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Process Validation Guidance

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0 Introduction

"Quality Management Systems – Process Validation Guidance", originally finalized in 1999, is being republished as "GHTF/SG3/N99-10:2004 (Edition 2)" after revisions due to the changes in ISO 13485:2003, which is utilized in some regulatory systems. The Process Validation Guidance has been revised in sections 0 through 3.4, Figure 1 and Annex B. The revisions can be generalized in two categories: 1.) Editorial revision of terminology to be consistent with ISO 13485:2003 (i.e., "quality system" to "quality management system" and "design controls" to "design and development controls"), and; 2.) Changes to Figure 1 and the corresponding text to reflect the new process validation requirements found in clause 7.5.2 of ISO 13485:2003.

This process validation guidance is intended to assist manufacturers in understanding quality management system requirements concerning process validation and has general applicability to manufacturing (including servicing and installation) processes for medical devices. The guidance provides general suggestions on ways manufacturers may prepare for and carry out process validations.

Process validation is a term used in the medical device industry to indicate that a process has been subject to such scrutiny that the result of the process (a product, a service or other outcome) can be practically guaranteed. This is vitally important if the predetermined requirements of the product can only be assured by destructive testing.

Processing deficiencies may only become apparent after an intermediate component is further processed or the finished product is in use. Validation of a process entails demonstrating that, when a process is operated within specified limits, it will consistently produce product complying with predetermined (design and development) requirements.

The medical device industry encompasses a wide range of technologies and applications, ranging from simple hand tools to complex computer-controlled surgical machines, from implantable screws to artificial organs, from blood-glucose test strips to diagnostic imaging systems and laboratory test equipment. These devices are manufactured by companies of varied size, structure, volume of production, manufacturing processes and management methods. These factors, especially production volume and number of manufacturing steps per unit (e.g. soldering or welding steps) significantly influence how process validation is actually applied. Given this diversity, this guidance does not suggest particular methods of implementation, and therefore, must not be used to assess compliance with quality management system requirements. Rather the intent is to expand on quality management system requirements with practical explanations and examples of process validation principles. Manufacturers can and should seek out/select technology-specific guidance on applying process validation to their particular situation.

This guidance provides general suggestions on ways manufacturers may prepare for and carry out process validations. Other ways may be equally acceptable; some regulatory requirements place the responsibility on the manufacturer to specify those processes which require validation and the qualification of personnel who operate validated processes. Regardless of the method used to validate the process, records of all validations activities should be kept and the final outcome documented.

While the completion of process validation is a regulatory requirement, a manufacturer may decide to validate a process to improve overall quality, eliminate scrap, reduce costs, improve customer satisfaction, or other reasons. Coupled with properly controlled design and development activities; a validated process may well result in a reduced time to market for new products.

In general, the validation of a process is the mechanism or system used by the manufacturer to plan,

obtain data, record data, and interpret data. These activities may be considered to fall into three phases: 1) an initial qualification of the equipment used and provision of necessary services – also know as installation qualification (IQ); 2) a demonstration that the process will produce acceptable results and establishment of limits (worst case) of the process parameters – also known as operational qualification (OQ); and 3) and establishment of long term process stability – also known as performance qualification (PQ).

Many processes are controlled by computers. While the computer software may be considered an integral part of the process, this guideline does not cover software validation.

While the theory of process validation is reasonably straightforward, the decision of the manufacturer to evaluate every process for potential validation may lead to uncertainty. Some regulatory requirements state that every process that cannot be verified by subsequent monitoring or measurement be validated. Guidance is provided for reaching decisions on whether to validate or not.

1 Purpose and scope

1.1 Purpose This process validation guidance is intended to assist manufacturers in understanding quality management system requirements concerning process validation.

1.2 Scope This document has general applicability to manufacturing (including servicing and installation) processes for medical devices. Specific recommendations for verification of design output and design validation is included in the GHTF document covering design control.

2 Definitions

For this document, the following definitions apply. Terms other than those defined herein may be found in the literature.

2.1 Installation qualification (IQ): establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

2.2 Operational qualification (OQ): establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

2.3 Performance qualification (PQ): establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

2.4 Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

2.5 Process validation protocol: a document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

2.6 Verification: confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

3 Process validation within the quality management system

Process validation is part of the integrated requirements of a quality management system. It is conducted in the context of a system including design and development control, quality assurance, process control, and corrective and preventive action.

The interrelationship of design control and process development may, for some technologies, be very closely related. For others the relationship may be remote. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Often this results in a very interactive product development and process development activity.

Daily measuring and monitoring activities are conducted as specified by the process control plan which is often largely developed during process validation.

Corrective actions often identify inadequate processes/process validations. Each corrective action applied to a manufacturing process should include the consideration for conducting process validation/revalidation.

3.1 Process validation decision

The following model may be useful in determining whether or not a process should be validated:

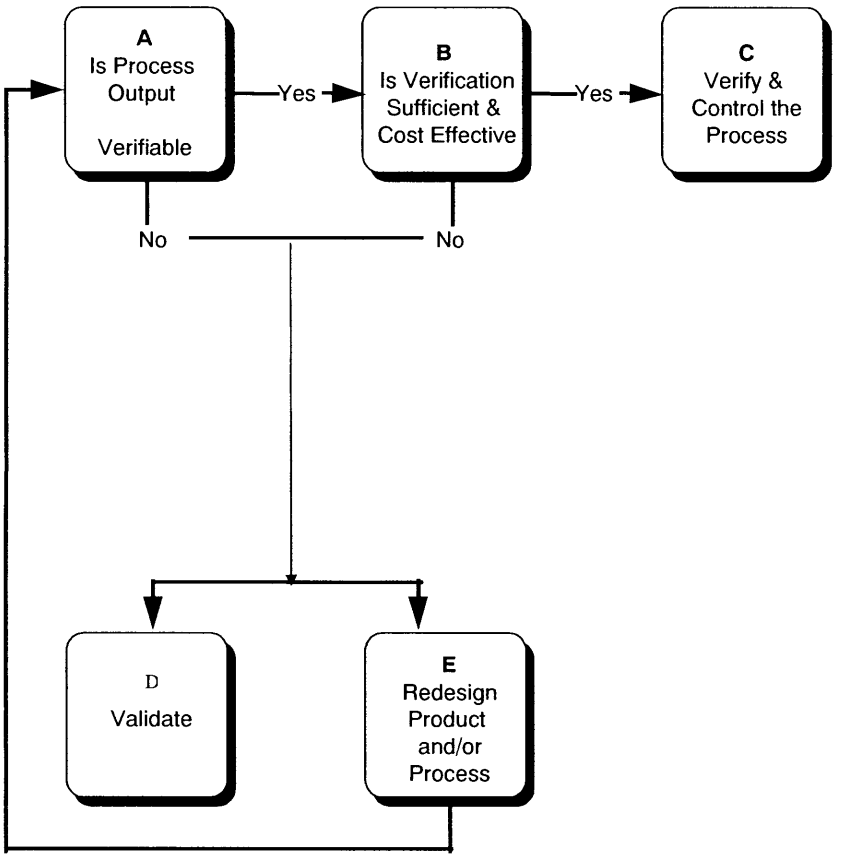

Figure 1: Process validation decision tree

The model shown describes a decision tree that a manufacturer can follow when deciding on whether a process needs to be validated. The process under consideration in this model is the simplest possible - many processes may be large and/or a complex set of sub-processes.

Each process should have a specification describing both the process parameters and the output desired. The manufacturer should consider whether the output can be verified by subsequent monitoring or measurement (**A**). If the answer is positive, then the consideration should be made as to whether or not verification alone is sufficient to eliminate unacceptable risk and is a cost effective solution (**B**). If yes, the output should be verified and the process should be appropriately controlled (**C**).

If the output of the process is not verifiable then the decision should be to validate the process (**D**); alternatively, it may become apparent that the product or process should be redesigned to reduce variation and improve the product or process (**E**). Also, a change in a manufacturing process may result in the need for process validation even though the process formerly only required verification and control.

The risk or cost may also be reduced by redesigning the product or process to a point where simple verification is an acceptable decision (**E**).

3.2 Examples

The following table is a list of examples of processes which: (1) should be validated, (2) may be satisfactorily covered by verification, and (3) processes which may be verifiable, but for business purposes, validation can be chosen.

(1) Processes which should be validated

- Sterilization processes
- Clean room ambient conditions
- Aseptic filling processes
- Sterile packaging sealing processes
- Lyophilization process
- Heat treating processes
- Plating processes
- Plastic injection molding processes

(2) Processes which may be satisfactorily covered by verification

- Manual cutting processes
- Testing for color, turbidity, total pH for solutions
- Visual inspection of printed circuit boards
- Manufacturing and testing of wiring harnesses

(3) Processes for which the above model may be useful in determining the need for validation

- Certain cleaning processes
- Certain human assembly processes
- Numerical control cutting processes
- Certain filling processes

While the output of a process may be verifiable, application of software used in that process should be validated for its intended use.

