THE BEST OF 2012
As competitive pressures continue to increase, pharmaceutical manufacturing professionals are challenged every day to do more with less, and to do it right the first time, without compromising product quality or patient safety.

This selection of articles, chosen by readers and our editors as among the most useful of 2012, offer insights into trends as well as practical guidance for improving process understanding, compliance, product quality and operational efficiency. Most are written by independent consultants and your peers.

We hope that you find them useful in your quest for continuous improvement.
ESTIMATING CAPITAL project budgets can be a tricky business. There are many factors to include as inputs to the budget: vendor quotes, capital labor, permits, third-party inspections, expenditure data from previous projects, material escalation . . . the list goes on and on. Unfortunately, each input can itself be an estimate, and each input can present cost uncertainty risks. Because it is impossible to calculate a precise, infallible budget (owing to the nature of project risk and cost uncertainty), numerical analysis is a good option for arriving at a solution. In the case of predicting capital budgets, the Monte Carlo Simulation (MCS) is the numerical method of choice.

What is MCS? In terms of project cost risk, MCS is a tool for calculating the statistical likelihood of exceeding a base budget by a given value. The goal is to assign a statistically derived dollar value to the various risks associated with the project. The MCS calculates budget values and likelihoods based on two key inputs for each budget line item: 1) the forecasted cost distribution for the expenditure; and 2) the chance of incurring the expenditure. For example, in Table 1, Item A should cost between $70,000 and $85,000, and there is a 100% likelihood of incurring the cost; Item B should cost between $10,000 and $15,000, but there is only an 80% chance of incurring the cost.

<table>
<thead>
<tr>
<th>Budget Line Item</th>
<th>Low Cost</th>
<th>High Cost</th>
<th>Probability of Occurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item A</td>
<td>$70,000</td>
<td>$85,000</td>
<td>100% (decimal value 1.0)</td>
</tr>
<tr>
<td>Item B</td>
<td>$10,000</td>
<td>$15,000</td>
<td>80% (decimal value 0.8)</td>
</tr>
</tbody>
</table>

Table 1: Example Monte Carlo Inputs

How to Apply Monte Carlo Simulation to Engineering Capital Projects

By Keith Melchior, Biogen Idec
The MCS generates random numbers and applies them to the cost and likelihood-of-occurrence for each line item. The sum of all line items is a resulting budget scenario—also called an iteration. The first iteration may yield a budget of $93,561 because Item B occurs. The second iteration may yield a budget of $74,829 because Item B doesn’t occur (Table 2).

Using this random “roll of the dice” calculation method, the MCS generates thousands of budget iterations. A simple results chart then tabulates the iterations and calculates the budget contingency required to have X% certainty of staying within budget. MCS overall results typically read like this: for a $90,000 baseline budget, a contingency of $2,950 should be allocated to assure that the project doesn’t go over budget—assuming management accepts an 80% likelihood of staying within budget. For a 90% likelihood of staying within budget, the MCS may calculate that $5,820 contingency is required.

At this point, many project managers and engineers will say, “OK, fine, I’ll try using an MCS to estimate my budget—where can I download one, and how much does it cost?” There certainly are commercially available MCS software packages, and some are very affordable (less than $100 for a single license). The problem lies in using a black-box method to estimate a budget. Regardless of how poorly or how well an MCS package performs, it is likely that the end user doesn’t fully understand its internal workings. What probability distributions are used? Is the random number generator truly random? How many iterations are performed? For that matter, how many iterations are required?

For those willing to remove the MCS from within its black box, the rewards are great. The only requirements for creating an MCS from scratch are: 1) a spreadsheet program; 2) familiarity with basic spreadsheet functions; and 3) following along with the example below. The end product will be an MCS spreadsheet that is user-friendly, documented, fully understood, and similar in function to commercially-available options.

**BUILDING YOUR OWN MCS TOOL**

The most important aspect of understanding MCS mechanics is knowing how to generate meaningful cost probability distributions. There are many probability distributions that could be used to describe forecasted cost: normal distribution (standard bell curve), uniform distribution (see Table 2), log-normal distribution, beta distribution, etc. The problem lies in translating straightforward cost data into statistical distribution lingo. It takes a skilled statistician to, for example, analyze limited data and generate the $\alpha$ and $\beta$ parameters of a beta distribution. Moreover, how does “$\alpha=2$, $\beta=5$” translate to a $10,000,000 line item? The beta parameters have no clear meaning on the surface.

Fortunately, there exists a straightforward and easy-to-generate distribution that is well suited to MCS’s: the triangular distribution (TriD) shown in Figure 1. A TriD has three simple parameters: low limit $a$, high limit $b$, and likely value $c$. The TriD’s Probability Distribution Function (PDF, a function that describes the likelihood of a random variable having any given value) shows the characteristic triangular shape, with the “likely value” having the highest chance of occurring. The chance of occurring drops to 0% at the high and low values (Figure 1).

---

**Table 2: Example Monte Carlo Iteration Results**

<table>
<thead>
<tr>
<th>Iteration</th>
<th>Item A</th>
<th>Item B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost RAND</td>
<td>Occur RAND</td>
<td>Cost</td>
</tr>
<tr>
<td>1</td>
<td>0.8251</td>
<td>0.1167</td>
<td>$82,377</td>
</tr>
<tr>
<td>2</td>
<td>0.3219</td>
<td>0.6178</td>
<td>$74,829</td>
</tr>
</tbody>
</table>

Notes:
- All RAND columns are randomly generated values between 0 and 1.
- An item’s “Occur RAND” must be less than the input “Probability of Occurring” to incur the cost.
- Uniform cost probability distribution is assumed, implying even chances of obtaining any value between Low and High inputs. Hence, the “Cost RAND” simply scales between the input Low and High costs.

---

**Figure 1: Triangular Distribution (Probability Density Function)**
The TriD is a good choice for MCS’s for multiple reasons. First, the parameters \((a, b, c)\) used to define the distribution are easily superimposed onto a budget line item: lowest possible cost, highest possible cost, and most likely cost, respectively. This aids in easy comprehension of the cost inputs. Additionally, the triangular shape of the distribution is versatile enough to approximate forecasted cost for a variety of possible line items. For example, “time & material” line items can place the Likely Cost centrally between the Low and High Costs (roughly approximating a bell curve)—this accounts for the risk of either less or more T&M cost. For lump-sum and not-to-exceed budget items, the Likely Cost can be set closer to (or equal to) the High Cost, indicating low likelihood of exceeding the line item cost. If using expired vendor quotations to forecast future projects, the Likely Cost can be set equal to the Low Cost, indicating likelihood of future cost being higher than current benchmark data.

Important Note: For each line item, the MCS user must carefully consider the Low, High and Likely values. Obtaining early consensus on MCS inputs with vested internal parties can prevent questions and challenges in later project stages.

Returning to the previous MCS input example (Table 1), Item A was assigned a low limit of $70,000 and a high limit of $85,000. To generate a TriD for Item A, the only missing input is assignment of the likely value. Assuming that a vendor has quoted Item A at $75,000, our TriD specification is complete \((a=70,000, b=85,000, c=75,000)\). The only remaining hurdle is to transform the three TriD parameters into a randomly-generated cost data sample that takes on the triangular distribution when tabulated.

Using a spreadsheet’s random number generator, infinite random decimal numbers between 0 and 1 can be created. Kotz and van Dorp [1] provide the equations necessary to transform this random variate into a triangular distribution with Low Value = \(a\), High Value = \(b\), and Likely Value = \(c\). The TriD transformed line item cost \(\text{Cost}_{\text{TriD}}\) for a random cost variable \(x\) in any iteration is given by Equations 1 and 2 (for \(0 \leq x \leq 1\)):
Because the likelihood of occurrence may not be 100% for all line items, an additional check is performed to determine if the line item’s cost is included in the iteration total cost. The assigned iteration cost “CostI” of each line item, based on random occurrence variable y is given by Equations 3 and 4 (for \(0 \leq y \leq 1\)):

\[
Cost_I = \begin{cases} 
\text{IF}(y < \text{Likelihood}, \text{IF}(c-a)/(b-a) > x, a + x(b-a)(c-a)^0.5, b-(1-x)(b-a)(b-c)^0.5, 0) 
\end{cases}
\]

Formula 1

\[a = \text{TriD low value}\]
\[b = \text{TriD high value}\]
\[c = \text{TriD likely value}\]
\[x = \text{random variable between 0 and 1, for transforming a random variable into a TriD data point}\]
\[y = \text{random variable between 0 and 1, to test if line item cost occurs}\]
\[
\text{Likelihood} = \text{line item chance of occurring}\]
\[
\text{Cost,} = \text{line item’s assigned iteration cost, based on TriD calculation and likelihood of occurrence}\]

By referencing previously entered TriD inputs \((a, b, c, \text{ and likelihood})\), along with two long columns of random numbers \(x\) and \(y\) for each iteration, Formula 1 will generate the TriD data points for each line item.

To transform this data set into a meaningful visual representation, the individual points must be sorted into a Cost Frequency Distribution—a graph showing how frequently the Cost, results fall into various cost brackets. To accomplish this, create a column of 20 numbers: from the line item’s Low Value to High Value, with intervals of \((\text{High-Low})/20\). This column will be the values of the \(x\) axis for the cost frequency distribution. To sort each randomly generated Cost, into a cost frequency distribution bracket, a vlookup is performed and a bracket for the cost selected using Formula 2.

\[\text{Cost,}’s \text{ Selected Bracket} = \text{vlookup}(\text{Cost,}, \{\text{range of 20 bracket values}\}, 1, \text{TRUE})\]

Formula 2

Assuming 1,000 iterations were calculated, Formula 2 will be used to sort each of the 1,000 Cost, values into a cost bracket. This creates a column of 1,000 numbers, each being a value from the list of 20 brackets. Now, a CountIf formula (Formula 3) can be used to tally the Formula 2 results for each of the 20 brackets:

\[\text{Sum of Data Points for Each Bracket} = \text{CountIf}(\{\text{entire range of Formula 2 results}\}, \{\text{individual bracket from the table of 20}\})\]

Formula 3

By graphing the Formula 3 results against the list of 20 bracket values, a visual representation of the TriD is created. In Figure 2, each bar represents the number of data points randomly generated between the indicated \(x\) axis value and the next higher \(x\) axis value. For example, 51 data points fall between Cost, of $79,000 and $79,750. Only 2 data points fall between $84,250 and $85,000. It should be noted that Figure 2 does not take on a perfectly triangular shape—this is to be expected. Because the dataset is based on a random number generator, there

Table 3: Vessel Procurement Monte Carlo Inputs

<table>
<thead>
<tr>
<th>Budget Line Item</th>
<th>Low Cost</th>
<th>High Cost</th>
<th>Likely Cost</th>
<th>Probability of Occurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel</td>
<td>$70,000</td>
<td>$85,000</td>
<td>$75,000</td>
<td>100% (decimal value 1.0)</td>
</tr>
<tr>
<td>Agitator</td>
<td>$10,000</td>
<td>$15,000</td>
<td>$14,000</td>
<td>80% (decimal value 0.8)</td>
</tr>
<tr>
<td>Piping</td>
<td>$8,000</td>
<td>$10,000</td>
<td>$8,000</td>
<td>100% (decimal value 1.0)</td>
</tr>
</tbody>
</table>

\[
\text{Cost}_{\text{min}} = a + \sqrt{x(c-a)(b-a)}, \text{for } 0 \leq x \leq \frac{c-a}{b-a}
\]

Equation 1

\[
\text{Cost}_{\text{max}} = b - \sqrt{(1-x)(b-c)(b-a)}, \text{for } \frac{c-a}{b-a} \leq x \leq 1
\]

Equation 2

Because the likelihood of occurrence may not be 100% for all line items, an additional check is performed to determine if the line item’s cost is included in the iteration total cost. The assigned iteration cost “Cost,” of each line item, based on random occurrence variable y is given by Equations 3 and 4 (for \(0 \leq y \leq 1\)):

\[Cost_I = \text{Cost}_{\text{min}} \text{ for } y < \text{Item Likelihood of Occurrence}\]

Equation 3

\[Cost_I = 0 \text{ for } y \geq \text{Item Likelihood of Occurrence}\]

Equation 4

When translated to spreadsheet language, Equations 1-4 can be condensed to this formula:

\[Cost_I = \text{IF}(y<\text{Likelihood}, \text{IF}(c-a)/(b-a)>x, a+x(b-a)(c-a)^0.5, b-(1-x)(b-a)(b-c)^0.5, 0)\]

Formula 1
is an extremely small likelihood of the triangle being perfectly formed. For Figure 2, 1,000 data points were used. For a sample size of only 100 data points, the triangle shape would be much less pronounced. For a sample size of 50,000 data points, for example, the triangle would appear much more precisely formed.

