Needed Math Project

Award # 2100062

Developed by Professor James Martin, Wake Technical College Community College, NC

<u>Company and Contact inspiring Topic:</u>

AstraZeneca

Durham, NC

Elliott Locke – NCSU graduate and now Process Engineer

Elliott is now a Process Engineer at Eli Lily and Company and works with manufacturing technicians. Eli Lilly and Company is an American pharmaceutical company headquartered in Indianapolis, Indiana, with offices in 18 countries. Elliott is employed at the Cary site in North Carolina. The company's products are sold in approximately 125 countries. The company was founded in 1876 by, and named after, Colonel Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War. They both test and manufacture pharmaceuticals.

PROBLEM STATEMENT

A technician needs to take samples, make measurements, determine if the manufactured projects fall within specified tolerances, and recognize patterns in data to anticipate production problems.

SCENARIO DESCRIPTION–SPECIFIC EXAMPLE

The manufacturing of Inhalers requires an assembly of several parts including the canister that contains the medication and the pump valve that dispenses the medication (see Figure 1). A manufacturing line crimps the pump valve onto the canister, pulls a vacuum on the canister, and injects the precise amount of medication into the canister. Whether the manufacturing is still in the research and development phase or the large-volume manufacturing phase, in-process checks (sampling of product) must be done to ensure measured parameters are within acceptable tolerances. Pulling samples at regular intervals and measuring parameters will ensure quality products are being manufactured. Most manufacturing companies follow a GMP (Good Manufacturing Practice) model, and quality products are kept at the highest standards.

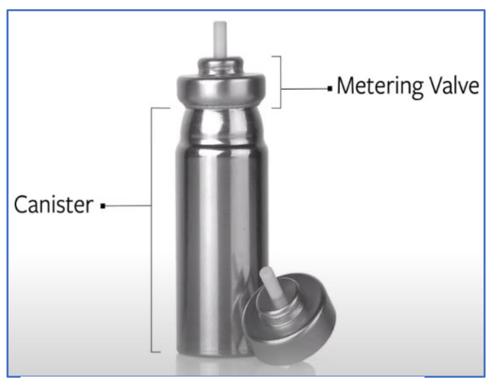

Figure 1. Metered-Dose Inhaler

During the manufacturing of the Metered Dose Inhaler canisters, the valves are crimped onto the canister. To ensure integrity of the product, In-Process Checks are conducted on the crimped canisters and they are sampled at regular intervals. Each selected Canister is measured for Crimp Height (mm), Crimp Diameter (mm), and Net Fill Weight (g) (see Figure 2). Also, during the manufacturing process, the suspension (active medicine along with additives) is recirculated to fill the canisters with the proper drug concentration or mixture. To ensure integrity of the product, In-Process Checks are conducted on the suspension parameters, specifically Temperature (°C), Stir Rate (rpm), and the Recirculation Rate (L/min) are measured and recorded. All parameters that are measured and recorded have a target and a tolerance. Data from samples are analyzed for “staying in tolerance” and for any occurring trends. For issues that arise from the data analysis, manufacturing machinery will need to be adjusted or possibly replaced to maintain high quality standards.

TOLERANCES

	Target Value	RANGE ±
Crimp Height (mm)	4.96	0.1
Crimp Diameter (mm)	15.8	0.30
Net Fill Wt. (g)	6.5	0.60

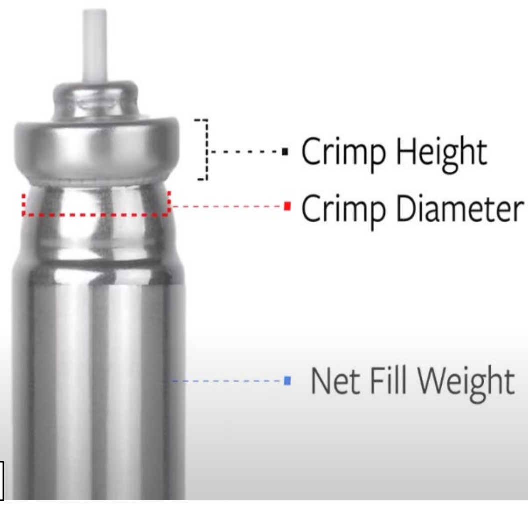

Figure 2. Parameters and Tolerances

ISSUES TO BE ADDRESSED

In manufacturing of the inhalers, the machinery will on occasion produce inhalers that either are not crimped together properly and therefore could possibly dispense incorrectly or the amount of medicine injected into the canister could be too little or too much in volume. Technicians pull sample canisters off the manufacturing line and take measurements to determine if the canisters are being manufactured according to design. Each measurement must be within a specified tolerance (range). Technicians need to determine when a measurement is out of the given tolerance range. Also, technicians need to recognize patterns that exist in the data being recorded on the measurements to predict when the measurements will probably go out of tolerance.

WHERE DOES MATHEMATICS COME IN

Tolerances, creating and reading line graphs (MS Excel), mean and standard deviation, sampling to determine any trends.

