where there are 12 ports are available in a feel wheel then sub group size shall be 12. So selection of chart will be **XBAR-S chart**
- After making the sub group, standard deviation (S.D) & Average values shall be calculated for each subgroup. From the values available, $(\bar{S})$ i.e. average of the standard deviation to be calculated. The averages we have calculated for each subgroup, from there average of averages to be calculated i.e. $\bar{X}$.

UCL & LCL can be calculated by using the following formula:

- **UCL = LSL+T_2 ; LCL= LSL+T_1**

Sigma calculation

- $\sigma = \frac{\bar{S}}{d2}$

Note: d2 values shall be chosen from the statistical table as per the size of the sub-groups.

Calculating Capability Indices using the following formula:

Process Capability Index $(Cp) = \frac{USL-LSL}{6 x \sigma}$

Process performance index $(Cpk) Min \left[\frac{USL-\bar{X}}{3x\sigma} \text{ or } \frac{\bar{X}-LSL}{3 x \sigma}\right]$

For CPV, Statistical Trends (for individual observations) the type of control chart to be made is $(XBar - S)$ chart.

STEPS IN CONSTRUCTING AN $\bar{X}$-S CHART

- X Bar S charts often used control chart to examine the process mean and standard deviation over the time. These charts are used when the subgroups have large sample size and S chart provides better understanding of the spread of subgroup data than range.
- X bar S charts are also similar to X Bar R Control chart, the basic difference is that X bar S charts plots the subgroup standard deviation whereas R charts plots the subgroup range
- Selection of appropriate control chart is very important in control charts mapping, otherwise ended up with inaccurate control limits for the data.

1. Gather the data.

a. Select the subgroup size (n). The concept of rational subgrouping should be considered. The objective is to minimize the amount of variation within a subgroup. This helps us see the variation in the averages chart more easily.

b. Select the frequency with which the data will be collected. Data should be collected in the order in which it is generated.

c. Select the number of subgroups (k) to be collected before control limits are calculated. It should start with initial control limits after ten subgroups, but recalculate the limits each time until you get to twenty subgroups.
d. For each subgroup, record the individual, independent sample results.
e. For each subgroup, calculate the subgroup average:

$$\bar{X} = \frac{\sum X_i}{n} = \frac{X_1 + X_2 + \ldots X_n}{n}$$

f. For each subgroup, calculate the subgroup range:
Tolerance = Xmax - Xmin
Where, Xmax is the maximum individual sample result in the subgroup and Xmin is the minimum individual sample result in the subgroup.

2. Plot the data.

a. Select the scales for the x and y axes for both the $\bar{X}$ and S charts.

b. Plot the subgroup ranges on the S chart and connect consecutive points with a straight line.
c. Plot the subgroup averages on the $\bar{X}$ chart and connect consecutive points with a straight line.

3. Calculate the overall process averages and control limits.

a. Calculate the average range (S bar):

$$\bar{s} = \frac{\sum s_i}{k} = \frac{s_1 + s_2 + \ldots + s_k}{k}$$

where k is the number of subgroups. b. Plot S bar on the range chart as a solid line and label.
c. Calculate the overall process average (X bar):

$$\bar{\bar{X}} = \frac{\sum \bar{X}_i}{k} = \frac{\bar{X}_1 + \bar{X}_2 + \ldots \bar{X}_k}{k}$$

d. Calculate the control limits for the S chart. The upper control limit is given by UCL. The lower control limit is given by LCL.

$$UCL_s = B_4 \bar{s}$$
$$LCL_s = B_3 \bar{s}$$

Where B4, B3, are control chart constants that depend on subgroup size.
f. Plot the control limits on the R chart as dashed lines and label.
g. Calculate the control limits for the X chart. The upper control limit is given by UCLx. The lower control limit is given by LCLx.

$$UCL_X = \bar{\bar{X}} + A_3 \bar{s}$$
$$LCL_X = \bar{\bar{X}} - A_3 \bar{s}$$

Where A3 is a control chart constant that depends on subgroup size. Plot the control limits on the $\bar{X}$ chart as dashed lines and label.

4. Interpret both charts for statistical control.

a. Always consider variation first. If the S chart is out of control, the control limits on the $\bar{X}$ chart are not valid since you do not have a good estimate. All tests for statistical control apply to the $\bar{X}$ chart. Points beyond the limits, number of runs and length of runs tests apply to the S chart.

5. Calculate the process standard deviation, if appropriate.

a. If the R chart is in statistical control, the process standard deviation, s, can be calculated as:

$$\sigma' = \frac{\bar{s}}{c_4}$$

Where C4 is a control chart constant that depends on subgroup size.

RESULTS AND DISCUSSION

a. Quality of incoming raw material

Quality of incoming raw materials of commercial and PV batches are checked and the parameters are given in Table 1.

