SPECIAL REPORT

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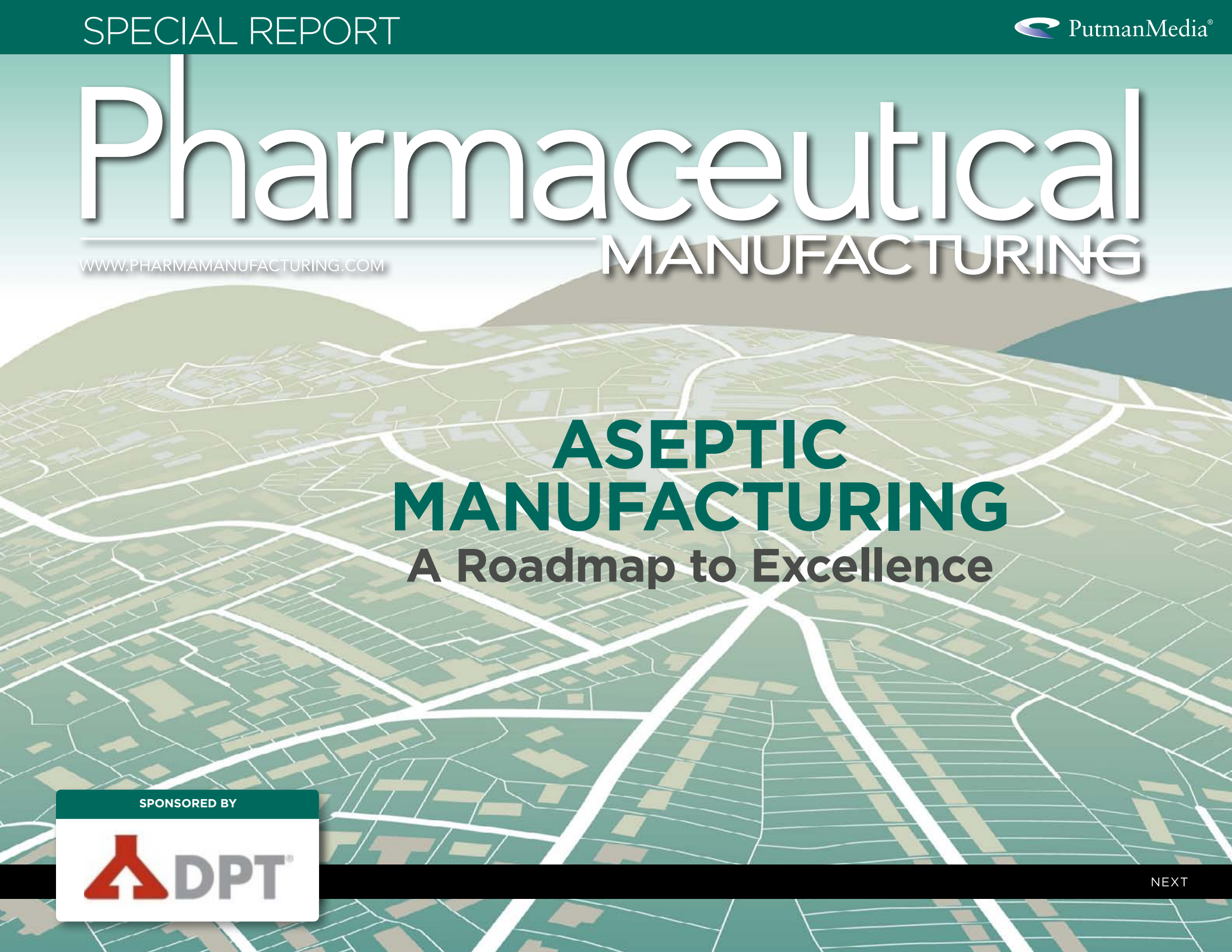

# ASEPTIC MANUFACTURING

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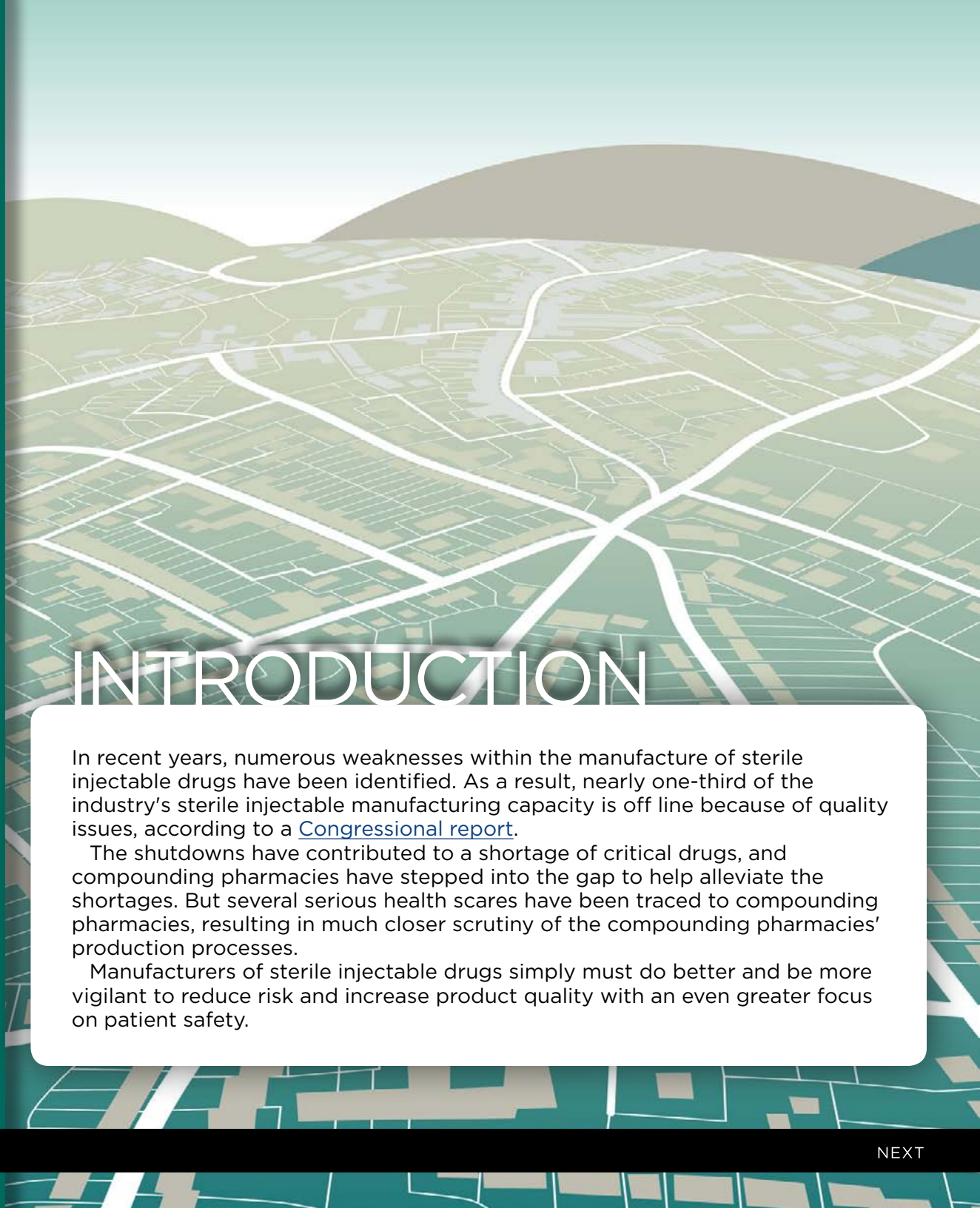


# INTRODUCTION

In recent years, numerous weaknesses within the manufacture of sterile injectable drugs have been identified. As a result, nearly one-third of the industry's sterile injectable manufacturing capacity is off line because of quality issues, according to a Congressional report.

The shutdowns have contributed to a shortage of critical drugs, and compounding pharmacies have stepped into the gap to help alleviate the shortages. But several serious health scares have been traced to compounding pharmacies, resulting in much closer scrutiny of the compounding pharmacies' production processes.

Manufacturers of sterile injectable drugs simply must do better and be more vigilant to reduce risk and increase product quality with an even greater focus on patient safety.

# Risk Management in Sterile Environments

A look at how HACCP and FMEA can be applied in the pharma micro lab and other sterile environments.

BY TIM SANDLE, PH.D., HEAD OF MICROBIOLOGY, BIO PRODUCTS LABORATORY

Within microbiology, a shift is taking place from simple laboratory studies toward greater use of risk assessment and management [1]. Sometimes these approaches form part of a drug company's total quality system; sometimes they exist as stand-alone techniques. The most important guidelines for pharmaceutical microbiology are described in ICH Q9, including the tools of FMEA (Failure Modes and Effects Analysis); FTA (Fault Tree Analysis); and HACCP (Hazard Analysis Critical Control Points).

The two most commonly used within microbiology are HACCP (which originated in the food industry) and FMEA (developed for engineering). This article explores these two approaches, first with a description of HACCP, followed by a description and case study of FMEA in sterility testing. (Please visit PharmaManufacturing.com for more from this chapter and other book excerpts.)

## HACCP: RISK-BASED APPROACH IN ENVIRONMENTAL MONITORING

Hazard Analysis and Critical Control Point is a risk assessment approach that addresses physical, chemical, and biological hazards [2]. HACCP is designed so that key actions, known as Critical Control Points (CCPs) can be taken to reduce or eliminate the risk of the hazards being realized. HACCP involves focusing on where the control points in a process are. Once these are established, critical limits are set. The critical limits are then monitored and the process is verified as being in control (or not) [3]. There are different variants of HACCP. The "Lifecycle Approach" is similar to that contained in FDA's "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" [4].

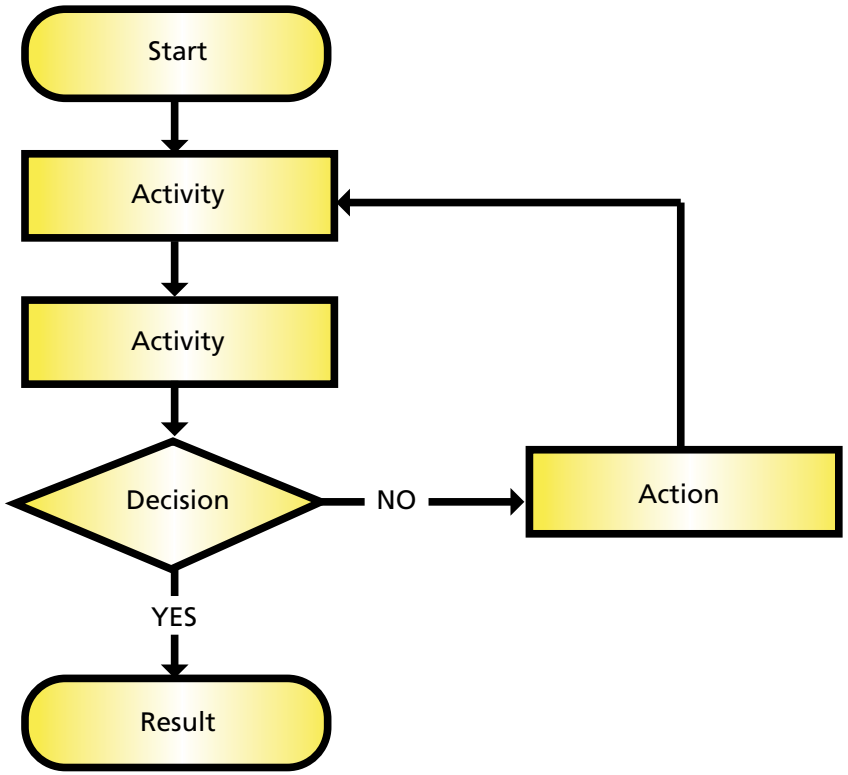
There are two key components of HACCP:

- ***Hazard Analysis:*** Determining what microbiological, physical or chemical risks are associated with a process.
- ***Critical Control Point:*** A point, step or procedure at which control can be applied.