Questions to Address:

1. Analyze the In-Process Check Data (Task 1 Tab in DATA) to determine if any product has one or more measurements that are not within specifications. Record a “flag”, or note, for any canister with a measurement that is outside the tolerance of specified design value:
   - ➢ The Crimp Height must be within 0.08mm of the design spec of 6.96mm.
   - ➢ The Crimp Diameter must be within 0.10mm of the design spec of 17.80mm.
   - ➢ The Net Fill Weight must be within 0.30g of the specified 6.50g.

   a) Do you notice any trends in the data? Explain below.
   b) Does the data cluster around a particular value, or is it spread out?
   c) Briefly explain how you identified the information requested above. Could a graphical representation of the data be helpful? What might that look like?
   d) Create a line graphic of each parameter that also displays the maximum and minimum allowed measurements.
   e) Compute the mean and standard deviation for each parameter. Explain what the mean and standard deviation tell you about the crimp height, crimp diameter, and fill weight of a run of canisters. What would you expect the mean to be? Explain. What would you hope the standard deviation would be? Explain. Explain what the mean and standard deviation tell you about each measurement.
   f) What recommendations would you make to the manufacturer based on the results you’ve gathered?

2. Analyze the In-Process Check Data (Task 2 Tab in DATA) to determine if any product has one or more measurements that are not within specifications. Record a “flag”, or note, for any canister with a measurement that is outside the tolerance of specified design value:
   - ➢ The temperature must be within 2.00℃ of 21.00℃.
   - ➢ The Stir Rate should be within 5rpm of 200rpm.
   - ➢ The Recirculation Rate must be within 0.10L/min of 2.50L/min.

   a) Do you notice any trends in the data? Explain below.
   b) Does the data cluster around a particular value, or is it spread out?
   c) Create a line graphic of each parameter that also displays the maximum and minimum allowed measurements.
   d) Compute the mean and standard deviation for each parameter. Explain what the mean and standard deviation tell you about the crimp height, crimp diameter, and fill weight of a run of canisters. What would you expect the mean to be? Explain. What would you hope the standard deviation would be? Explain. Explain what the mean and standard deviation tell you about each measurement.

e) What recommendations would you make to the manufacturer based on the results you've gathered?

3. Analyze the In-Process Check Data (Task 3 Tab in DATA) to determine if any product has one or more measurements that are not within specifications. Record a "flag", or note, for any canister with a measurement that is outside the tolerance of specified design value:
   - The Crimp Height must be within 0.08mm of the design spec of 6.96mm.
   - The Crimp Diameter must be within 0.10mm of the design spec of 17.80mm.
   - The Net Fill Weight must be within 0.30g of the specified 6.50g.
     a) Since this data set is large, is there a better way to determine "out of tolerance rather than graphics?

4. For each of the following data patterns, make a conjecture for each situation.
   a) Near the end of a production run, the Crimp Diameter was increasing over the final 15 samples. What might cause this?
   b) In the middle of a production run, a "clump" of medication clogged the filling valve to the canisters. How might you be able to recognize this event from a set of sample data?
   c) The Crimp Height was below the specified tolerance in the first 18 samples but fell within the tolerance for nearly all the remainder of the samples. What might cause this event?
   d) Every item in five consecutive production samples has been within specifications on all parameters. Is this likely? What might be the cause?

Teacher Resources and Notes

Video that introduces Inhaler Production and GMP, Elliott Locke's success story, and a contextual introduction to the design problem:

https://www.youtube.com/watch?v=nnOmaMzIkUI&t=254s

Teacher Desmos activity that contains pre-requisite math skills:

https://teacher.desmos.com/activitybuilder/custom/5ff4859fc52e860d05268c42?collections=5f6cae0049988f0bfcd6f9f8

Solutions:

1. Analyze the In-Process Check Data in order to determine if any product has one or more measurements that are not within specifications. Record a "flag", or note, for any canister with a measurement that is outside the tolerance of specified design value:
   - The Crimp Height must be within 0.08*mm* of the design spec of 6.96*mm*.
   - The Crimp Diameter must be within 0.10*mm* of the design spec of 17.80*mm*
   - The Net Fill Weight must be within 0.30*g* of the specified 6.50*g*.

a. Do you notice any trends in the data? Be sure to examine columns as well as rows. Explain below.
In Samples 1 & 2, Fill Weights are increasing for the last several samples. Most are still within tolerance, but this could indicate the need for an adjustment in the equipment. In Sample 3, the mean for the Crimp Height measurements is high, suggesting a possible need to adjust the machine.

b. Does the data cluster around a particular value, or is it spread out?
Answers may vary. Since canisters are expected to be uniform, we would hope the data clusters around the designed value.

c. Briefly explain how you identified the information requested above. Could a graphical representation of the data be helpful? What might that look like? Encourage students to be as specific as possible.
Most students will have visually scanned the data for readings that are outside the range of tolerance, i.e., below 6.96-0.08, or 6.88, or above 6.96+0.08 or 7.04, etc. Some may have generated a graph of the data in the spreadsheet or in a graphing tool such as Desmos to see any data points that may fall outside the interval of tolerance.

