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Quality Assessment of A Generic Pharmaceutical Filling Operation by Loss Function And Quality Sampling Plan

Guangming Chen and Andrew Ezekiel
Department of Industrial and Systems Engineering
Morgan State University
Baltimore, Maryland 21251
USA

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Abstract

This paper deals with the filling process of a liquid generic medicine in a pharmaceutical company where quality control is implemented by sampling periodically. According to Federal regulation, all liquid generic medicines cannot be under-filled (under the lower specification limit LSL). The company's products are classified into two different categories: Class A and Class B, based on whether an upper specification limit (USL) may be exceeded. Both products cannot be filled below the lower spec limit. However, product A has an USL while product B has no USL restriction. To evaluate the filling process of the pharmaceutical company, Taguchi's loss function and the sampling plan currently used by the company are considered to develop the assessment on the expected quality loss for symmetric and asymmetric quality loss functions for optimization of process mean and sampling plan design.

1. Introduction

A key to be competitive in today's economy is to produce high-quality products at low production cost, to meet or exceed customer's requirements. Products and process variations cost manufacturing industry significant amount of money in terms of high rework cost, scrap, and costly inspection. Currently, governmental regulation on consumer protection requires that the amount of pharmaceutical product dispensed into the containers, on average, must be at least the label-stated amount. Furthermore, the Food and Drug Administration (FDA) expects pharmaceutical industry to have appropriate validation processes for quality assurance, where the validation has been defined by FDA as "establishing documented evidence to provide a high degree of assurance that the specific process will consistently meet the predetermined specification and quality attributes. Under-filled containers put the pharmaceutical company at risk with the liability due to this regulation (i.e., the company may face recalls or serious fines). Therefore, a common practice in pharmaceutical industry is to set the process mean sufficiently higher than the target value to avoid the risk of producing under-filled units, consequently to ensure the conformance to the specification. However, using higher process mean or over-filling containers results in substantial loss to the producer. Consumers consistently receive 102-108% of the declared label weight (2% - 8% of excess quantity of product) for volume products (Kloos and Clark 1981).

Sampling inspection is a tool widely used by pharmaceutical companies to identify and monitor the variation, and also to control the variability in the production process to insure that the units produced are within the required and acceptable range. Also, sampling inspection is used for decision-making on product disposition and there is a possibility of

making an incorrect decision because the sampling plan bases the decision on a sample rather than the entire lot.

2. Quality Evaluation System

Quality evaluation system is usually based on specification limits. If the characteristic of the product being measured is within the specification limits, the product is classified as good or conforming unit, otherwise it is classified as bad or non-conforming. The loss function is used to evaluate quality on a continuous base. The loss function states that as product deviates from the target value, the loss becomes greater. It is a way to relate product variation to a monetary loss, results in a loss to the society and the company. A commonly-accepted relationship is a parabolic function that estimates the quality loss, in terms of money, when a quality characteristic *y* deviates from its target value *T*.

In this paper quality loss function is used to measure the deviation of products from the target, as well as the variability in the products in terms of monetary value. The basis of the loss function is that products should be produced close to their target.

To account for the loss to the company due to deviation from the target, Taguchi's quadratic loss function was used. The formula to calculate the quality loss *L* per unit of product is given by:

$$L(y) = k(y - T)^2 \qquad (1)$$

where y is the quality characteristic and T is the target and *k* is a cost-related numerical constant (Bai and Lee 1993; Melloy 1991; Thomas, Mohsen and Jafari 1991). When there is more than one unit, the expected quality loss is given by:

$$L = k[\sigma^2 + (\bar{y} - T)^2] \qquad (2)$$

where $\bar{y}$ is the average deviation from the target and σ^2 is the variance. The advantage of the loss function is that we can evaluate quality loss in terms of average and variance. To reduce quality loss, we can focus on adjusting the average to the target as well as reducing the variance σ^2.

3. The Compounding Process

In a typical pharmaceutical company, the industrial application involves compounding of raw materials into finished products, and the packaging of the finished products. The packaging process is accomplished with the aid of filling machines. The compounding process consists of a number of steps after the raw materials arrive at the facility. Quality Assurance (QA) department is responsible for receiving the incoming materials (liquid, powder or solution), and collects samples for testing. If the test results are within the required specification limits, the raw materials are released from QA incoming department to compounding department for production.