Now that the TriD is generated (and visually verified) for line item 1, the same methodology is used to create the TriDs for each line item. Using the F9 key to refresh the calculations will update the random numbers, and will show how variable the triangular shape can be. Note, however, that the peak will always be at or near the Likely Value assigned to each line item, and the trend will decrease to 0 at the Low and High limits.

Let’s speculate that our MCS is being created for a vessel procurement project (Table 3). A new agitated process vessel must be purchased and connected to an existing piping system, but there is a 20% chance that the agitator can be sourced internally from a decommissioned vessel at another site.

Using the methods described previously, a 1,000-iteration MCS results table is generated, and the Cost Frequency Distribution graph for each line item indicates that the calculations are behaving as intended, with the statistics summarized in Table 4 (broken down into four parts on p. 26). To generate the MCS total budget, the CostI of each line item is simply summed.
for each iteration into a column of 1,000 budget total data points. The 20 bracket values for the budget total data set can be determined by using the \( \text{MIN()} \) and \( \text{MAX()} \) functions and referencing the range of budget totals. By applying the vlookup and countif methods to the budget total data column (use \( \frac{\text{MAX}() - \text{MIN}()}{20} \) to determine the bracket intervals), a cost frequency distribution for the overall budget can be generated (Figure 3).

Because not all line items had a 100% chance of occurring, the cost frequency distribution shows a dip that might not have been anticipated without the use of an MCS. Though illustrative, Figure 3 does not provide the critical result that will determine the final budget and contingency. The final budget result comes from using a few simple statistical analysis functions.

To form the baseline budget (Base Cost) against which analysis is performed, Likely values are summed. The previous spreadsheet functions (referencing the column of total budget results) will yield informative statistical indicators: \( \text{MIN()} \), \( \text{MAX()} \), \( \text{AVERAGE()} \), \( \text{MEDIAN()} \), \( \text{STDE.D.P()} \), \( \text{KURT()} \), \( \text{SKEW()} \). See Table 4 for examples of these calculations and the MCS result, which uses a simple formula to calculate the total budget required to guarantee an X% chance of staying within budget:

\[
\text{PERCENTILEINC(}[\text{dataset}],[\text{percentile}]).
\]

This function references the range of 1,000 budget total data points as the \( [\text{dataset}] \), along with a desired confidence \( \text{[percentile]} \). The formula’s result is the budget value that falls at the desired percentile. For example, at the 90th percentile (90% of the budgets calculated fall below this budget), the total budget happens to be $102,738. Comparing this to the Base Cost of $97,000, a contingency of $5,738 should be allocated. It is also helpful to calculate each percentile’s contingency as a percentage of the Base Cost. The only subjective decision is to select the cost confidence percentile that is acceptable to management.

Note that this MCS example was performed with 1,000 iterations for illustrative purposes. To increase the statistical robustness of the MCS result, the MCS spreadsheet creator should consider using a very large number of iterations: targeting a minimum of 20,000. Fifty thousand iterations or more are desirable, but will result in a large spreadsheet file. For the spreadsheet power-user, there is a method of transforming the standard TriD into a Modified TriD (TriMod)—similar to the TriGen function in the Excel @ Risk add-on. The TriMod allows the user to specify a small chance of under- or over-running the budget line item. This is useful in cases where there is low confidence in the selected High and Low cost inputs. The TriMod calculations determine the new High and Low values that would be required to generate the desired percentages of area outside the original High and Low values. See Figure 4: The area of right-triangle 0 represents the percentage of the TriMod triangle that falls outside of Low value a, and inside of new Low value m. The area of right-triangle \( \Phi \) represents the percentage of the TriMod triangle that falls outside of High value b, and inside of new High value n.

For the complete version of this article, visit www.pharmamanufacturing.com.

References


ABOUT THE AUTHOR

Keith Melchiors is currently a process engineer at Biogen Idec in Research Triangle Park, North Carolina. During the writing of this article, he was senior process engineer with Integrated Process Technologies in Cary, N.C. Keith earned his B.S. ChE from Purdue University in 2002, and has 10 years experience in biopharmaceutical process design and capital project execution.
RECENTLY, AN international regulatory agency challenged Elan Drug Technologies’ manufacturing services business, now part of Alkermes plc, to develop an approach for managing risk at its multiproduct facility in Athlone, Ireland. The plant processes many different active pharmaceutical ingredients, including high-potency ones (HAPIs).

Working closely with PharmaConsult Ltd.’s Stephanie Wilkins, cochair of ISPE’s Risk-MaPP task team, the facility responded with a Master Matrix based on Risk-MaPP, a risk-based framework derived from principles outlined in ICH Q9. Risk-MaPP is designed to allow manufacturers to focus on critical risk areas to help prevent cross-contamination and ensure that controls applied are appropriate and commensurate to risk. The Master Matrix, in turn, is a spreadsheet that offers an effective way to see where cross-contamination risks, process- and product-related, are highest, allowing appropriate actions to be taken. This tool allows Alkermes to assign a numeric value to each potential source of cross-contamination risk, and to products vulnerable to cross-contamination.

This article will summarize how the Master Matrix was implemented and what results it has shown so far. (For more on this and Risk-MaPP, see PharmaManufacturing.com.)

Alkermes considers the “opportunity to contaminate” as a function of the frequency of a given product’s manufacture. In addition, the company characterizes source batches or dosage forms at risk of cross-contamination by evaluating:

- toxicity
- quantity of active used per batch
- process train used in product manufacture
- level of containment and the energies employed in processing
- proximity to other products and the use of shared equipment
- opportunity to contaminate
- dosing regime of the product and in particular the number of daily doses contained in a batch
- frequency of ingredient’s/product’s manufacture
- proximity to other potentially contaminating products
- any other products manufactured on site that may be contra-indicated for users of the target drug.
TABLE 1. PRODUCT DATA INPUT PROCEDURE

<table>
<thead>
<tr>
<th>Material Number</th>
<th>Therapeutic Area</th>
<th>Dosage Type</th>
<th>Route of Admin</th>
<th>Controlled Substance</th>
<th>ADI (mg/day)</th>
<th>Pediatric Use</th>
<th>Lactating Females</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000132</td>
<td>Anti-inflammatory, anti-tumour</td>
<td>Liquid</td>
<td>Oral</td>
<td>N</td>
<td>0.007</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000057</td>
<td>Angina</td>
<td>Tablet</td>
<td>Oral</td>
<td>N</td>
<td>0.350</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000057</td>
<td>Angina</td>
<td>Tablet</td>
<td>Oral</td>
<td>N</td>
<td>0.350</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000011</td>
<td>Hypertension</td>
<td>Capsule</td>
<td>Oral</td>
<td>N</td>
<td>0.500</td>
<td>CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3001530</td>
<td>Antiemetic</td>
<td>Capsule</td>
<td>Oral</td>
<td>N</td>
<td>5.000</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000018</td>
<td>Hypertension</td>
<td>Capsule</td>
<td>Oral</td>
<td>N</td>
<td>6.000</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000018</td>
<td>Hypertension</td>
<td>Capsule</td>
<td>Oral</td>
<td>N</td>
<td>6.000</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3001271</td>
<td>Hyperactivity</td>
<td>Capsule</td>
<td>Oral</td>
<td>N</td>
<td>1.000</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3000014</td>
<td>Pain/Athritis</td>
<td>Tablet</td>
<td>Oral</td>
<td>N</td>
<td>0.100</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>8500259</td>
<td>Post operative/Dental</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>N</td>
<td>0.075</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>8001472</td>
<td>Anorexia/AIDS patients</td>
<td>Oral</td>
<td>Oral</td>
<td>N</td>
<td>0.005</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>3001460</td>
<td>MS</td>
<td>Tablet</td>
<td>Oral</td>
<td>N</td>
<td>0.100</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
</tbody>
</table>

The goal is to identify and highlight points at which high risk and high vulnerability coexist. The elements of the matrix can be divided into five subsections:

1. **PRODUCT DATA**
   The first step was to list products manufactured on site. Internally, to simplify communication, product names were used, while externally product numbers were employed to ensure confidentiality (See Table 1).

2. **POPULATING THE COLUMNS**
   For each product, the applicable therapeutic area, dosage type, and route of administration are described. While Alkermes’ Ireland facility is primarily a solid dose producer, liquids and a small number of injectable products are also manufactured. Clearly, information on the route of administration and on the targeted use of the drug informs those reviewing the matrix as to how compromised the defenses of patients using these products might be.

   The matrix also notes the “contra-indication” of drugs. This highlights any areas where a product may be manufactured adjacent to or sharing equipment with another product whose patient information leaflet (PIL) recommends that the two not be used in combination.

   At the Athlone site, Alkermes also handles (largely in development) a small amount of controlled substances or scheduled drugs. While not of any special concern in cross-contamination assessments, a column to highlight such APIs has been included on the matrix.

TABLE 2. CALCULATION OF “UNINTENDED” ACTIVE AMOUNT NECESSARY TO CONTAMINATE DRUG PRODUCT

<table>
<thead>
<tr>
<th>Material Number</th>
<th>Doses Batch</th>
<th>Dose Size</th>
<th>Largest Daily Dose (mg)</th>
<th>Daily Doses per Batch</th>
<th>API/Batch in kg</th>
<th>Batches per Year (approx)</th>
<th>Daily Doses per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000132</td>
<td>10,000,000</td>
<td>1</td>
<td>40</td>
<td>250000</td>
<td>10</td>
<td>12</td>
<td>3,000,000</td>
</tr>
<tr>
<td>3000057</td>
<td>1,800,000</td>
<td>30</td>
<td>60</td>
<td>900000</td>
<td>54</td>
<td>9</td>
<td>8,100,000</td>
</tr>
<tr>
<td>3000057</td>
<td>433,333</td>
<td>60</td>
<td>60</td>
<td>433333</td>
<td>26</td>
<td>27</td>
<td>11,700,000</td>
</tr>
<tr>
<td>3000011</td>
<td>1,387,000</td>
<td>120</td>
<td>400</td>
<td>416100</td>
<td>166</td>
<td>20</td>
<td>8,322,000</td>
</tr>
<tr>
<td>3001530</td>
<td>366,000</td>
<td>125</td>
<td>125</td>
<td>366000</td>
<td>46</td>
<td>4</td>
<td>1,464,000</td>
</tr>
<tr>
<td>3000018</td>
<td>2,420,000</td>
<td>60</td>
<td>360</td>
<td>403333</td>
<td>145</td>
<td>11</td>
<td>4,436,667</td>
</tr>
<tr>
<td>3000018</td>
<td>879,000</td>
<td>120</td>
<td>360</td>
<td>293000</td>
<td>105</td>
<td>32</td>
<td>9,376,000</td>
</tr>
<tr>
<td>3001271</td>
<td>450,000</td>
<td>100</td>
<td>300</td>
<td>150000</td>
<td>45</td>
<td>42</td>
<td>6,300,000</td>
</tr>
<tr>
<td>3000014</td>
<td>430,000</td>
<td>375</td>
<td>1000</td>
<td>161250</td>
<td>161</td>
<td>82</td>
<td>13,222,500</td>
</tr>
<tr>
<td>3000412</td>
<td>2,985,000</td>
<td>2</td>
<td>36</td>
<td>197667</td>
<td>7</td>
<td>8</td>
<td>1,581,333</td>
</tr>
<tr>
<td>8500259</td>
<td>167,000</td>
<td>30</td>
<td>30</td>
<td>166667</td>
<td>5</td>
<td>6</td>
<td>1,000,000</td>
</tr>
<tr>
<td>801472</td>
<td>60,240</td>
<td>625</td>
<td>800</td>
<td>46875</td>
<td>38</td>
<td>1</td>
<td>1,000,000</td>
</tr>
<tr>
<td>3001460</td>
<td>750,000</td>
<td>10</td>
<td>20</td>
<td>375000</td>
<td>8</td>
<td>14</td>
<td>5,250,000</td>
</tr>
</tbody>
</table>
NUMERIC VALUES
The first significant numeric value entered in the matrix is the Acceptable Daily Exposure (ADE)—a measure of an active ingredient’s toxicity. This measurement was interpreted as the maximum allowable daily amount of contaminated active present in a manufactured product to which a patient could be exposed without experiencing the therapeutic/adverse effect. Alkermes’ view that the ADE should in all cases consider all potential sub-populations negates the need to highlight susceptible (contraindicated) sub-populations in the matrix.