In general HACCP involves the following:

1) Conducting a hazard analysis. This involves listing all potential hazards associated with each step, conduct a hazard analysis, and consider any measures to control

**FIGURE 1. GENERALIZED HACCP FLOW CHART**




identified hazards. For this, process flows are useful. For example, **see Figure 1:**

2) Determining the Critical Control Points (CCPs).
3) Establishing critical limit(s).
4) Establishing a system to monitor control of the CCP.
5) Establishing the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
6) Establishing procedures for verification to confirm that the HACCP system is working effectively.
7) Establishing documentation and record keeping.

The general methodologies of HACCP are also similar to the principles used in qualification and validation, and the critical control points are often the same as critical process parameters. This allows for several synergies with other aspects of pharmaceutical quality systems.

There are, nonetheless, some limitations with HACCP. It often has to be combined with other risk assessment tools, like FMEA, in order to allow risks to be prioritized and quantified. HACCP is also less useful for complex processes or if the process is not well known.

## FMEA: RISK-BASED APPROACH IN STERILITY TESTING

A failure modes and effects analysis (FMEA) examines potential failure modes within a system for classification by severity or determination of the effect of failures on the system. Failure modes are any errors or defects in a process, design or equipment — potential or actual.

Effects analysis refers to studying the consequences of those failures. FMEA looks at the risk of failure at each process step by evaluating the potential failure modes for the process. It then proceeds to evaluate and document the impact of the failure upon product quality or the next stage in the process. Once the process has been mapped, the emphasis is on eliminating, reducing or controlling performance failures through risk reduction techniques.

Although FMEA can be a powerful tool, it is better applied to equipment, where complex items can be broken down to their key components or operational steps, rather than to process manufacture (where HACCP arguably has the advantage in spotting potential microbiological risks). It also relies upon a detailed process understanding; if the process is not well understood, then key steps can be easily missed. Some organizations have attempted to combine both HACCP and FMEA together to overcome the disadvantages with both models.

An example of the application of FMEA is outlined in the case study that follows. FMEA was applied to assess risk in a barrier isolator system [5] used for sterility testing. The following steps were taken:

a) Setting the scope;
b) Defining the problem;
c) Setting scales for factors of severity, occurrence and detection (see Table 1);
d) Process mapping;
e) Defining failure modes;
f) Listing the potential effects of each failure mode;
g) Assigning severity ratings to each process step;
h) Listing potential causes of each failure mode;
i) Assigning an occurrence rating for each failure mode;
j) Examining current controls;
k) Examining mechanisms for detection;
l) Calculating the risk;
m) Examining outcomes and proposing actions to minimize risks.

Where the number of risk is very high, the ICH Q9 guideline proposes the use of a risk filter.

## STERILITY TESTING ISOLATOR: THE CASE STUDY

The definition of an isolator is a device [6]:

a) Provided with microbial retentive filtered air (and which does not exchange any other air with the surrounding environment)
b) Has a decontamination cycle (for the isolator itself and for material entering)
c) Has a means for material transfer and/or connection to another isolator
d) No human part directly enters the isolator

All isolators are at risk from contamination [7]. Although isolators are superior in many ways to clean rooms, the approach of regulators, such as the FDA, is: "Barrier Isolators cannot prevent contamination caused by GMP deficiencies such as poor aseptic procedures and inadequate training of...operators" [8].

The main risks which different isolators (those used for both sterility testing and for aseptic filling) are susceptible include [9]:

- leaks;
- gloves/operator manipulations;
- filters;

**TABLE 1**

| Risk Category | Score | Definition of Risk |
|---|---|---|
| Severity | 5 | Specification limits exceeded. Probable rejection of test or shutdown of system. |
| | 3 | Observed trend takes place, but no critical excursions. Requires investigation. |
| | 1 | No excursion has taken place. No upward trends and no investigation is required. |
| Occurrence | 5 | Expected to occur >50% time. |
| | 3 | Expected to occur ≥10-≤50% time. |
| | 1 | Expected to occur ≤10% time. |
| Detection | 5 | No way to detect the failure mode. |
| | 3 | Can be partially detected but detection could be improved. |
| | 1 | Good detection systems in place. |

- other airborne contamination;
- transfer of material into and out of the Isolator;
- the isolator room;
- decontamination cycle;
- cleaning/environmental monitoring issues.

## APPLICATION

The isolator system is used for the sole purpose of performing final product sterility testing on a range of plasma-derived parenteral products according to Ph. Eur. 2.6.1 or USP <71>. The methods used are membrane filtration and direct inoculation. A variety of environmental monitoring methods are performed during and after testing: air-samples (passive settle plates and an active volumetric air-sample); finger plates; contact plates and swabs. A spray bottle of a sporicidal disinfectant remains in the isolator for spillages and for a post-test clean down.

Monthly monitoring is performed in the isolator room. A number of daily, weekly and six-monthly physical tests are performed on the isolator system using pressure charts; cleaning and formal classification as a Grade A clean zone (to ISO 14644-1).

A score from 1 to 5 (most severe) was assigned to each of the following categories describing risk: i) Severity; ii) Occurrence;

and iii) Detection; where:

i) Severity is the consequence of a failure, should it occur;
ii) Occurrence is the likelihood of the failure happening (based on past experience);
iii) Detection is based on the monitoring systems in place and on how likely a failure can be detected.

The following questions were asked of every main part of the isolator system:

i) What is the function of the equipment? How are its performance requirements?
ii) How can it fail to fulfill these functions?
iii) What can cause each failure?
iv) What happens when each failure occurs?
v) How much does each failure matter? What are its consequences?
vi) What can be done to predict or prevent each failure?
vii) What should be done if a suitable proactive task cannot be found?

The scoring system was based on the Table 1. Using these criteria, a final FMEA score or "risk priority number" is produced:

$$\frac{x}{125}$$

The total of 125 is derived from: severity score x occurrence score x detect score, or:

$$5 \times 5 \times 5 = 125$$

Depending upon the score produced it can be decided whether further action is needed. There is no published guidance on what the score that dictates action should be. In this study, the company adopted 27 as the cut-off value where action was required. This was based on 27 being the score derived when the mid-score is applied to all three categories [i.e. the numerical value "3" from severity (3) x occurrence (3) x detect (3)] and the supposition that if the mid-rating (or higher) was scored for all three categories then at minimum the system should be examined in greater detail.

**THE ISOLATOR ROOM**

| Process Step | Failure Mode | Significance of Failure | Severity of Consequence (score) |
|---|---|---|---|
| Loading isolators pre-sanitization / performing sterility testing | That contamination from the room could enter transfer or main isolators | Reduced efficiency of transfer isolator sanitization / contamination inside main isolator | 3 |

| Measures to Detect Failure | Occurrence (score) | Detection Systems | Detection (score) |
|---|---|---|---|
| Would be shown from reduced evaporation rate for isolator sanitization / poor environmental monitoring results in main isolator/ potential sterility test failures / sanitization cycle has been validated using BIs of $10^6$ spores | 1 | Isolator room is monitored monthly for viable microorganisms and papers / staff wear over-shoes on entry / Dycem mat in place / entry to room has controlled access / environmental monitoring performed inside main isolator/ isolators are at positive pressure to the room and air is HEPA filtered | 1 |

## THE FMEA EXERCISE

To conduct the exercise, the company used the defined scheme on the isolator system, the isolator set-up was broken down into a number of critical areas, and each area was subsequently assessed. Several of these steps are examined below.

*Examination: The Isolator Room*

*Description of critical area:* The isolator is situated in an unclassified room. There is no requirement to place a sterility testing isolator in a classified room.

*FMEA schematic (above):*
*FMEA score: 3 x 1 x 1 = 3*

*Risk Evaluation:* There is no problem considered from the room environment. Entry to the room is controlled;

**POTENTIAL OF SANITIZATION CYCLE FAILURE**

| Process Step | Failure Mode | Significance of Failure | Severity of Consequence (score) |
|---|---|---|---|
| Performing sanitization cycles on transfer or main isolator | An isolator is not correctly sanitized | Contaminated items enter main isolator or main isolator itself is contaminated | 4 |

| Measures to Detect Failure | Occurrence (score) | Detection Systems | Detection (score) |
|---|---|---|---|
| Evaporation rate / pre- and post-lot testing of acid / sanitization cycles developed using BIs | 1 | Sterilizer parameters checked after sanitization and before use / acid potency checked for each lot / post-sanitization environmental monitoring performed for main isolator | 1 |

the sanitization cycle has been challenged with a level of microorganisms far greater than would ever be found in the environment (spores of Geobacillus stearothermophilus); all items entering the isolator are sanitized (using a chlorine dioxide based sporicidal disinfectant) and the isolator itself is an effective positive pressure barrier to the outside (at >15 Pascal). As detailed earlier, environmental monitoring is performed inside the isolator during testing [10]. This monitoring, which has an action level of 1 cfu, is designed to detect any potential contamination inside the isolator environment.

*Examination: Potential of Sanitization Cycle Failure*

*FMEA schematic (above):*

*FMEA score:* $4 \times 1 \times 1 = 4$

Risk Evaluation: The severity of an ineffective sanitization cycle is a potential sterility test failure. However, the sterilizer parameters are checked for every transfer and main isolator cycle and post-sanitization environmental monitoring is performed on the main isolator. This has a long history of producing no growth of viable microorganisms.

The isolators are loaded with a set amount of equipment and consumables. This is described in authorized procedures and the maximum load has been determined through BI studies. One potential area of weakness for the sanitization of the main isolator are valves for the removal of waste during the membrane filtration sterility test. These are autoclaved prior to each sanitization and during the first hour of the cycle they are opened — both inside and outside — to allow the sanitization agent to penetrate. A further preventative measure is taken post-sterility testing where the valve which has been used is rinsed through with disinfectant.