4 Statistical methods and tools for process validation

There are many methods and tools that can be used in process validation. A primer on statistics and process validation is provided in **Annex A** as a guide through the basic concepts. Control charts, capability studies, designed experiments, tolerance analysis, robust design methods, failure modes and effects analysis, sampling plans, and mistake proofing are some of the examples.

5 Conduct of a validation

5.1 Getting started

A consideration should be given to form a multi-functional team to plan and oversee the validation activities. A team approach will help assure the validation processes are well thought out, the protocols are comprehensive and that the final packages are well documented and easy to follow. The team should advise "what could go wrong". The team also provides an opportunity for key functional areas to communicate early about important new and changed products and processes and can foster cooperation.

Members of the validation team could include representatives from or personnel with expertise in:

- Quality Assurance
- Engineering
- Manufacturing
- Others depending on company organization and product types:
  - Laboratory
  - Technical Services
  - Research & Development
  - Regulatory Affairs
  - Clinical Engineering
  - Purchasing/Planning

Once the validation team has been formed, the next step is to plan the approach and define the requirements. Many manufacturers develop what is referred to as a master validation plan which identifies those processes to be validated, the schedule for validations, interrelationships between processes requiring validation and timing for revalidations. Once these have been established, and the purpose and scope for validations are clearly stated and known, protocol development can commence.

Following is a list of activities which may be used as a checklist to review validation activity:

- Form multi-functional team for validation
- Plan the approach and define the requirements
- Identify and describe the processes
- Specify process parameters and desired output
- Decide on verification and/or validation
- Create a master validation plan
- Select methods and tools for validation
- Create validation protocols
- Perform IQ, OQ, PQ and document results
- Determine continuous process controls

- Control the process continuously

5.2 Protocol development

Detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

- Identification of the process to be validated
- Identification of device(s) to be manufactured using this process
- Objective and measurable criteria for a successful validation
- Length and duration of the validation
- Shifts, operators, equipment to be used in the process
- Identification of utilities for the process equipment and quality of the utilities
- Identification of operators and required operator qualification
- Complete description of the process
- Relevant specifications that relate to the product, components, manufacturing materials, etc.
- Any special controls or conditions to be placed on preceding processes during the validation
- Process parameters to be monitored, and methods for controlling and monitoring
- Product characteristics to be monitored and method for monitoring
- Any subjective criteria used to evaluate the product
- Definition of what constitutes non-conformance for both measurable and subjective criteria
- Statistical methods for data collection and analysis
- Consideration of maintenance and repairs of manufacturing equipment
- Criteria for revalidation

For all three phases, IQ, OQ, and PQ, based on product/process requirements:

- Determine <u>what</u> to verify/measure
- Determine <u>how</u> to verify/measure
- Determine <u>how many</u> to verify/measure, i.e. statistical significance
- Determine when to verify/measure
- Define acceptance/rejection criteria
- Define required documentation

Knowing exactly what the product requirements are and what key parameters will be necessary to answer the questions of what to measure. Seal thickness, seal strength, pressure testing and visual defects of samples are examples of measurable parameters.

Utilizing statistically valid techniques such as sampling, design experiments, Taguchi methods, response surface studies and component swapping are statistically valid techniques to answer the questions of how many to measure. Utilization of standard test methods such as such as those contained in international or national standards will provide guidance in how to measure specific parameters. Also, it is important to ensure test methods replicate actual use conditions.

During the conduct of various phases of validation, the protocol should address the resolution of discrepancies. Some deviations in established protocol may not negate the results. Each deviation should be addressed, evaluated and a conclusion drawn as to acceptance or rejection of the results. As a result, process control procedures may require modification and those modifications should be validated as part of the overall process.

Addressing all product and process requirements and the establishment of specific criteria for each requirement, upper and lower limits based on product specifications and established standards will help define the acceptance/rejection criteria.

5.3 Installation qualification (IQ)

Simply put, IQ means is it installed correctly? Important IQ considerations are:

- Equipment design features (i.e. materials of construction cleanability, etc.)
- Installation conditions (wiring, utilities, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules
- Safety features
- Supplier documentation, prints, drawings and manuals
- Software documentation
- Spare parts list
- Environmental conditions (such as clean room requirements, temperature, humidity)

Sometimes activities are conducted at the equipment supplier's site location prior to equipment shipment. Equipment suppliers may perform test runs at their facilities and analyze the results to determine that the equipment is ready to be delivered. Copies of the suppliers' qualification studies should be used as guides, to obtain basic data, and to supplement installation qualification. However, it is usually insufficient to rely solely upon the validation results of the equipment supplier. Each medical device manufacturer is ultimately responsible for evaluating, challenging, and testing the equipment and deciding whether the equipment is suitable for use in the manufacture of a specific device(s). The evaluations may result in changes to the equipment or process.

5.4 Operational qualification - (OQ)

In this phase the process parameters should be challenged to assure that they will result in a product that meets all defined requirements under all anticipated conditions of manufacturing, i.e., worst case testing. During routine production and process control, it is desirable to measure process parameters and/or product characteristics to allow for the adjustment of the manufacturing process at various action level(s) and maintain a state of control. These action levels should be evaluated, established and documented during process validation to determine the robustness of the process and ability to avoid approaching "worst case conditions."

OQ considerations include:

- Process control limits (time, temperature, pressure, linespeed, setup conditions, etc.)
- Software parameters
- Raw material specifications
- Process operating procedures
- Material handling requirements
- Process change control
- Training
- Short term stability and capability of the process, (latitude studies or control charts)
- Potential failure modes, action levels and worst-case conditions (Failure Mode and Effects Analysis, Fault Tree Analysis)

- The use of statistically valid techniques such as screening experiments to establish key process parameters and statistically designed experiments to optimize the process can be used during this phase.

5.5 Performance qualification - (PQ)

In this phase the key objective is to demonstrate the process will consistently produce acceptable

product under normal operating conditions. Please note the guidance for process stability in Annexes A and B "Methods and tools for process validation".

PQ considerations include:

- Actual product and process parameters and procedures established in OQ
- Acceptability of the product
- Assurance of process capability as established in OQ
- Process repeatability, long term process stability

Challenges to the process should simulate conditions that will be encountered during actual manufacturing. Challenges should include the range of conditions as defined by the various action levels allowed in written standard operating procedures as established in the OQ phase. The challenges should be repeated enough times to assure that the results are meaningful and consistent.

Process and product data should be analyzed to determine what the normal range of variation is for the process output. Knowing the normal variation of the output is crucial in determining whether a process is operating in a state of control and is capable of consistently producing the specified output.

One of the outputs of OQ and PQ is the development of attributes for continuous monitoring and maintenance. Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- Temperature
- Humidity
- Variations in electrical supply
- Vibration
- Environmental contaminants
- Purity of process water
- Light
- Human factors (training, ergonomic factors, stress, etc.)
- Variability of materials
- Wear and tear of equipment

Appropriate measures should be taken to eliminate controllable causes of variation. Eliminating controllable causes of variation will reduce variation in the process output and result in a higher degree of assurance that the output will consistently meet specifications.

5.6 Final report

At the conclusion of validation activities, a final report should be prepared. This report should summarize and reference all protocols and results. It should derive conclusions regarding the validation status of the process. The final report should be reviewed and approved by the validation team and appropriate management.

6 Maintaining a state of validation

6.1 Monitor and control

Trends in the process should be monitored to ensure the process remains within the established

parameters. When monitoring data on quality characteristics demonstrates a negative trend, the cause should be investigated, corrective action may be taken and revalidation considered.

6.2 Changes in processes and/or product

Any changes in the process and /or product including changes in procedures, equipment, personnel, etc. should be evaluated to determine the affects of those changes and the extent of revalidation considered.

6.3 Continued state of control

Various changes may occur in raw materials and/or processes, which are undetected, or considered at the time to be inconsequencial. (An example of this type of process is sterilization.) These changes may cumulatively affect the validation status of the process. Periodic revalidation should be considered for these types of processes.

6.4 Examples of reasons for revalidation

Revalidation may be necessary under such conditions as:

- change(s) in the actual process that may affect quality or its validation status
- negative trend(s) in quality indicators
- change(s) in the product design which affects the process
- transfer of processes from one facility to another
- change of the application of the process

The need for revalidation should be evaluated and documented. This evaluation should include historical results from quality indicators, product changes, process changes, changes in external requirements (regulations or standards) and other such circumstances.

Revalidation may not be as extensive as the initial validation if the situation does not require that all aspects of the original validation be repeated. If a new piece of equipment is purchased for a validated process, obviously the IQ portion of the validation needs to be repeated. However, most of the OQ aspects are already established. Some elements of PQ may need to be repeated, depending on the impact of the new equipment.