Of particular importance is that the ADE information is provided in a consistent and auditable way. Alkermes has based its approach on that described in Section 5.3 of the ISPE Risk-MaPP guidelines. Additional requirements—such as the availability of key source data for audit review and qualification of toxicologists performing analysis—have also been added.

2. AMOUNT OF API NEEDED TO CONTAMINATE PRODUCT
Having conservatively established the ADE limits to include all potential sub-populations, it is next important to understand how much unintended active would be needed to contaminate a drug product in order to harm. Simply, it is necessary to relate the maximum potentially prescribed daily dose of all products in manufacture to the actual manufacturing batch size.

Consider “x” grams of contaminating active getting into a blend. Assume that contaminant is evenly spread through the blend during processing. If the blend produces 1,000 (maximum) daily doses, each will contain 0.1% of the contaminating material. If instead the blend produces 1,000,000 daily doses, then the patient will receive 0.0001% of the unwanted contaminating material. Clearly the potential to exceed the ADE is far greater where the blend produces fewer daily doses. (See Table 2.)

3. DETERMINATION OF PROCESS RISK
Proximity of processing is a major consideration in the estimation of risk. As a result, Alkermes’ manufacturing areas were separated into zones based on processing rooms that shared a common corridor. These zones were then assigned a color and number to allow for easy identification. The process stages were then mapped for each product in these zones.

In the matrix (Table 3), the steps employed in each product’s manufacture (material number shown in left-hand column) are identified (across the top row) by coloring the cell at the intersection point of column and row. For each zone of the facility, a different color is used.

TABLE 3. IDENTIFICATION OF THE PROCESSING STEPS EMPLOYED IN EACH PRODUCT’S MANUFACTURE

<table>
<thead>
<tr>
<th>Material Number</th>
<th>Simple</th>
<th>Wiping</th>
<th>Etching</th>
<th>DSA</th>
<th>BCr</th>
<th>Blender</th>
<th>2Cr V Blender</th>
<th>Gald 300</th>
<th>Suspension Vessel (NMO)</th>
<th>C5 Generator</th>
<th>Gate 120</th>
<th>Gate 130</th>
<th>Savoio</th>
<th>Sweco Siew</th>
<th>Fill</th>
<th>P1200</th>
<th>Fill</th>
<th>P1600</th>
<th>Gelburt open</th>
<th>Dispersive unit</th>
<th>Cambour Go 2000</th>
<th>Cambour</th>
<th>Cambour</th>
<th>Cambour</th>
<th>GMS</th>
<th>Cambour</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>300132</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>3000057</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>3000057</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>3000011</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>308</td>
</tr>
<tr>
<td>3001530</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>3000018</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>354</td>
</tr>
<tr>
<td>3000018</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>361</td>
</tr>
<tr>
<td>8600647</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>3001271</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>135</td>
</tr>
<tr>
<td>3000014</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>325</td>
</tr>
<tr>
<td>3000412</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>8600259</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>8601472</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>3001460</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>52</td>
</tr>
</tbody>
</table>

TABLE 4. SCALE OF PROCESS RISK

<table>
<thead>
<tr>
<th>Scale</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully closed process with good confirming data, low surface area, easily cleaned, dedicated</td>
</tr>
<tr>
<td>5</td>
<td>Closed process low risk of fugitive emissions or coated material</td>
</tr>
<tr>
<td>10</td>
<td>Semi-open process (open charge/discharge), low to medium energy, medium surface area, relatively easy to clean, medium risk of mechanical transfer, multiproduct</td>
</tr>
<tr>
<td>15</td>
<td>Open process, medium to high energy, small to medium surface area, easily cleaned, high risk of mechanical transfer, multiproduct</td>
</tr>
<tr>
<td>20</td>
<td>Open process, high energy, large surface area, not easily cleaned, high risk of mechanical transfer, multiproduct</td>
</tr>
</tbody>
</table>
In this way, it is immediately evident which products are manufactured in the same area(s) of the plant.

The format in Table 3 has since been refined. However, what is important is that processes are not equally likely to generate contamination. Factors such as level of containment, mechanical energy input, ratio of product quantity to surface area of equipment, as well as the physical state of material (e.g., in solution, a coated bead, or a dry powder?) all affect the potential to contaminate. Alkermes uses a number of sources to grade the potential of processes to generate contaminants (process risk). For instance, assessment is informed by industrial hygiene (IH) data gathered during operator exposure testing. The scale in Table 4 is used to represent process risk.

The facility’s initial approach to scoring of processes is also shown in Table 3. Note that some boxes have scores greater than 20. This occurs for two reasons:

- **Everything is related to a finished batch size;** where multiple components are combined in that final batch, multiplication of each individual component score by the number of components combined in a batch is undertaken. For example, coated beads are manufactured in the CF granulators in component batch sizes of 60-80 kg, but finished (encapsulation) batch sizes are bulked up by combining four of these in a blend. As a result, a 4x “component score” is entered in the matrix.
- **A number of Alkermes’ processes are iterative.** Again, taking the example of our CF coated beads, typically multiple layers are used. The first is when active material is coated directly onto a non-pareil core. Such a process is “semi-open” with “medium to high” energy input and is scored a 12. The next coating is of a polymer onto the active core—the potential for active “release” is much reduced as all active has adhered to the bead. As polymer coating covers more of the bead surface, the product design virtually eliminates potential for contaminants. The second coat is scored a 10 and all subsequent coats as 5 or 2. Scores from these iterations are then combined.

### 4. Determination of Product Risk

By adding all steps used to manufacture a product, an overall process score or “Process Risk” is derived. This number reflects process design, the level of mechanical energy input, and containment. It does not, however, consider the potency, toxicity, or amount of API or the opportunity to contaminate other products.

The potency of a batch can be described by:

\[
\text{Product Risk} = \left(\frac{\text{API/batch}}{\text{ADE}}\right) \times \text{Process Risk}
\]

Calculating “Product Risk” for all products manufactured allows them to be ranked and process trains presenting the greatest potential contaminating risk to others immediately highlighted (Figure 1).

### 5. Determination of Product Vulnerability

Consideration must now be given to the potential for a product to be become contaminated, or “Product Vulnerability.” If a patient takes less than the ADE of a drug, even if the patient takes it over an extended period, one can assume that there will be no effect. Clearly the patient most at risk is the patient prescribed the largest envisaged daily dose. As remarked above, the smaller the

---

**FIGURE 1. GRAPHICAL REPRESENTATION OF ALKERMES’ PRODUCT RISK**

**FIGURE 2. GRAPHICAL REPRESENTATION OF ALKERMES’ PRODUCT VULNERABILITY**
batch, the less the dilution of contaminant and the greater its concentration in the finished product. These two considerations were combined (with opportunity) to rank the “vulnerability” of products manufactured.

\[
\text{Vulnerability} = \frac{\# \text{ batches manufacture/year}}{\# \text{ maximum-daily-dose/batch}}
\]

Again, this is a function of the number of times a product is manufactured. See Figure 2.

**LESSONS LEARNED**

Table 5 highlights that the greatest potential source of contaminant currently manufactured at the Athlone site is product “3000011.” The product most vulnerable is “3000014.” The analysis indicates that there should be a focus on where these products are manufactured and where they may come in contact with each other. In short, attention should be focused on anywhere a product presenting a relatively high “product risk” is manufactured in proximity to a product of relatively high “vulnerability.” This is shown in the flowchart in Figure 3.

**REFINEMENT OF APPROACH**

While developing the matrix has been very useful and informative, limitations have been observed.

1. The matrix needs to be regularly updated to reflect changing manufacturing volumes.
2. Overall site scores do not immediately highlight potential issues in a shared zone or corridor.
3. The matrix does not provide an immediate under-

---

**TABLE 5. IDENTIFICATION OF CONTAMINANT AND VULNERABLE PRODUCTS**

<table>
<thead>
<tr>
<th>Material Number</th>
<th>Doses Batch</th>
<th>Dose Size</th>
<th>Largest Daily Dose (mg/day)</th>
<th>Dose Size</th>
<th>API/Batch in kg</th>
<th>Batches Year (approx)</th>
<th>Daily Doses Year</th>
<th>Risk</th>
<th>Vulnerability (*1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000132</td>
<td>10,000,000</td>
<td>1</td>
<td>40</td>
<td>250000</td>
<td>10</td>
<td>12</td>
<td>3,000,000</td>
<td>154,286</td>
<td>0.000000</td>
</tr>
<tr>
<td>3000057</td>
<td>1,800,000</td>
<td>30</td>
<td>60</td>
<td>900000</td>
<td>54</td>
<td>9</td>
<td>8,100,000</td>
<td>72,206</td>
<td>0.070000</td>
</tr>
<tr>
<td>3000057</td>
<td>433,333</td>
<td>60</td>
<td>60</td>
<td>433333</td>
<td>26</td>
<td>27</td>
<td>11,700,000</td>
<td>144,411</td>
<td>0.436154</td>
</tr>
<tr>
<td>3000011</td>
<td>1,387,000</td>
<td>120</td>
<td>400</td>
<td>416100</td>
<td>166</td>
<td>20</td>
<td>8,322,000</td>
<td>2,164,770</td>
<td>1.355443</td>
</tr>
<tr>
<td>3001530</td>
<td>366,000</td>
<td>125</td>
<td>125</td>
<td>366000</td>
<td>46</td>
<td>4</td>
<td>1,146,000</td>
<td>3,001</td>
<td>0.098361</td>
</tr>
<tr>
<td>3000018</td>
<td>2,420,000</td>
<td>60</td>
<td>360</td>
<td>403333</td>
<td>145</td>
<td>11</td>
<td>4,436,667</td>
<td>38,653</td>
<td>0.495868</td>
</tr>
<tr>
<td>3000018</td>
<td>879,000</td>
<td>120</td>
<td>360</td>
<td>293000</td>
<td>105</td>
<td>32</td>
<td>9,376,000</td>
<td>105,759</td>
<td>2.017065</td>
</tr>
<tr>
<td>3001271</td>
<td>450,000</td>
<td>100</td>
<td>300</td>
<td>150000</td>
<td>45</td>
<td>42</td>
<td>6,300,000</td>
<td>146,213</td>
<td>1.140000</td>
</tr>
<tr>
<td>3000014</td>
<td>430,000</td>
<td>375</td>
<td>1000</td>
<td>161250</td>
<td>161</td>
<td>82</td>
<td>13,222,500</td>
<td>467,237</td>
<td>10.201550</td>
</tr>
<tr>
<td>3000412</td>
<td>2,985,000</td>
<td>2</td>
<td>36</td>
<td>197667</td>
<td>7</td>
<td>8</td>
<td>1,581,333</td>
<td>38,142</td>
<td>0.000000</td>
</tr>
<tr>
<td>8500259</td>
<td>167,000</td>
<td>120</td>
<td>30</td>
<td>166667</td>
<td>5</td>
<td>6</td>
<td>1,000,000</td>
<td>3,799</td>
<td>0.108000</td>
</tr>
<tr>
<td>8001472</td>
<td>60,240</td>
<td>625</td>
<td>800</td>
<td>46875</td>
<td>38</td>
<td>1</td>
<td>1,000,000</td>
<td>82,500</td>
<td>0.000000</td>
</tr>
<tr>
<td>3001460</td>
<td>750,000</td>
<td>10</td>
<td>12</td>
<td>375000</td>
<td>8</td>
<td>14</td>
<td>5,250,000</td>
<td>44,250</td>
<td>0.226667</td>
</tr>
</tbody>
</table>

**FIGURE 3. ALKERMES’ PROCESS OF ELIMINATING OR REDUCING CROSS-CONTAMINATION RISK**
standing of a “vulnerable” process—e.g., if the product at risk of contamination is itself highly contained, whether the level of risk is reduced.