*Examination: Frequency of Isolator Sanitizations*

*FMEA schematic (below):*
*FMEA score:* $4 \times 2 \times 1 = 8$

Risk Evaluation: Each transfer isolator was sanitized, each run using a validated cycle and the Sanitization physical parameters were checked each run (evaporation rate and

**FREQUENCY OF ISOLATOR SANITIZATIONS**

| Process Step | Failure Mode | Significance of Failure | Severity of Consequence (score) |
|---|---|---|---|
| Performing sanitizations on transfer (each batch) and main isolator (three monthly) | Isolators are not sanitized frequently enough and allow contamination buildup | Environment inside isolator becomes contaminated thereby increasing likelihood of sterility test failure | 4 |

| Measures to Detect Failure | Occurrence (score) | Detection Systems | Detection (score) |
|---|---|---|---|
| Environmental monitoring inside main isolator / physical checks | 2 | Analysis of environmental monitoring / physical checks performed daily, weekly, six-monthly service and calibration | 1 |

pressure chart recorder). The main isolator is sanitized every three months (this has been set by monitoring trends in biocontamination over time). Environmental monitoring is performed during each sterility test and examined monthly for trends.

Testing showed that, if contamination occurred in the main isolator it did not recur when repeat monitoring is performed. It is reasoned that this is because the level of post-test disinfection is sufficient; that the air-changes in the isolator are such that most contamination will be removed every hour. Furthermore, the main isolator was continuously monitored to show that it remained at positive pressure to the outside. Every six months a range of physical tests were performed: pressure decay, HEPA filter integrity and particle classification.

*Examination: Pressure Leaks to Gloves*

*FMEA schematic (right):*
*FMEA score:* 4 x 2 x 3 = 24

Risk Evaluation: This FMEA has been given an occurrence of 2 because weekly checks on the gloves do show, on occasions, holes in gloves. A detection of 3 has been given due to reasons outlined below.

The weakest spot on the Isolator is considered to be the glove ports [11], therefore, the gloves have been subject to a separate FMEA. Although these are tested after each test using finger plates and are visually inspected by the testing technician pre-test and weekly, such visual checks are unable to detect pin-pricks leading to slow leakage. Pressure monitoring would show a significant leak from torn gloves, but is not subtle enough to detect tiny holes [12]. In order to improve detection, the organization undertook to purchase a glove-leak tester. This reduced the FMEA score by improving the detection rate from 3 to 1.

The probability of contamination is further reduced by the use of aseptic technique by the testing technician at all times. Tests are performed to the same level of aseptic technique

**PRESSURE LEAKS TO GLOVES**

| Process Step | Failure Mode | Significance of Failure | Severity of Consequence (score) |
|---|---|---|---|
| Use of gloves to transfer material or to perform sterility test (sterile gloves may be worn underneath isolator gloves) | Contamination from technician into isolator or weak area of positive pressure to allow contamination in | Contamination present in isolator / compromise of aseptic technique | 4 |

| Measures to Detect Failure | Occurrence (score) | Detection Systems | Detection (score) |
|---|---|---|---|
| Environmental monitoring (post-use finger plates) / pressure charts | 2 | Environmental monitoring is performed post-test on gloves / gloves are wiped with disinfectant / gloves are visually examined weekly and changed as appropriate | 3 |

that would be provided to performing a sterility test in a clean room. Furthermore all technicians are trained in aseptic technique prior to testing final product for batch release.

In addition technicians wear a pair of sterile gloves underneath the isolator gloves and procedures are in place for an aseptic change of gloves. Spare gloves are held in the Isolator for this purpose.

Despite the pre-glove leak testing system FMEA rating of 24—as a possible risk—the exceedingly favorable history of environmental monitoring gives assurance that there is little contamination in the isolator and no adverse trends. Therefore the gloves are a potential weak spot, but this has not been observed in practice. A further weakness is associated with the glove change procedure, which could also be explored as an area for improvement.

Other leaks associated with the isolator also pose a risk and could be similarly examined through FMEA.

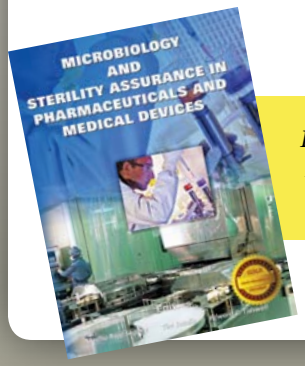
## CONCLUSION

The tools explored in this article, HACCP and FMEA, are

not without their limitations and indeed there is no single risk assessment approach applicable to every situation. Nevertheless, the application of risk assessment is increasingly a key part of pharmaceutical microbiology, and the microbiologist is increasingly called upon to use tools such as those shown here as part of contamination control.

## REFERENCES


1. *Whyte, W. and Eaton, T. (2004): "Microbiological contamination models for use in risk assessment during pharmaceutical production," European Journal of Parenteral and Pharmaceutical Sciences, Vol. 9, No.1, pp. 11-15.*
2. *Sidor, L. and Lewus, P. (2007): "Using risk analysis in Process Validation," BioPharm International, Vol. 20, Issue 2. pp. 50-57.*
3. *Notermans, S., Barendsz , A., Rombouts, F. (2002): "The evolution of microbiological risk assessment in food production," Foundation Food Micro & Innovation, Netherlands.*
4. *World Health Organization (2003): "Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals," WHO Technical Report Series No 908, Annex 7, World Health Organization, Geneva, 2003.*
5. *De Abreu, C., Pinto, T. and Oliveira, D. (2004): "Environmental Monitoring: A Correlation Study Between Viable and Nonviable Particles in Clean Rooms," Journal of Pharmaceutical Science and Technology, Vol. 58, No.1, January-February 2004, pp. 45-53.*
6. *The FMEA centre at: http://www.fmeainfocentre.com/introductions.htm.*
7. *Sandle, T. (2003): "The use of a risk assessment in the pharmaceutical industry – the application of FMEA to a sterility testing isolator: a case study," European Journal of Parenteral and Pharmaceutical Sciences, 2003; 8(2): 43-49.*
8. *PDA Technical Report No. 13 (revised): "Fundamentals of an Environmental Monitoring Programme," September / October 2001.*
9. *EU GMP: "Rules and Guidance for Pharmaceutical Manufacturers," TSO, UK.*
10. *Farquarharson, G. and Whyte, W. (2000): "Isolators and Barrier Devices in Pharmaceutical Manufacturing," PDA Journal of Pharmaceutical Science and Technology, Vol. 54, No.1, January-February 2000, pp. 33-43.*
11. *Sandle, T. (2004): "General Considerations for the Risk Assessment of Isolators used for Aseptic Processes," Pharmaceutical Manufacturing and Packaging Sourcer, Samedan Ltd, Winter 2004, pp43-47.*
12. *Whipple, A. (1999): "Practical validation and monitoring of Isolators used for sterility testing," European Journal of Parenteral Sciences, 1999, Vol. 4, No.2, pp49-53.*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# Tech Transfer's New Framework, Part I

How process validation guidance simplifies tech transfer, especially for legacy products.

BY BIKASH CHATTERJEE AND MARK MITCHELL, PHARMATECH ASSOCIATES

The technology transfer of a process, whether it is from R&D to commercial manufacturing or to another site or contract manufacturing organization (CMO) is a critical step in the lifecycle of any drug product, involving many steps. As major blockbuster drugs come off patent and large pharmaceutical companies look to bolster their pipeline through acquisition, the control and consistency of development data can vary dramatically. To make matters more complicated, the new Process Validation (PV) Guidance issued by FDA in January 2011 now defines three major stages of process validation that must be satisfied to consider the process validated. With the present article, we will lay out a practical approach that addresses this complexity and propose to discuss and summarize the diverse factors required to describe the process, establish the control strategy and specify the acceptance criteria to successfully transfer a legacy or newly acquired process to another process train and satisfy the new guidance.

To illustrate, we will take a closer look at the methodologies employed and the challenges encountered as part of a recent technology transfer process validation exercise executed for a legacy product for a client organization, with references to the business unit and technology transfer team assembled for the project.

Through this real-life example, Part I will discuss the approach taken to establish the design and control space for the final process. Part II will describe the Process Performance Qualification (PPQ) study design and acceptance criteria for Stage 2 and the approach taken to satisfy Stage 3 of the new PV guidance.

## THE NEW PV MODEL

Under FDA's 1987 guidance, Process Validation could be characterized as "quality by sampling and testing," while the new guidance would more appropriately describe validation as "quality by design and control." Let's look closer at the three distinct stages that make up the new definition of process validation:

- Stage 1: Process Design: The commercial manufacturing process is based on knowledge gained through development and scale-up activities.

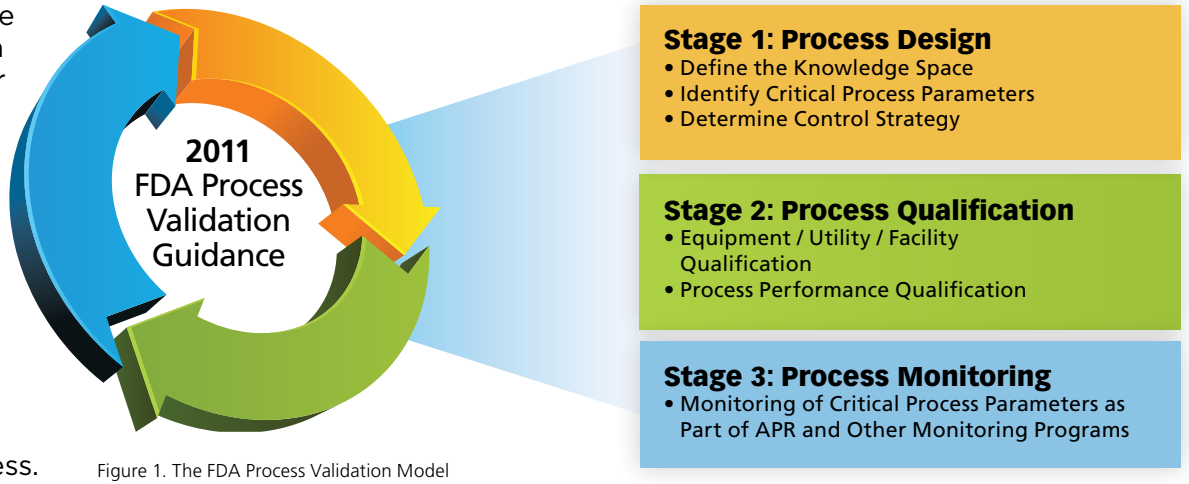


Figure 1. The FDA Process Validation Model

- Stage 2: Process Qualification: The process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3: Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

The PV roadmap uses a milestone-driven framework creating a phase-gate process for each stage of the new process validation lifecycle as shown in Figure 1.

## FOCUS ON THE CONTROL OF PARAMETERS INSTEAD OF THE TESTING OF ATTRIBUTES

As the new PV guidance states:

- Quality, safety and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and final product inspection and testing.
- Each step of a manufacturing process is controlled to assure the finished product meets all quality attributes including specifications [1].