Another example might be if a raw material supplier is changed, the impact of that change on the process and resultant product should be considered. Parts of OQ and PQ might need to be redone, as the interaction between the new raw material and the process may not be fully understood.

7 Use of historical data for validation

Validation of a process can be partially based on accumulated historical manufacturing, testing, control, and other data related to a product or process. This historical data may be found in batch records, manufacturing log books, lot records, control charts, test and inspection results, customer feedback, field failure reports, service reports, and audit reports. A complete validation based on historical data is not feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis. Historical manufacturing data of a pass/fail nature is usually not adequate.

If historical data is determined to be adequate and representative, an analysis can be conducted per a

written protocol to determine whether the process has been operating in a state of control and has consistently produced product which meets its predetermined requirements. The analysis should be documented.

The terms "retrospective validation", "concurrent validation" and "prospective validation" are often used. Any validation can use historical data in the manner described above, regardless of the term used.

8 Summary of activities

Initial considerations include:

- Identify and describe the processes
- Decide on verification and/or validation
- Create a master validation plan

If the decision is to validate:

- Form multi-functional team for validation
- Plan the approach and define the requirements
- Identify and describe the processes
- Specify process parameters and desired output
- Create a master validation plan
- Select methods and tools for validation
- Create validation protocols
- Perform IQ, OQ, PQ and document results
- Determine continuous process controls
- Prepare final report and secure management approval
- Control the process continuously

Maintaining a state of validation:

- Monitor and control the process continuously
- Revalidate as appropriate

Annex A Statistical methods and tools for process validation

A.1 Introduction

Process validation requires that a process is established that can consistently conform to requirements and then studies are conducted demonstrating that this is the case. Process development and optimization may lead directly to the validation of the process. In other words, the methods for developing and optimizing a process may be used (and the data developed) to demonstrate process capability and stability. Thus there is often not a clear distinction between process development and process validation.

However, many processes are well established and subject to routine process validation. Many of the methods and tools described here may already be used for these processes. As validation methods and tools are reviewed for existing processes, some of these may be helpful to improve validation protocols and improve processes.

This annex describes the many contributions that statistical methods and tools can make to validation. Each tool appearing in bold is further described in **Annex A.3**.

Nonconformities often occur because of errors made and because of excessive variation. Obtaining a process that consistently conforms to requirements requires a balanced approach using both mistake proofing and variation reduction tools. When a nonconformance occurs because of an error, **mistake proofing methods** should be used. Mistake proofing attempts to make it impossible for the error to occur or at least to go undetected.

However, many nonconformities are not the result of errors, instead they are the result of excessive variation and off-target processes. Reducing variation and proper targeting of a process requires identifying the key input variables and establishing controls on these inputs to ensure that the outputs conform to requirements.

One output of process validation is the development of a control plan. The final phase of validation requires demonstrating that this control plan works, i.e., that it results in a process that can consistently conform to requirements. One key tool here is a **capability study**. A capability study measures the ability of the process to consistently meet the specifications. It is appropriate for measurable characteristics where nonconformities are due to variation and off-target conditions. Testing should be performed not only at nominal, but also under worst-case conditions. In the event of potential errors, **challenge tests** should be performed to demonstrate that mistake proofing methods designed to detect or prevent such errors are working. **Acceptance sampling plans** can be useful in optimizing the number of samples to be tested and to demonstrate conformance to specification.

A.2 Primer on statistics and process validation

Each unit of product differs to some small degree from all other units of product. These differences, no matter how small, are referred to as variation. Variation can be characterized by measuring a sample of the product and drawing a histogram. For example, one operation involves cutting wire into 100 cm lengths. The tolerance is 100 ± 5 cm. A sample of 12 wires is selected at random and the following results obtained:

98.7	99.3	100.4	97.6	101.4	102.0
100.2	96.4	103.4	102.0	98.0	100.5

A histogram of this data is shown below. The width of the histogram represents the variation.

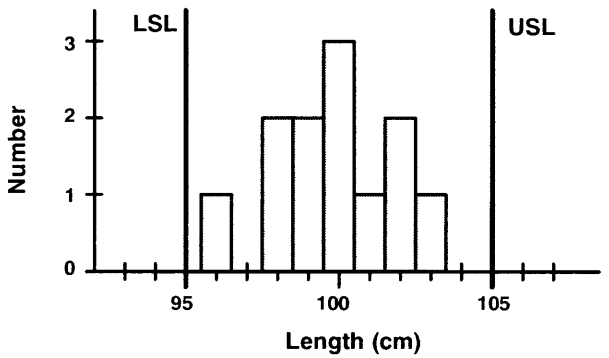

Figure 2: Histogram of data

Of special interest is whether the histogram is properly centered and whether the histogram is narrow enough to easily fit within the specification limits. The center of the histogram is estimated by calculating the average of the 12 readings. The average is 99.99 cm. The width of the histogram is estimated by calculating either the range or standard deviation. The range of the above readings is 7.0 cm. The standard deviation is 2.06 cm. The standard deviation represents the typical distance a unit is from the average. Approximately half of the units are within ±1 standard deviation of the average and about half of the units are more than one standard deviation away from the average. On the other hand, the range represents an interval containing all the units. The range is typically 3 to 6 times the standard deviation.

Frequently, histograms take on a bell-shaped appearance that is referred to as the normal curve as shown below. For the normal curve, 99.73% of the units fall within ± 3 standard deviations of the average.

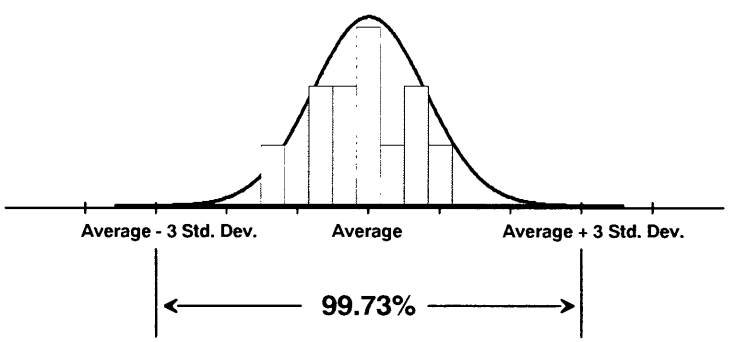

Figure 3: Normal curve applied to histogram

For measurable characteristics like wire length, fill volume, and seal strength, the goal is to optimize the average and reduce the variation. Optimization of the average may mean to center the process as in the case of fill volumes, to maximize the average as is the case with seal strengths, or to minimize the average as is the case with harmful emissions. In all cases, variation reduction is also required to ensure all units are within specifications. Reducing variation requires the achievement of stable and capable processes. Figure 4 shows an unstable process. The process is constantly changing. The average shifts up and down. The variation increases and decreases. The total variation increases due to the shifting.

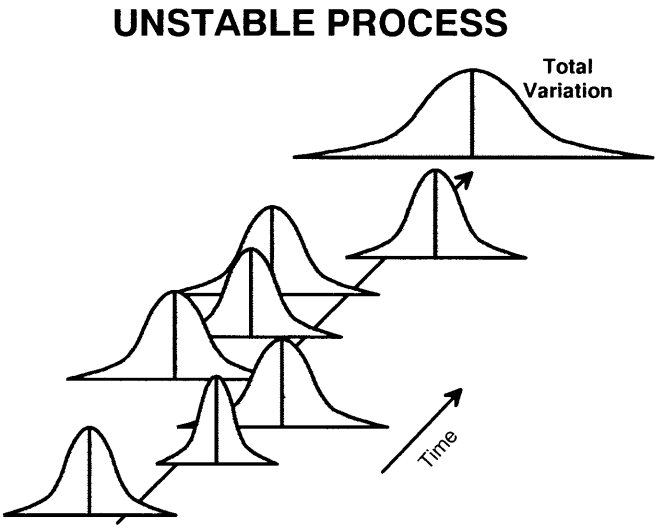

Figure 4: Unstable process

Instead, stable processes are desired as shown in figure 5. Stable processes produce a consistent level of performance. The total variation is reduced. The process is more predictable.