4. The matrix does not differentiate short-run products (e.g., clinical or registration batch manufacture) where timing and lack of familiarity would heighten concern.

Addressing the first of these issues allows for the relatively easy resolution of the other three and provides a very local assessment of cross-contamination potential. Because “vulnerability” does not include a measure of process containment, a “process risk” rating has been included in the revised spreadsheet.

The revised sequence of matrix review is now:

1. Identify highest “product-risk” and “vulnerability” products manufactured on site to provide an immediate high level focus on most important areas.

2. Track products through zones of manufacture at a component level in the body of the matrix.

3. Where high-risk sources coexist with the manufacture of vulnerable products, target detailed risk assessment to ensure the adequacy of in-place measures.

There remains much to be done on education, on calibration with others in industry, and on honing the entire process, but the Master Matrix has provided Alkermes a very strong foundation and framework on which to build.

About the Authors
Mark O’Reilly is Alkermes’ Senior Director of Engineering. His responsibilities include process train and facility design, industrial hygiene and validation. Aisling Horan works in Alkermes’ validation department with a focus on process & cleaning validation and cross-contamination.

### Table 6. Revised Matrix Reflecting Refined Approach

<table>
<thead>
<tr>
<th>Material Number</th>
<th>V</th>
<th>P</th>
<th>O</th>
<th>Q</th>
<th>W</th>
<th>B</th>
<th>R</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
</tr>
</thead>
<tbody>
<tr>
<td>3001312</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000057</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000056</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000011</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3001530</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000018</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30001271</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000014</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000412</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8602250</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8001472</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3001460</td>
<td>R</td>
<td>V</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Not all columns shown due to page-width restrictions)
The NEW GEMÜ 4242 Combi Switchbox with microprocessor-controlled set point determination offers unprecedented repeatability and reliability.

Featuring:

- Highly visible GLOWTOP indicator
- Self-setting without cover removal
- Integrated 3/2 pilot valve with manual override
- Local or remote programming
- Local and remote diagnostics
- 24 VDC, AS-I or DeviceNet
Biopharma’s Flexible Imperative

Business forces, bioterror and pandemic risks demand new approaches

By Robert F. Dream, Principal, HDR Company, LLC

RECENTLY, A number of different trends have converged to demand a new type of biopharmaceutical facility, one that emphasizes flexibility and agility. Drawing this new blueprint are:

- business needs to minimize timelines and financial risks;
- “biotech on demand,” and the ability to shore up local manufacturing capacity, quickly, to meet market needs;
- national security needs for systems that can easily and rapidly respond to biological attacks;
- urgent national health needs to protect the public from large-scale, fast moving epidemics and pandemics.

Today’s biopharmaceutical manufacturing facilities are smaller and more flexible, efficient and cost-effective than those of the 1990s, and they are able to adapt quickly to market changes.

The goal isn’t technology in and of itself, but greater product and process knowhow for speed to market. With modular systems, we can now place an entire small-scale clinical production line inside an 18’x42’x13’ (W x L x H) environment.

Based on defense and health department standards, vaccine manufacturing facilities have been blazing new trails. Traditionally, it has taken between 14 and 20 years to move from pathogen identification to vaccine safety and efficacy trials. The new goal, set by the U.S. Defense Department’s DARPA (Defense Advanced Research Projects Agency), and repeated in specs set by BARDA, is to cover the same ground in less than 22 weeks.

The lifeblood of this flexible, multiproduct and multitechnology future will be the Mobile Bioprocessing Unit (MBU), which has already been built for manufacturing small, clinical-scale quantities of some therapies. (Figures 1-4 illustrate the National Center for Therapeutics Manufacturing, housed at Texas A&M University in College Station, Texas.) The key feature of these mobile units is that they are self-contained, with inherent air handling and other critical equipment and controls built in and standard.

Figure 1. National Center for Therapeutics Manufacturing, designed and built based on Flexible Manufacturing Criteria
Each MBU is used for a single, biologically distinct technology (bacteria, mammalian cells, plants, etc.), thereby eliminating any cross-contamination issues with regulatory agencies. When they are not being used, MBUs are designed to be moved to cleaning and refurbishing areas, and ready to connect when needed. The goal is to:

- Enable low-cost, rapid production of proteins/products, all of which are correctly folded and biologically active, as well as cGMP-qualified master virus banks and cell lines;
- Draw on extensive clinical use and regulatory history;
- Scale MBUs to large volumes and high cell densities;
- Feature FDA-qualified cell lines and virus banks;
- Produce cGMP clinical materials affordably and to provide manufacturing and treatment capacity on a moment’s notice.

The Strategic National Stockpile facility for flu vaccine, for instance, calls for 8 to 10 modular process trains for surge production, and allows surge capability to 10 times baseline capacity within 24 hours.

Key features of these facilities will be stockpile pods containing complete process lines, and a lifecycle management program, with scheduled rotation through production.

In addition, DARPA is considering construction of adjacent facilities to integrate and validate “clinic ready” emerging technology platforms. These facilities will be closely integrated with other operations, including animal model development and validation, biomarker evaluation, imaging, GLP pre-clinical studies and animal rule efficacy, and human Phase 1 clinical trials.

**VACCINES, BIOREAPERAPUTICS AND PERSONALIZED MEDICINE DEMAND AGILITY**

Business demands are also demanding new facility designs and technologies. By 2016, five of the top 10 biopharmaceuticals are expected to be monoclonal antibodies (MAb’s). Follow-on (biosimilar) versions of these will most likely become available in the coming years due to patent expiry and the introduction of legislation for
biosimilars. Personalized therapies will further drive the fractionation of the biopharmaceuticals market, thus increasing the need for smaller batch sizes and campaign-based production schemes.

Business realities, combined with demographic and market forces, will accentuate the national imperative for flexible and more cost-effective manufacturing. Compared with other biopharmaceutical products, monoclonal antibodies are large proteins that require relatively high doses—and traditionally necessitate high-volume manufacturing process equipments/systems and facilities. Many biopharmaceutical facilities are still designed as traditional fixed equipment/systems and facilities, with fixed piping and vessel layout and large bioreactor volumes. Such facilities require a significant financial investment along with high total installation costs.

Recent increases in cell culture yields/titer have led to significantly reduced bioreactor volume requirements, which again have opened the door for single-use manufacturing technologies such as pre-sterilized assemblies of single-use bags, tubing and filters that are only used once and then disposed of. With a financial investment reduction and simplified installation, single-use technology could be more appealing than other fixed technologies.

Combining single-use technology and high-yield processes could further reduce the price tag for comparable facilities by 50 percent. This combination is being pursued in a number of biopharmaceutical facilities today—the full effect is truly a paradigm shift.

Additionally, single-use technology runs a much lower risk of batch-to-batch contamination, which is of particular importance in multipurpose facilities. A facility based on single-use technology is easy to reconfigure and can therefore be ready for a new product in a matter of days. This flexibility translates to reduced development timelines and thus accelerated time-to-market peak.

In an increasingly fractionated market, the need for speed to secure market shares is more important than initial minimal cost of manufacturing. And with remarkably increased cell titer, the cost contribution from the manufacturing facility is limited compared with development costs.

With single-use technology, it becomes possible to optimize facility installations based on anticipated product lifecycle stages. For instance, to start with, the strategy could be to use just one single-use bioreactor to get material for clinical trials and then upgrade the...
facility with additional bioreactors later in anticipation of market supply production while clinical trials are taking place. As the next pipeline product must be developed, the facility can change the lifecycle stage back to clinical production and the extra bioreactors moved to a market supply expansion facility. Such a strategy becomes possible because single-use technology is so decoupled from the facility building itself.

As an interesting side effect, environmental impact studies show that single-use technology is up to 50% less energy intensive than fixed reusable manufacturing. It may appear counterintuitive, but the emissions from disposing single-use material are more than offset by elimination of the cleaning and sterilization processes required for reusable technology, basically because heating up many tons of water and metal is extremely energy intensive. Full implementation of high-yield processes and single-use technology results in facilities with a markedly reduced carbon footprint per kilogram of product compared to the fixed facilities of the 1990s. Usually 60% of piping in a fixed facility is installed to perform CIP/SIP.

The need for local biopharma manufacturing capacity is increasing in the fast-growing emerging markets as the customer base expands and national initiatives manage the markets. The trend is being amplified by blockbuster patent expiry and the implementation of regulatory legislation for accelerated pathways for biosimilars. For biopharmaceuticals, emerging markets are not about low-cost manufacturing hubs, but about being on location to get access to the local market. Consequently, many big pharmaceutical companies as well as local manufacturers are investing in new facilities in these countries. A blueprint facility concept that can be established as interesting markets develop will become an important strategic asset for biopharmaceutical players with global aspirations.

In reality, the important issue is not stainless steel or single-use technology, but rather how technologies could be combined to provide the most productive and cost-effective process in a fast and predictable way. Choosing one or the other technology concept or a hybrid of the two depends on both strategic considerations and feasibility studies of each individual case.

Clearly, biopharmaceutical manufacturing’s paradigm is changing from stainless steel to hybrid combinations of single-use and stainless steel, and complete single-use facilities. Manufacturers are already exploring opportunities, aggressively, and we can expect this trend to continue.
Wisdom From Within

Eliminate reliance on transmitters with Arc intelligence engineered into your sensor head.

The Arc sensor head enables the first fully integrated intelligent sensors that do not rely on a transmitter. Arc can be integrated into existing 4-20 mA or digital environments to improve signal quality and data efficiency. Calibration statistics, usage history, and diagnostics are stored in the sensor for quality management and troubleshooting. Increase the productivity and quality of your analytical process.

For more information on how the Arc can improve your process analysis, visit www.ham-info.com/0615

1-888-525-2123
www.hamiltoncompany.com

Visit us at BioProcess International
Oct. 8 – 12, 2012 • Providence, RI
Booth #120
Manufacturing Strategies for Biosimilars

Regulators have paved the way for low-cost biologics, but it’s up to manufacturers to select the right technologies and define quality

By Tom Fritz, Christine Lightcap, Ph.D., and Kundini Shah, M.S., Swiftwater Group

AMIDST BIOLOGICS patent expirations and the push for personalized (yet low-cost) medicines, the age of biosimilars is upon us. The European Union has paved the way with its biosimilar approval pathway, while FDA passed the Biologics Price Competition and Innovation Act (BPCIA) in 2010. The Act codified into law the 351(k) abbreviated regulatory pathway for biosimilars approval, and formally opened the door for biosimilars product approval in the U.S. However, the law provided no advice regarding what requirements the FDA would need for approval, so in early 2012, the Agency issued draft guidelines describing CMC considerations in demonstrating biosimilarity to a reference protein product (U.S.-approved or foreign innovator biologic) [1].

Like their reference products, biosimilars are complex, difficult to characterize, typically have more than one biological effect, and frequently generate immune responses. Because of this, the guidance necessarily lacks a list of specific steps for developing biosimilars, leaving developers to integrate quality attributes on a case-by-case basis using the totality of evidence approach. Although approval of a biosimilar will rely on current data of the reference product, the guidance paves the way for producing biosimilar proteins through the use of alternative expression systems and novel manufacturing technologies. To do this, however, developers must ensure they use the principles of Integrated Drug Development to incorporate robust quality considerations in their development programs.

