PROCESS ROBUSTNESS

PQRI WHITE PAPER

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TABLE OF CONTENTS

1. INTRODUCTION

1.1 OBJECTIVE

The ability of a manufacturing process to tolerate the expected variability of raw materials, operating conditions, process equipment, environmental conditions and human factors is referred to as robustness.

The objective of this paper is to unify understanding of the current concepts of process robustness and how they apply to pharmaceutical manufacturing. The paper also provides recommendations on development and maintenance of a robust process. The concepts presented here are general in nature and can apply to many manufacturing situations; however, the focus of the discussion is application of robustness principles to non-sterile solid dosage form manufacturing. The tools, case studies, and discussion presented in this paper center around new product development and commercialization as, ideally, process robustness activities start at the earliest stages of process design and continue throughout the life of the product. It is also recognized that concepts of robustness can be applied retrospectively to established products in order to enhance process understanding.

1.2 BACKGROUND

There is a heightened emphasis on greater process understanding in the pharmaceutical industry. There is great incentive from a manufacturer's point of view to develop robust processes. Well understood, robust processes suggest greater process certainty in terms of yields, cycle times, and level of discards. Lower final product inventories may be carried if the manufacturing process is reliable.

There is a growing expectation from global regulatory agencies that firms demonstrate a comprehensive understanding of their processes and controls. The finalized FDA report entitled "Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach" clearly expresses the expectation that firms strive for "the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate process change to support continuous process improvement." As evidenced by recent draft guidelines, the other

members of the ICH tripartite have also adopted the philosophy embraced by this “Risk-Based Approach”. The eventual implementation of recommendations contained in ICH Q8 and Q9 should establish the linkage between “knowledge” and “associated risk”. An underlying principle of ICH Q8 is that an assessment of process robustness can be useful in risk assessment and risk reduction. Furthermore, such an assessment of process robustness can potentially be used to support future manufacturing and process optimization, especially in conjunction with the use of structured risk management tools outlined in the draft ICH Q9 guidance. The establishment of well-controlled processes serves the best interests of the patients, global regulatory agencies, and firms. It is anticipated that such processes will consistently produce safe and efficacious products in a cost effective manner. While not in the scope of this document, it is also anticipated that regulatory agencies will adjust their oversight requirements for processes that are demonstrated to be robust, as such processes are anticipated to present low risk for product quality and performance.

There is more to a robust process than having a dosage form pass final specifications. Robustness cannot be tested into a product; rather, it must be incorporated into the design and development of the product. Performance of the product and process must be monitored throughout scale up, introduction, and routine manufacturing to ensure robustness is maintained and to make adjustments to the process and associated controls if necessary. Process understanding - how process inputs affect key product attributes - is the key to developing and operating a robust process.

This paper presents key concepts associated with process robustness, defines common terms, details a methodical approach to robust process development, and discusses tools and metrics that can be used during development or for ongoing process monitoring. Where appropriate, case studies are used to demonstrate concepts. The tools, approaches, and techniques discussed are commonly understood concepts and are routinely used in other industries. Many pharmaceutical development and manufacturing programs are employing some or all of the

techniques. The intent is to organize the approaches and show how, when used together, they can lead to greater process understanding and control.

2. PRINCIPLES OF PROCESS ROBUSTNESS

2.1 DEFINING ROBUSTNESS

The ability of a process to demonstrate acceptable quality and performance while tolerating variability in inputs is referred to as robustness. Robustness is a function of both formulation and process design. Formulation design variables include the qualitative and quantitative composition of raw materials, both API and excipients. Process design variables include the process selected, the manufacturing sequence or steps, the equipment settings, such as speeds and feed rates, and environmental conditions. In this discussion, all process inputs will be referred to as parameters.

Performance and variability are factors impacting robustness and may be managed through process design and product composition. Elements of product composition for consideration include the choice of API form, since some API forms are more robust than others, and the choice of the excipients, e.g. the grades and concentrations.

Process performance and variability may be managed through the choice of manufacturing technology. Setting appropriate parameter ranges for a robust process requires consideration of the manufacturing technology selected. Well designed processes reduce the potential for human mistakes, thereby contributing to increased robustness.

A typical pharmaceutical manufacturing process is comprised of a series of unit operations. A unit operation is a discrete activity e.g. blending, granulation, milling, or compression. Parameters for a unit operation include: machinery; methods; people; material (API, excipients, material used for processing); measurement systems; and environmental conditions. The outputs of a unit operation are defined as attributes, e.g. particle size distribution or tablet hardness.

During product and process development both the inputs and outputs of the process are studied. The purpose of these studies is to determine the critical parameters and attributes for the process, the tolerances for those parameters, and how best to control them. Various experimental and analytical techniques may be used for process characterization. The goal of this development phase is to have a good understanding of the process and the relationships of

the parameters to the attributes. The body of knowledge available for a specific product and process, including critical quality attributes and process parameters, process capability, manufacturing and process control technologies and the quality systems infrastructure is referred to as the Manufacturing Science underlying a product and process.

2.2 Critical Quality Attributes (CQAs)

There are some measured attributes that are deemed critical to ensure the quality requirements of either an intermediate or final product. The identified attributes are termed Critical Quality Attributes (CQAs).

CQAs are quantifiable properties of an intermediate or final product that are considered critical for establishing the intended purity, efficacy, and safety of the product. That is, the attribute must be within a predetermined range to ensure final product quality. There may be other non-quality specific attributes that may be identified, e.g. business related attributes, however, and they are outside the scope of CQAs.