Defining a knowledge space relating process parameters and material attributes to quality attributes allows us to establish a control strategy around the most critical process parameters. Stage 1, Process Design, encompasses identification and control of critical process parameters to provide a high level of assurance that the critical quality attributes for the entire lot will meet the defined limits. In-process and finished product inspection and testing on a relatively small sample of the lot become merely a confirmation of that control. Stage 2, Process Qualification, is a demonstration of that control of critical process parameters and their prediction of critical quality attributes, both within lot and lot-to-lot. Stage 3, Process Monitoring, is the ongoing verification that critical process parameters remain in control and continue to predict the outcome of the testing of critical quality attributes. Process Monitoring also provides the continuing opportunity to evaluate any emergent critical process parameters, which

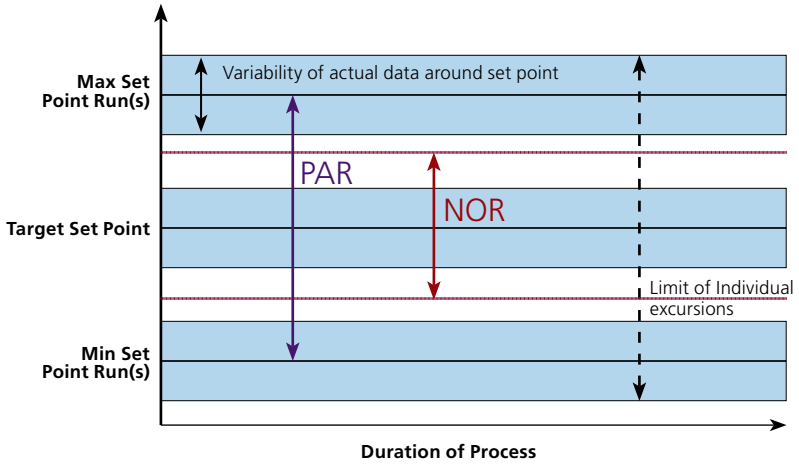


Figure 2. Relationship between PAR and NOR

may occur as a process, or as materials, equipment and facilities mature and potentially drift over time.

The key to control of a critical process parameter is to characterize the range for which operation within this range, keeping other parameters constant, will result in producing product that meets certain critical quality attributes, or the Proven Acceptable Range (PAR) as defined in ICH Q8. The PAR is established with data; these data are usually gathered during Process Design. Commercial production lots produced outside a PAR for a critical process parameter represent unknown quality and would be technically unsuitable for release despite acceptable in-process and final product inspection and testing.

Many companies establish a tighter range for production control called a Normal Operating Range (NOR), frequently seen on batch records. In these cases, excursions of a critical process parameter outside the NOR require a quality investigation to confirm that the PAR has not been exceeded. The NOR frequently represents the qualified limits of the control system used for the critical process parameter.

One possible relationship between the PAR and NOR is

shown in Figure 2. The PAR limits are set by the minimum and maximum set point runs for the critical process parameter where the product meets its quality attributes. The actual data for the parameter will vary around the chosen set point, shown in the diagram by the shaded areas around the set point. Here, the NOR is shown as a narrower limit than the PAR. The NOR was determined by the qualified control limits of the parameter when operating at its set point; the NOR is used for the batch record limits of normal production data. The extremes of individual excursions around the set point limits of the PAR may be used to justify limited duration deviations, which may occur in production.

## LEGACY PRODUCTS VS. NEW MOLECULAR ENTITIES

Legacy products represent a unique challenge for technology transfer and PV because of the inconsistency in terms of the development information available. NMEs have the advantage of gaining process understanding at small scale, with a focus on scale-up and/or tech transfer. The ability to identify critical process parameters at small scale has economic advantages and also provides greater flexibility in terms of experimental design. Using the ICH Q8 definition, it is possible to move from the knowledge space to the design space quickly and efficiently. The new PV guidance recognizes this and states: "Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3.1."

The big difference with legacy products vs. NMEs as they relate to PV is that the baseline data gathering activity begins in Stage 3 of the PV lifecycle rather than Stage 1.

## THE TECHNOLOGY TRANSFER FRAMEWORK

Gone are the days of simply comparing product

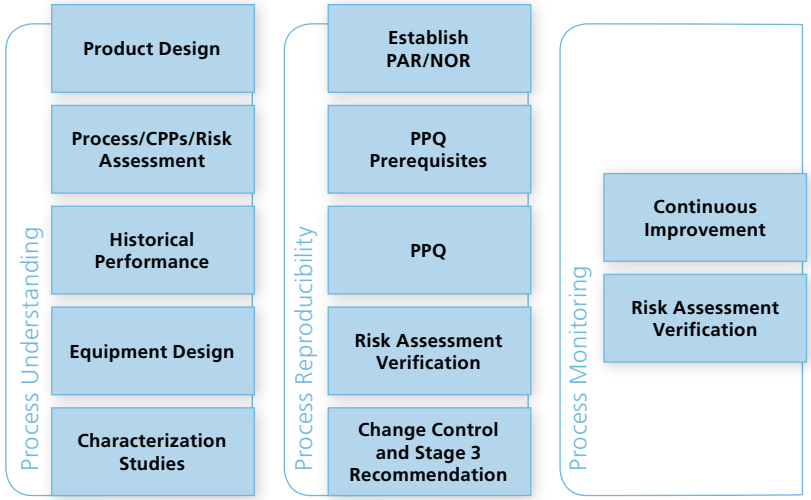


Figure 3. Technology Transfer/PV Framework

performance against its release specification. The objective of technology transfer is to acquire the necessary process and product knowledge to establish a PAR and NOR for each unit operation that is consistent with the predicate process being transferred. Thus, the new PV guidance requires the demonstration of process reproducibility in the PPQ phase of Stage 2. Reproducibility effectively requires establishing acceptance criteria that are consistent with the process stability demonstrated in the predicate process. Reproducibility must be defined for within lot and between lot variability as part of the PPQ exercise. The technology transfer framework used for this project is based upon Pharmatech Associates' PV model shown in Figure 3 and will be discussed as follows:

## PRODUCT REQUIREMENTS SPECIFICATION (PRS)

To illustrate, here is a case in point: the business unit of a pharmaceutical company acquired the rights to a controlled release anti-hypertensive tablet. The tablet had been

**Table 1. Formulation Details**

| Raw Material | %w/w | Function |
|---|---|---|
| API | 60 | Active ingredient |
| Microcrystalline cellulose | 22 | Excipient filler |
| Povidone K 29-32 | 5 | Granulation binder |
| Lactose | 12 | Excipient filler |
| Mg Stearate | 1 | Lubricant |
| Purified water | QS | Solvent |
| **Coating Solution Raw Material** | **%w/w** | **Function** |
| Eudragit Coating Solution | 12 | Controlled release polymer |
| Triethyl Citrate | 1 | Plasticiser |
| Talc | 1.5 | Glidant |
| Water | QS | Solvent |

manufactured for 15 years outside the U.S. and was to be transferred to the acquiring company's main manufacturing site. A PRS was given to the development team defining the critical-to-quality attributes for the final tablet, including:

- Greater than 50 percent Active Pharmaceutical Ingredient (API)
- Round 200-mg tablet
- Coated to mask taste
- 12-hour drug release with the following specifications:
- 4-hour dissolution 20-40 percent
- 8-hour dissolution 65-85 percent

**Table 2. Comparison of Process Equipment**

| Process Step | Original Process | Transferred Process |
|---|---|---|
| Compounding | 100 Liter tank with integrated Impeller | 250 Liter Tank with Tri-blender |
| Fluid Bed Granulation | Same Mfg. 350 kg product bed | Same Mfg. 350 kg product bed |
| Milling | Fitzmill | Comil |
| Blending | 30 cu ft. Blender | 100 cu ft. Blender |
| Compression | 24 station tablet press, manual control with pre-compression | 36 station tablet press closed loop control, and pre-compression |
| Coating | 36" coating pan, 3 spray guns, peristaltic pump | 48" coating pan, 4 spray guns, peristaltic pump |

## TECHNOLOGY TRANSFER MODEL: PROCESS UNDERSTANDING

### PRODUCT DESIGN

The technology transfer package included the formulation, raw material, API and finished product specifications and master batch records. No development report was ever written for the product. The team looked at the Chemistry, Manufacturing and Control (CMC) section of the non-disclosure agreement to understand the composition and functionality of each component of the formulation. The formulation is shown at left.

The final product design revealed two key considerations for the downstream process characterization studies. First, the product has a fairly large loaded dose. This translates to a potentially lower risk of content uniformity issues, which could translate to a more forgiving PAR and NOR for the final blend step. Second, the primary controlled release component is limited to the coating step, which means if the upstream process steps can be shown not to impact the final drug release profile this will simplify the final process validation argument. The raw material specifications were either compendial or cut-sheet specifications from the supplier. Limited API characterization studies had been performed. A comparison of the original process train and the new process train is shown in Table 2.

### CRITICAL PROCESS PARAMETERS/RISK ASSESSMENT

In the absence of a development report, the team turned to a tiered risk-

Table 3. Process Unit Operation Risk Assessment

| CQA | Process Steps | | | | | |
|---|---|---|---|---|---|---|
| | Granulation | Drying | Milling | Blending | Compression | Coating |
| Appearance | Low | Low | Low | Low | Medium | **High** |
| Assay | Low | Low | Low | Medium | Low | Low |
| Impurity | Low | Low | Low | Low | Low | Low |
| Blend Uniformity | Low | Low | Medium | **High** | **High** | Low |
| Drug Release | Low | Low | Low | Medium | Medium | **High** |
| Particle Size Distribution | Medium | Low | **High** | Low | Low | Low |
| Justifications for High Rating | N/A | N/A | Milling screen size and speed can affect the PSD and therefore the powder flow and tablet fill weight control | Blending can affect blend uniformity, assay, and drug release profile | Compression can affect drug uniformity in the tablet based upon particle size variability and flow | The final appearance and drug release rate are affected by the coating quality and reproducibility |

assessment approach for insight into the process design and sources of variability. The risk assessment was divided into two parts. The first evaluation compared each process step against the defined Critical Quality Attributes (CQA) in order to identify which process steps would require close characterization. Process steps with a High rating were then further evaluated. The second tier of the risk assessment evaluated the potential impact of the process parameters. Parameters were divided into scale independent and scale dependent variables. Those parameters that were identified as having a High potential impact on CQAs were targeted for further study. Scale-dependent parameters required further experimental characterization. Scale-independent parameters focused on an analysis of historical performance. An example of the risk assessment at the process level is shown in Table 3.

The team also defined a process parameter as critical when it had an impact on the CQAs across the final PAR and NOR. This was a significant definition, which could have a profound impact on the number of parameters tracked in the Stage 3, Continuous monitoring portion of the PV process. Since the objective of every process development exercise is to identify a process design and control space which does not have an impact on the final product CQAs, parameters that did not move the product CQAs based upon their final PAR and NOR were not considered Critical Process Parameters (CPP) and would not become part of the final Stage 3 monitoring program.