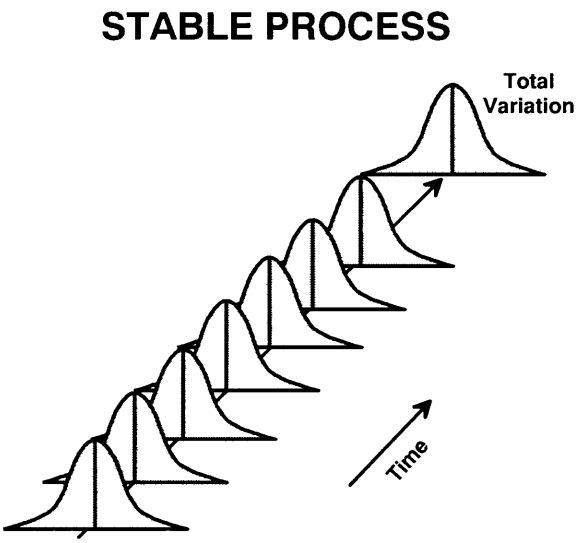

Figure 5: Stable process

However, stability is not the only thing required. Once a consistent performance has been achieved, the remaining variation must be made to safely fit within the upper and lower specification limits. Such a process is then said to be stable and capable. Such a process can be relied on to consistently produce good product as illustrated in figure 6.

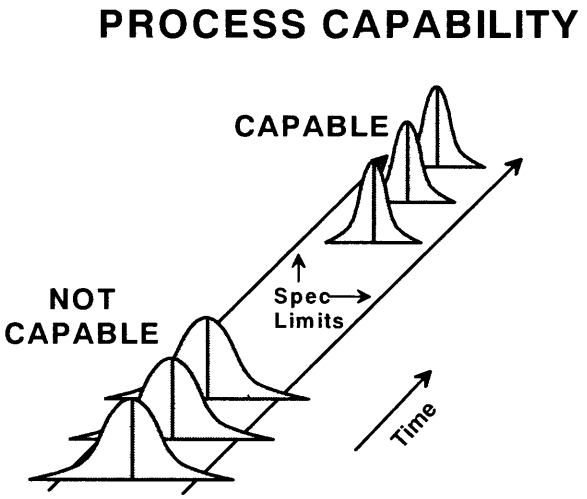

Figure 6: Process capability

A **capability study** is used to determine whether a process is stable and capable. It involves collecting samples over a period of time. The average and standard deviation of each time period is estimated and these estimates plotted in the form of a **control chart**. These **control charts** are used to determine if the process is stable. If it is, the data can be combined into a single histogram to determine its capability. To help determine if the process is capable, several capability indices are used to measure how well the histogram fits within the specification limits. One index called C_p is used to evaluate the variation. Another index C_{pk} is used to evaluate the centering of the process. Together these two indices are used to decide whether the process meets its requirements. The values required to pass depend on the severity of the defect (major, minor, critical) that the manufacturer considers acceptable.

While capability studies evaluate the ability of a process to consistently produce good product, these studies do little to help achieve such processes. Reducing variation and the achievement of stable processes requires the use of numerous variation reduction tools. Variation of the output is caused by variation of the inputs. Consider the example of a simple system, such as a pump for moving fluids:

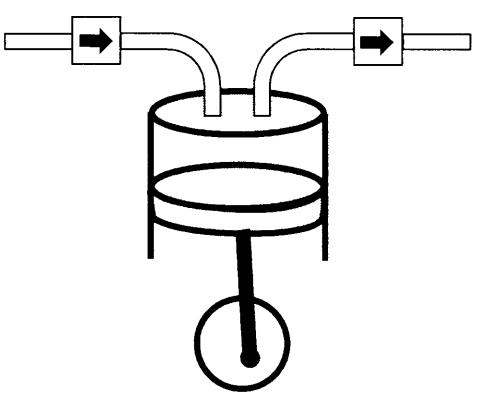

Figure 7: The pump

An output is flow rate. The pump uses a piston to draw a fluid into a chamber through one opening and then pushes it back out another opening. Valves are used to keep the fluid moving in the right direction. Flow rate will be affected by piston radius, stroke length, motor speed and valve backflow to name a few. The target flow rate is achieved by designing the piston radius, stroke length, motor speed, etc. The actual flow rate will vary due to variation in wear of the piston, wear of the bearings, wear of the valves, variation of the motor speed, temperature/viscosity of the fluid, etc. Variation of the inputs is transmitted to the output as shown below.

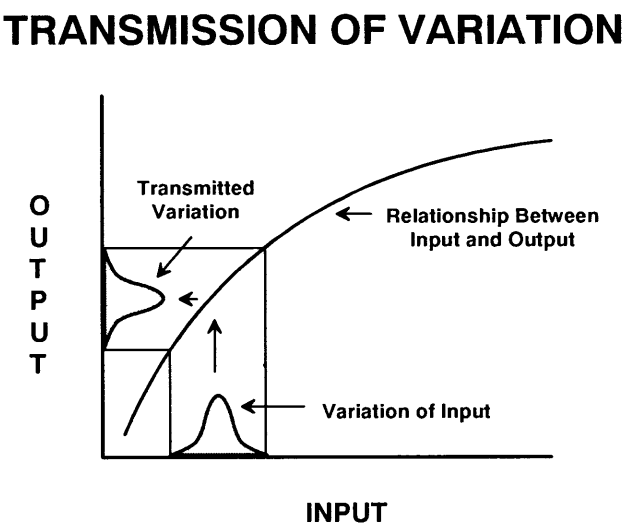

Figure 8: Transmission of variation

Reducing variation requires identifying the key input variables affecting the outputs, designing the process to take advantage of relative input sensitivities (the relationships between cylinder radius, stroke length, motor speed and output) and establishing controls on input variation (wear, motor speed, temperature/viscosity, etc.) to ensure that the outputs conform to their established specifications. In general one should, identify the key input variables, understand the effect of these inputs on the output, understand how the inputs behave and finally, use this information to establish targets (nominals) and tolerances (windows) for the inputs. Various techniques can be used.

One type of designed experiment called a **screening experiment** can be used to identify the key inputs. Another type of designed experiment called a **response surface study** can be used to obtain a detailed understanding of the effects of the key inputs on the outputs. **Capability studies** can be used to understand the behavior of the key inputs. Armed with this knowledge, **robust design methods** can be used to identify optimal targets for the inputs and **tolerance analysis** can be used to establish operating windows or control schemes that ensure the output consistently conforms to requirements.

The obvious approach to reducing variation is to tighten tolerances on the inputs. This improves quality but generally drives up costs. The robust design methods provide an alternative. Robust design works by selecting targets for the inputs that make the outputs less sensitive (more robust) to the variation of the inputs as shown below. The result is less variation and higher quality but without the added costs. Several approaches to robust design exist including **Taguchi methods**, **dual response approach** and **robust tolerance analysis**.

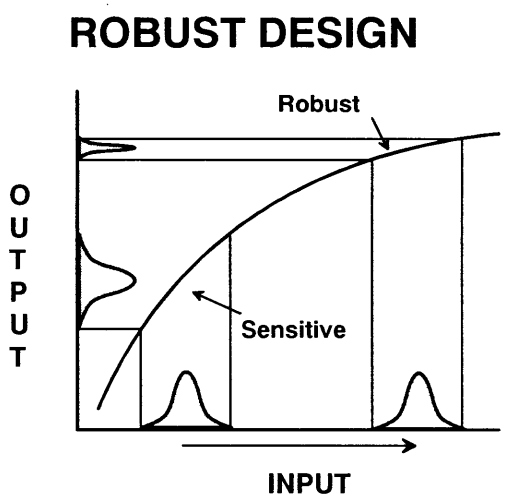

Figure 9: Robust design

Another important tool is a **control chart**.

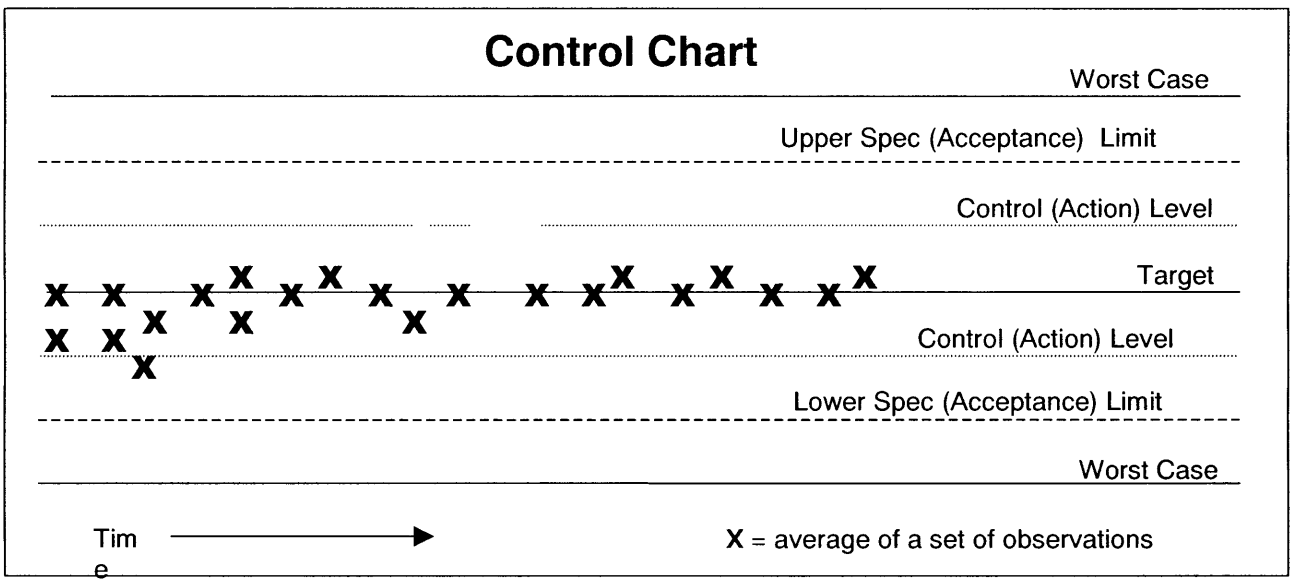

Figure 10: Control Chart

By monitoring the results of changes of inputs through control charting, the resultant variation in output can be determined and inherent variation of the process identified. Ultimately, control charting may be used to continuously monitor the process and assure a state of validated control. Control or action levels can be determined to adjust the process and maintain the process within the control limits.