A batch cycle begins with the weighing of ingredients and ends with dispensing the finished product into containers. The following four basic operations make up a complete cycle: weighing, heating/cooling, mixing, and packaging. Each individual operation is very important to the overall performance of the product, i.e., the sequence of weighing and introducing the ingredients into the mixing tank affects the quality of the final product. In some steps, mixing and cooling are performed at the same time. The compounding of each batch usually takes a couple of days depending on the specific product. During compounding of the ingredients, the batch is closely monitored and controlled by experienced compounders or technicians. Electronic devices continuously measure the process variables, such as viscosity, density, hydration, temperature and pH value. Visual inspections of the reacting ingredients (clarity, color, dissolution, dispersion, hydration etc.) are used to determine the reaction end points.

4. The Filling Process

During a packaging process, the product to be packaged is transferred from compounding area through overhead lines to the filler located in the packaging area. Figure 1 depicts a consolidated rotary piston filler/capper that is used to package some of the company's products. The Consolidated Rotary Piston Filler consists of 21 filling stations. Empty bottles are sent to an in-feed assembly (consisting of a feed star and a conveyor) from the bottle blower. The feed star transfers the bottles to holding chucks that position them under the filling stations and move them around the filling head. The containers travel around the head on a bottle rail.

The filling stations are mounted outside the bowl. Each filling station consists of a cylinder, a piston, and a valve. As the bowl rotates, rollers attached to the upper outside of the pistons travel around the machine on a stationary inclined track, lifting them during the first 180 degrees of rotation and forcing them down during the second 180 degrees.

Figure 1. Consolidated Rotary Piston Filler/Capper

The following sequential steps describe the operation of the filler:

- On its upstroke, a piston draws product from the filler bowl into the cylinder through its valve intake port.
- As the piston reaches the top of its stroke, a trip cam rotates the valve plug to its discharge position. The down stroke of the piston then forces the product through the discharge port via the fill heads of a filling machine into the container.
- At the beginning of the next upstroke, a second cam rotates the valve plug back to its intake position and the cycle is repeated.

An adjustment jackscrew is provided to raise or lower track as required. This track movement adjusts the fill at all stations simultaneously, and can be accomplished while the machine is operating. Volume of fill is governed by the length of the piston stroke, which in turn is controlled by the height of the

cam track. The entire bowl and valve assembly rotates about a central axis during the filling cycle. Filled bottles are conveyed from the filler through a conveyor belt to the capper for cap application. Figure 2 illustrates a typical filling and capping machine. To determine fill weight accuracy during a filling process, we consider a sampling plan in which samples are collected manually from each fill head. The samples are weighed. Detection of process shifts is important during a filling process so that the necessary corrective action can be implemented (Lanning, Montgomery & Runger, 2003). These shifts might result in either over-filled or under-filled containers. Under-fill is a concern in terms of federal government regulations, and consumer satisfaction. Over-fill is another concern because of the higher cost and lost revenue.