This article provides a review of the essentials of developing and manufacturing biosimilars today. We review current animal-, yeast-, and plant-based expression systems, predominant manufacturing technologies, and key quality considerations for developers and manufacturers of biosimilars—all with an eye toward the integration of these elements.

Figure 1. Expression Systems Used for Manufacture of Approved Drugs

ALTERNATE EXPRESSION SYSTEMS

For more than two decades, most biologics have been manufactured in well-known, well-characterized, FDA-approved cell lines that were developed by the innovator manufacturers. Figure 1 shows global product approvals from January 2006 to June 2010 by distribution of these cell lines [2].

Historically, CHO cells have shown the highest expression rates and are easily cultured and sustained. Bacterial and yeast cell lines like E. coli and S. cerevisiae require minimal growth media conditions and are fast growing, making them economical. However, these traditional cell lines are inherently prone to host cell protein contamination and adventitious agents such as endotoxins. Developers often opt to use traditional cell lines because they have established upstream and downstream purification processes, historical literature data is available for reference, and regulatory agencies are familiar with the expression systems. For biosimilars developers, however, these cell lines provide less opportunity for innovation, fewer intellectual property advantages, and minimal patent protection.
A NIMAL- OR YEAST-BASED ALTERNATIVE EXPRESSION SYSTEMS

FDA has approved novel products using animal or yeast-based alternative expression systems (Table 1).

- **YF-Vax** was developed in Avian Leukosis Virus (ALV)-free chicken embryos. Chicken embryos have historically been used for protein expression and experimentation, and are economical and easily accessible. Most importantly, chicken embryos lack an immune system, making them ideal candidates for production.

- Due to their susceptibility to a wide range of viruses, VERO cells, a kidney epithelial line isolated from the African Green Monkey, have served as a popular expression system for vaccines, such as RotaTeq, Rotarix, ACAM2000, and Ixiaro.

- **HEK293** cells (Human Embryonic Kidney cells) have also been used in the manufacture of an approved drug, Xigris. (Note: Xigris was withdrawn from the market in 2011 due to lack of efficacy, not due to any manufacturing deficiencies.) Similar to CHO cells, HEK293 cell lines are easy to culture, have higher rates of expression for proteins of interest, and are easily scaleable.

- The baculovirus insect cell line, used to produce Ceravix for the treatment of HPV, produces large quantities of proteins in cultured insect cells or insect larvae and these proteins are easily purified with tags or using affinity chromatography techniques.

- In 2009, Kalbitor produced from *P. pastoris* (a yeast) was also approved. These yeast cells can grow to high densities compared to the more common yeast *S. cerevisiae*. *S. cerevisiae* is also known to release ethanol during the fermentation process, which can deter cell growth and protein production.

- In 2011, Benlysta was approved for the treatment of lupus and was expressed in the mouse myeloma cell line NS0. The NS0 cell line cannot produce endogenous antibodies, making it an attractive platform for protein production. However, as seen with CHO cells, NS0 cells have the potential to generate glycosylated proteins, which are known to produce immunogenic effects.

P LANT-BASED ALTERNATIVE EXPRESSION SYSTEMS

FDA has also been open to plant-based expression systems (i.e., plant cell cultures and whole plants), (See Table 2.) These systems have gained increasing popularity due to...

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Stage of Development</th>
<th>Sponsor</th>
<th>Cell Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xigris (withdrawn in 2011)</td>
<td>Sepsis</td>
<td>Approved 2001</td>
<td>Eli Lilly &amp; Company</td>
<td>HEK293 cells</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>Rotavirus gastroenteritis</td>
<td>Approved 2006</td>
<td>Merck Sharp and Dohme Corp.</td>
<td>VERO cells</td>
</tr>
<tr>
<td>ACAM2000</td>
<td>Small Pox</td>
<td>Approved 2007</td>
<td>Sanofi Pasteur</td>
<td>VERO cells</td>
</tr>
<tr>
<td>Rotarix</td>
<td>Rotavirus gastroenteritis</td>
<td>Approved 2008</td>
<td>GlaxoSmithKline</td>
<td>VERO cells</td>
</tr>
<tr>
<td>YF-Vax</td>
<td>Yellow Fever</td>
<td>Approved 2008</td>
<td>Sanofi Pasteur</td>
<td>ALV-Free Chicken Embryos</td>
</tr>
<tr>
<td>Kalbitor</td>
<td>Hereditary angioedema (HAE)</td>
<td>Approved 2009</td>
<td>Dyax Corp.</td>
<td><em>P. pastoris</em> cells</td>
</tr>
<tr>
<td>Ixiaro</td>
<td>Japanese Encephalitis</td>
<td>Approved 2009</td>
<td>Intercell Biomedical</td>
<td>VERO cells</td>
</tr>
<tr>
<td>Ceravix</td>
<td>Human Papillomavirus (HPV)</td>
<td>Approved 2011</td>
<td>GlaxoSmithKline</td>
<td>Baculovirus Insect cell</td>
</tr>
<tr>
<td>Benlysta</td>
<td>Lupus</td>
<td>Approved 2011</td>
<td>Human Genome Sciences</td>
<td>NS0 cells</td>
</tr>
</tbody>
</table>

Table 1. Recent FDA-Approved Products Using Animal/Yeast Alternative Expression Systems

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Stage of Development</th>
<th>Sponsor</th>
<th>Cell Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elelyso</td>
<td>Gaucher disease</td>
<td>Approved 2012</td>
<td>Protalix Therapeutics</td>
<td>Carrot</td>
</tr>
<tr>
<td>Locteron</td>
<td>Hepatitis C Virus (HCV)</td>
<td>Phase 2</td>
<td>Biolex Therapeutics</td>
<td>Lemna (duckweed)</td>
</tr>
<tr>
<td>H5N1</td>
<td>Influenza</td>
<td>Phase 2/3</td>
<td>Medicago Inc.</td>
<td>Tobacco</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>Antibiotic Associated Diarrhea</td>
<td>Phase 3</td>
<td>Ventria Bioscience</td>
<td>Rice</td>
</tr>
</tbody>
</table>

Table 2. Biologic Products Using Plant-based Alternative Expression Systems
to attractive protein yields; simpler methods of expression, cultivation, and manufacturing; and economical developmental requirements when compared to mammalian cell lines. One of the most enticing benefits to using a plant-based production system is the decreased likelihood of clinical immunogenic responses, since plants do not contain mammalian pathogens or endotoxins. However, when working with plant-based expression systems, extensive DNA or protein characterization is required, unlike with mammalian cell lines. These systems also show greater potential for aflatoxin contamination.

FDA approved the first plant-based recombinant therapeutic protein, Elelyso, in 2012. Protalix developed Elelyso using ProCellEx (ProCellRx Platform Overview), a proprietary carrot cell expression system in combination with a closed novel bioreactor system using disposable plastic bags. The 12-month delay in approval was due to a lack of efficacy data, not FDA’s concerns about the novel cell line. Although not discussed here, companies are pursuing expression systems outside even these novel systems, including ciliates, alternative yeast and bacterial species, and cell-free expression systems. One day these expression systems may have the same degree of success as animal and plant-based systems.

### SELECTED MANUFACTURING TECHNOLOGIES

Several innovative manufacturing technologies are available for both high throughput screening of recombinant protein variants as well as rapid protein production. Principles of synthetic biology and industrial engineering are used to enhance product expression and development.

### HIGH THROUGHPUT SCREENING

These principles form the basis of Intrexon’s proprietary UltraVector Platform which offers a dynamic library of modular components to customize, test, and optimize various protein candidates in a cell line of interest based on host cell performance. Combined with its Laser-Enabled Analysis and Processing (LEAP), developers have the option to rapidly identify and select high-secreting, genetically modified mammalian cell lines producing the protein of interest.

### PRODUCTION TECHNOLOGY

The need to get to the market quickly will lead companies to explore flexible, cost-effective manufacturing tools such as single-use technology (SUT). SUTs have reduced cleaning validation requirements between product change-overs and batch-to-batch processing. Single-use portable bioreactors, for example, are available at various capacities, providing linear scalability throughout the manufacturing process for biosimilars using alternate cell lines.

According to technology provider Xcellerex, the SUT platform allows production lines to start up within 15-18 months, and manufacturers benefit from a decrease in total capital cost by 50-75% and operating cost by 20%. This presents biosimilars developers with the ability to accelerate upstream manufacturing processes and dedicate the upfront cost savings towards commercial production needs.

### PURIFICATION PROCESSING

While high-producing alternative cell lines and less complex upstream manufacturing techniques offer some advantages, downstream purification processing can be a significant bottleneck to CMC development. For some development programs, downstream purification accounts for 80% of the total manufacturing cost [2]. Streamlining purification and reducing the number of steps required in the purification process are two commonly used techniques. However, more emphasis is being placed on optimizing purification systems. For example, 3M Purification’s Zeta Plus line of single-use, depth-filtration systems

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>DNA Sequencing</td>
</tr>
<tr>
<td></td>
<td>Enzyme-linked immunosorbent assay (ELISA)</td>
</tr>
<tr>
<td></td>
<td>Mass Spectrometry - Peptide Mapping</td>
</tr>
<tr>
<td>Identity and Purity</td>
<td>Mass Spectrometry - Intact Molecular Mass</td>
</tr>
<tr>
<td></td>
<td>Western Blot</td>
</tr>
<tr>
<td></td>
<td>High Pressure Liquid Chromatography (HPLC) such as reverse phase (RP), size exclusion (SEC), and ion-exchange (IEC)</td>
</tr>
<tr>
<td>Purity</td>
<td>SDS-PAGE</td>
</tr>
<tr>
<td>Functionality</td>
<td>Binding Capacity</td>
</tr>
<tr>
<td></td>
<td>In vitro and in vivo biopotency</td>
</tr>
</tbody>
</table>

Table 3. Protein Assays for Product Characterization
can remove cells and selected contaminants and host cell proteins from cell culture media at the primary recovery step using charge-modified depth filters. This system can also be applied to mammalian cell harvest or bacteria, yeast, and insect cell lysates clarification. The specialty media has been shown to reduce host cell proteins, protein aggregates, and endotoxins. This not only provides time and cost efficiency but reduces protein yield loss observed during multiple purification steps.

QUALITY CONSIDERATIONS FOR BIOSIMILAR DEVELOPMENT

If using a different expression system, it is impossible to generate a biosimilar which is identical to the reference product. However, it is possible to develop highly similar products with no clinically meaningful differences by remembering that “the process is the product.” Upstream production and downstream processing techniques can yield protein fluctuations and impurity profiles that vary among expression systems.

When using alternate cell lines, the FDA expects developers to provide sufficient justification that the construct encodes the same primary amino acid sequence as the reference product, with data supporting that minor modifications do not affect safety, purity, or potency of the product. Comprehensive cell line development and characterization data shared early in the development process with the FDA will enable the developers to collect sufficient safety and efficacy data.

Products that are highly similar to reference products can be developed by implementing consistent and complete product characterization testing per International Conference on Harmonization (ICH) quality guidelines. This includes identity testing and structure confirmation during all stages of protein folding (primary through quaternary). A purity assessment accounting for all host cell-related protein availability, and those impurities associated with the protein itself, such as truncated forms, aggregates, or modifications (e.g., glycosylation) should be completed. These impurities could have an effect on protein quality, potency, and the amount of safety and efficacy data required during development. Protein function should also be assessed. Table 3 lists recommended assays for product characterization, which will vary based on the type of protein and production process.

Once fully characterized, a master cell bank (or seed bank when working with plant expression systems) is generated based on the quality traits desired. This banking system is designed to ensure consistent production of a highly similar protein product. A stability protocol using many of the assays used to characterize the original protein should be in place to control for changes during storage and shelf-life of the product. Agency reviewers expect that the stability protocol assesses phenotypic traits, such as protein production and titre, as well as genotypic stability. DNA sequencing and segregation analysis can be used to monitor potential changes to the protein construct on a DNA level, prior to the expression of the protein itself.