## HISTORICAL DATA ANALYSIS

The absence of development data establishing the PAR and NOR for the CPP can be ascertained to some extent by evaluating the historical behavior of each parameter along with the corresponding behavior of the CQAs for the unit operation. Data should be extracted from multiple batch records to determine whether the process is stable within lot and between lots. In some cases, only mean data or composite data may be available. To do this, the team went back into the batch records of approximately 30 lots across a period of one year to extract the necessary data. This exercise also gave some indication as to whether the parameter was truly a CPP, based upon whether it had an impact on the corresponding CQA for the unit operation. The data for each unit operation

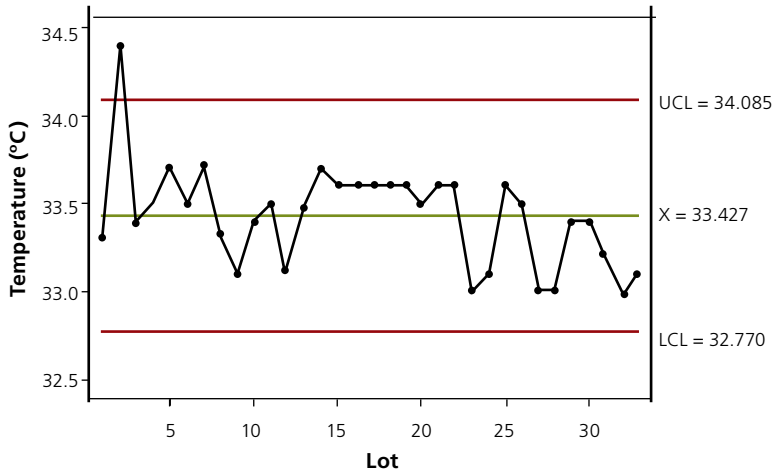


Figure 4. Control Chart of Product Bed Temperature for the Granulation Process

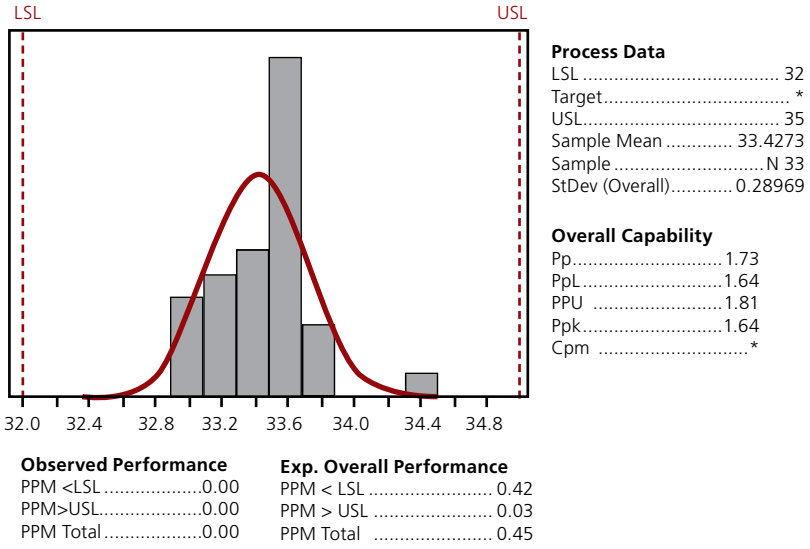


Figure 5. Product Bed Temperature for the Granulation Process

were plotted as control charts and the process capability was determined. Excursions outside the 3 sigma limit of the control charts were investigated to determine if there were deviations associated with the events. An example of the control chart and capability histogram for fluid bed product bed temperature is shown at left in Figures 4 and 5. Capability limits are based on a previously established PAR for the product bed temperature.

In addition, the corresponding CQA for the process—particle size—was evaluated to determine if there was any impact from the excursion. Figure 6 shows the control chart for the particle size, the CQA for this process. A linear regression between the process parameter and the critical quality attribute is shown in Figure 7. This indicates no statistically significant relationship between the product bed temperature and the particle size through the range of data examined. It is likely that product bed temperature would not meet our definition of "critical process parameter" from this data. However, since historical analysis is not a controlled experiment where all other parameters are necessarily held constant, there may be other parameters or material attributes influencing the particle size data and disrupting the correlation.

This approach was repeated based upon the parameters that had a medium or high rating in the risk table. For these scale independent parameters, the existing PAR ranges were used for the next phase of scale-up studies.

## CHARACTERIZATION STUDIES

For those parameters that were scale dependent, additional characterization studies were required to establish PAR and NOR that were consistent with the predicate process. For simply scalable processes like blending, single time-based blend uniformity studies may be adequate to identify the PAR and NOR for the new scale. For more complex unit operations, such as the coating operation, a Design of Experiments (DOE) approach may be more appropriate. The team developed a series of balanced orthogonal experiments to establish the PAR for these parameters. This raises another good point to consider when confirming CPPs. By conducting the historical analysis first, it is

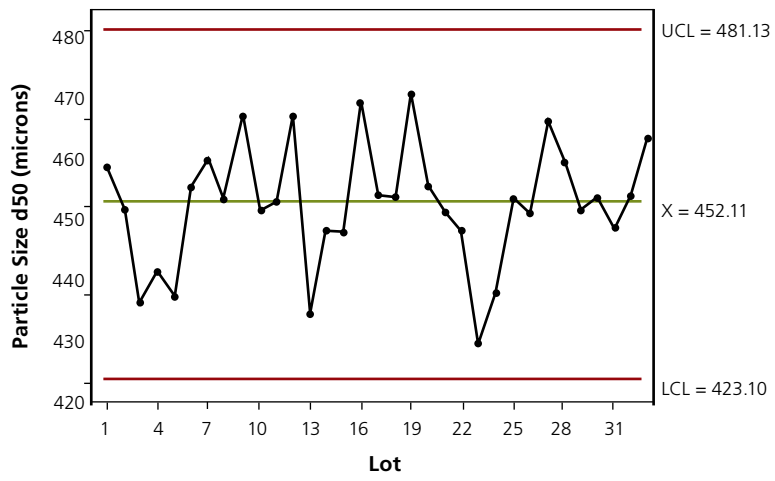


Figure 6. Particle Size for the Granulation Process

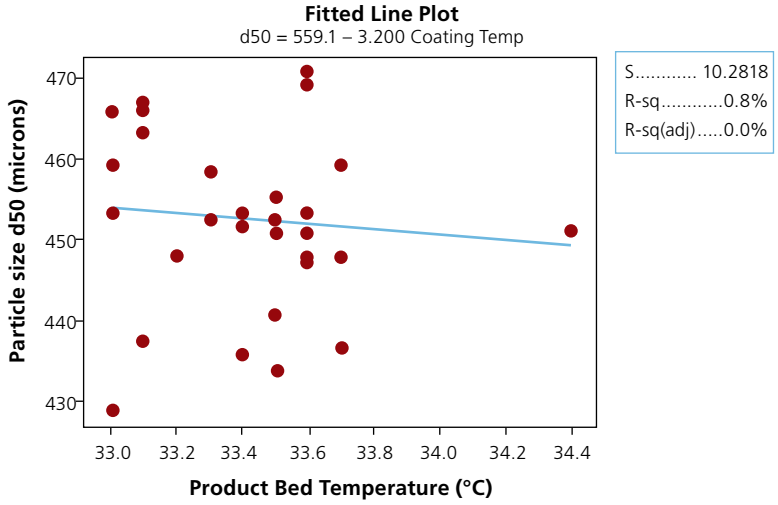


Figure 7. Correlation Between Particle Size and Bed Temperature

possible to reduce the number of variables in the experimental design which reduces the number of runs required.

## CONCLUSION

The new guidance is moving the industry toward a quality-by-design philosophy for process validation. This translates to a more parametric approach rather than an attribute-based approach to process design. The application of a risk-based model, considering the process and product design at the outset of the technology transfer project, allows the application of scientific understanding to filter the potential list of parameters that may affect the process and product CQAs to a limited few. The analysis of historical performance reduces the number of factors that may need to be characterized at the next scale. It also provides a foundation for establishing a baseline PAR and NOR for scale independent parameters when moving to the next scale, factoring in the larger scale equipment design and configuration. Finally, applying a DOE approach to the few remaining scale dependent parameters will establish the corresponding PAR and NOR for the transferred process before moving to the process Control Stage of the roadmap.

In Part II of this case study, we will discuss the considerations in developing an effective sampling plan and acceptance criteria for the Stage 2 PPQ along with how to transition to the Continuous Monitoring stage of the new PV guidance.

## REFERENCES:

1. *Guidance for Industry: Process Validation General Principles and Practices - FDA, January 2011.*
2. *Wheeler, Donald. Understanding Variation: The Key to Managing Chaos, ISBN 0-945320-35-3, SPC Press, Knoxville, TN.*
3. *Chatterjee, Wong, and Rafa. Using Operational Excellence to Meet the New Process Validation Guidance, Pharmaceutical Engineering, Sept. 2011.*

# Tech Transfer's New Framework, Part II

Developing an effective sampling plan and acceptance criteria.

BY BIKASH CHATTERJEE AND MARK MITCHELL, PHARMATECH ASSOCIATES

In this part of the article, we will discuss the considerations in developing an effective sampling plan and acceptance criteria for the Stage 2 Process Performance Qualification (PPQ) and how to transition to the Stage 3 Continuous Monitoring phase of the new PV guidance. With the new guidance, as in the original 1987 guidance, moving to PPQ requires completion of the following:

- Facility and Utility qualification
  - Equipment qualification (IQ,OQ and PQ or equivalent)
  - Analytical Method Validation is complete and Measurement System Analysis (MSA) has concluded that the resolution of the method is appropriate
  - Cleaning Validation protocol; Cleaning method development and validation
  - Upstream processing validation such as Gamma irradiation of components, for the new batch size
  - Environmental Monitoring program for the new facility
  - Master Batch Record
  - Qualification of in-process testing equipment, SMA, validation of method and SOP in place.

In a technology transfer exercise, these elements must be applied to the new equipment and include the larger commercial batch size consideration. If all the elements are not complete prior to beginning the PPQ runs then a strategy may be developed, with the participation of QA, to allow concurrent processing of the PPQ lot and process prerequisites. For example, if cleaning validation has not been completed prior to the PPQ runs, and the PPQ lots are intended for commercial release, then a risk-based approach to the cleaning validation may be adopted with studies conducted concurrently with the manufacture of the lots with the caveat that the lots are not releasable until the cleaning validation program is complete.

If such an approach is adopted then consideration must be given to both the major clean procedure, typically performed on equipment when changing products, and the minor clean procedure, typically performed during a product campaign.

In our case study process, all prerequisites were complete with the exception of cleaning validation, which was conducted concurrently. The new process site used a matrix approach to cleaning validation, bracketing its products based upon an assessment of the API/Formulation solubility, potency, LD50 and difficulty-to-clean profiles. For the purposes of the PPQ runs, only the major clean procedure was used between lots since the minor clean procedure had not been qualified. To establish a PPQ plan that is efficient in demonstrating process reproducibility, the considerations for sampling testing and establishing acceptance criteria must be thoughtfully considered, especially for products with limited development or performance data.

To cite the PV guidance, the objective of the Process Performance Qualification is to "confirm the process design and demonstrate that the commercial manufacturing process performs as expected." The PPQ must "establish scientific evidence that the process is reproducible and will deliver quality products consistently." It is clear that producing three commercial lots in a row to meet its specification limits is no longer sufficient to meet process

qualification objectives. We must develop a statistical prediction for the acceptance criteria of quality attributes, which is typically much more rigorous than simply meeting the specification limit.