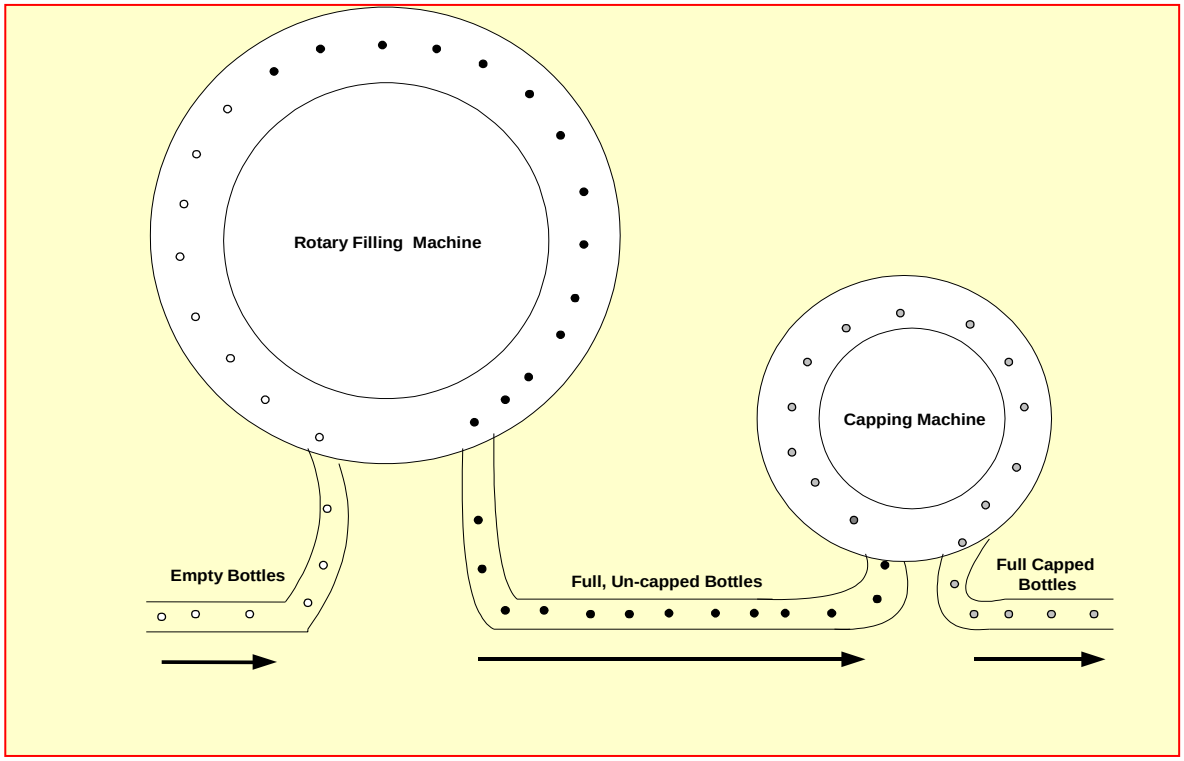

Figure 2. Filling and Capping machine.

5. Modeling Assumption

The output from the filling process is the fill weight Y (response variable), and it is assumed to be a random variable with known distribution and parameters. Furthermore, we assume Y is normally distributed with mean μ and variance σ^2, *i. e.* $N(\mu,\sigma^2)$ and that the random variable Y_i (characteristic of the ith unit. $i = 1, 2, 3, - - - n$), are statistically independent. The company sets T the target fill weight for each product. The gross weight of each packaged unit G includes both the net weight of the product and the tare weight t (weight of empty bottles and caps).

$$G = Y + t \qquad (3)$$

The weight of the empty bottles and caps varies according to a known distribution and is independent of the net weight of the product. Due to the variability in the tare weight, it is difficult to assess the net weight of the product correctly; as a result, estimates of the net weight are subject to error. These package

errors can result in under-filled or over-filled packaged units, which increase the possibility of noncompliance and giveaway, respectively. Therefore, to compensate for both the uncertainty of the fills and tare weight, the company imposes minimum and maximum fill weight specifications on the gross weight, denoted by g_l and g_u, respectively. Due to the variability in the filling process, *Y* can be in one of two possible states: within specifications or out of specifications. In addition, we assume *X* is the number of units that are out of specification (defective units) in time period t. Then *X* is a Poisson random variable with parameter λ, where λ is the mean rate of defective occurrence per unit of time. Also, we assume a symmetrical (same quality loss for equal deviation on both sides of the target) quality loss function is applicable to the company. As stated earlier, the company's products is classified into two different categories; *A* and *B.* During filling process for product *A*, a unit of filled product with a fill weight outside the specification limits is defective and is discarded. While for category *B*, underfilled products are destroyed or discarded, but overfilled units are sold for the same price as good units. We consider three types of losses; loss due to variability of the units produced within specification limits, inspection cost, and scrap cost, and hence we derive the model to determine the expected quality loss to the company based on the above scenarios.

6. Problem Domain

As stated earlier, the company's products are classified into two different categories; *A* and *B.* During a filling process, the filler operator collects samples (one sample per fill head) every thirty minutes and weighs the samples (periodic fill checks). If any of the units is not within the fill weight specification limits, for product *A*, the operator is required to pull 3 additional consecutive samples from the same fill head and weigh the units. If any of the additional samples is out of specifications, the operator is required to stop the line, and segregates the units produced since the last acceptable fill check, including the test samples. For product *A*, containers can not be filled below or above the specification limits. In this case, both the lower and upper specification limits are of interest. All isolated units are inspected and acceptable units are reintroduced to the line. Note that the cost of inspecting a container filled below the lower specification limit is the same as inspecting a container filled above the upper specification limit.

To evaluate the quality of all units for product *A*, we derive the expected quality loss to the company.

Let a = lower specification limit
b = upper specification limit
y = weight of a container
Cr = cost of re-inspection per unit
Q = production rate
t = time interval between sampling
Cs = scrap cost per unit
x = number of defectives in time period t

Then # of units produced for a period of time *t* = Qt

Total scrap cost = xCs

Total inspection cost = CrQt

Therefore, a defective product will lead to a loss equivalent to total inspection cost + total scrap cost in time t = CrQt + *x*Cs

Note: If it is determined that an out of spec situation has occurred, all units produced right from the last acceptable fill check to the time the out of spec is confirmed are subject to inspection. An inspection was performed for all units produced in time period *t* due to a defective.