2.3 Critical Process Parameter (CPPs)

During development, process characterization studies identify the critical process parameters (CPPs). A Critical Process Parameter is a process input that has a direct and significant influence on a Critical Quality Attribute. Failure to stay within the defined range of the CPP leads to a high likelihood of failing to conform to a CQA.

It is also important to distinguish between parameters that affect critical quality attributes and parameters that affect efficiency, yield or worker safety or other business objectives. Parameters influencing yield and worker safety are not typically considered critical process parameters unless they also impact product quality.

Most processes are required to report an overall yield from bulk to semi-finished or finished product. A low yield of a normally higher yielding process should receive additional scrutiny since the root cause for the low yield may be indicative of a manufacturing issue or may be resultant from a lack of process control. In the event a process produces a lower than

expected yield, it becomes relevant to demonstrate thorough process understanding and control why the low yield occurred.

Development of comprehensive manufacturing science for the product will produce the process understanding necessary to define the relationship between a CPP and CQA. Often the relationship is not directly linked within the same unit operation or even the next operation. It is also important to have an understanding of the impact of raw materials, manufacturing equipment control, and degree of automation or prescriptive procedure necessary to assure adequate control. The goal of a well characterized product development effort is to transfer a robust process which can be demonstrated, with a high level of assurance, to consistently produce product meeting pre-determined quality criteria when operated within the defined boundaries. A well characterized process and a thorough understanding of the relationships between parameters and attributes will also assist in determining the impact of input parameter excursions on product attributes. CPPs are intrinsic to the process, and their impact on quality attributes is mitigated by process controls.

2.4 Normal Operating Range (NOR), Proven Acceptable Range (PAR)

During the early stages of process development, parameter target values and tolerance limits are based on good scientific rationale and experimental knowledge gained from the laboratory and pilot scale studies. A parameter that shows a strong relationship to a critical quality attribute becomes a key focal point for further study. In developing the manufacturing science, a body of experimental data is obtained, and the initially selected parameter tolerances are confirmed or adjusted to reflect the data. This becomes the proven acceptable range (PAR) for the parameter, and within the PAR an operating range is set based on the typical or normal operating range (NOR) for the given parameter. Tolerance ranges may be rationalized and adjusted as increased process understanding is gained.

Further study of parameters is a prelude to determining those that are critical process parameters. If varying a parameter beyond a limited range has a detrimental effect on a critical quality attribute, it is defined as a critical process parameter (CPP). Final selection and

characterization of the critical process parameters should be completed prior to executing the commercial scale batches.

In subsequent product development the parameters and attributes of the process are characterized to determine the critical parameters for the process, the limits for those parameters, and how best to control them. Controllable parameters may be parameters that are adjustable, e.g., drying time or temperature. At other times it may be desirable to 'fix' a parameter by specifically setting one value and not testing around the variability. A cause and effect relationship may be established for parameters and desired attributes. As an example, the drying time and temperature are parameters to a granulation process that affect the moisture level, an attribute of the granulation.

In a robust process, critical process parameters have been identified and characterized so the process can be controlled within defined limits. The normal operating range (NOR) of the process is positioned within the proven acceptable range (PAR) for each of the critical process parameters. The PAR is a function of the process and reflects the range over which a parameter can vary without impacting critical quality attributes. A process that operates consistently in a narrow NOR demonstrates low process variability and good process control. The ability to operate in the NOR is a function of the process equipment, defined process controls and process capability. If the difference, delta, between the NOR and PAR is relatively large, the process is considered robust with respect to that parameter. Refer to Figure 1. Where the delta between the NOR and PAR is relatively small, adequate process control and justification should be provided to assure the process consistently operates within the PAR.

PROVEN ACCEPTABLE RANGE

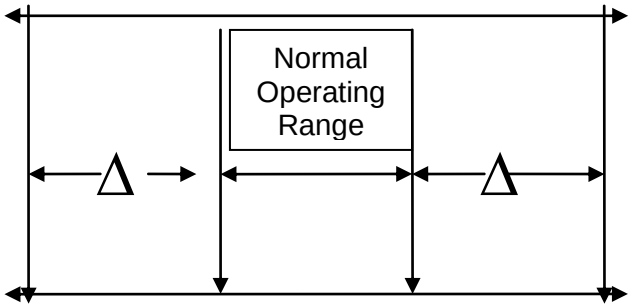

Figure 1

Characterizing and defining parameters may take a path of first defining the normal operating range (NOR) and range midpoint where the commercial product would be expected to be consistently manufactured, followed by defining the boundaries of the proven acceptable range (PAR). A process that operates in a NOR that is close in limits to the PAR may experience excursions beyond the PAR. In this case, the process may lack robustness

In processes that contain CPPs, and where the Δ between the NOR and PAR is relatively small, the concern of excursions beyond the PAR drives the need for a greater understanding of the tolerances of the CPPs. This is warranted to assure adequate process control is provided within the process.

Further characterization of parameters is achieved as manufacturing experience is gained and the state of robustness of the process is assessed at a pre-determined frequency.

2.5 Variability: Sources and Control

Typical sources of variability may include process equipment capabilities and calibration limits, testing method variability, raw materials (e.g. API and excipient variability between lots and vendors), human factors for non-automated processes, sampling variability and environmental factors within the plant facility. A myriad of systems are available to monitor and control many of the input factors listed.

Variability in operator technique may contribute to process variability. In assessing robustness of a process it may be necessary to evaluate operator-to-operator variability and day-to-day variability of the same operators.