Many other tools also exist for identifying key inputs and sources of variation including **component swapping studies**, **multi-vari charts**, **analysis of means** (ANOM), and **variance components analysis**, and **analysis of variance** (ANOVA).

When studying variation, good measurements are required. Many times an evaluation of the measurement system should be performed using a **gauge R&R** or similar study.

A.3 Descriptions of the tools

A brief description of each of the cited tools follows:

Acceptance Sampling Plan – An acceptance sampling plan takes a sample of product and uses this sample to make an accept or reject decision. Acceptance sampling plans are commonly used in manufacturing to decide whether to accept (release) or to reject (hold) lots of product. However, they can also be used during validation to accept (pass) or to reject (fail) the process. Following the acceptance by a sampling plan, one can make a confidence statement such as: "With 95% confidence, the defect rate is below 1% defective."

Analysis of Means (ANOM) – Statistical study for determining if significant differences exist between cavities, instruments, etc. It has many uses including determining if a measurement device is reproducible with respect to operators and determining if differences exists between fill heads, etc. Simpler and more graphical alternative to Analysis of Variance (ANOVA).

Analysis of Variance (ANOVA) – Statistical study for determining if significant differences exist between cavities, instruments, etc. Statistically, this is defined as a methodology for evaluating the results of factorial experiments designed to determine the relative influence of the factors and interactions which cause variation in a process. Alternative to Analysis of Means (ANOM).

Capability Study – Capability studies are performed to evaluate the ability of a process to consistently meet a specification. A capability study is performed by selecting a small number of units periodically over time. Each period of time is called a subgroup. For each subgroup, the average and range is calculated. The averages and ranges are plotted over time using a control chart to determine if the process is stable or consistent over time. If so, the samples are then combined to determine whether the process is adequately centered and the variation is sufficiently small. This is accomplished by calculating capability indexes. The most commonly used capability indices are C_p and C_{pk}. If acceptable values are obtained, the process consistently produces product that meets the specification limits. Capability studies are frequently used towards the end of the validation to demonstrate that the outputs consistently meet the specifications. However, they can also be used to study the behavior of the inputs in order to perform a tolerance analysis.

Challenge Test – A challenge test is a test or check performed to demonstrate that a feature or function is working. For example, to demonstrate that the power backup is functioning, power could be cut to the process. To demonstrate that a sensor designed to detect bubbles in a line works, bubbles could be purposely introduced.

Component Swapping Study – Study to isolate the cause of a difference between two units of product or two pieces of equipment. Requires the ability to disassemble units and swap components in order to determine if the difference remains with original units or moves with the swapped components.

Control Chart – Control charts are used to detect changes in the process. A sample, typically consisting of 5 consecutive units, is selected periodically. The average and range of each sample is calculated and plotted. The plot of the averages is used to determine if the process average changes. The plot of the ranges is used to determine if the process variation changes. To aid in determining if a change has occurred, control limits are calculated and added to the plots. The control limits represent the maximum amount that the average or range should vary if the process does not change. A point outside the control limits indicates that the process has changed. When a change is identified by the control chart, an investigation should be made as to the cause of the change. Control charts help to identify key input variables causing the process to shift and aid in the reduction of the variation. Control charts are also used as part of a capability study to demonstrate that the process is stable or consistent.

Designed Experiment (Design of Experiments or DOE) – The term designed experiment is a general term that encompasses screening experiments, response surface studies, and analysis of variance. In general, a designed experiment involves purposely changing one or more inputs and measuring resulting effect on one or more outputs.

Dual Response Approach to Robust Design – One of three approaches to robust design. Involves running response surface studies to model the average and variation of the outputs separately. The results are then used to select targets for the inputs that minimize the variation while centering the average on the target. Requires that the variation during the study be representative of long term manufacturing. Alternatives are Taguchi methods and robust tolerance analysis.

Failure Modes and Effects Analysis (FMEA) – An FMEA is systematic analysis of the potential failure modes. It includes the identification of possible failure modes, determination of the potential causes and consequences and an analysis of the associated risk. It also includes a record of corrective actions or controls implemented resulting in a detailed control plan. FMEAs can be performed on both the product and the process. Typically an FMEA is performed at the component level, starting with potential failures and then tracing up to the consequences. This is a bottom up approach. A variation is a Fault Tree Analysis, which starts with possible consequences and traces down to the potential causes. This is the top down approach. An FMEA tends to be more detailed and better at identifying potential problems. However, a fault tree analysis can be performed earlier in the design process before the design has been resolved down to individual components.

Fault Tree Analysis (FTA) – A variation of a failure analysis. See FMEA for a comparison.

Gauge R&R Study – Study for evaluating the precision and accuracy of a measurement device and the reproducibility of the device with respect to operators.

Mistake Proofing Methods – Mistake proofing refers to the broad array of methods used to either make the occurrence of a defect impossible or to ensure that the defect does not pass undetected. The Japanese refer to mistake proofing as Poka-Yoke. The general strategy is to first attempt to make it impossible for the defect to occur. For example, to make it impossible for a part to be assembled backwards, make the ends of the part different sizes or shapes so that the part only fits one way. If this is not possible, attempt to ensure the defect is detected. This might involve mounting a bar above a chute that will stop any parts that are too high from continuing down the line. Other possibilities include mitigating the effect of a defect (seat belts in cars) and to lessen the chance of human errors by implementing self-checks.

Multi-Vari Chart – Graphical procedure for isolating the largest source of variation so that further efforts concentrate on the largest source of variation.

Response Surface Study – A response surface study is a special type of designed experiment whose purpose is to model the relationship between the key input variables and the outputs. Performing a response surface study involves running the process at different settings for the inputs, called trials,

and measuring the resulting outputs. An equation can then be fit to the data to model the affects of the inputs on the outputs. This equation can then be used to find optimal targets using robust design methods and to establish targets or operating windows using a tolerance analysis. The number of trials required by a response surface study increases exponentially with the number of inputs. It is desirable to keep the number of inputs studied to a minimum. However, failure to include a key input can compromise the results. To ensure that only the key input variables are included in the study, a screening experiment is frequently performed first.

Robust Design Methods – Robust design methods refers collectively to the different methods of selecting optimal targets for the inputs. Generally, when one thinks of reducing variation, tightening tolerances comes to mind. However, as demonstrated by Taguchi, variation can also be reduced by the careful selection of targets. When nonlinear relationships exist between the inputs and the outputs, one can select targets for the inputs that make the outputs less sensitive to the inputs. The result is that while the inputs continue to vary, less of this variation is transmitted to the output. The result is that the output varies less. Reducing variation by adjusting targets is called robust design. In robust design the objective is to select targets for the inputs that result in on-target performance with minimum variation. Several methods of obtaining robust designs exist including robust tolerance analysis, dual response approach and Taguchi methods.

Robust Tolerance Analysis – One of three approaches to robust design. Involves running a designed experiment to model the output's average and then using the statistical approach to tolerance analysis to predict the output's variation. Requires estimates of the amounts that the inputs will vary during long-term manufacturing. Alternatives are Taguchi methods and robust tolerance analysis.

Screening Experiment – A screening experiment is a special type of designed experiment whose primary purpose is to identify the key input variables. Screening experiments are also referred to as fractional factorial experiments or Taguchi L-arrays. Performing a screening experiment involves running the process at different settings for the inputs, called trials, and measuring the resulting outputs. From this, it can be determined which inputs affect the outputs. Screening experiments typically require twice as many trials as input variables. For example, 8 variables can be studied in 16 trials. This makes it possible to study a large number of inputs in a reasonable amount of time. Starting with a larger number of variables reduces the chances of missing an important variable. Frequently a response surface study is performed following a screening experiment to gain further understanding of the affects of the key input variables on the outputs.