A developer must keep in mind that, although a full protein characterization may initially support a highly similar protein product, the expression system can introduce new, and specific, product- and process-related impurities and substances. This is especially true if the reference product was made using a different system.

Not all impurities are detrimental to development. Levels should be based on ICH-guided drug substance and drug product impurity specifications and knowledge gained from the production process and batch history analysis. FDA requires a functionality and potency assessment. In many cases, as long as the safety and efficacy of the protein drug is maintained, the additional substances are not a concern. If the specific impurities are shown to impact functionality, further upstream and downstream process optimization may be required. This can impact the product development plan from a safety and efficacy perspective as well.

AN INTEGRATED APPROACH

CMC challenges related to upstream scale-up and downstream purification strategies and the growing cost of product development have contributed to a shift in innovation and evaluation of product candidates in alternative systems and other technologies. Developers are considering new ways to expand product pipelines and will move to integrate those systems that provide them with a competitive advantage. The 351(k) pathway for biosimilars development will compel manufacturers to build quality into the process in the early stages, use a risk-based approach to proving comparability and characterization of their product, and to work together with key subject matter experts and the FDA to create a successful development program.

References

ABOUT THE AUTHORS
Tom Fritz is the Managing Partner of Swifitwater Group, while Christine Lightcap, Ph.D., is a Senior Associate, and Kundini Shah, M.S., is a Manager at Swifitwater.
Federal Equipment Company has more than 50-years experience in the processing equipment industry, providing quality used equipment at competitive prices to the pharmaceutical and related process industries.

Federal Equipment is your source for Pfizer process and packaging equipment. Go to fedequip.com and check out the latest additions to our inventory from Pfizer sites around the world.

Buy the best, from the best!

Your Source for Pfizer Surplus Equipment

- Blister Lines
- Bottling Lines
- Capsule Fillers
- Centrifuges
- Coating Pans
- Dryers
- Filters
- Fluid Bed Dryers
- Fluid Bed Granulators
- High Shear Mixers
- Lab Equipment
- Mixers
- Tablet Presses
- Tanks
- Roller Compactors

Contact Us At 1.800.652.2466 or by email at pharmaceutical@fedequip.com to get a Fast Quote.

View Our Entire Inventory Online at www.fedequip.com

8200 Bessemer Ave. • Cleveland, Ohio 44127 • T (800) 652-2466
www.fedequip.com • pharmaceutical@fedequip.com
Studying Outliers

TO ENSURE PRODUCT QUALITY

Out-of-trend results from APRs offer unique insights into ingredients and finished products

When the U.S. FDA rewrote its current good manufacturing practices (cGMPs) for drug products back in 1976, it added the requirement that manufacturers review the quality standards for each drug product every year, and that they write up results in an Annual Product Review (APR). After some manufacturers commented on the proposed regulation, objecting to FDA’s initial report requirements, the Agency revised the proposal to allow each manufacturer to establish its own procedures for evaluating product quality standards. They were to base the final report on records required by cGMPs. The final requirement became law in 1979, as 21 CFR 211.180(e) [1].

Conducted for each commercial product, the APR provides the basis for deciding on steps needed to improve quality. The APR must include all batches of product, whether they were accepted or rejected and/or stability testing performed during the last 12-month period. The APR must cover a one-year period, but does not necessarily have to coincide with the calendar year. A report for the APR addresses the assessment of data, documents and electronic records reviewed.

The data generated from the batch or product are trended using appropriate statistical techniques such as time series plots, control charts and process capability studies. Control limits are established through trending, and specs for both starting materials and finished products are revisited. If any process is found to be out of control, or to have low capability indices, improvement plans and corrective and/or preventive actions must be taken.

Out-of-specification (OOS) regulatory issues have been well understood and documented in the literature [2]. However, out-of-trend (OOT) issues, for product stability, raw materials (RM) and finished products (FP) data identification and investigation are less well understood, but rapidly gaining regulatory interest.

An OOT result in stability, RM or FP is a result that may be within specifications but does not follow the expected trend, either in comparison with historical data of other stability, RM or FP batches respectively, or with respect to previous results collected during a stability study.

The result is not necessarily OOS but does not look like a typical data point. Identifying OOT results is a complicated issue and further research and discussion are helpful.

By Bir (Barry) Gujral and Peter Amanatides, Noven Pharmaceuticals
The lot numbers and ranges shown above in the table are not related to any product or company specific. The table has been built up to make use of all the statistical tools in the paper.

<table>
<thead>
<tr>
<th>Lot</th>
<th>Potency (mg/unit)</th>
<th>Mean</th>
<th>Mean + σ</th>
<th>Mean - σ</th>
<th>Mean + 2σ</th>
<th>Mean - 2σ</th>
<th>Mean + 3σ</th>
<th>Mean - 3σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 46062*</td>
<td>54.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46065</td>
<td>54.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46266</td>
<td>54.5</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46269</td>
<td>55.5</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46272</td>
<td>56.5</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46120</td>
<td>54.8</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46121</td>
<td>54.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 46678</td>
<td>55.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47311</td>
<td>55.1</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47313</td>
<td>56.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47526</td>
<td>55.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47527</td>
<td>55.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47937</td>
<td>55.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47941</td>
<td>55.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47952</td>
<td>54.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47952-2</td>
<td>54.8</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47955</td>
<td>54.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47955-2</td>
<td>54.1</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47958</td>
<td>54.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 47958-2</td>
<td>54.5</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 49235</td>
<td>53.9</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 49203</td>
<td>54.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 49638</td>
<td>55.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 49724</td>
<td>55.8</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50796</td>
<td>54.5</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50797</td>
<td>54.7</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50260</td>
<td>55.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50261</td>
<td>55.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50265</td>
<td>54.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50297</td>
<td>54.6</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50301</td>
<td>55.2</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50304</td>
<td>54.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50319</td>
<td>54.9</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 50322</td>
<td>54.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 52320</td>
<td>54.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 52702</td>
<td>55.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 52927</td>
<td>55.4</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 52931</td>
<td>53.7</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 52999</td>
<td>54.3</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
<tr>
<td>A 53999</td>
<td>56.9</td>
<td>54.9</td>
<td>55.6</td>
<td>54.2</td>
<td>56.3</td>
<td>53.5</td>
<td>57.0</td>
<td>52.8</td>
</tr>
</tbody>
</table>

**Mean**: 54.9

**SD**: 0.7

**Mean + 3σ**: 57.0

**Mean - 3σ**: 52.8
United States v. Barr Laboratories stated that the history of the product must be considered when evaluating the analytical result and deciding on the disposition of the batch. It seems obvious that trend analysis could predict the likelihood of future OOS results.

Avoiding potential issues with marketed product, as well as potential regulatory issues, is a sufficient basis to apply OOT analysis as a best practice in the industry [5]. The extrapolation of OOT should be limited and scientifically justified, just as the use of extrapolation of analytical data is limited in regulatory guidance (ICH, FDA). The identification of an OOT data point only notes that the observation is atypical.

This article discusses the possible statistical approaches and implementation challenges to the identification of OOT results. It is not a detailed proposal but is meant to start a dialogue on this topic, with the aim of achieving more clarity about how to address the identification of out-of-trend results.

This article will focus on studying the OOT trends in finished products and raw materials only. A different approach would be necessary to identify and control OOT in stability, and will be discussed in subsequent articles.

DIFFERENCES BETWEEN OOS AND OOT
Out-of-specification (OOS) is the comparison of one result versus a predetermined specification criterion. OOS investigations focus on determining the truth about that one value while out-of-trend (OOT) is the comparison of many historical data values versus time and OOT investigations focus on understanding non-random changes. For example:

The specification limit of an impurity is not more than 0.10%:

Case 1: For a particular batch, the result obtained is 0.11%. This result is out of the specification limit and is called OOS. An investigation is required. Root cause analysis (RCA) is required for OOS investigation. Once a root cause is identified, corrective and preventive measures need to be taken.

Case 2: The result obtained is 0.08%. Although the result is well within the specifications, we should compare the result with the previous batches’ trend. If we find the average value of the trend as 0.05%, then this batch result (0.08%) is called out-of-trend. Any result greater than 0.05% will be atypical results. A systematic root cause analysis is required. After identifying the root cause, we can decide the fate of the batch. OOT is dealt with on a case-by-case approach. A thorough understanding and control of the process is required.

We used the following tools to analyze data in this paper:
- Microsoft Excel
- Minitab
- Crystal Ball
In addition, we used the data set of 40 batches of potency shown as Table 1. The data is amended to satisfy the scope of this article.

**STATISTICAL APPROACH BACKGROUND**

There is a need for an efficient and practical statistical approach to identify OOT results to detect when a batch is not behaving as expected. To judge whether a particular result is OOT, one must first decide what is expected and in particular what data comparisons are appropriate.

**Methodology, 3 sigma (3σ):**

- Data of 40 batch results has been compiled for fixing the Trend range. A minimum of 25 batches data could be used
- Results of 40 batches are tabulated, mean, minimum and maximum values are established.
- Standard deviation is calculated for these 40 batch results. Excel spreadsheet has been used for Standard deviation calculation.
- Standard deviation will be multiplied by 3 to get the 3 sigma (3σ) value.
- Maximum limit is arrived at by adding the 3σ value to the mean of 40 batch results.
- Minimum limit is arrived at by subtracting the 3σ value from the mean of 40 batch results. Minimum value may come in negative also at times.
- The above maximum and minimum limits shall be taken as the Trend range for upper and lower limits.

- Any value that is out of this range will be considered as out-of-trend (OOT) value or outlier value.
- Wherever a specification has only “not more than,” then only maximum limit for a trend can be considered. Minimum limit should be excluded.
- Wherever a specification has range, then both the Maximum and Minimum limits for trend should be considered.

**RESULTS AND DISCUSSIONS**

Once we arrived at our OOT limits by mean + - 3σ values, we further authenticated these limits using:

**PROCESS CONTROL**

To make sure if the process was under control when we established OOT limits, the following charting was done:

- **Run Chart**: Run charts (often known as line graphs outside the quality management field) display process performance over time. Upward and downward trends, cycles, and large aberrations may be spotted and investigated further. In the run chart (Figure 1), potencies, shown on the y axis, are graphed against batches on the x axis. This run chart clearly indicates that Lot # 52999 with potency value of 56.9 is not an atypical result as it is inside of mean +3σ value, but is borderline to the 57.0 limit.

- **Control Charts**: The control chart is a graph used to study how a process changes over time. Data are plotted in time order. A control chart always has a central line for the average, an upper line for the upper control limit and a lower line for the lower control limit. Normality test passed (p-value = 0.422)
and a lower line for the lower control limit. These lines are determined from historical data. By comparing current data to these lines, we can draw conclusions about whether the process variation is consistent (in control) or is unpredictable (out of control, affected by special causes of variation). In the control chart of given data 40 lots (Figure 2), it is evident that lot #52999 is borderline to the control limit of Mean + 3 \( \sigma \).

**Statistical Process Control:** SPC involves using statistical techniques to measure and analyze the variation in processes. Most often used for manufacturing processes, the intent of SPC is to monitor product quality and maintain processes to fixed targets. Statistical quality control refers to using statistical techniques for measuring and improving the quality of processes and includes SPC and other techniques, such as sampling plans, experimental design, variation reduction, process capability analysis, and process improvement plans.

A primary tool used for SPC is the control chart, a graphical representation of certain descriptive statistics for specific quantitative measurements of the manufacturing process. These descriptive statistics are displayed in the control chart in comparison to their “in-control” sampling distributions. The comparison detects any unusual variation in the manufacturing process, which could indicate a problem with the process.

Several different descriptive statistics can be used in control charts and there are several different types of control charts that can test for different causes, such as how quickly major vs. minor shifts in process means are detected. Control charts are also used with product measurements to analyze process capability and for continuous process improvement efforts.

Figure 3 describes Statistical Process Control Chart of Potency versus Lots of Finished Products. We have taken the mean of 40 lots (54.9) as the target value and mean +3 sigma (57.0) as upper control limit and mean -3 sigma (52.8) as the lower control limit. Figure 3 shows that all the data is shifted right to the mean.