Table 1: Quality of incoming raw materials of commercial and PV batches

Quality parameters	Limits	Results
Potency	870-1015mcg	*Satisfactory*
Ph	4.5-6.5	*Satisfactory*
Water content	NMT 5.0%	*Satisfactory*
Assay	870-1015mcg	*Satisfactory*
Particulate matter	NMT 600pc/container	*Satisfactory*
Related substance	NMT 4.5%	*Satisfactory*
Bulk density	NLT 0.5% g/ml	*Satisfactory*
Bacterial endotoxin	NMT 0.20EU/mg	*Satisfactory*
Sterility	To be sterile	*Satisfactory*

b. Quality of in-process materials

Quality of in process materials of commercial and PV batches are checked and the parameters are given in Table 2.

Table 2: Quality of in process materials of commercial and PV batches

In process checks	Limits	Results
Dummy vials and rubber stopper sterility tests	To be sterile	*Satisfactory*
Rubber stopper moisture content	NMT 0.2%	*Satisfactory*
Leak test	No leakage	*Satisfactory*

c. Weight variation of PV and commercial batch filling

- Weight variation of PV batch at different hopper levels and hopper speed are recorded and statistical analysis was performed.
- Weight variation of commercial batch during filling was recorded and statistical analysis were done.

d. Comparison of previous batch and current batch using trend chart analysis

- Collect the data of previous batch and create a trend chart by taking average and standard deviation
- With this value find out the limits for UCL, LCL.
- Keeping UCL, LCL constant create a trend chart for current batch and find out Cp,Cpk

e. Finished product analysis of PV batch and commercial batch

Finished product analysis should be checked routinely and the parameters are shown in Table 3.

Table 3: Finished product analysis of PV batch and commercial batch

Parameters		Limits	Results
PH		4.0-6.5	*Satisfactory*
BET		NMT 0.2 EU/mg	*Satisfactory*
Sterility		To be sterile	*Satisfactory*
Particulate count	**≥10µm**	NMT 6000pc/container	*Satisfactory*
	≥25µm	NMT 600pc/container	
Related substance	Individual impurity	NMT 1.5%	*Satisfactory*
	Total impurity	NMT 4.5%	
Water content		NMT 4.0%	*Satisfactory*
Assay		90-115%	*Satisfactory*

f. Comparison of finished product analysis of PV batch and commercial batch

Keeping the average of PV batch data and create a trend chart for commercial batch and results are found to be within the limits.

g. Yield trend analysis of PV batch and commercial batch

Yield trend charts are made using the average of PV batch and commercial batch and the limits are NLT 96%

h. Yield trend comparison of PV batch and commercial batch

Keeping average of PV batch data and create a trend chart for commercial batch and results are found to be within the limits.

SUMMARY

The analytical results obtained were manufactured as per approved specification/SMP respectively shows that the manufacturing process of **sterile product** is capable of delivering quality product and assuring that during routine production, the process is in a state of control. The data obtained during manufacturing process to the product process are as follows:

Quality of incoming raw materials

- The quality of incoming raw materials of commercial batches was found to be satisfactory as per ICH guidelines Q8, Q9, Q10 and the manufacture of product were from reputed supplier and were found to be of standard quality.

Weight variation during filling

- The weight variation carried out for the commercial batches determined at different hopper levels and different speeds were found to be within the stated limits as per ICH guidelines Q8, Q9, Q10 demonstrating that the process was capable of reliably and repeatedly rendering a product of desired dosage.

Finished products

- The moisture content of the powder in the vials was found to be satisfactory as per ICH guidelines Q8, Q9, Q10 suggestive of suitable drying of rubber stoppers and vials, and appropriate maintenance of temperature and relative humidity of the filling cabinet and filling room
- The pH of the powder in the vials was found to be satisfactory as per ICH guidelines Q8, Q9, Q10 demonstrating an appropriate washing process.
- The contents of the active pharmaceutical ingredients in all commercial batches were satisfactory as per ICH guidelines Q8, Q9, Q10.All commercial batches comply with the Tests for sterility demonstrating proper sterilization of vials and rubber stoppers, an appropriate aseptic environment for filling and suitable aseptic manoeuvres and techniques followed by filling personnel.
- The particulate matter present on the container of all commercial batches was found to be satisfactory as per ICH guidelines Q8, Q9, Q10.
- The impurities present on powder of all the commercial batches was found to be satisfactory as per ICH guidelines Q8, Q9, Q10

Yield trends

Actual / practical yield in all commercial batches was found to be satisfactory and not less than 96 % which is within the acceptable limits.

CONCLUSION

The process outlined in this represents a general recommendation for implementation of CPV for new or legacy products. These high-level steps can be useful in driving alignment of understanding across the pharmaceutical industry. The steps could also be used within a company or among companies to aid in the planning and implementation of a CPV program. A risk- and fact-based approach to process revalidation based on CPV data can support focusing effort on value-adding and quality-improving activities.

- Implementation of a CPV program is a current compliance expectation and is expected to influence regulatory inspections and reviews to an increasing degree in the future.
- Beyond compliance, significant business value can be created through implementing CPV systems that highlight risk, motivate improvement, and document increases in process reliability and performance.

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