Taguchi Methods – One of three approaches to robust design. Involves running a designed experiment to get a rough understanding of the effects of the input targets on the average and variation. The results are then used to select targets for the inputs that minimize the variation while centering the average on the target. Similar to the dual response approach except that while the study is being performed, the inputs are purposely adjusted by small amounts to mimic long-term manufacturing variation. Alternatives are the dual response approach and robust tolerance analysis.

Tolerance Analysis – Using tolerance analysis, operating windows can be set for the inputs that ensure the outputs will conform to requirements. Performing a tolerance analysis requires an equation describing the effects of the inputs on the output. If such an equation is not available, a response surface study can be performed to obtain one. To help ensure manufacturability, tolerances for the inputs should initially be based on the plants and suppliers ability to control them. Capability studies can be used to estimate the ranges that the inputs currently vary over. If this does not result in an acceptable range for the output, the tolerance of at least one input must be tightened. However, tightening a tolerance beyond the current capability of the plant or supplier requires that improvements be made or that a new plant or supplier be selected. Before tightening any tolerances, robust design methods should be considered.

Variance Components Analysis – Statistical study used to estimate the relative contributions of

several sources of variation. For example, variation on a multi-head filler could be the result of shifting of the process average over time, filling head differences and short-term variation within a fill head. A variance components analysis can be used to estimate the amount of variation contributed by each source.

Annex B Example validation

Foreword

Heat sealing processes, as described in this example, use equipment to seal plastic pouches which perform as sterility barriers for disposable medical devices. Seal integrity is crucial for maintenance of sterility. Testing of seal integrity is usually destructive testing, and the process therefor is a special process which requires validation.

This Annex is presented only to give a simple and brief example of the nature of a process validation. The heat seal process described should not be considered a model for all heat seal validations. Additionally, this example may be modified according to different quality management systems, documentation methods and cultures of regions and/or countries which use this guidance.

There are many other circumstances and variables that might be considered when validating an actual heat seal process. This example uses only three simple input variables: time, temperature and pressure. There may be many more input variables, such as operator training, material thickness and melt indexes of the plastic pouches. Additionally, all the details surrounding the rationale for specific sample sizes, control limits, etc. are not given.

ABC Medical Device Company
Process Validation Protocol
PVP 98-101

Title: Heat Sealer Validation

Products to be covered: Sterile Gizmos – Codes 12345 through 12789

Equipment/Process to be Validated: Supplier Co., Model xyz, ABC Manufacturing Equipment Register: MER 98-1248 / Heat Sealing Process: SOP 20-12-14

Process/Product Change Control Number: PPCN 98-364

Objective:

Supplier Co. has developed a new and improved heat sealer, which should improve process flow and reduce setup time. The heat sealer will be validated to assure it performs with existing sterile barrier pouch materials and existing process procedure SOP 20-12-14. SOP 20-12-14 identifies a design requirement for a seal strength of 2 to 4 kg and a target of 3 kg. The most difficult pouches to seal are the smallest (PN 96-122) and the largest (PN 88-010). The target process capability is a C_{pk} of >1.

Reference Documents:
1. Heat Seal Process Procedure, SOP 20-12-14
2. Statistical Methodologies, SOP 3-8-51, SOP 3-9-12, SOP 3-13-81
3. Master Device Records, Codes 12xxx
4. Manufacturing Equipment Register, MER 98-1248
5. Supplier Co. Model xyz Heat Sealer Operating Manual
6. Process Validation Master Plan: PVP-98001
7. Lab Processes and Calibration: SOP 9-2-5
8. Production Processes and Calibration: SOP 20-1-2
9. Clean Room Procedures: SOP 1-12-77

Validation Plan:

The Supplier Co. Model xyz Heat Sealer will be subjected to the Installation Qualification, Operational Qualification and Performance Qualification procedures outlined in the Master Validation Plan: PVP-98001. Statistical methods in SOP 3-x-x will be used as appropriate.

The Installation Qualification will utilize the heat sealer operating manual to define requirements for electrical and air pressure requirements. The heat sealer will be installed, checked and calibrated in Clean Room 3 during a weekend, before the weekend scrub-down. Particular attention will be paid to the exhaust of pressurized air into the clean room, so that the requirement for integrity of the environment is not compromised. A checklist of requirements will be completed and results approved.

Operational Qualification will be completed in three phases. First, during production down time, the heat sealer will be subjected to an initial burn-in to observe the stability of the measurements of clamp closure time, temperature build and pressures. Pouches will be sealed, but detailed assessments of seal integrity will not be completed. Data for clamp closure time, temperature build and pressures will be recorded. Variations in these measures will be subjected to a screening experiment (SOP 3-8-51) to determine possible worst case situations and the risk of weak seals or overburning of the pouches. Initial optimal heat seal settings will also be established.

The second phase of operational qualification will center the process and determine initial process

capability. The process will be conducted off line, but during production, in the clean room and with production personnel. Production personnel will be trained on the use of the new heat sealer. Heat seals will be completed for pouches PN 96-122 and PN 88-010. Heat sealer settings for the time, temperature and pressure will be used which were determined to be optimal during the initial phase of operational qualification. Accelerated sampling plan 1-A from SOP 3-9-12 will be used and the results control charted. The seal strength target result will be 3 kg and the variation monitored. The number of runs, samples and evaluations will continue until it is determined that the C_p is >1 per SOP 3-13-81. Optimal heat sealer settings will be determined for the next phase.

The third phase of operational qualification will determine the sensitivity of the process to variations in time, temperature and pressure. The normal production process will be used. Production personnel will be trained on the use of the new heat sealer. Worst case combinations of time, temperature and pressure will be evaluated. Runs will be completed 1) with the optimal settings, 2) with a short dwell time, low temperature and low pressure; and 3) long dwell time, high temperature and high pressure. Action levels for adjustment of the heat sealer will be determined as a result of this phase.

Performance qualification will commence after satisfactory completion of operational qualification. Optimal settings for the heat sealer will be used and the heat seal action levels for adjustment of time, temperature and pressure will be used. Accelerated sampling plan 2-C from SOP 3-9-12 will be used and the results control charted. Variations in seal strength will be investigated and root causes determined. When process stability is demonstrated, and the process variation demonstrates a value of $C_{pk} > 1$ per SOP 3-13-81, the process will be considered validated and SOP 20-12-14 will be used to control the process.

Measurement / Testing Equipment and Calibration:

1. Stopwatch, Process Development Lab, Calibrated per SOP 9-2-5
2. Remote IR Thermometer RST-12, Process Development Lab, Calibrated per SOP 9-2-5
3. Pressure gauge, 0 – 500kPa, Process Development Lab, Calibrated per SOP 9-2-5
4. VAR meter, ID 683, Process Development Lab, Calibrated per SOP 9-2-5
5. Heat Seal Pull Tester, PE 8167, Production, Calibrated per SOP 20-1-2

Equipment Maintenance:

During validation the heat sealer will be maintained per the Supplier Co. Operating Manual. Upon completion of the validation, Manufacturing Equipment Register, MER 98-1248 will be updated to include maintenance and calibration of the heat sealer.

Revalidation:

Upon completion of the validation, the Process Validation Master Plan: PVP-98001 will be updated to include the heat sealer in the master validation schedule.

Validation Team Protocol Approval

John Smith Date: 15 Nov. 1998 Title: Sr. Quality Engineer
John Smith

Paula Johnson Date: 15 Nov. 1998 Title: Production
Supervisor
Paula Johnson

Randy Jacoby Date: 15 Nov. 1998 Title: Plant Manager
Randy Jacoby

Sue Brown Date: 15 Nov. 1998 Title: R&D Project Leader
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Claudia Becker Date: 15 Nov. 1998 Title: Plant Quality
Manager
Claudia Becker

Protocol Registered in Doc Center:

Priscilla Johnson Date: 18 Nov. 1998 Title: Document Center
Manager
Priscilla Johnson

Installation Qualification Results
PVP 98-101

Installation Checklist

Requirements were established from the heat sealer operating manual, clean room procedures (SOP 1-12-77) and heat seal process procedure (SOP 20-12-14).

Requirement	Source	Status
Electrical supply	heat sealer operating manual	conforms
Air pressure	heat sealer operating manual	conforms
Ergonomic positioning	heat sealer operating manual	conforms
Spare parts	heat sealer operating manual & SOP 20-12-14	conforms
Clean air exhaust	SOP 1-12-77	conforms
Cleanability around equipment	SOP 1-12-77	conforms
Accessibility for maintenance	SOP 20-12-14	conforms
Capability for sizes of pouches	SOP 20-12-14	conforms

Initial Burn-in

The heat sealer operated as described in the heat sealer operating manual and as required by SOP 20-12-14.