This graph indicates that the process is under control but not centered to the mean as per given specifications. The product specifications given by R&D are always subject to update based upon the manufacturing data.

**PROCESS CAPABILITY INDICES CP AND CPK**

Cp is the capability index. It measures how well the data fits between the upper and lower specification limits. The higher the value, the better the fit. Cpk is the centering capability index. It measures how well the data is centered between the specification limits. The higher the value, the more centered the data.

Thus the Cp and Cpk indices are the primary capability indices. Cp shows whether the distribution can potentially fit inside the specification, while Cpk shows whether the overall average is centrally located. If the overall average is in the center of the specification, the Cp and Cpk values will be the same.
Cpk values are different, the overall average is not centrally located. The larger the difference in the values, the more offset the overall average.

A process capability study is used to determine whether a process is stable and capable. Process capability indices are used to measure how well the data fits into the specification limits. Frequently used process capability indices include Cp and Cpk. Cp is used to evaluate the variation of the process, and Cpk is used to evaluate the centering of the process.

It is important for manufacturers to calculate and analyze the values of Cp and Cpk for their processes and understand the interpretation of such data. It is recommended that the Cp / Cpk values be targeted at 1.33 or above [6]. Process capability studies assist manufacturers in determining if the specifications limits set are appropriate, and also to highlight processes that are not capable. Manufacturers would then be required to take necessary improvement plans / actions.

**CALCULATIONS OF Cp AND Cpk FOR POTENCY OF GIVEN DATA**

Lower Specification Limit= 53.4
Upper Specification Limit= 57.8
Mean= 54.9

**Cp**

Cp= Upper Specification Limit-Lower Specification limit/6*SD
\[
Cp = (57.8-53.4)/6*0.7
\]
\[
Cp = (4.4/4.2) = 1.048
\]

Similarly

Cpk=0.714

Cpk can never exceed Cp, so Cp can be seen as the potential Cpk if the overall average is centrally set. In Figure 4, Cp is 1.048 and Cpk is 0.714. This shows that the distribution can potentially fit within the specification. However, the overall average is currently off center.

**RATIO OF Cp AND Cpk**

Cp/Cpk=1.048/0.714

Cp/Cpk=1.47 which is greater than 1.33 as required Process Capability by Minitab

Note that the results obtained by Minitab agree with Cp and Cpk results.

**RISK ANALYSIS USING MONTE CARLO SIMULATIONS**

Risk Analysis is applied to deal with uncertainty. The criti-
Monte Carlo simulation is a computerized mathematical technique that allows pharmaceutical manufacturers to account for risk in the quantitative analysis of manufacturing and quality data and decision making. This technique has already been used by professionals in fields such as finance, project management, energy, engineering, research and development, insurance, oil & gas, transportation, and the environment.

Monte Carlo simulation performs risk analysis by building models of possible results by substituting a range of values—a probability distribution—for any factor that has inherent uncertainty. It then calculates results over and over, each time using a different set of random values from the probability functions.

In order to analyze OOT data from the APR, a probability distribution function is assigned to the unknown variables, and then Monte Carlo simulations are run to determine the combined effect of multiple variables. The seed value of the individual variables is calculated by the probability density definition of each variable.

A standard sensitivity study shows us the sensitivity of the resulting improvements from the range of outputs from a single variable.

Monte Carlo simulations furnish the decision-maker with a range of possible outcomes and the probabilities that they will occur for any choice of action. Monte Carlo simulations can be run for extremes (either the ‘go for broke’ or ultraconservative approaches) or for middle-of-the-road decisions to show possible consequences.

Depending upon the number of uncertainties and the ranges specified for them, a Monte Carlo simulation could involve thousands or tens of thousands of recalculations before it is complete. Monte Carlo simulation produces distributions of possible outcome values. By using probability distributions, variables can have different probabilities of different outcomes occurring. Probability distributions are a much more realistic way of describing uncertainty in variables of a risk analysis.

**DETERMINATION OF CP AND CPK VALUES FROM SIMULATIONS**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Forecast Values</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials</td>
<td>5000</td>
<td>0.</td>
</tr>
<tr>
<td>Mean</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Dev</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Variation</td>
<td>0.0</td>
<td>0.</td>
</tr>
<tr>
<td>Skewness</td>
<td>-0.0339</td>
<td>0.0852</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>2.93</td>
<td>7.68</td>
</tr>
<tr>
<td>Coefficient of Variations</td>
<td>0.0915</td>
<td>0.0365</td>
</tr>
<tr>
<td>Min</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Max</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean Standard Error</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Precision is calculated at 95.00%

In Figure 5, the ratio of Cp and Cpk of simulations has gone down from 1.47 to 1.11. This gives us an opportunity to look at Sensitivity Analysis to find out the drivers of Risk Analysis. This is an alert to improve our future APR reports. There is also a shift of all our batches to the left to the target values in the simulated model. This is a contrast to the model that we have on Statistical Process Control. The Statistical Process Control model was based upon controls while the simulated model is based upon our specifications. That means that the variability of shifting the model is coming up not only from specifications but from individual lots.
Figure 6 and Figure 7 are Monte Carlo Simulations for Potency Data on Standard Deviation and Sensitivity Analysis respectively. Figure 7 clearly indicates that the drivers of Risk are three lots with lot #s A53999, A47313 and A46272. These lots contribute 27.4%, 11.2% and 7.7% to the variance. The raw materials and production parameters used in these lots should be further investigated to use as a mirror for future years APRs.

LIMITATIONS

One advantage of the Monte Carlo Simulation approach is that, as long as the assumptions are met, the rate of false positives can be set when one calculates the limits. However, a disadvantage is that, when applied to products with limited data, the appropriate limits may be difficult to determine. This can lead to wrongly centered, too narrow, or too wide OOT limits.

So far, we have studied trending for Annual Product Reviews using the data of one calendar year. We are in a process of extending the scope of this project for evaluating trending from year to year, which we expect to give us improved process understanding. Our ultimate goal is scoping out the Knowledge Space, and using APR’s to build the Design Space and Control Strategy fundamental to Quality by Design.

References

6. Investigating OOS test results for pharmaceutical production, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2006, Pharmaceutical CGMPs

About the Authors

Bir (Barry) Gujral is Director Quality Engineering and Peter Amanatidis is Vice President QA and QC with Noven Pharmaceuticals Inc., Miami, Fl 33186. Mr. Gujral can be reached by email, at bgujral@noven.com

Acknowledgments

We sincerely thank Mike Lewis, Director of Validations, and Paul Johnson, Senior Director Analytical Research at Noven Pharmaceuticals Inc for not only reviewing this paper but also for providing their valuable comments. We are also indebted to Joe Jones, VP Corporate Affairs and Jeff Eisenberg, CEO of this company, for their encouragement and kind permission to publish this paper.
Working Together to Perfect Your Tableting Process

There are a number of factors that can affect tablet quality, and failing to address them could cause serious production problems. Choosing a tooling provider who has the experience and foresight to avoid such costly mistakes can be critical to your success.

The tableting experts at Natoli have decades of experience and know just what to look for to prevent common production problems. When you invest in quality Natoli tooling you gain instant access to first-class customer service, extensive technical resources and expert support to help make production problems a thing of the past.

Contact us today to begin a partnership with endless possibilities.
The big picture has changed very little in 10 years. While pointing out root causes, observers also see reasons for optimism.

During the past decade, pharmaceutical manufacturing and quality functions were thrust into an unaccustomed spotlight. After an extended spate of consent decrees, noncompliance and drug quality problems, FDA began to look for root causes and to consider lessons in manufacturing science that regulators and manufacturers might learn from other industries.

At FDA's Center for Drug Evaluation and Research, the Office of Pharmaceutical Sciences held a series of meetings to analyze these issues. In quick succession the Process Analytical Technology (PAT) team was formed in 2002, the 21st Century cGMP's were published, outlining a risk-based approach to regulation and compliance, and the PAT Guidance appeared in 2004.

During this period, a challenge was issued to drug companies by then-Commissioner Mark McClellan, who was quoted by *The Wall Street Journal* as saying that the science of drug manufacturing was "behind that of potato chip and soap making."

Today, drug companies still face quality and compliance problems ranging from supply shortages to consent decrees and warning letters. We asked a number of expert industry observers, including some who had led the call for change last decade, to share their thoughts on how pharmaceutical manufacturing has progressed, and whether anything had actually changed. This is a brief summary of some of what they had to say. (For more, visit PharmaManufacturing.com.)

Examining the big picture, experts agree that the "sea change" predicted for drug manufacturing still hasn’t occurred. "McClellan’s quote still resonates today," says Bikash Chatterjee, President and CTO of Pharmatech Associates, Inc. "Our processes have not demanded the level of sophistication required in other market segments where margins are much tighter, so it’s natural to expect them to evolve at a different rate."

Although some companies have implemented processes that run at 6 Sigma, the industry overall still operates at the same Sigma level of 2.5 to 3 that it did last decade, says G.K. Raju, Executive Director of the Pharmaceutical Manufacturing Initiative at MIT, and President of Light Pharma, Inc. At FDA’s Science Advisory Board meetings last decade, Mr. Raju documented the high cost of traditional QC and its contributions to pharma’s unusually high cycle times.

"Progress seems to be slow when one looks at reports on shortages, recalls and other quality issues," says Ajaz Hussain, CSO at Philip Morris International, and former Deputy Director of OPS and head of the PAT Team at FDA. FDA had launched PAT and the 21st Century initiatives, in part, to prevent just these types of problems from recurring. "Efforts towards developing guidelines have been laudable," he says, "but additional emphasis is needed on certain fundamental aspects of quality such as effective QMS, training, root-cause investigations and setting of specifications based on an analysis of variance.”

However, there are bright spots. More people seem to realize that changing operations is not simply doing some Lean Sigma training, but changing mindsets, says Thomas Friedli, professor at the University of St. Gallen, whose research group has been closely tracking pharmaceutical operational excellence progress for a number of years. "The complexity that drug plants have to..."
master has increased, so a plant that maintains operational performance over the years has in fact improved,” he says.

Traditional pharma leads in Lean and Six Sigma efforts, but biopharma is now devoting more resources to operational excellence in manufacturing, and to consolidating isolated improvement activities, Friedli says. Currently, the University of California Berkeley and NSF have launched the Initiative for Research in Biopharmaceutical Operations to study this issue (right), while, funded by the Sloan Foundation, MIT and Georgetown are exploring related issues and the impact of globalization on regulation and innovation.

**INCREASED USE OF MODERN MANUFACTURING TOOLS**

Another positive sign, Raju says, is the fact that more drug companies are applying established industrial engineering tools such as process capability analysis and statistical process control.

These methods are specifically called out in FDA’s Process Validation Guidance, says biopharmaceutical consultant James Blackwell, but more companies are realizing their value in catching trend deviations, providing new process insights and driving continuous improvement. “Looking for trends once a year is not cGMP anymore,” he says.

“Today, even generic manufacturers routinely have control charts on the shop floor, a big change from a decade ago,” Chatterjee notes, “while most companies use some kind of scorecard for product performance.” In addition, he says, inline detection, vision systems and barcode readers are common at most facilities. Ten years ago, they were still a novelty.

Chatterjee notes the need for greater flexibility, particularly where shift changeovers are concerned. Mergers and acquisitions are driving manufacturing to greater agility, since many companies now must accommodate technologies rapidly, even with limited or no development understanding. He points to flu vaccine manufacturing, and the push to cell-based vaccines, as a success story. A few years ago, there was only one cell-based vaccine pilot. Today there are eight. “The market needed something, and we applied the innovation engine to figure out how to do it,” he says.

FDA enforcement and guidance trends are also having a positive, if painful, impact. For one thing, the Agency’s emphasis on science- and risk-based reviews and inspections will likely change the short-sighted emphasis that some companies give on “delivering quality to the regulator rather than the consumer,” says Gawayne Mahboubian-Jones, manager of Quality by Design at Philip Morris, and a frequent speaker and trainer at FDA staff training workshops.