d. Create a line graphic of each parameter that also displays the maximum and minimum allowed measurements. (in MS Excel spreadsheet)

e. Compute the mean and standard deviation for each parameter (measurement) in your worksheet.
   i. Explain what the mean and standard deviation tell you about the crimp height, crimp diameter, and fill weight of a run of canisters.
   The mean gives the typical measure. If the mean is noticeably out of tolerance, equipment may need adjustment. The standard deviation describes the variance in measures of the data set. If this number is large, the equipment is not producing canisters consistently indicating a need for service.
   ii. What would you expect the mean to be? Explain.
   Crimp Height: 6.96*mm* or very close, because this is the design specification.
   Crimp diameter: 17.80*mm* or very close.
   Net Fill Weight: 6.50*g* or very close.
   iii. What would you hope the standard deviation would be? Explain.
   We would like the standard deviation to be very close to 0. If the equipment is operating within close tolerances, there should be very little variance in the readings.
   iii. Explain what the mean and standard deviation tell you about each measurement, and how you would use these values to make recommendations.
   The mean tells you how closely to tolerance the products are being produced. The Standard Deviation indicates how consistently the equipment is operating. If the Mean is off, but the standard deviation is very close to zero, the machine is running consistently, but its settings need adjustment. If the Mean is on-target, but the standard deviation gets large, the equipment may need maintenance.

f. What recommendations would you make based on these results?
With the increasing trend in Fill Volume measurements in samples 1 & 2, the machine or the measurement device may be having problems and needs attention. With the CrimpHeights running high in Sample 3, that machine or measuring device may need adjustment.

2. Analyze the In-Process Check Data in order to determine if the product is within specifications. Record a "flag", or note, for any canister with a measurement that is outside the tolerance of specified design value.
    - The temperature must be within 2.00°C of 21.00°C
    - The Stir Rate should be within 5*rpm* of 200*rpm*
    - The Recirculation Rate must be within 0.10*L/min* of 2.50*L/min*

a. Do you notice any trends in the data? Explain below.
At samples 9-12, temperature and recirculation rates were off together. These two variances may be related.
All the Stir Rates are within tolerance; no adjustments necessary. This does not happen often in classroom exercises, but it does happen in industry.

b. Does the data cluster around a particular value, or is it spread out?
Answers may vary. Since canisters are expected to be uniform, we would hope the data clusters around the designed value.

c. Create a line graphic of each parameter that also displays the maximum and minimum allowed measurements. (in MS Excel spreadsheet)

d. Compute the mean and standard deviation for these measurements. What do these results tell you about the mixing process?
The Mean for Temperature is a little higher than the intended value, but the readings are just what we would expect for Stir Rate and Recirculation Rate. The Standard Deviation for temperature is more than half the tolerance. It might work fine, but attention to this reading may be needed to avoid an interruption in production for maintenance. Stir Rate is very consistent at the intended value with very little variance. The standard deviation value for the Recirculation Rate is very close to the tolerance, suggesting that this reading could be out of tolerance fairly often.

3. Analyze the In-Process Check Data to determine if any product has one or more measurements that are not within specifications. Record a "flag", or note, for any canister with a measurement that is outside the tolerance of specified design value:
    - The Crimp Height must be within 0.08mm of the design spec of 6.96mm.
    - The Crimp Diameter must be within 0.10mm of the design spec of 17.80mm.
    - The Net Fill Weight must be within 0.30g of the specified 6.50g.

    Since this data set is large, is there a better way to determine "out of tolerance" rather than graphics?

Students will likely suggest there must be a way to have the computer check for them, but may not know how this can happen. Connect the IF commands in spreadsheets with the language they will likely use "If the crimp height is less than 6.88, then it is out of tolerance". Students may not have the tools to construct the spreadsheet commands. Possible command:
=IF(((E5<6.88)+(E5>7.04)+(F5<17.70)+(F5>17.90)+(G5<6.20)+(G5>6.80))>0, "Out of Range", "") Visual inspection would probably take a long time, and a graph may not be helpful due to its size - a very long x-interval, with a relatively small y-interval.

4. For each of the following data patterns, make a conjecture for each situation. Possible answers. Students should be encouraged to use their imaginations.

a. Near the end of a production run, the Crimp Diameter was increasing over the final 15 samples. What might cause this? Mechanical failure, a component is wearing out or coming loose, etc.

b. In the middle of a production run, a "clump" of medication clogged the filling valve to the canisters. How might you be able to recognize this event from a set of sample data? Since the medication is a fine powder, the fill valve may have gotten clogged with lumps. Temperature variation could affect viscosity.

c. The Crimp Height was below the specified tolerance in the first 18 samples, but fell within the tolerance for nearly all the remainder of the samples. What might cause this event? The machine started out misaligned and settled in. Or something in the machine was dirty, but slowly rubbed itself clean, with the dirt ending up in a dump.

d. Every item in five consecutive production samples has been within specifications on all parameters. Is this likely? What might be a cause? Could be a pleasant surprise with machinery running properly. Measuring tools might be out of adjustment. Or both.