## SAMPLING

Since the new PV guidance focuses on quality by design and control, there is greater interest in the identification and control of critical parameters to ensure that critical quality attributes throughout the lot are predictable. We cannot test the entire lot for the quality attributes, but we can control the parameters, and they should predict those quality attributes. Sampling and testing now become a verification of what we should already expect to occur.

A sample from a lot does not tell us the value of a quality attribute since that quality attribute could be variable throughout the lot. In statistical terms, this is known as the population. However, statistics can help us infer a likely range of a lot's mean value for a quality attribute, expressed as a confidence interval. We could also calculate a similar confidence interval for the standard deviation of the lot.

The mean of the sample values is not as important as the calculated confidence interval (usually chosen as 95 percent confidence) for the lot's mean. This is because it is the limit of the confidence interval that must meet our acceptance criteria, since we want to be able to infer that the true mean—and the true standard deviation—meets the acceptance criteria, not just individual tested samples.

To determine the acceptance criteria for PPQ lots, we use the process knowledge from the process design to make an estimate of the process mean—in other words, where the process centers—and the process standard deviation—or how the process varies around the center—for each critical quality attribute. This allows for a statistical comparison of the PPQ lots' means to the expected process mean.

The comparison between two means is done using the "t-Test," to evaluate any difference in two independent samples. The acceptance criteria is successful when the t-Test concludes that the difference between the lot's population mean and the predicted process mean is less than the largest predicted variation of the predicted process mean, calculated from the process standard deviation. In statistical terms, this describes the alternative hypothesis (H1) of the t-Test:

$$H_1: \mu_1 - \mu_2 < (\text{Target Difference})$$

Where, $\mu_1$ and $\mu_2$ are the predicted process mean and the population mean of the PPQ lot and the Target Difference is the predicted variation in the process mean. For the t-test, when the null hypothesis ($H_0$) is not significant, the alternative hypothesis ($H_1$) is concluded to be true.

There are several methods of predicting the process mean and its variation from process design data:

1) **Use a predictive model:** When DOEs are used during process design and a strong relationship (correlation and mechanism) is shown between critical process parameters and critical quality attributes, a mathematical model can be used to predict how variation in the process parameter affects the quality attribute. It is assumed that the PAR of the process parameter is such that the quality attribute will be within specification. Variation in the model itself must be considered since the model equation usually predicts the quality attribute on average rather than for individual PPQ lots, which will vary from the average. Alternatively, scale-up models can also be useful.
2) **Analyze Historical Performance:** When performing a technical transfer from one commercial site to another, the historical process mean and its variation can be calculated to predict performance at the new site.
3) **Analyze Development Performance:** Development lots produced during Process Design are used to determine the PAR for critical parameters. Consequently, these extreme set point runs will produce critical quality attributes at their highest deviation from the process mean.

Variation in the raw materials lot (and any critical material attributes) must be considered in the predicted process variation. A limited number of development lots may not have experienced the full variation due to the limited number of raw material lots used.

As mentioned before, the t-Test is a statistical comparison of means. To compare standard deviations between lots, the statistical test is the F-test (for normally distributed data) or Levene's test (no assumption of normal distribution). The acceptance criteria for the standard deviation of a quality attribute (variation between samples in a lot) must consider how the attribute varies from lot to lot in addition to the variation within each lot to ensure all portions of the lot have a high likelihood of meeting specification.

Certain sampling plans commonly used during PPQ are predefined in various guidance and standards. One example is blend uniformity in which both the minimum sampling requirements and the acceptance criteria are defined. Another is Bergum's Method for Content Uniformity. For user-defined plans (e.g., t-Test) the minimum number of samples must be calculated to ensure that a valid statistical conclusion may be drawn.

For the t-Test, F-test, or Levene test the number of samples is calculated using a power calculation for the specific test. The power calculation uses the conceptions of alpha risk (Type I error, the risk of failing a criteria which actually passes) and beta risk (Type II error, the risk of passing a criteria which actually fails). Power is 1– beta is targeted at either 0.8 (20 percent beta risk) or 0.9 (10 percent beta risk); the actual risk of the sampling plan is determined after the number of samples is known. Calculating the sample size using a power calculation will require the significance level (alpha risk), the estimated maximum standard deviation (between samples), and a target difference.

Figure 1 is an example power curve showing the number of samples for different target power (0.8 and 0.9) with a standard deviation of 1. The sample size is determined by the first curve above the target power for a given target difference. Our choice of target difference is determined by the t-Test acceptance criteria: the largest variation predicted in the process mean.

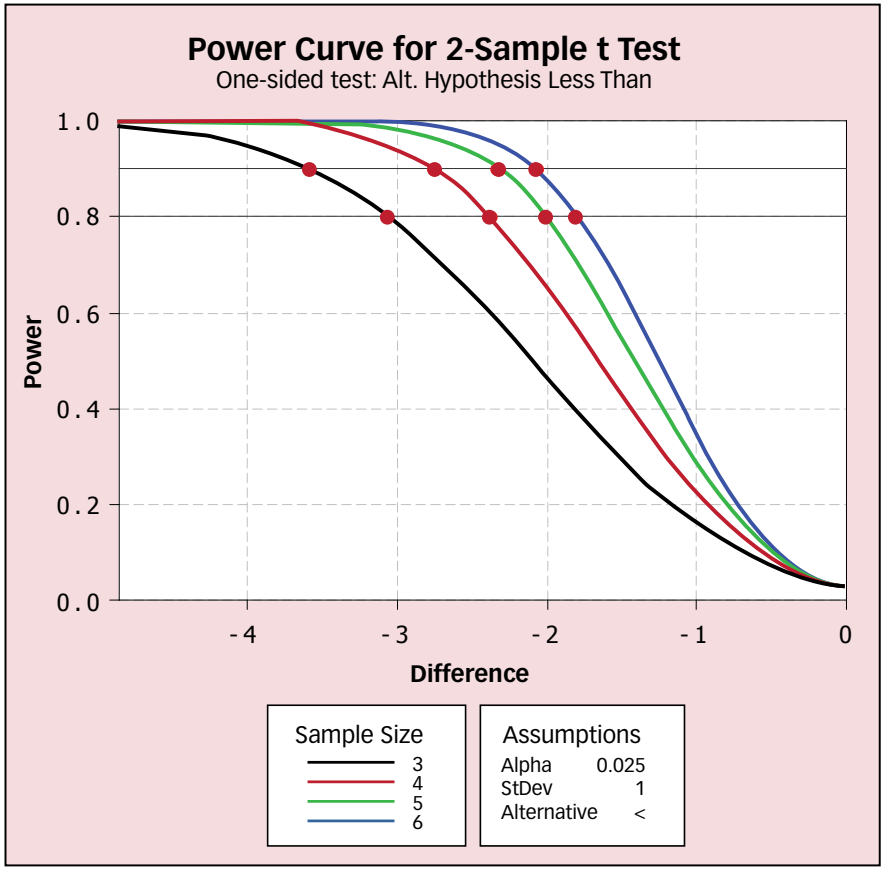


Figure 1: Sample Size by Power Curve for T-test

## LOT ACCEPTANCE SAMPLING PLANS

When sampling for attributes that are discrete (pass/fail) rather than continuous (a numeric value), the sampling plan

is determined by an operating characteristic curve instead of a power curve. Frequently used for visual defects, these plans are either calculated or selected from the ANSI Z1.4-2008 standard for sampling by attributes. In our case, the manufacturer's quality assurance group chose the Acceptance Quality Level (AQL) for the attribute, because it represented the maximum process average of defects for that attribute over time.

The desire for PPQ lots is to increase the number of samples (i.e. discrimination of the sample plan). However, shifting the AQL is not recommended since the AQL is not representative for individual lots in isolation. To create a more discriminating sampling plan for PPQ, the Limiting Quality (LQ, also called Lot Tolerance Percent Defective, LTPD) is the preferred method for creating a more discriminating plan for PPQ.

Figure 2 compares a standard lot plan under Z1.4 (General Inspection Level II) to a more discriminating PPQ lot plan (General Inspection Level III). The number of samples increases from 500 to 800 and the LQ at 10 percent acceptance changes from approximately 0.77 percent defective to 0.65 percent defective.

These types of sampling plans are only suitable for individual lot acceptance; they do not determine the actual percent defective for a lot. These plans only assure that lots above the LQ have a low (10 percent or less) probability of being accepted under this plan.

The PV Guidance no longer defines the number of lots required for PPQ; it is left to individual manufacturers to justify how many lots are sufficient. There is no safe harbor for producing three PPQ lots since justification must be made for any number of lots. In order to make any reasonable argument of reproducibility, it would be expected that the minimum number of lots be no less than two to three. It is usually not necessary to operate process parameters at the extremes of the NOR since this should have been previously established. As such, the setpoints of process parameters are not changed between PPQ lots and do not impact the number of PPQ lots required. In determining the number of lots consideration should be given to understanding the source and impact of variation

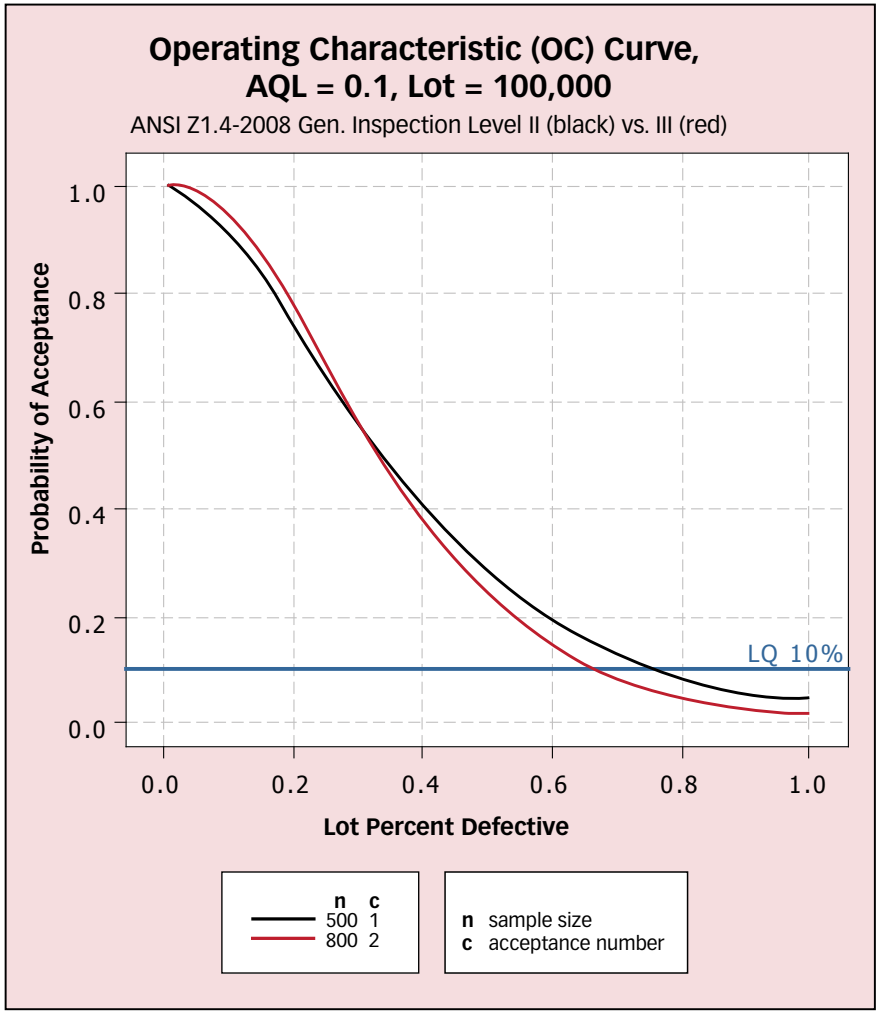


Figure 2: Limiting Quality Comparison between Z1.4 Sample Plans

on quality attributes. Suggested sources of variation to consider are:

- Number of raw material lots, especially when a critical material attribute is identified;
- Number of commercial scale lots previously produced during Process Design;
- Number of equipment trains intended for use;
- Process complexity and number of intermediate steps;
- History of performance of commercial scale equipment on similar products;
- Number of drug strengths;
- Variation of lot size within commercial equipment;
- In-process hold times between process steps;
- Number of intermediate lots and mixing for downstream processes.