2.6 SETTING TOLERANCE LIMITS

Upper and lower tolerances around a midpoint within the PAR of a parameter should be established to provide acceptable attributes. In setting the acceptable tolerances of a CPP often the point of failure does not get defined. It is acknowledged that the acceptance limits set for a CPP may be self-limited by the initially selected design space. In this case the manufacturing science knowledge base is limited; however, within the tolerance limits selected, conformance to the desired quality attribute limits will be achieved.

It is not necessary to take a process to the edge of failure to determine the upper and lower limits of a defined process. The defined limits, however, should be practical and selected to accommodate the expected variability of parameters, while conforming to the quality attribute acceptance criteria.

3. DEVELOPMENT OF A ROBUST PROCESS

A systematic team-based approach to development is one way to gain process understanding and to ensure that a robust process is developed. However, there is presently no guidance on how to develop a robust process. The purpose of this section is to define a systematic approach to developing a robust process and to determine which parameters are critical process parameters. This section will also present a case study to give practical examples of tools that can be used in the development of a robust process.

3.1 STEPS FOR DEVELOPING A ROBUST PROCESS

Six steps are described for the development of a robust process:

1. Form the team
2. Define the process (process flow diagram, parameters, attributes)
3. Prioritize experiments
4. Analyze measurement capability
5. Identify functional relationships
6. Confirm critical quality attributes and critical process parameters

It is important to note that documentation of results is a critical part of this process, and appropriate records should capture all findings of the development process.

Step 1: Form the team

Development of a robust process should involve a team of technical experts from R&D, technology transfer, manufacturing, statistical sciences, and other appropriate disciplines. The scientists and engineers most knowledgeable about the product, the production process, the analytical methodology, and the statistical tools should form and/or lead the team. This team approach to jointly develop the dosage form eliminates the virtual walls between functions, improves collaboration and allows for early alignment around technical decisions leading to a more robust product. This team should be formed as early as possible, before optimization and scale-up has been initiated.

Step 2: Define the process

A typical process consists of a series of unit operations. Before the team can proceed with development of a robust process they must agree on the unit operations they are studying and define the process parameters and attributes. Typically, flow charts or process flow diagrams are used to define the process. This flowchart should have sufficient detail to readily understand the primary function of each step. Figure 2 illustrates a simple process flow diagram for the case study of a direct compression tablet.

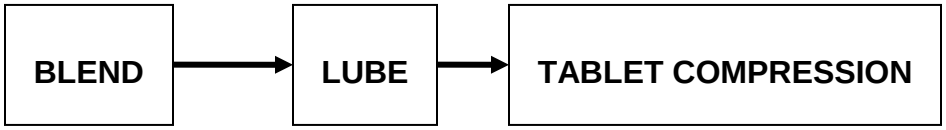

Figure 2 – Case study example: process flow diagram for a direct compression tablet

The next step in defining the process is to list all possible product attributes, and agree on *potential* critical quality attributes (CQAs). This list of product attributes is typically generated by the team using expert knowledge, scientific judgment, and historical information on the product of interest and similar products. It should be emphasized that some attributes are evaluated or monitored for process reproducibility, i.e., process yield, and some are for final product quality, i.e., the critical quality attributes. For example, critical quality attributes could include (but are not limited to) assay, dissolution, degradants, uniformity, lack of microbial growth, and appearance. For the case study of a direct compression tablet, Table 1 lists the potential critical quality attributes that the team generated.

Critical Quality Attributes
Dissolution
Assay
Tablet uniformity
Blend uniformity
Stability

Table 1 – Case study example: Table of critical quality attributes for a direct compression tablet
(Note that this list is for the case study example only and may not be all inclusive).

The final step in defining the process is determining process parameters. Categories of parameters to consider are materials, methods, machine, people, measurement, and environment. In some cases, the parameters may be some or all of the actual attributes of a previous unit operation. Several methods or tools can be used to capture the parameters. One suggested tool is called a Fishbone or Ishikawa diagram. The general concept is illustrated in Figure 3. A fishbone diagram for the case study of a direct compression tablet process is shown in Figure 4.