Calibration

All gauges and measuring devices on the heat sealer were successfully calibrated per SOP 20-1-2.

Lab Notebook Reference

Quality Engineering Lab Notebook, JWS, 98-4, pages 46 – 62.

Issues / Commentary

No new issues were identified.

The environmental challenge of the air exhaust was met by adding an oil based air filter to the exhaust line of the heat sealer. The particulate matter was monitored per SOP 9-15-84 and no changes from normal levels were detected.

The heat sealer installation was successful.

Validation Team IQ Results Approval

John Smith John Smith	Date: 15 Dec. 1998	Title: Sr. Quality Engineer
Paula Johnson Supervisor Paula Johnson	Date: 15 Dec. 1998	Title: Production
Randy Jacoby Randy Jacoby	Date: 15 Dec. 1998	Title: Plant Manager
Sue Brown Sue Brown	Date: 15 Dec. 1998	Title: R&D Project Leader
Claudia Becker Manager Claudia Becker	Date: 15 Dec. 1998	Title: Plant Quality

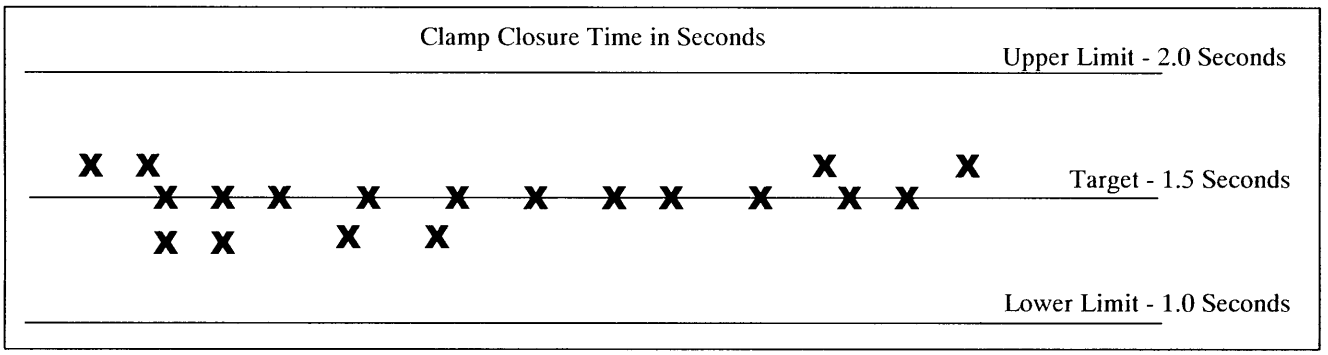
IQ Results Registered in Doc Center:

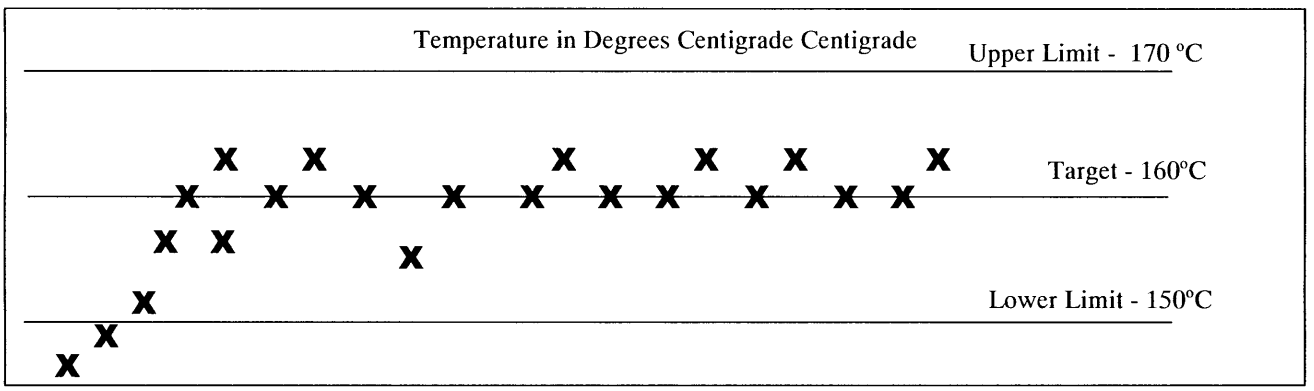
Priscilla Johnson Manager Priscilla Johnson	Date: 18 Dec. 1998	Title: Document Center

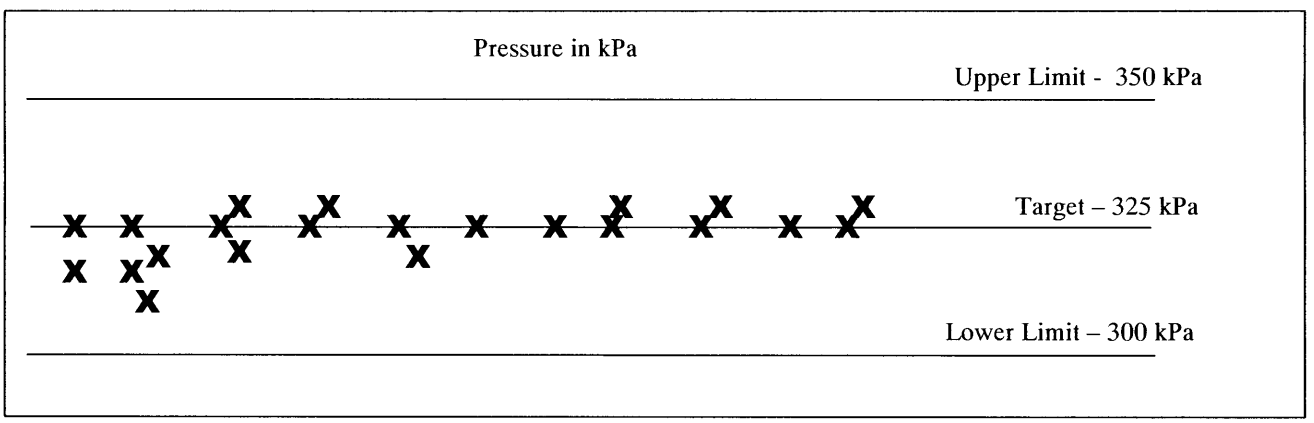
Operational Qualification Results
PVP 98-101

Phase One

Clamp closure time, temperature build and pressures were measured over a four-hour time frame with initial heat seal settings for time, temperature and pressure. Control charts were completed as follows:







From this analysis, it is apparent that the temperature is the most variable within the lower and upper limits for temperature. Also, temperatures were under the limit for the first fifteen to twenty minutes, as the sealer requires this time to warm up. This screening experiment demonstrated that temperature might be the primary factor influencing heat seal integrity.

Initial optimal heat sealer settings were established: temperature controller setting of 7.5, closure time setting of 1.5 seconds and pressure setting of 325 kPa.

Phase Two

Response surface studies were conducted to determine the effects of key inputs on seal strength. Variations in settings were used and the resultant seal strength for ten pouches was calculated. The following table summarizes the results:

Trial Run	Pouch Size	Time	Temperature	Pressure	Seal Strength
1	Small	1.0	150	300	Average 2.1, 6σ 1.2
2	Large	1.0	150	300	Average 2.3, 6σ 1.8
3	Small	1.5	150	300	Average 2.2, 6σ 1.6
4	Large	1.5	150	300	Average 2.5, 6σ 1.3
5	Small	2.0	150	300	Average 2.4, 6σ 1.5
6	Large	2.0	150	300	Average 2.8, 6σ 1.0
7	Small	1.0	160	300	Average 3.0, 6σ 0.4
8	Large	1.0	160	300	Average 3.1, 6σ 0.6
9	Small	1.5	160	300	Average 3.3, 6σ 0.5
10	Large	1.5	160	300	Average 3.4, 6σ 0.6
11	Small	2.0	160	300	Average 2.9, 6σ 0.3
12	Large	2.0	160	300	Average 2.8, 6σ 0.4
13	Small	1.0	170	300	Average 3.1, 6σ 0.6
14	Large	1.0	170	300	Average 3.2, 6σ 0.5
15	Small	1.5	170	300	Average 2.7, 6σ 0.6
16	Large	1.5	170	300	Average 2.9, 6σ 0.4
17	Small	2.0	170	300	Average 2.8, 6σ 0.6
18	Large	2.0	170	300	Average 3.0, 6σ 0.7
19	Small	1.0	150	325	Average 2.2, 6σ 1.7
20	Large	1.0	150	325	Average 2.3, 6σ 1.5
21	Small	1.5	150	325	Average 2.2, 6σ 1.3
22	Large	1.5	150	325	Average 2.5, 6σ 1.4
23	Small	2.0	150	325	Average 2.4, 6σ 1.7
24	Large	2.0	150	325	Average 2.8, 6σ 1.2
25	Small	1.0	160	325	Average 3.0, 6σ 0.3
26	Large	1.0	160	325	Average 3.1, 6σ 0.5
27	Small	1.5	160	325	Average 3.3, 6σ 0.4