It is recommended to perform a risk analysis of these sources of variability. The number of PPQ lots can then be determined by matrix design of the sources with the highest risk to variation of quality attributes. Those sources of variability, which cannot be included in the PPQ, should be considered for monitoring during Stage 3 - Continuous Process Verification.

After completing the PPQ analysis, the team revisited the risk matrix to reflect the commercial operation. This data was included in the Stage 2 final report.

## STAGE 3 – DATA MONITORING

The last stage of the new PV lifecycle is process monitoring. While monitoring has been part of the normal drug quality management system (QMS), the new PV guidance advocates moving beyond the normal CQAs reported in a product's Annual Product Review (APR) and extending them to include the CPPs that have been identified as critical to process stability. For the product in question, a protocol was drafted to gather data over the next 20 lots to establish alert and action limits relating to process variability. This data was intended to be reported in the product scorecard and included in the APR.

## REFERENCES


1. *Guidance for Industry-Process Validation: General Principles and Practices, January 2010, Rev. 1.*
2. *ANSI/ASQ Z1.4-2008, "Sampling Procedures and Tables for Inspection by Attributes."*
3. *Kenneth Stephens, The Handbook of Applied Acceptance Sampling Plans, Procedures and Principles, ISBN 0-87389-475-8, ASQ, 2001.*
4. *G.E.P Box, W.G. Hunter, and J.S. Hunter, Statistics for Experimenters, ISBN 0-471-09315-7, Wiley Interscience Series, 1978.*
5. *Douglas C. Montgomery, Design and Analysis of Experiments, 5th Ed., ISBN 0-471-31649-0, Wiley & Sons, 2001.*
6. *Schmidt & Launsby, Understanding Industrial Designed Experiments, 4th Ed., ISBN 1-880156-03-2, Air Academy Press, Colorado Springs, CO, 2000.*
7. *Donald Wheeler, Understanding Variation: The Key to Managing Chaos, ISBN 0-945320-35-3, SPC Press, Knoxville, TN.*
8. *W.G. Cochran and G.M. Cox, Experimental Designs, ISBN0-471-16203-5, Wiley and Sons, 1957.*
9. *Box, G.E.P., Evolutionary Operation: A method for increasing industrial productivity, Applied Statistics 6 (1957) 81-101.*
10. *Box, G.E.P. and Draper, N.R., Evolutionary Operation: A Statistical Method for Process Improvement, ISBN 0-471-25551-3, Wiley and Sons, 1969.*
11. *Pramote C, Use of the Bergum Method and MS Excel to Determine the Probability of Passing the USP Content Uniformity Test, Pharmaceutical Technology, September 2004.*

# Overview: Methods of Sterilization

Sterile semi-solids and liquids can either be made in a sterile environment using sterile ingredients, or can be made in a clean environment and then sterilized once they are completed (terminal sterilization). "Terminal sterilization is the most economical process, and the one that regulatory authorities prefer, because it gives higher levels of assurance," says Charles Shaw, scientific advisor at DPT Laboratories. The choice of method of sterilization will depend on the product, and those semi solids and liquids that cannot withstand terminal sterilization, including injectables, infusions, vaccines and protein- or peptide-based products, or whose packaging will be damaged in the terminal sterilization process, will have to be manufactured and packaged in a sterile environment using aseptic processing techniques (1). Semi solid and liquid products and ingredients can be sterilized using filtration, heat, ethylene oxide gas or gamma radiation. The stability and solubility of the API will determine how it is sterilized and manufactured, for example, and the level of sterility required may vary from product to product.

- **Filtration** is used for liquids that are sensitive to heat or irradiation. Microfiltration uses a filter with 0.2 µm pores to remove bacteria and fungi; nanofiltration uses a filter with 20 -50 nm pores to remove viruses, and smaller pores mean lower filtration rates.
- **Heat sterilization** can be used for equipment and heat-stable liquids and semi-solids. This process will inactivate bacteria, fungi and viruses, but will degrade protein-based drugs.
- **Ethylene oxide gas** is a powerful antioxidant, and can be used to sterilize solid materials that are sensitive to heat or irradiation. However, it is highly flammable and toxic for the operators.
- **Gamma radiation** is an effective sterilizing method but has limited ability to penetrate formulations containing water.

The use of any method of sterilization will need to be validated, to ensure that the process doesn't add anything and is only removing or inactivating contaminating microorganisms, with no impact on the product's safety or efficacy.

## HANDLING SEMI-SOLIDS AND LIQUIDS

Semi-solids and liquids do have to be handled differently from solid products, both in the process of sterilization and in the techniques of packaging. Liquids are generally sterilized using filtration, with the sterile product then held in a presterilized storage tank. The oil and aqueous phase of an emulsion can be sterilized separately and then combined in a pre-sterilized tank. Ointments or gels can be too viscous to filter, but petrolatum (petroleum jelly) and other ointment and gel bases can become thin enough to filter when heated.

The ointment or gel is then sent to a pre-sterilized tank where it is cooled and mixed with the sterilized API (active pharmaceutical ingredient) using a sterile glove box. The API is introduced using isolator technology over the hatch, and the isolator environment is sterilized before opening the hatch. The whole process is qualified through a media fill.

Generally, liquid manufacturing and sterilization is an onstage process, whereas semi-solids will require a number of stages. Increasing the number of stages increases the cost and complexity, as each step will need to be validated, and may increase the need for human intervention and the risk of contamination.

Types of packaging also differ for liquids and semi-solids—gels and ointments are likely to be packaged in tubes, whereas liquids will mostly likely be filled into a vial or a pre-filled syringe.

"There are differences in the primary components, but the basic rules of sterile manufacturing and processing remain the same," said Gene Ciolfi, Vice President & General Manager Lakewood Site Operations, DPT Laboratories.

# Cutting Contamination Within Sterile Processing

Sterile processing and manufacturing needs to remove or prevent contamination, and the most common source of contamination is from people, because of the microbial fauna naturally colonizing the body, including the hair, skin, mouth and nose."

A fully gowned operator may release as many as 10,000 colony forming units [CFUs] per hour using controlled and defined movements, with certain movements exacerbating the situation as his or her clothing essentially pumps air, and therefore microbes, through the openings," says John Erdner, VP of sales and marketing, IMA Life North America Inc.

The fundamentals of sterile processing are based on keeping operator intervention to a minimum, by separating or removing people from the aseptic environment(1). Other necessary steps include increasing automation, training employees, qualifying the processes, reducing contamination during processing, and ensuring that material and personnel transfer does not violate the integrity of the system.

"You can fix machines and processes, but it is harder to fix human failings, so the best thing is to simply take the operator out of the equation through isolation and automation, reducing variability," says Jim Agalloco of Agalloco &Associates, a provider of technical services to the pharmaceutical and biotechnology industries. "It is only possible to have a good product if the materials, controls and people are right."

## KEEPING OPERATOR INTERVENTION TO A MINIMUM

Systems such as restricted access barrier systems (RABS) and isolators reduce the contact that operators have with the sterile products (1).

"It is easy to sterilize the packaging and the environment — it is the people that are the problem; any way that will keep people away from the products will improve the process," says Shaw.

RABS setups use the following Quality by Design characteristics (2, 3):

- A rigid wall or enclosure separating the workers from the sterile processing area
- A one-way airflow from the clean area (ISO 5/class 100 standard)
- Passive RABS uses a laminar flow from the cleanroom venting system; active RABS has its own HEPA filter and laminar air flow drawing air from the cleanroom and exhausting it back; closed RABS (cRABS) is a sealed system that can be operated under pressure and the air is circulated within the enclosure
- Sterilization-in-place (SIP) for parts contacting liquids and semi-solids, with the transfer of autoclavable parts aseptically
- A transfer system for consumables and other equipment
- Automation for the filling operations, or glove ports or half suits for operators who are involved with the process
- High level disinfection of all non-product contact surfaces
- The system should be in a room that is ISO 7/class 10,000 minimum
- The access doors should be lockable and/or alarmed
- Controlling contamination during processes that involve an open door intervention through disinfection, positive airflow, and maintaining ISO 5/class 100 standards around the area of the door using a unidirectional laminar airflow.

As an example, IMA Life North America has installed a RABS system for DPT Laboratories. "This system is not completely sealed but is contained within solid walls, and the pressure can be increased in the enclosure," says Erdner.

An isolator is a sealed system that completely segregates the worker from the sterile processing space. The equipment

can be designed to separate different zones within the isolator and create pressure gradients. The air within both the isolators and RABS only travels in one direction (3). RABS and isolators use glove ports, for example in filling areas and stoppering and capping areas, to allow human interaction while minimizing the risk of contamination. RABS may be simpler to operate, lower cost and more flexible than isolators, but are not sealed systems, so there are some areas that are vulnerable to contamination (1).

## INCREASING AUTOMATION

Manual processes increase variability, so introducing as much automation as possible makes the process easier to validate and more reproducible.

"Every manual step is an opportunity for contamination, and the best scenario would be vials in at one end, product out at the other, without human intervention," says Erdner.

Automated systems do also reduce the number of people that need to be involved, again reducing the contamination risks as well as the operational costs.

## EMPLOYEE TRAINING

To reduce variability for the steps that still require operators, training is a vital part of the process.

"Operator's variability is a weak point in the process," says Agalloco. "Everyone has good and bad days, and the aim should be to make the process so robust and so reproducible that people can succeed even on their worst day."

Training needs to be robust and detailed, and include how to gown or suit-up and enter the cleanroom, how to operate the system, processing, and filling using aseptic techniques if manual steps are required, and how to clean the system. Employees will need to qualify at each step.

"One of our training focuses is on the behavior in the cleanroom, making sure that people use aseptic technique, such as not leaning over open vials. Better training reduces the variability, and qualifies both the people and the process," says Ciolfi.

## DESIGNING AND QUALIFYING THE PROCESS

Sterile processing needs to have standard operating protocols (SOPs)in place, including risk mitigation approaches and checks and balances for every step. However, to put SOPs in place, the facility design has to be optimum — as Shaw says, it is important to design in quality rather than bolt it on. It's then possible to create the best and most effective processes and procedures.