7. The Model

The following model describes the loss function:

$$L(y) = \begin{cases} k(y-T)^2, & a \le y \le b \\ CrQt + xCs, & \text{otherwise} \end{cases} \quad (4)$$

The Poisson probability function for X units of defectives is given by:

P(X = *x*: # of defects in time period t)

$$= \frac{(\lambda t)^x}{x!} e^{-\lambda t}, \quad x = 0,1,2,... \qquad (5)$$

then

$$E(X) = \sum_{x=1}^{\infty} x \frac{(\lambda t)}{x!} e^{-\lambda t} \qquad (6)$$

$$= \sum_{x=1}^{\infty} x \frac{(\lambda t)^x}{x(x-1)!} e^{-\lambda t}$$

$$= (\lambda t) e^{-\lambda t} \sum_{x=1}^{\infty} \frac{(\lambda t)^{x-1}}{(x-1)!}$$

The expected quality loss is given by:

$$E[L(y)] = \int_{all\ y} L(y) f(y) dy \qquad (7)$$

The expected loss is based on all values of y and not just the values of y that are outside the specification limits. Therefore,

E[L(y)] =

$$\int_0^a L(y) f(y) dy + \int_a^b L(y) f(y) dy + \int_b^{\infty} L(y) f(y) dy$$

$$= \int_a^b L(y) f(y) dy + (C_r Qt + xC_s)[P(y < a) + P(y > b)] \qquad (9)$$

$$E[TL] = \int_a^b k(y-T)^2 f(y) dy + \quad (10)$$

$$(C_r Qt + C_s \sum x \frac{(\lambda t)^x}{x!} e^{-\lambda t}) [\int_0^a f(y) dy + \int_b^{+\infty} f(y) dy]$$

Equation (10) represents the expected quality loss due to the variability within the specification limits, inspection cost, and scrap cost. Let us evaluate each integral in equation (10) separately,

By using the transformation $z = \frac{y-\mu}{\sigma}$, $y = z\sigma + \mu$, and $dy = \sigma dz$, let $\phi(z)$ and $\Phi(z)$ be the standard normal density function and the standard cumulative normal distribution function respectively. Then we have

$$\int_a^b k(y-T)^2 f(y) dy = k \int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} (z\sigma + \mu - T)^2 \phi(z) dz \qquad (11)$$

$$= k[\sigma^2 \int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} z^2 \phi(z) dz + 2\sigma(\mu - T)[\int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} z \phi(z) dz + (\mu - T)^2 \int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} \phi(z) dz] \qquad (12)$$

But

$$\int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} z^2 \phi(z) dz = \Phi\left(\frac{b-\mu}{\sigma}\right) - \Phi\left(\frac{a-\mu}{\sigma}\right) + \left(\frac{a-\mu}{\sigma}\right)\phi\left(\frac{a-\mu}{\sigma}\right) - \left(\frac{b-\mu}{\sigma}\right)\phi\left(\frac{b-\mu}{\sigma}\right) \qquad (13)$$

$$\int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} z \phi(z) dz = \phi\left(\frac{a-\mu}{\sigma}\right) - \phi\left(\frac{b-\mu}{\sigma}\right) \qquad (14)$$

$$\int_{\frac{(a-\mu)}{\sigma}}^{\frac{(b-\mu)}{\sigma}} \phi(z) dz = \Phi\left(\frac{b-\mu}{\sigma}\right) - \Phi\left(\frac{a-\mu}{\sigma}\right) \qquad (15)$$

Substitute equation (13), (14), and (15) into (12). The expected quality loss within specification limits is given by:

$$\int_a^b k(y-T)^2 f(y) dy = k[\sigma^2 \{\Phi\left(\frac{b-\mu}{\sigma}\right) - \Phi\left(\frac{a-\mu}{\sigma}\right) + \left(\frac{a-\mu}{\sigma}\right)\phi\left(\frac{a-\mu}{\sigma}\right) - \left(\frac{b-\mu}{\sigma}\right)\phi\left(\frac{b-\mu}{\sigma}\right)\} + 2\sigma(\mu - T)(\phi\left(\frac{a-\mu}{\sigma}\right) - \phi\left(\frac{b-\mu}{\sigma}\right)) + (\mu - T)^2 (\Phi\left(\frac{b-\mu}{\sigma}\right) - \Phi\left(\frac{a-\mu}{\sigma}\right))] \qquad (16)$$