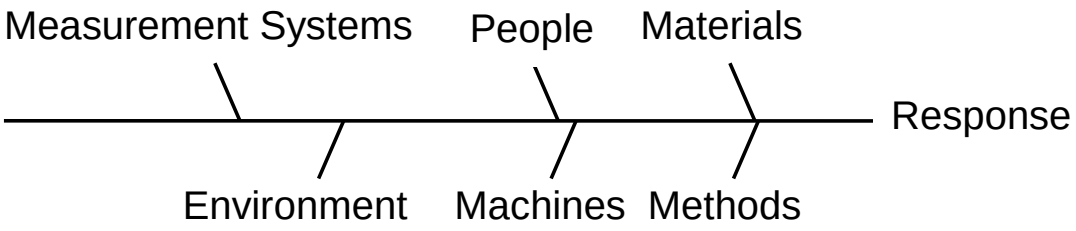

Figure 3 - General concept for Fishbone (Ishikawa) diagram

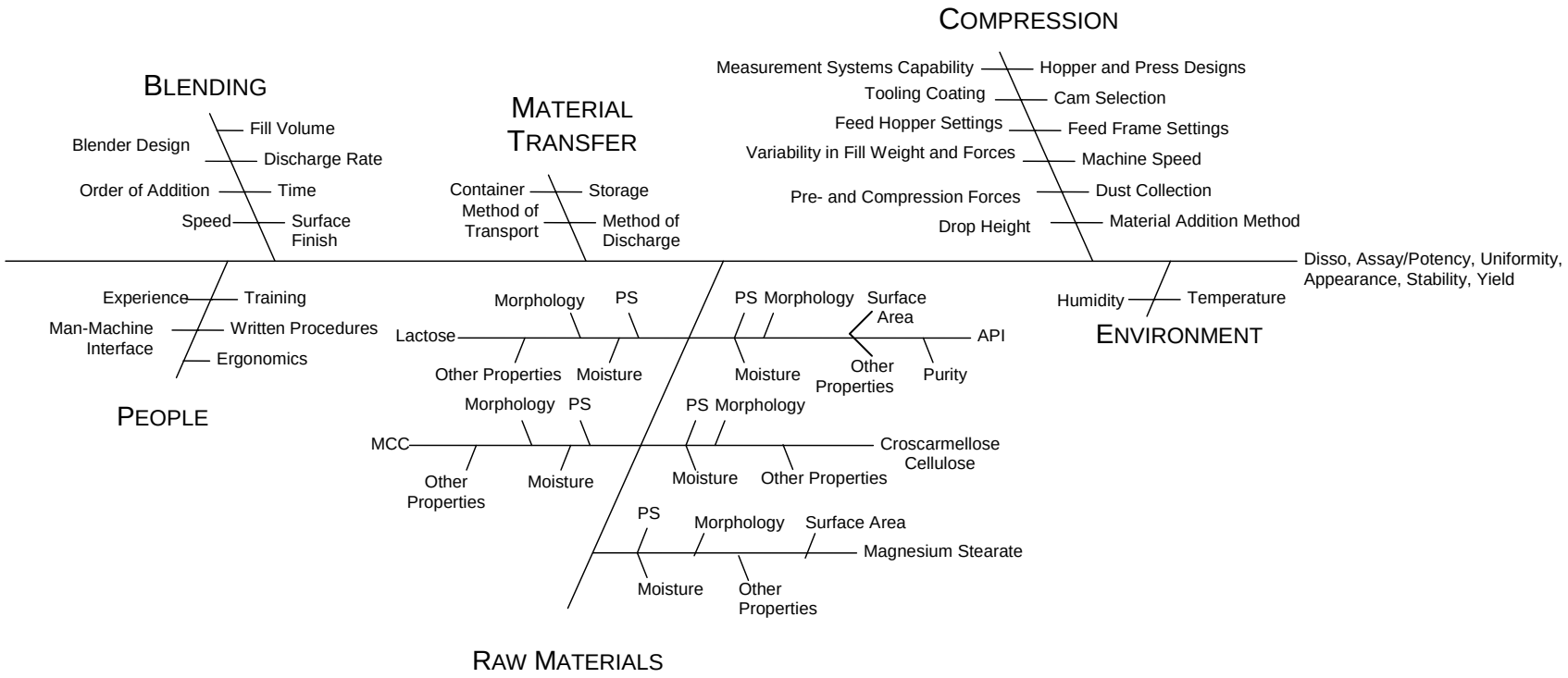

FIGURE 4 - Case study example: Fishbone diagram for a direct compression tablet (CASE STUDY)

Step 3: Prioritize experiments

A thorough understanding of the process and the process parameters is needed to develop a robust process. However, it is not practical or necessary to study every possible relationship between process parameters and attributes. It is recommended that the team initially use a structured analysis method such as a prioritization matrix to identify and prioritize both process parameters and attributes for further study. Unlike more statistically-oriented techniques, the use of a prioritization matrix generally relies on the process knowledge and subjective judgment of the team members involved in the process under study, although data may be included from designed experiments.

A case study example of a prioritization matrix for a direct compression tablet is shown in Table 2. In the table is placed a quantitative measure of the effect that a particular parameter is expected to have on a measured product characteristic. This effect is typically expressed on a scale from 0 (no influence) to 10 (directly correlated). A ranking of parameters of importance is calculated by considering the expected impact of a parameter on attributes as well as the relative importance of the attributes. In this case study, three process parameters, API particle size, compression force and compressing speed are anticipated to be the most important (based on the ranking totals at the bottom of the table). Therefore, for this case study, it makes sense to prioritize studies that focus on the effects of these 3 parameters. The parameters that were of lower importance may not be studied at all, or may be studied at a later date.

PROCESS PARAMETERS

Quality Attributes	Blend Time	Lube Time	API Particle Size	Pre-Compression Force	Compression Force	Compressing Speed	Feed Frame Setting	Excipient Particle Size	Importance
Dissolution	1	7	9	1	9	1	3	1	**10**
Assay/ Potency	1					5	3		**10**
Uniformity	7	1	9			5	3	5	**10**
Appearance	1	3			3	3			**5**
Stability			1		3				**7**
Yield						3			**3**
Ranking Total	**95**	**95**	**187**	**10**	**126**	**134**	**90**	**60**	
Percent	**13**	**13**	**25**	**1**	**17**	**18**	**12**	**8**	

Table 2 – Case study example: Prioritization matrix for a direct compression tablet (Note that this matrix is for the case study example only and may not be all inclusive).

Step 4. Analyze measurement capability

All measurements are subject to variability. Therefore, the analysis of a process cannot be meaningful unless the measuring instrument used to collect data is both repeatable and reproducible. A Gage R&R study (repeatability and reproducibility) or similar analysis should be performed to assess the capability of the measurement system for both parameters and attributes. Measurement tools and techniques should be of the appropriate precision over the range of interest for each parameter and attribute.