Results, continued:

28	Large	1.5	160	325	Average 3.4, 6σ 0.3
29	Small	2.0	160	325	Average 2.9, 6σ 0.2
30	Large	2.0	160	325	Average 2.8, 6σ 0.3
31	Small	1.0	170	325	Average 3.1, 6σ 0.5
32	Large	1.0	170	325	Average 3.2, 6σ 0.4
38	Large	1.0	150	350	Average 2.3, 6σ 1.8
39	Small	1.5	150	350	Average 2.2, 6σ 1.6
40	Large	1.5	150	350	Average 2.5, 6σ 1.3
41	Small	2.0	150	350	Average 2.4, 6σ 1.5
42	Large	2.0	150	350	Average 2.8, 6σ 1.0
43	Small	1.0	160	350	Average 3.0, 6σ 0.4
44	Large	1.0	160	350	Average 3.1, 6σ 0.6
45	Small	1.5	160	350	Average 3.3, 6σ 0.5
46	Large	1.5	160	350	Average 3.4, 6σ 0.6
47	Small	2.0	160	350	Average 2.9, 6σ 0.3
48	Large	2.0	160	350	Average 2.8, 6σ 0.4
49	Small	1.0	170	350	Average 3.1, 6σ 0.6
50	Large	1.0	170	350	Average 3.2, 6σ 0.5
51	Small	1.5	170	350	Average 2.7, 6σ 0.6
52	Large	1.5	170	350	Average 2.9, 6σ 0.4
53	Small	2.0	170	350	Average 2.8, 6σ 0.6
54	Large	2.0	170	350	Average 3.0, 6σ 0.7

Based on these results, it is apparent that the lower temperature limit of 150 °C will result in unacceptable variations in seal strength (overall average of 2.38 kg, 6σ of 1.42). Variations in time and pressure within specified limits have little to do with seal strength.

An additional 36 runs were repeated with a lower temperature limit of 155 °C and variations of time and pressure similar to the first 54 runs. The data is not included in this report, but is available in the lab notebook referenced below. The results of these runs demonstrated an overall average of 2.92 kg, 6σ of 0.5. The C_p for these runs had a value of 1.8. Optimal heat sealer settings were determined to be a temperature controller setting of 8.2, a time of 1.5 seconds and pressure of 325 kPa.

Phase Three

Normal production processes were used to seal pouches with product and heat seal settings at 1) optimal levels; 2) low temperature, low pressure and short time, and 3) high temperature, high pressure and long time. 190 products were produced at each combination of settings.

Results:

The run with optimal levels resulted in an average seal strength of 3.08 kg, 6σ of 0.3, the run with low settings resulted in an average seal strength of 2.8 kg, 6σ of 0.5, and the run with high settings resulted in an average seal strength of 2.9 kg, 6σ of 0.6.

Lab Notebook Reference

Quality Engineering Lab Notebook, JWS, 98-4, pages 63-98.

Issues / Commentary

The input which transmits the most variation to the heat sealing process is temperature. The lower limit of temperature was adjusted to 155 °C from 150 °C.

The heat sealer must have a warm-up time period of at least twenty minutes with normal cycling to have stable temperature control.

Based on these results, when the process is run within input limits, the seal strength target of 3.0 kg should be met with a C_{pk} of 1.8 per SOP 3-13-81. Initial action levels for adjustment of the heat sealer should be seal strengths of 2.6 kg and 3.2 kg, which should be 3σ variation from the average of 2.9 during operational qualification.

The heat sealer Operational Qualification was successful.

Validation Team OQ Results Approval

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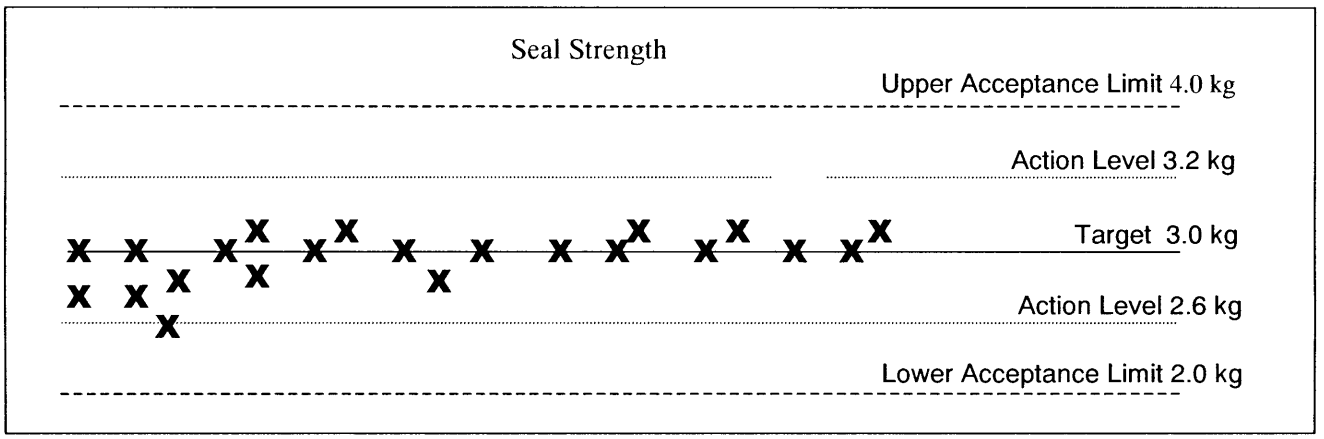
Performance Qualification Results
PVP 98-101

Normal production of codes 12345 and 12789 were run utilizing pouches PN 96-122 and PN 88-010. Optimal heat sealer settings were used. The heat sealer was allowed to warm-up with normal cycling for one half-hour prior to use. A week of production was completed for each code. Accelerated sampling plan 2-C from SOP 3-9-12 was used and the results control charted. Following is a typical control chart:



The resultant C_{pk} was 1.75 for the overall process during this performance qualification. The comparison of the C_p results for each day demonstrated that the process was both stable and capable. The following C_p values were calculated:

PN 96-122: 1.8, 1.9, 1.7, 1.6, 1.7;
PN 88-010: 1.6, 1.8, 1.7, 1.9, 2.0.

The centering of results about the target was very close: overall average seal strength was 2.93 kg with a target of 3.0 kg

The action levels were never reached, and therefore no adjustments were made and no root causes identified.

Lab Notebook Reference:

Quality Engineering Lab Notebook, JWS, 99-1, pages 1 – 48.

Issues / Commentary

The process has demonstrated stability and capability.

The Manufacturing Equipment Register, MER 98-1248, has been updated to include maintenance and calibration of the new heat sealer.

The Process Validation Master Plan, PVP-98001 has been updated to include the new heat sealer in the revalidation process.

The Heat Seal Process Procedure, SOP 20-12-14, has been updated to include the new heat sealer and the revised operating procedure for temperature warm-up and lower temperature control limit has been changed from 150 °C to 155 °C.

All production and QA employees have been trained and the training schedule in SOP 20-12-14 has been revised accordingly.

Validation Team PQ Results Approval

John Smith John Smith	Date: 31 Jan. 1999	Title: Sr. Quality Engineer
Paula Johnson Supervisor Paula Johnson	Date: 31 Jan. 1999	Title: Production
Randy Jacoby Randy Jacoby	Date: 31 Jan. 1999	Title: Plant Manager
Sue Brown Sue Brown	Date: 31 Jan. 1999	Title: R&D Project Leader
Claudia Becker Manager Claudia Becker	Date: 31 Jan. 1999	Title: Plant Quality

PQ Results Registered in Doc Center:

Priscilla Johnson Manager Priscilla Johnson	Date: 5 Feb. 1999	Title: Document Center

Final Report
PVP 98-101

We have reviewed the requirements of the protocol; the IQ, OQ and PQ reports and compared these to the requirements of the reference documents. All requirements have been met and the process is validated.

Validation Team Final Report Approval

John Smith
John Smith
Date: 5 Feb. 1999 Title: Sr. Quality Engineer

Paula Johnson
Supervisor
Paula Johnson
Date: 5 Feb. 1999 Title: Production

Randy Jacoby
Randy Jacoby
Date: 5 Feb. 1999 Title: Plant Manager

Sue Brown
Sue Brown
Date: 5 Feb. 1999 Title: R&D Project Leader

Claudia Becker
Manager
Claudia Becker
Date: 5 Feb. 1999 Title: Plant Quality

Final Report Registered in Doc Center:

Priscilla Johnson
Manager
Priscilla Johnson
Date: 10 Feb. 1999 Title: Document Center