Substitute equation (16) in equation (10), the expected quality loss that is due to the

variability in the process, inspection cost and scrap cost is given by:

$$E[TL]= k[\sigma^2\{\Phi\left(\frac{b-\mu}{\sigma}\right)-\Phi\left(\frac{a-\mu}{\sigma}\right) + \left(\frac{a-\mu}{\sigma}\right)\phi\left(\frac{a-\mu}{\sigma}\right)-\left(\frac{b-\mu}{\sigma}\right)\phi\left(\frac{b-\mu}{\sigma}\right)\}+ 2\sigma(\mu-T)(\phi\left(\frac{a-\mu}{\sigma}\right)-\phi\left(\frac{b-\mu}{\sigma}\right)) + (\mu-T)^2(\Phi\left(\frac{b-\mu}{\sigma}\right)-\Phi\left(\frac{a-\mu}{\sigma}\right))] + (C_rQt+(\lambda t)e^{-\lambda t}C_s\sum_{x=1}^{\infty}\frac{(\lambda t)^{x-1}}{(x-1)!})[\Phi\left(\frac{a-\mu}{\sigma}\right)+ 1-\Phi\left(\frac{b-\mu}{\sigma}\right)] \quad (17)$$

$$Let \quad \lambda_1 = \frac{a-\mu}{\sigma} \quad (18)$$

$$Let \quad \lambda_2 = \frac{b-\mu}{\sigma} \quad (19)$$

Substitute equations (18) and (19) into equation (17). The expected quality loss to the company is given by:

$$E[TL] = k[\sigma^2\{\Phi(\lambda_2)-\Phi(\lambda_1)+(\lambda_1)\phi(\lambda_1)- (\lambda_2)\phi(\lambda_2)\}+2\sigma(\mu-T)(\phi(\lambda_1)-\phi(\lambda_2))+ (\mu-T)^2(\Phi(\lambda_2)-\Phi(\lambda_1))]+(C_rQt + (\lambda t)e^{-\lambda t}C_s\sum_{x=1}^{\infty}\frac{(\lambda t)^{x-1}}{(x-1)!})[\Phi(\lambda_1)+1-\Phi(\lambda_2)] \quad (20)$$

Equation (20) consists of the expected quality loss within the specification limits that is due to variability in the process, inspection cost, and scrap cost.

8. **Numerical Example**

A numerical example to illustrate an application of the proposed model (equation 20) to determine the expected quality loss within the specification limits that is due to the variability in the process, inspection cost, and scrap cost follows. Given the following information:

Minimum weight (a) = 400.0 grams
Target weight (T) = 403.0 grams
Maximum weight (b) = 413.0 grams
Process mean (□) = 410.2 grams
Standard deviation = 1.0135
Cost price/unit (A_0) = \$42.50
Production rate Q = 80 bpm
Scrap cost per unit C_s = 12.00
# of defectives X = 1 unit

Δ_0 = (USL-LSL)/2 = (413-400)/2 = 6.5

$k = A_0/\Delta_0^2 = 42.50/(6.5)^2 = 1.006$

Now suppose that:
Inspection cost per unit or C_r = \$0.14
Time interval between sampling t =30 min
Average rate of producing a defective λ = 0.001. By using equation (18), (19), and (20), we obtain

$$□_1 = \frac{a-\mu}{\sigma} = -10.0641$$

$$□_2 = \frac{b-\mu}{\sigma} = 2.7627$$

Thus,

$\phi(\lambda_1) = \phi(-10.0641) = 0.0000$
$\Phi(\lambda_1) = \Phi(-10.0641) = 0.0000$
$\phi(\lambda_2) = \phi(2.7627) = 0.0035$
$\Phi(\lambda_2) = \Phi(2.7627) = 0.9971$

Substitute these values into equation (20), then the expected quality loss for the filling process of the company is given by:

E[TL] = \$53.85/unit

9. **Concluding Remarks**

Sampling plan is often used in industries to accept or reject a lot. In this paper we have evaluated the expected quality loss of the filling process of a pharmaceutical industry by using loss function and quality sampling plans. The developed model for the expected

quality loss considers several losses occurring to the pharmaceutical company and the customer: loss to the manufacturer and loss to the consumer, such as the cost due to product variability, inspection cost and scrap cost.

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