Step 5. Identify functional relationship between parameters and attributes

The next step is to identify the functional relationships between parameters and attributes, and to gather information on potential sources of variability. The functional relationships can be identified through many different ways, including computational approaches, simulations (small scale unit ops) or correlative approaches. Where experimental approaches are needed, one-factor-at-a time experiments can be used, but are least preferred. Design of

experiments (DOE) is the recommended approach because of the ability to find and quantitate interaction effects of different parameters

Properly designed experiments can help maximize scientific insights while minimizing resources because of the following:

- The time spent planning experiments in advance can reduce the need for additional experiments.
- Fewer studies are required
- Each study is more comprehensive, and
- Multiple factors are varied simultaneously.

Design of experiments can often be a two-stage process, involving screening experiments to identify main factors to consider as well as response surface methodologies to refine the understanding of functional relationships between key parameters and attributes. An example of a statistical DOE for the case study of a direct compression tablet is shown in Table 3.

Run order	Compression. Pressure (megaPascals)	Press Speed (1000 tab/h)	Dissolution (Average% dissolved at 30 min)	Disso SD
1	350	160	83.12	2.14
2	150	160	81.54	2.40
3	250	280	96.05	3.73
4	150	260	80.38	6.18
5	390	210	69.32	6.08
6	250	140	94.81	1.14
7	250	210	96.27	3.59
8	250	210	94.27	6.37
9	110	210	70.76	4.03
10	350	260	83.71	7.10

Table 3 – Case study example: DOE results for a direct compression tablet study

In this example the effect of compression pressure and press speed on dissolution were studied. The results, plotted in Figures 5 and 6 showed that compression pressure affected average dissolution, while tablet press speed affected dissolution variability.

Step 6. Confirm Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)

After a sufficient amount of process understanding is gained, it is possible to confirm the CQAs previously identified (step 2). In the case study for a direct compression tablet, the critical quality attributes were dissolution, assay, tablet uniformity, and stability. As defined in a previous section, a CPP is defined as a process input that has a direct and significant influence on a CQA. CPPs are typically identified or confirmed using the functional relationships from step 5. In the case study for a direct compression tablet, tablet press speed and compression pressure were found to impact the CQA of dissolution, and were identified as CPPs. In figure 5, it can be seen that there is an optimum compaction pressure to obtain the highest dissolution. In figure 6, it can be seen that increasing the tablet press speed resulted in increasing variability in dissolution.

These functional relationships can be used and various optimizing strategies employed to identify optimal process set points or operating regions for press speed and compaction pressure. Suppose the product's goal is to achieve an average dissolution greater than 80% with less than a 5% standard deviation on dissolution. One summary source providing information on a potential operating region is an overlay plot; see Figure 7 for the case study of a direct compression tablet. This visual presents a predicted (yellow) area of goodness where average dissolution is greater than 80% and simultaneously the standard deviation of dissolution is less than 5%. The area where either or both of these conditions fails to hold is colored grey; the actual experimental design points are shown as red dots on the plot.

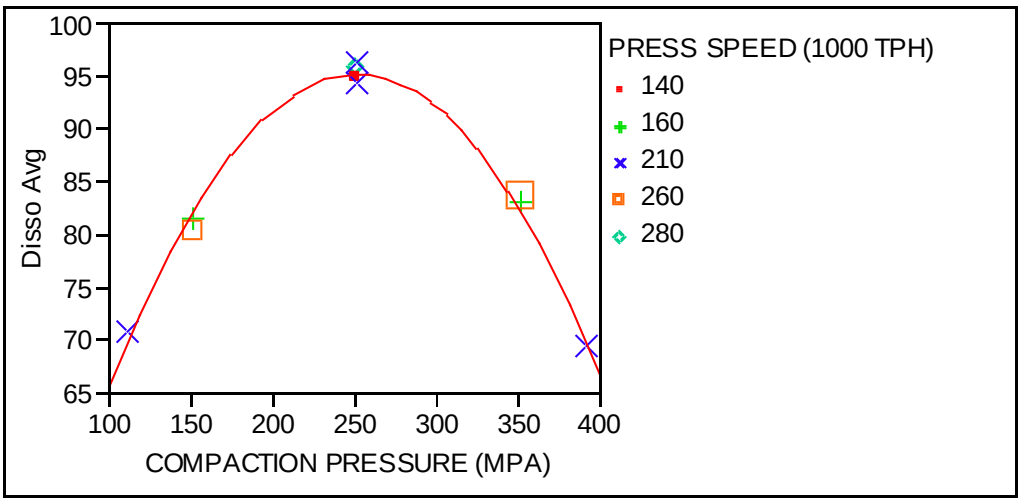

Figure 5 – Case study example: DOE results showing effect of compaction pressure on dissolution

