WHITEPAPER: PROCESS VALIDATION – A SYSTEMATIC APPROACH

White paper produced by Maetrics

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Introduction

Over the last few years Process Validation has become a buzz word across all sectors of the medical device industry. Implemented properly it can be used as a very powerful tool for ensuring high quality products are manufactured time and time again. Not only does this contribute to patient safety but it also helps to protect that all important bottom line by minimising rejected products and aborted production run and worse still… product recalls. However, the route to ensuring that a process is fully validated isn’t always a clear one which can all too often result in an inadequately validated process.

The purpose of this paper is to guide you through the key milestones required to successfully validate a process to meet both European and US requirements.

Validate or Verify?

The requirements of ISO 13485 and 21 CFR Part 820, with regards to process validation, are clear – where a process cannot be verified by subsequent monitoring or measurement then the process needs to be validated.

Before starting any form of process validation you need to ask yourself whether the process is suited to a validation approach or if a process of continuous verification is more applicable.

Validation and verification can easily be confused and are often, wrongly, used interchangeably but they are two very different approaches to ensuring product conformity.

The objective of verification is the same as that for validation: to ensure that a process consistently meets the predefined quality attributes, however verification will involve the inspection and/or measurement on 100% of the processes output, i.e. every single unit is checked to ensure that the outputs of the process equals your predetermined design inputs. It would not be adequate to consider a method of routine sampling sufficient enough to verify a product for release. A review of the FDA database will reveal a number of FDA 483 observations and warning letters to companies who have tried to adopt an approach of routine sampling in place of validating a process or 100% verification. There are no halfway measures as far as the regulatory requirements are concerned – you either validate or 100% verify.
Process verification allows for continuous “real time” quality assurance. If you have adopted this approach and later find that a problem occurs with a device as a result of a production issue once it has been released to market, this would suggest that verification of the process is not adequate and a validation approach needs to be considered.

Part of the validation process is to identify where variability in the process may exist and to determine what an acceptable level of variation would be whilst still ensuring the desired output is achieved – this might sound like a bit of a juggling act but if done properly you should find you are hardly ever dropping a ball.

Variation will exist in all processes and will need to be minimised and controlled as far possible, this is much easier to achieve in automated and semi-automated processes. In manual processes where there is potential for human differences between operating staff then variation becomes much more difficult to control and therefore validation becomes more difficult to achieve and is potentially unreliable.

For a process to be verifiable the output has to be easily detectable/measurable. For example you could not use the 100% verification approach for ensuring a medical device is sterile since this would involve opening every packet to verify that your sterility acceptance level has been achieved – you would never get anything out the door! Therefore some methods are much more suited to a process validation approach using statistical techniques than others and careful consideration is required.

The former Global Harmonization task force (GHTF), now the International Medical Device Regulators Forum (IMDRF) issued a guidance document which gives some excellent examples of processes that may and may not be suitable for validating.

The IMDRF and the FDA define process validation as:

“Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined..."
The GHTF guidance document provides an excellent decision diagram to help you to determine which process to adopt, this is shown in Figure 1 below.

![Decision Diagram](Image)

**Figure 1: Adapted from GHTF/SG3/N99-10:2004 (Edition 2)**

**Planning the validation**

A requirement of the FDA is that a documented plan of validation activities, commonly called a Validation Master Plan, is created. Although this isn’t specifically stated in ISO 13485 it makes good sense to plan and document where you intend to go and how you are going to get there. It is very rare that any form of process validation will only require the activities of a single individual so early adoption from all parties involved will help determine how and when the installation, operational and performance qualification activities will take place. This is the perfect time to establish your pass/fail criteria and to determine who shall be responsible for completing, reviewing and approving each of the activities.
Installation Qualification (IQ)

Installation qualification involves providing documented evidence that all the associated equipment being used in a particular process have been suitably installed as per the requirements of the manufacturer and that they operate within the tolerance limits specified. This may include taking into account the environmental conditions and utility supplies. For example is the machinery connected to a distilled water supply as per the manufacturing instructions? Are the environmental conditions likely to exceed the temperature limits provided by the manufacturer on a hot summer’s day?

Whilst the definitions may vary slightly between 21 CFR Part 820 and ISO 13485 their expectations in terms of the robustness of the validation remain the same.

With regards to exactly what sort of data you should be collecting we need to look more closely at 21 CFR §820.70(g) Equipment and combine it with the requirements set out in ISO 13485:2012 Section 7.5.1 Control of Production and Service Provision. To summarise, the requirements of European and US quality systems emphasise the need to have equipment that is suitable for its intended purpose and this is exactly what you need to demonstrate. Figure 2 describes some of the elements you should take into consideration.