**BENEFITS OF NEW PROCESS VALIDATION GUIDANCE**

FDA’s revised Process Validation Guidance will stimulate improvements in manufacturing, some say. “It has already increased the industry’s awareness of the need to take a lifecycle view of product quality and the importance of good science and process characterization and increased efforts,” says Blackwell.

Chatterjee notes that the guidance will allow manufacturers to take overall equipment effectiveness (OEE), SPC and Lean, and drive manufacturing equipment performance levels up far more rapidly. In addition, he says, it will facilitate the implementation of platform-based technologies.

“This may be the most significant byproduct of the guidance, which is lost on those who remain fixated on the three stages,” he says. “If we can, during those stages, demonstrate that we not only understand and are monitoring those variables that affect our process, and setting limits around them, we can improve processes without

---

**IS BIOPHARMA OPEX GROWING UP?**

New research suggests that biopharma manufacturers desire operational excellence but are not using sophisticated methods common in other industries.

Biopharma is usually looked at as a progressive industry, with innovative companies pushing the envelope in pursuit of the next big drug or technology. There may be one area, however, where bio is lagging behind—operational excellence. Early results from surveys of biopharmaceutical professionals taken by the newly formed UC Berkeley Initiative for Research in Biopharmaceutical Operations suggest that biopharma is, for example, preoccupied with risk, but has not yet developed analytical, data-driven means to assess and manage that risk.

The Berkeley Initiative was launched last summer with funding from the university, three founding members—Bayer, Genentech, and BioMarin—and the National Science Foundation. The impetus for the effort is to develop collective, “precompetitive” research and intelligence for the industry regarding its operations, said Phil Kaminsky, a Berkeley professor and director of the program.

“When you look at the progression of this industry, it’s similar to progression of the semiconductor industry, offset by 20 or 25 years,” said Kaminsky, speaking February 28 at the Biopharmaceutical Development & Production Week in San Diego. “There were big players in that industry and they were making lots of money, then the realization dawned that production control, inventory control, efficiency, supply chain management, and so on were going to be important.”

Kaminsky and his graduate assistants are just beginning to churn out data from the some 300 industry members that have provided input thus far. For more on this, visit PharmaManufacturing.com.

– Paul Thomas, Witt-Keifer
having to revalidate everything; now we are able to make improvements to our manufacturing approach.”

Of special significance is the use of matrix validation, he says. “When you do this, you allow people to use more nimble or continuous manufacturing solutions, and qualify them for new or existing applications.”

**CLUELESS ON THE COST OF POOR QUALITY?**

One obstacle to more scientific manufacturing has been a persistent lack of understanding of the cost of quality. “Until the industry grasps the fact that this is an essential driver, and that the Taguchi Loss Function is not a digital (1 or 0) function, they cannot start down the road toward significant improvement,” says Mahboubian-Jones.

Blackwell agrees. “More efficient development and manufacturing come from a better understanding of the cost of quality throughout the product lifecycle, and the more efficient use of resources and technology to develop robust processes and to approach scaledown, platform technologies, and DOE,” he says. “Most pharma managers still don’t have a handle on the cost and risk of noncompliance.”

---

**“Most pharma managers still don’t have a handle on the cost and risk of noncompliance.” — James Blackwell**

---

Chatterjee notes past progress in this area, in the late 1980s for instance with activity-based costing, which “came and went,” and with Lean accounting, which tied product costs not to work centers but to areas between them and allowed companies like Procter & Gamble to achieve quick and significant results.

Today, he says, at most pharma companies, the financial buckets are not measured to the same magnitude. “If I have to make 100 lots of a drug to meet a market forecast this month and I only make 80 because the rest failed, those 20 are now accounted for in a different bucket. Nobody actually calculates the true loss, the true cost of those lots; they just track the scrap costs,” Chatterjee says. “The reality is that you lost that market share, that revenue opportunity,” he adds.

For OTC drugs, it can take six months to a year before you realize the impact. “If you’re trying to meet a minimum order for Costco, Walmart or Sam’s Club, if you don’t ship that number on that day in that quantity, you’ve lost that shelf space, possibly forever. How do you measure that, and its impact on your business revenue?”

That’s where cost of poor quality becomes a very important number,” he says. “Then, when you factor in the cost of deviation and CAPA investigation, sales and forecast inaccuracies, material on hold, inability to ship on time, the numbers are tremendous and it doesn’t take much to realize much of that gain back, but we’re not connecting these pieces together and considering what the true cost is of our inability to supply.”

**RIGHT FIRST TIME**

The key to improving manufacturing lies in improving drug development. “We develop drugs using methods from the 1950s and 1960s,” says U.K.-based consultant Hedley Rees. “You need to scotch the idea that you discover drugs by accident by screening thousands of compounds and then getting into clinical as soon as possible. It’s only when we have hard clinical evidence in Phase III that people begin to think about how we actually make these products, and by then it’s too late.” The key, he says, is Quality by Design, but not in doing it as a scientific and technical activity but by reengineering the whole process, by involving all stakeholders at an early stage, not just R&D but CMC and procurement.

The current approach also limits pharma’s ability to connect manufacturing issues to impact on the patient, says PMI’s Hussain. “This is especially true,” he says, “if we only focus on the ‘mean values’ of attributes of a product used in clinical trials. Prior-knowledge, pilot studies, Phase I–Phase II studies are a means to reduce uncertainty on which product attributes are critical or not,” he says, “while structured experiments and databases can provide relevant information.”

“If you were to see side-by-side case studies of companies that had adopted QbD vs. those that didn’t, you’d see clear benefits in terms of the cost of poor quality, scrap rate, inability to meet market demand,” says Pharmatech’s Chatterjee. “The benefits are clear. But that kind of comparison is never done.”

The new FDA guidance on applying QbD for generic drugs is very much in line with what brand-name pharma should do and what generic companies don’t do, Chatterjee says. “If a generic company were to adopt three-quarters of the methodology, not only would their bioequivalency lots match their scaleup lots the first time out of the box, but the variability they would see as they go to commercial manufacturing would be significantly less.”

**REGULATORY UNCERTAINTY**

Hussain sees the connection between IT for data, information and knowledge management and how it is integrated with Quality Management Systems to
be critical to quality assurance and efficiency improvements in drug manufacturing. Pharmaceutical manufacturers have not been investing in the types of technology and IT required to better handle knowledge management and quality, says Raju, instead focusing on transactional systems. In the end, he says, this only encourages the documentation of 2.5-to-3-Sigma processes, rather than helping in transformation.

In addition, he says, industry may be reluctant to invest in technology that may reveal problems. Are regulators to blame for this? Since the last decade, FDA has invited companies to discuss such issues openly with them, and those who have report mixed results. Critics and surveys have suggested lack of coordination between reviewers and inspectors as a major source of problems. Recently, Raju's company, Light Pharma, is working under contract with FDA to help improve those connections.

Strengthening those ties will be critical, says Hussain. "The PAT Guidance and PAT team, which united CMC review, cGMP compliance and inspection, recognized the need to reduce technical and regulatory uncertainty. At the moment, I can't see such an integrated approach," he says. Since 2000, FDA has swung from "carrot" to "stick" mode. However, the end result will be positive, observers say, if it drives manufacturers to acquire better knowledge of their processes. Industry didn't take the carrot [for instance, with PAT], so regulators are now using the stick, but this stick is based on product and process understanding, a much more effective weapon than the blunt "quality and compliance" approach they took in the past, says Mahboubian-Jones.

One ongoing challenge is the fact that manufacturing's role is viewed as less of a priority than R&D and marketing. Although pharma is hiring more experts from other industries, says Sam Venugopal, consultant with PricewaterhouseCoopers in Cleveland, it is not likely that a CEO will come from the operations track any time soon.

"Companies need to understand that manufacturing skills and understanding are an essential component of the mix in a boardroom. Until that happens, decisions will continue to be made which look sensible on the balance sheet, but are disastrous on the factory floor," says Mahboubian-Jones.

The future of drug manufacturing belongs, he says, to small, flexible, forward-looking companies which create a base by filling niches deemed "uncompetitive" by Big Pharma. "Once this base is established, they will progressively out-compete the current generation of companies. There are clear signs that this process has started, and it seems to be most vibrant away from the conventional manufacturing centers in the Western world," he says.

Overall, there is reason for optimism, he says. "Today's positive examples suggest that pharma is capable of transforming its manufacturing and the quality of its products. The future has great potential. The question is: Will that potential be realized by the current generation of companies, or will it be a new generation of more flexible, more responsive, less autocratic companies which take up the gauntlet and bring about the transformation which is required?"
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.
- **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 ensure 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 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.

TECH TRANSFER FRAMEWORK

Gone are the days of simply comparing product 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 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

**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 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.

**Table 1. Formulation Details**

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>%w/w</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>60</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>22</td>
<td>Excipient filler</td>
</tr>
<tr>
<td>Povidone K 29-32</td>
<td>5</td>
<td>Granulation binder</td>
</tr>
<tr>
<td>Lactose</td>
<td>12</td>
<td>Excipient filler</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>1</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Purified water</td>
<td>QS</td>
<td>Solvent</td>
</tr>
<tr>
<td>Coating Solution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>%w/w</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit Coating Solution</td>
<td>12</td>
<td>Controlled release polymer</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>1</td>
<td>Plasticiser</td>
</tr>
<tr>
<td>Talc</td>
<td>1.5</td>
<td>Glidant</td>
</tr>
<tr>
<td>Water</td>
<td>QS</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

**Table 3. Process Unit Operation Risk Assessment**

<table>
<thead>
<tr>
<th>CQA</th>
<th>Granulation</th>
<th>Drying</th>
<th>Milling</th>
<th>Blending</th>
<th>Compression</th>
<th>Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Assay</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Impurity</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Blend Uniformity</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Drug Release</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Particle Size Distribution</td>
<td>Medium</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Justifications for High Rating</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milling screen size and speed can affect the PSD and therefore the powder flow and tablet fill weight control</td>
<td>M&quot;illing can affect blend uniformity, assay, and drug release profile</td>
<td>Compression can affect drug uniformity in the tablet based upon particle size variability and flow</td>
</tr>
</tbody>
</table>
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.

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

CRITICAL PROCESS PARAMETERS/RISK ASSESSMENT
In the absence of a development report, the team turned to a tiered risk-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

---

Reduce your Risk
With Monitoring & Measurement Solutions Proven Reliable in GxP Environments

“Our customers need solutions that reduce the risks of ruined or adulterated product and regulatory non-compliance. They also need software and devices that are easy to integrate and allow for simple validation. Since a big part of my job involves visiting customers, I’m really glad that Vaisala’s solutions do all of that.”

Paul Daniel
Vaisala Senior Regulatory Compliance Expert

FREE GxP Compliance Kit Download:
www.vaisala.com/gxp-compliance-kit

www.vaisala.com/gxp-compliance-kit
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 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 below 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 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:
IN THIS second 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 (H<sub>1</sub>) 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<sub>0</sub>) is not significant, the alternative hypothesis (H<sub>1</sub>) 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 Bergumi’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.

**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 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 life-cycle 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**

Additional Resources Links

**GEMU**

Valves Product Line  
http://www.gemu.com/valves.html

Flow Measurement Product Line  
http://www.gemu.com/flow_measurement.html

Downloads  
http://www.gemu.com/downloads.html

**VAISALA**

Education & Resources : Application Notes, White Papers, Webinars & Articles  

Humidity Calculator  

Life Sciences Product Line  

**Federal Equipment Company**

Current Deals & Liquidations  

Sell to Federal Equipment  

Federal Equipment News & Events  
http://www.fedequip.com/NewsAndEvents.aspx

**DE-STA-CO**

Life Sciences Material Handling Solutions  
http://www.destaco.com/life-sciences-material-handling.html

Telemanipulators, Gloveport Systems, Transfer Products  
http://www.destaco.com/crl-products-equipment.html

Catalogs  
http://www.destaco.com/downloads.html

**Hamilton Company**

Biopharmaceutical Process Sensor Application Map  

Biopharmaceutical Process Sensor Solutions Brochure  

Biopharmaceutical Process Scale Up: Get It Right eResource  