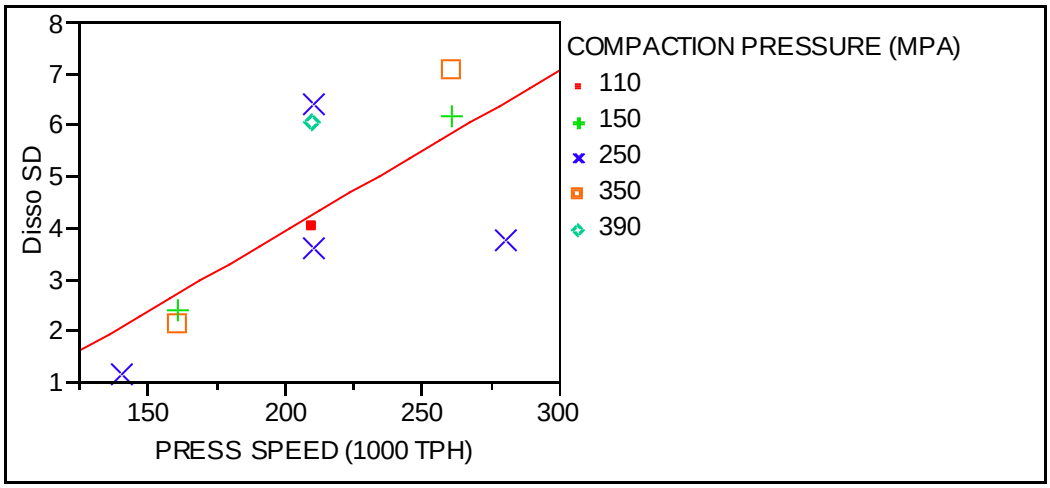

Figure 6 – Case study example: DOE results showing effect of press speed on dissolution variability (% standard deviation)

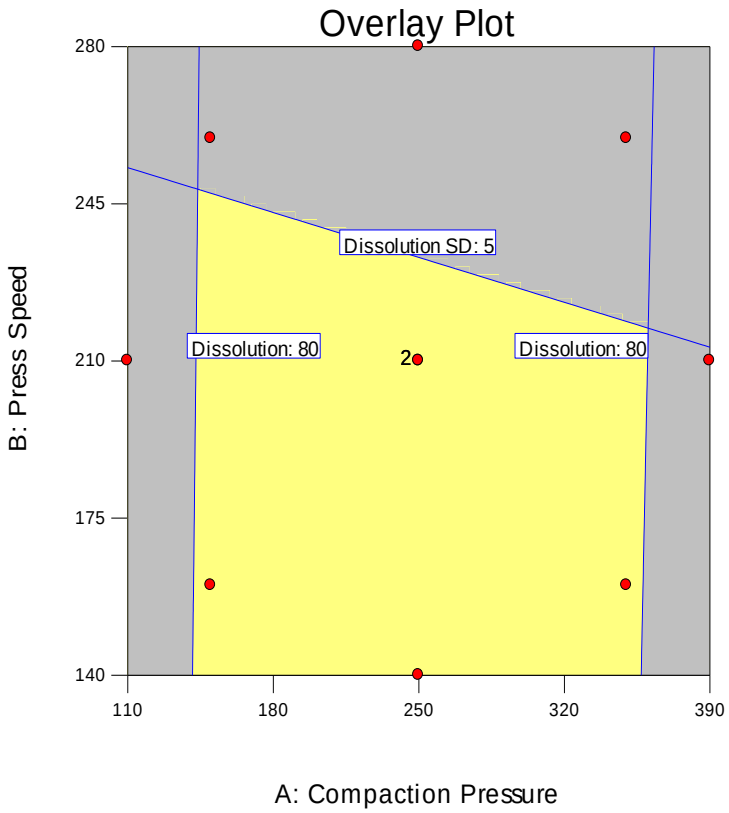

Figure 7 - Case study example: Overlay plot of DOE results showing effect of compaction pressure and press speed on dissolution. The potential operating window is shown in yellow.

3.2 TECHNOLOGY TRANSFER

Process understanding is necessary for development of a robust process. The systematic, step-wise approach described above may require several iterations before enough process understanding is achieved. This methodology will enable scientists and engineers to gain process understanding to set the groundwork for a robust operation in production. Important to the product technology transfer is a well-characterized formulation and process design. It is recognized that parameters identified during the research and development phase may need to be adjusted at scale-up to the pivotal (biobatch) or commercial batch size. Therefore employing similar steps that are used in the development of a robust process, scale-up activities will include the challenging of previously defined CPPs and CQAs and identification

and process optimization of newly identified process parameters. These activities will require an understanding of:

- The qualitative and quantitative composition of the product
- API, excipient specifications and functional attributes
- Potential increased variability in the API as a result of scale-up of the API manufacturing process
- Manufacturing process and controls, operator experience and skill sets
- Assessment of equipment, used at the development stage versus the identified commercial manufacturing equipment, to identify batch sizes and operating parameters. This equipment assessment should also include equipment controls and tolerances.

After critical quality attributes and critical process parameters have been defined, the team should generate a plan for controlling critical process parameters. This may involve, but is not limited to establishment of process operating limits, use of automation, procedural controls and specialized operator training and qualification. In addition, it is critical that the knowledge transfer is well documented for the development and technology transfer phases through to the commercial scale.

As presented in the manufacturing section, with more manufacturing history and data over time, assessment of robustness can be ascertained.

4. PROCESS ROBUSTNESS IN MANUFACTURING

The research and development phase is characterized by execution of a development plan consisting of a number of discrete experiments that are designed to develop a formulation, establish the proper manufacturing process and provide process and formulation understanding around the key relationships between parameters and attributes. When the product is transitioned to Manufacturing, it will most likely encounter a much wider range of variation on the parameters than seen in development. For example, attribute variability may increase due to a wider range in incoming raw material parameters that can't possibly be fully studied in R&D. It is upon transfer to Manufacturing that assessment of the true process capability and robustness as well as any process improvement or remediation will begin.

Manufacturing yields a large amount of empirical process performance data that may be used for a variety of purposes. It should be periodically analyzed to assess process capability and robustness and to prioritize improvement efforts; the data should be reviewed during the improvement effort to identify correlative relationships. Feedback to R&D may occur during these activities to further build quality into the design process. Although Manufacturing may benefit from a larger amount of empirical data, the ability to perform planned experimentation is not trivial. There are other techniques that have been successfully utilized to further process understanding and variability reduction. This section discusses techniques that are applicable to analyzing data to determine the state of process robustness and ensure the continuation of this state over time.