There are many different ways that you could collate the IQ section of your validation report, one such method would be in the form of a checklist whereby you verify each section as being complete by signing off against that particular requirement, this allows for easy review and approval of the outputs.
Figure 2: Installation Qualification Process – points to consider

Do calibration records exist and is the equipment within its calibration period?

Do work instructions exist? Are they adequate? Reference the ones specifically related to your process.

What is the process for cleaning to prevent contamination from previous production runs?

Is there evidence that the equipment has been installed as per the manufacturer’s instructions?

Are personnel involved in the process adequately trained?

Are there specific environmental conditions that need to be met? e.g. temperature limitations, cleanroom requirements etc.

Are the correct drawings being used and have they been formally approved? For example, for an injection moulding process this could include both the mould tool drawing and part drawing.

Is there a requirement for spare parts? Where is this recorded and is there sufficient stock?

Calibration Records

Work Instructions

Maintenance Schedule

Approved drawings

Operator training records

Installation records/Certificates

Environmental conditions

Cleaning schedule

List of spare parts

Calibration Records

Maintenance Schedule

Work Instructions

Installation records/Certificates

Environmental conditions

Cleaning schedule

Calibration Records

Maintenance Schedule

Work Instructions

Installation records/Certificates

Environmental conditions

Cleaning schedule
Operational Qualification (OQ)

A successful OQ phase is the result of a systematic approach that involves determining the optimal settings for the process and gaining an understanding of how much these settings would need to change to result in a non-conforming product. This section is about establishing your operating window and defining what your action limits are.

Within your process there are likely to be number of variable parameters. With injection moulding for example, variables include injection pressures, melt temperatures and injection times and with packaging sealing there are seal temperatures, crimp pressures and crimp times to name but a few. We need to fully understand how the process is going to respond to changes in each of these variables and what the worst case combinations are. If the worst case condition occurs (i.e. at one end of the operating window) are we still going to get acceptable products that form part of a repeatable process? In its simplistic form we can adjust the machine settings to determine at what point the process output stops conforming to the product/design specification. Once we have established where these upper and lower limits lie we have defined the operating window.

We need to have a high level of confidence that any product manufactured within this operating window will provide us with an acceptable output time and time again. To achieve this we need statistical evidence to show the process is capable at its extreme limits.

Sampling Plan

When it comes to determining a sampling plan you should be able to justify why the sample size you have selected is appropriate for the process you are validating. The larger the sample size the more accurate your understanding of the variability will be but naturally the more products you sample the more time and cost there is involved in analysing the data so you need to find a happy medium.

In determining your sample size you need to consider the associated risk level for that process. Thirty samples are often cited as an appropriate sample size but often with very little justification as to why this number has been selected. If you are going to use a sample size of thirty you need to be prepared to justify as to why this is an acceptable number. ISO 2859 ‘Sampling procedures for inspection attributes’ may be a useful reference in helping you to determine a suitable sample size for your process.

Process Capability
Having determined your sample size you can now assess the capability of the process at the extremes of your operating window. A common approach is to assess process capability at nominal settings and at the upper and lower limits. There are a number of process capability indices available; the most commonly used are $C_p$ and $C_{pk}$.

Ideally 100% of everything produced would fall within the limits specified but in reality where variation exists there is always the potential for a product to fall outside of these limits, therefore by looking at a sample of these and using the process capability indices we can determine what the likelihood of this is and whether or not it is at an acceptable level.

There are subtle differences between $C_p$ and $C_{pk}$ and these are described below.

$$C_p = \frac{USL - LSL}{6\sigma}$$

where

- $USL$ = upper specification limit
- $LSL$ = lower specification limit
- $\sigma$ = process standard deviation

$C_p$ will give you information on how well your data is grouped together, the higher the number the tighter the group and therefore the lower the variance. However it doesn’t tell you anything about how well grouped the data is relative to your nominal (centre) value, it may be that everything is falling close to an upper or lower limit. To determine this you need to look at the $C_{pk}$ value.

$$C_{pk} = \text{the lowest value from } USL - x3\sigma \text{ and } x - LSL3\sigma$$

where

- $USL$ = upper specification limit
- $LSL$ = lower specification limit
- $\sigma$ = process standard deviation
- $(x)$ = process mean

If you imagine you are learning to play darts - to start with you will probably find some of the darts hit the board and others totally miss - this would be the equivalent of a process that is not capable. As you start to improve you will get more and more proficient at hitting the board, you may find that every dart hits the board (falls within your specification limits) but are scattered all over the board. This would result in a low $C_p$ value and a low $C_{pk}$ value. As you become more and more consistent and every throw becomes more reproducible you will find the darts start to cluster together. If the darts are clustered towards the edge of the board you would have a high $C_p$ value and
a low $C_{pk}$ value, i.e. within your limits but off centre. When you can repeatedly hit the bulls eye (your nominal value) you have the ideal scenario – a high $C_p$ and $C_{pk}$ value.