Once the system and the SOPs are in place, the effectiveness of the sterility assurance controls can be checked using a 'media fill'. These are samples of microbiological culture growth medium that go through the manufacturing process following the usual procedures, ensuring that they contact the same surfaces that the product ingredients will during manufacturing. The media is then incubated for 14 days, and the presence of microbial growth will indicate any contamination in the system. Regulatory authorities may also require a media feasibility study to confirm that the media will still support growth after processing. Media fills are typically run twice a year.

"The role of these media fills is to confirm and validate the sterility of the process. A successful media fill means a qualified sterile manufacturing process," says Ciolfi.

If a media fill shows up evidence of contamination, then the whole process has to be examined to find the probable root cause.

"If the root cause is found, then the issue will be easy to fix,"

says Ciolfi. “However, if it can’t be found, then it is a case of going right back to the beginning, setting the process up all over again and revalidating it.

”However, the necessity for the media fills and the media feasibility studies adds to the burden of the development side of product manufacturing, particularly for small companies, and it’s possible that, now that sterile manufacturing is so automated, their necessity is becoming more limited.

“The costs of sterile manufacturing have fallen and the effectiveness has increased,” says Agalloco. “Now, most facilities are so good that the microbiological testing process is almost ‘ceremonial’, and only the very worst plants will fail. Some monitoring processes can even increase the risk of contamination. However, media fills are likely to remain in place as it will always be needed by the weakest companies, and regulators are unlikely to be happy with no testing.”

The products will also need to be tested for the stability of the active ingredient before and after processing.

## PROTECTING STERILITY DURING MATERIAL AND PERSONNEL TRANSFER

As mentioned before, sterile manufacturing systems will generally use cascading airflows to maintain sterility, with the highest (positive) air pressure in the cleanest area, reducing the risk of environmental contaminants and particles moving from ‘dirty’ to ‘clean’ areas, and the lowest pressure areas acting as ‘air sinks’. Workers entering the system will usually go through multiple gowning or suiting steps and pass through a number of cleanrooms or airlocks that become increasingly hygienic.

“The large pressure cascade gives greater assurance that the products are not contaminated with particles or pathogens,” says Erdner.

Generally, anything that has to come into the sterile environment is enclosed in multiple bags or wrappings, with layers removed in increasingly clean environments separated

## TWO WEBINARS ADDRESS RISK MANAGEMENT IN STERILE MANUFACTURING

- Examine best practices for risk management in sterile manufacturing
- Examine FDA’s process validation guidelines

**RISK MANAGEMENT IN STERILE MANUFACTURING–PART 1**
http://www.dptlabs.com/resource-center/webinars/risk-management-in-sterile-manufacturing/

- Michael Curry, Director of Operations
  DPT Lakewood, Center of Excellence for Aseptic and Specialty Products
- Hal Baseman, Chief Operating Officer and Principal at ValSource LLC
  Chair-Elect of the Parenteral Drug Association (PDA) Board of Directors, Vice-Chair of the PDA Science Advisory Board, and Co-Leader of the PDA Process Validation Interest Group
- Dr. Mike Long, MBB, Director and Senior Consultant with ConcordiaValSource LLC, Co-chair of the Parenteral Drug Association’s (PDA) Risk Management Task Force and member of PDA’s Science Advisory Board

**RISK MANAGEMENT IN STERILE MANUFACTURING–PART 2**
http://www.dptlabs.com/resource-center/webinars/risk-management-in-sterile-manufacturing-part-2/
Speakers:

- Michael Curry, Director of Operations
  DPT Lakewood, Center of Excellence for Aseptic and Specialty Products
- Hal Baseman, Chief Operating Officer and Principal at ValSource LLC, Chair-Elect of the Parenteral Drug Association (PDA) Board of Directors, Vice-Chair of the PDA Science Advisory Board, and Co-Leader of the PDA Process Validation Interest Group

by airlocks (4). Techniques include trapping the packaging in the airlock door, so that the item is transferred into the cleaner area and the packaging remains in the 'dirty' area. Any damage to the wrapping can cause problems.

"It is vital to think about what is needed and how it gets into the sterile system, from a piece of paper or a pen to a clock," says Agalloco. "However, getting things out of the system is not as hard as getting them in."

This process is effectively reversed when items are removed from the system, and the sterility is maintained by the positive airflow from 'clean' to 'dirty'.

## REDUCING CONTAMINATION DURING PROCESSING

Packaging components for semi solids and liquids, such as vials or syringes, can be supplied already sterile and double-bagged, or manually washed and then sterilized as part of the process. Techniques will vary according to the material — for example, vials can be decontaminated by heating to high temperatures in a depyrogenation tunnel, and plastic can be sterilized using gamma radiation. It is important to maintain the sterility of the vial between depyrogenation and filling, and reducing the distance that any sterile components or ingredients have to travel cuts the risk of contamination.

Increasing integration, keeping the processes within one piece of equipment or integrated system, will also reduce the risk of contamination by reducing the need for transfers from one piece of equipment to the next.

"The sterile manufacturing process should be as completely integrated as possible," says Ciolfi.

This doesn't necessarily mean buying a fully integrated system from the get-go; systems such as those from IMA can be created from modules that can be added on as required.

Increasing the efficiency of the system is also important, because any major intervention, such as blockages, repairs, or removing damaged vials, will generally require stopping the production line. This will expose other vials to potential microbial contamination, and may mean throwing contaminated vials, or even, occasionally, an entire batch.

In a sealed system, if the production line has to be stopped and the system opened up, the batch may have to be thrown away. Shaw says: "This kind of wastage can be built into the costs. Any sterility failures can shut plants down for months, so it is worthwhile writing off one single batch," says Shaw.

There are a number of approaches to increasing efficiency and reducing breakdowns, and IMA's approach is to make the whole process a little gentler.

"The line for smaller batch sizes runs at a slower speed of 120 vpm, which provides the opportunity for us to design the component-handling parts with a little wider tolerances. The entire system is more 'forgiving' of component variability, increasing the overall efficiency. We believe that running slower can sometimes result in increased net production," says Erdner.

Contamination doesn't just involve pathogens — fragments of stoppers or broken glass can also contaminate the finished product, creating a hazard for patients. As the rubber stoppers that seal vials move they generate particles, in what is known as the 'eraser' effect, and these can be transferred into the vial during stoppering and sealing.

"One way to avoid this," explains Erdner, "is to ensure that the stopper sorting and pick up is positioned below the neck of the vial and there is minimal component movement above the vial during placement of the stopper. In the capping process, we synchronize the rotation of the cap and vial, as well as limit the amount of rotation to 460° to minimize particulate generation. Particle count in this area will remain under 100 per cubic foot of air. A continuous vertical force is maintained and monitored to ensure consistent sealing results."

Once the products are filled and sealed, then the sterile part of the process is completed, but any labeling and secondary packaging must not affect the integrity.

# Training and Skill Development Concerns for Sterile Manufacturers

In January 2013, more than 235 pharmaceutical professionals completed *Pharmaceutical Manufacturing*'s Training Survey. The purpose of the study was to determine training and skill priorities in the industry and to identify potential weaknesses that have resulted from reduced staffing within the pharmaceutical industry.

**Do you see a skills "gap" or mismatch within your organization?**

| | |
|---|---|
| No. People are doing what they have been trained to do | 29.8% |
| Somewhat. Lately, we've all had to pitch in to do things outside our traditional domains | 44.5% |
| Yes. People are often not doing working that matches their skills and training & it is hurting productivity | 19.5% |
| Yes. We simply have not been able to find people to fulfill key responsibilities | 6.2% |

***70.2% of the pharmaceutical industry*** *has a at least some skills gap or skills mismatch within their organizations.*

**Pharmaceutical manufacturing professionals are being asked to do more, have constantly expanding skills and knowledge and respond to constant change – continuing education is needed to meet these challenges.**

*"As a result of mergers and layoffs, many have had to take on additional responsibilities."*

*"All are being encouraged to broaden their skill sets to better enable support as needed."*

*"Due to less personnel, we all have had to do tasks outside our normal positions."*

*"I am called upon to be both a generalist and a specialist."*

**Regulatory agencies are moving to enforcement based on better understanding of processes and risk. Do you feel your employees have sufficient training in what is required to demonstrate this understanding?**

| | |
|---|---|
| No | 57.9% |
| Yes | 42.1% |

**The most pressing needs for better validation skills listed in order of importance are:**

1. Process
2. Product
3. Cleaning
4. Software/IT
5. Building/Commissioning
6. IT

**What are the key areas of training required for your employees to better understand processes and risks?**

| | |
|---|---|
| Understanding sources of variability in final product | 95.3% |
| Understanding sources of variability in raw materials | 94.2% |
| Understanding the need to utilize CAPA information to optimize processes and product | 91.6% |
| Understanding of critical quality attributes | 96.9% |
| Understanding critical process parameters | 98.4% |
| Determining the design space | 79.9% |
| Determining the control space | 80.5% |
| Being able to use multivariate data | 81.3% |
| Correlating data from maintenance and asset management to batch and manufacturing | 79.3% |
| Understanding the potential cost of quality and compliance problems | 89.8% |
| Applying process capability analysis | 82.1% |
| Applying statistical process control | 83.3% |

## ABOUT DPT

With a specialized focus on semi-solids and liquids, DPT offers pharmaceutical companies the broadest range of capabilities in the industry. From R&D formulation to commercial-scale manufacturing, small batches to large, liquids to emulsions, cans to pumps, sterile or non-sterile, we offer clients of all sizes the most effective resources for meeting challenges.

Whether you're a startup operation or Big Pharma, we can take your project all the way from lab to production. Just as important, we continue to invest heavily in our capabilities, including centers specializing in semisolid and liquid manufacturing, aseptic manufacturing and R&D.

## SERVICES OFFERED

**Comprehensive Drug Development Services for Sterile & Non-sterile Dose Forms**

- Pre-formulation and formulation development
- Biopharmaceutical development
- Analytical and method development and validation
- Stability studies
- Process development and validation
- Pilot and proof-of-concept batches from 0.3 kg
- Clinical trial materials phase I-III Packaging Services
- Identification and sourcing of relevant packaging options
- Packaging specification development
- Formulation and package compatibility assessment
- Packaging equipment sourcing, design, and engineering services
- Turnkey sourcing services for unique and specialized packaging

**Manufacturing Services for Sterile & Non-Sterile Dosage Forms**

- Five cGMP facilities
- cGMP batch sizes from 0.3 kg - 25,000 kg Controlled substances Schedules II-V
- Extensive packaging capabilities for semi-solids and liquids
- Specialized equipment installation, operational qualification, and validation services

## FACILITIES

Headquartered in San Antonio, TX, DPT has four facilities there and one in Lakewood, NJ, with state-of-the-art development, manufacturing, packaging and distribution space.

## ADDITIONAL RESOURCES

DPT's Resource Center contains a variety of white papers, articles and webinars.
www.dptlabs.com/resource-center

**DPT**
318 McCullough, San Antonio, TX 78215
Tel: 210-476-8100
www.dptlabs.com