4.1 MONITORING THE STATE OF ROBUSTNESS

As R&D has established the desired operating range of parameters and attributes, Manufacturing should monitor both the parameters and attributes over time and review the information at a pre-determined frequency, with emphasis on critical or key parameters.

The state of robustness is monitored through using statistical process control (SPC) charts combined with capability index calculations. SPC tools such as control charts can be used to

ascertain the process' stability, provide warnings of any potential problems, and to assess the state of control. Capability indices assess the product or process ability to meet specifications. To evaluate the true state of robustness, information on process parameters and attributes should be collected as per a pre-determined SPC sampling plan. Process control charts (trend chart, run chart) are constructed and capability indices calculated.

- Run Chart/Trend Chart: A run chart or trend chart is an x-y plot that displays the data values (y) against the order in which they occurred (x). These plots are used to help visualize trends and shifts in a process or a change in variation over time.
- Control Charts: Similar to a run chart, a control chart is a plot of a process parameter or quality attribute over time. Overlaid on the plot is information about the process average and expected variability (control limits). Statistical probabilities form the basis for control chart rules that help identify odd process behavior. Identifying and removing assignable causes of variability to the extent that only smaller or common sources of variability remain produces a process that can be considered stable and predictable over time, or under statistical control and producing consistent output.
- Process Capability: After it has been determined that a process is in statistical control, i.e. all assignable sources of variability have been removed, the expected process capability can be calculated. The capability number provides an assessment as to what extent the process is capable of meeting specifications or other requirements. Common capability indices include:
    - Cp: This index relates the allowable process spread (the upper specification limit minus the lower specification limit) to the total estimated process spread, +/- 3σ. Generally, Cp should be as large as possible.
    - Cpk: This index relates the relationships of centeredness and spread of the process to the specification limits. If the Cpk value is significantly greater than 1, the process is judged capable of meeting specifications. Larger values of Cpk are better.

Much has been written about control charts and process capability indices; there are formulas and statistical methods available for a wide range of data types, distributions, and

specifications beyond the most common charts and indices for normally distributed, centered data with symmetric specifications. It should be noted that the distribution of the data under study must be matched to the appropriate control chart and capability index; data normality should not be assumed in all cases.

4.2 Process Specific Improvement or Remediation

It is Manufacturing's responsibility to work with the process within bounds defined by development and registration to attain and maintain a process in an ideal state. If a problem has been identified either by a trend within the operating range or a single point outside the operating range then an investigation should occur. Tools for investigation include:

- Flowcharts: A pictorial (graphical) representation of the process flow that shows the process inputs, activities, and outputs in the order in which they occur. Flowcharts aid process understanding.
- Ishikawa or Cause and Effect (Fishbone) Diagram: This tool helps organize and display the interrelationships of causes and effects. It is a form of tree diagram on its side and has the appearance of a fishbone.
- QFD: Quality Function Deployment is a structured analysis method generally used to translate customer requirements into appropriate technical requirements. It is used to capture and share process knowledge and may be used to identify and prioritize both process parameters (inputs) and characteristics (outputs).
- FMEA: Failure Modes and Effects Analysis provides a structured approach to identify, estimate, prioritize and evaluate risk with the intention to prevent failures. Historically this tool is used in the design of a new product, process, or procedure; it can also be used to limit the risk involved in changing a process.
- KT: Kepner-Tregoe has developed four rational processes (situational, problem, decision, opportunity) that provide systematic procedures for applying critical thinking to

information, data, and experience; application of this tool aids the team's understanding and decision making.

- Pareto Chart: A graphical means of summarizing and displaying data where the frequency of occurrence is plotted against the category being counted or measured. It is used to pictorially separate the significant few causes from the many and identify those areas that are of the most concern and should be addressed first.

If either the variability of the process is larger than expected or the process average is not as expected, historical data analysis through multivariate regression or other statistical analysis may be used to help provide root cause candidates. Process improvement or remediation activities may need to occur using Statistical Experimental Design.

- DOE (Design of Experiments): Uses a statistically based pattern of experimental runs to study process parameters and determine their effect on process attributes. The results of these experiments are used to improve or optimize the process and may be used to predict the process's ability to produce the product within the specifications.
- Regression/correlation analysis/ANOVA: These are mathematical approaches to examine the strength of the relationship between two or more variables. These methods and models are useful in determining root cause, in specification setting, and optimization. When applied to historical data analysis, care should be taken in concluding causal relationships.
- r/t-tests/F-tests: Statistically significant relationships are determined using these statistics; in regression the t-test is used, correlation analysis employs r, and ANOVA relies on the F-test.
- Scatter Diagrams: A visual display of data showing the association between two variables. The scatter diagram illustrates the strength of the correlation between the variables through the slope of a line. This correlation can point to, but does not prove, a causal relationship.

4.3 Plant-wide Variability Reduction Activities

In addition to the targeted improvement or remediation activities just discussed, process variability may be reduced through plant-wide process improvement initiatives aimed at general sources of variability. Recent industry initiatives and programs targeted at variability and cost reductions and efficiency and flow improvements include 6-sigma, lean manufacturing, and even lean sigma.

General sources of process variability include machines, methods, people, materials, measurement systems, and environment. Examples of variability reduction/process improvement activities that address the general sources of variability and will lead to improved processes include: instrumentation calibration and maintenance, gage R&R studies, operator skills assessment, general plant layout, and clearly written work instructions.