Relatively small variations in the $C_{pk}$ values can result in large differences in the number of potential failures. Table 1 below demonstrates the potential number of part per million defects (ppm) produced for a given $C_{pk}$ value.

<table>
<thead>
<tr>
<th>$C_{pk}$</th>
<th>Sigma</th>
<th>ppm defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>1.50</td>
<td>133,614</td>
</tr>
<tr>
<td>1.00</td>
<td>3.00</td>
<td>2,700</td>
</tr>
<tr>
<td>1.16</td>
<td>3.50</td>
<td>465</td>
</tr>
<tr>
<td>1.33</td>
<td>4.00</td>
<td>63</td>
</tr>
<tr>
<td>1.50</td>
<td>4.50</td>
<td>7</td>
</tr>
<tr>
<td>1.60</td>
<td>5.00</td>
<td>0.57</td>
</tr>
<tr>
<td>2.00</td>
<td>6.00</td>
<td>0.002</td>
</tr>
</tbody>
</table>

You will need to determine a target $C_{pk}$ value for your particular device and this will generally be based upon your perceived risk that the non-conforming products may have.

Performing a process capability analysis at both extremes of your operating window should give you confidence that, providing you operate within that window, you have a consistent, repeatable process.

A common mistake is to calculate $C_{pk}$ indices from data that does not have a normal distribution, i.e. does not produce a bell like curve which may result in an unrepresentative $C_{pk}$ result, this risk here is that you approve a process that is not stable.

Another common mistake is to group samples together from a process that is producing several samples simultaneously, e.g. a multi-impression injection mould tool. Each cavity will produce its own variations and therefore should be assessed individually.

As part of the OQ phase it is important to record any unexpected observations and to detail any corrective action or changes that have been made to the process – a fully documented history can prevent the same errors from being made again.

**Performance Qualification (PQ)**
If you have managed to get this far you should now be able to see the light at the end of the tunnel. Rather than assuming that the processing parameters established in the OQ phase will forevermore produce consistent results you need to show documented evidence of this occurring under actual manufacturing conditions. This stage usually involves statistical analysis of data in much the same way as that conducted in the OQ phase and you are checking to ensure that the data remains stable and the process is capable over several machine starts and stops.

This is typically conducted over three batches/production runs but you may wish to consider additional runs for higher risk products. Assuming each batch meets the acceptance criteria and the relevant controls are in place these batches can be treated as saleable products.

As with both the IQ and OQ phase it is important that each stage is fully documented, including any variations and that the activities and the results are conducted, reviewed and approved by those with the necessary authority and training to do so.

**Maintaining a state of validation**

Having successfully validated a process it would be nice to assume that the process could be left alone without any concern of variability creeping in. Unfortunately as tools and equipment age and wear there is potential for the process to drift towards one of the limits and this may result in non-conforming products or an unstable process. A process of continued process verification should be adopted to gain ongoing approval that the process remains in control. One approach is trend data to detect any shifts in the process early on so they can be corrected before non-conforming products are produced.

**Revalidation**

Providing the process does not change and your sample inspection process shows that the manufactured parts are stable there should be no need to revalidate the process. However, should you need to change a process parameter, replace the equipment/machine that is being used then you will need to consider revalidating the process. Any revalidation process or justification for not revalidating should be recorded, reviewed and approved much in the same way as each of the IQ, OQ and PQ stages were.
Conclusion

For any processes involved in the manufacture of a medical device careful consideration needs to be given to determine whether a process of verification or validation is adopted. When process validation is selected a thorough review of the regulatory requirements, in addition to careful planning and implementation is required. Where the skills to support these activities do not exist in house then external specialists should be utilised.

There needs to be mechanisms in place to allow for the review and approval of the validation process at each of the stage gates. Validation records and results need to be maintained as part of the design history file (DHF) and should identify the major equipment used and the date and signature of the person(s) approving the validation activities.

When a process has been successfully validated procedures should be implemented that allow for the monitoring and control of the process.

When there is information to suggest that a process has changed or a number of process deviations are detected then consideration should be given to determine if the process needs to be revalidated.
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