- Materials can be a significant source of process variability. It is important that the material functionality and specific physiochemical specifications are well understood and controlled.
- Instrumentation and Machine Calibration and Maintenance: Machine and measurement systems are two of the process components whose variability can contribute adversely to the product. Planned maintenance, repeatability, reproducibility, and accuracy checks should be performed as per a systematic schedule. The schedule frequency should be appropriate for maintaining calibration. In addition, it is critical that the preventative maintenance program addresses equipment parameters that are process critical, i.e. granulator impeller speeds; air flow in fluid-bed equipment and film coaters.
- Gage R&R Studies: It is difficult/impossible to place a response in control if the measurement system is not capable. The gage or measurement system repeatability and reproducibility (R&R) experimental design study provides information about the repeatability (inherent equipment variation) and reproducibility (operator to operator variation) of the measurement system's actual vs. required performance. More generally,

a measurement system analysis can be used to study bias, linearity, and stability of a system.

- Human Factors: This contribution to variability is best minimized through education and training. The operator skills assessment provides a tool to track required skills vs. personnel capability. Variability in how a task is performed can be reduced if the work instructions are clear and concise. These instructions along with the general process flow should be periodically reviewed and discussed. Systematically error proofing is also a way to reduce the influence of the human factor.
- Plant Layout: Along with other environmental factors of temperature, pressure, and humidity, etc., the general cleanliness, orderliness and layout of an area provides an indirect effect on the variation of a product. Environmental plans should be developed and maintained.

5. CONCLUSION

Creating a system that facilitates increased process understanding and leads to process robustness benefits the manufacturer through quality improvements and cost reduction. Table 4 summarizes the robustness roles by product life cycle along with useful tools for each stage.

This system for robustness begins in R&D at the design phase of the formulation and manufacturing processes; emphasis on building quality into the product at this stage is the most cost effective strategy. R&D quantifies relationships between the inputs and outputs; the processes are established to produce the best predicted output with the targeted amount of variability.

Information about the process settings and key relationships are communicated to Manufacturing. Upon transfer, Manufacturing begins to verify R&D's information on process robustness through process monitoring and data analysis. Both general and process specific improvement activities help Manufacturing attain and maintain its goals.

Table 4: Development of Robustness at Various Stages in the Product Life Cycle

Process Robustness The ability of a manufacturing process to tolerate the variability of raw materials, process equipment, operating conditions, environmental conditions and human factors is referred to as robustness. Robustness is an attribute of both process and product design.			
R&D	Scale-Up & TT	Commercialization	Post-Commercialization
Establish basis for formulation, process and product design.	Generate detailed characterization of process and product being transferred.	Maintain ideal process state and assess process robustness.	After a sufficient time of manufacture, the commercial scale assessment of robustness can be ascertained.
Understand relationship between critical process parameters (CPP) and critical to quality product attributes (CQA).	Establish the ability to manufacture product routinely and predictably to the desired quality and cost, in compliance with appropriate regulations.	Monitor and if possible, actively control process.	Understand process capability and modify process if necessary to improve robustness.
Determine a design space that integrates various unit operations to achieve an output in the most robust, efficient and cost effective manner.	Confirm relationship between CPP and CQA.		Confirm relationship between CPP and CQA
Tools: Flowcharts, Ishikawa Diagram, FMEA, QFD, KT, Gage R&R, DOE, Regression Analysis & Other Statistical Methods, PAT	**Tools:** Flowcharts, Ishikawa Diagram, FMEA, QFD, KT, Gage R&R, DOE, Regression Analysis & Other Statistical Methods, OC Curves, Tolerance and Confidence Intervals, PAT, Tolerance Analysis	**Tools:** SPC, Trend Plots/Run Charts, Gage R&R, Process Capability – Cpk	**Tools:** APR, SPC, Trend Plots/Run Charts, FMEA, QFD, KT, Ishikawa Diagram, Flow Charts, Pareto, DOE, Regression Analysis & Other Statistical Methods

6. GLOSSARY

Critical Process Parameter (**CPP**): A Critical Process Parameter is a process input that has a direct and significant influence on a Critical Quality Attribute

Critical Quality Attribute (**CQA**): A quantifiable property of an intermediate or final product that is considered critical for establishing the intended purity, efficacy, and safety of the product. That is, the property must be within a predetermined range to ensure final product quality

Design Space: the design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes.

Manufacturing Science: the body of knowledge available for a specific product and process, including critical-to-quality product attributes and process parameters, process capability, manufacturing and process control technologies and the quality systems infrastructure.

Normal Operating Range (NOR): a defined range, within the Proven Acceptable Range, specified in the manufacturing instructions as the target and range at which a process parameter should be controlled, while producing unit operation material or final product meeting release criteria and Critical Quality Attributes

Process Analytical Technologies (PAT): a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of assuring final product quality.

Proven Acceptable Range (PAR): A characterized range at which a process parameter may be operated within, while producing unit operation material or final product meeting release criteria and Critical Quality Attributes

Quality: degree to which a set of inherent properties of a product, system or process fulfils requirements

Quality System: formalized system that documents the structure, responsibilities and procedures required to achieve effective quality management.

Requirements: needs or expectations that are stated, generally implied or obligatory by the patients or their surrogates (e.g. health care professionals, regulators and legislators)

Repeatability: the variability obtained with one gage used several times by one operator

Reproducibility: the variability due to different operators using the same gage on the same part

Robustness – The ability of a product/process to demonstrate acceptable quality and performance while tolerating variability in inputs

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