EFFECT OF TEMPERATURE ON ACTIVE INGREDIENT IN PHARMACEUTICAL MANUFACTURING PROCESS

RELEVANT JMP PLATFORMS AND STATISTICAL TECHNIQUES

Graph Builder :	Scatterplot, Line of Fit (Linear and Polynomial Regression)
Fit Y by X :	Linear and Polynomial Regression

PROBLEM STATEMENT

The manufacturing of pharmaceuticals requires the control of a wide array of ingredients, equipment, and process conditions. Temperature plays a critical role in the manufacturing of pharmaceutical drugs, influencing various stages of production from raw material handling to final formulation and storage. During the synthesis of the active pharmaceutical ingredient (API), precise temperature control is vital for a process to consistently produce the desired API with very minimal amount of impurities.

A process engineering team at a pharmaceutical company is working on establishing conditions to scale-up production of a new drug formulation. To understand the effect that temperature at one of the process stages has on the amount of API, a pilot run of the process was planned. The target API for this product is 350 +/-2.5 mg/mL. The engineering team has decided to test 6 different temperatures (125ºC, 127.5ºC, 130ºC, 132.5ºC, 135ºC, 137.5ºC, 140ºC). The experiment was conducted as follows:

The process was set at the lowest temperature of 125ºC, and 2 batches produced. The API was measured for each batch. The process was then set to 127.5 and 2 batches of formulation run. The temperature was increased at each step by 2.5 ºC until the 2 batches were produced at the highest temperature of 140ºC. This part of the experiment took an entire day to complete. On the next day, the process was set at the highest temperature of 140ºC, and 2 batches of produced. The temperature was lowered at each step by 2.5 ºC until the process was run at the lowest temperature of 125ºC.

This resulted in having API measured for four separate batches at each temperature level. In addition, the amount of impurities for each batch was also measured. This product requires impurities levels to be below 0.1%.

DATA SET

Effect_of_Temperature_on_API.jmp

Day	Day of Experiment (1, 2)
Temperature	Temperature set for the process (6 values: 125°C, 127.5°C, 130°C, ... , 140°C)
API	Amount of Active Pharmaceutical Ingredient (Target: 350 +/-2.5 mg/mL)
Impurities	Amount of impurities (Target: < 0.1%)

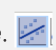
EXERCISES

The exercises consist of first creating a graphical display of the data (using Graph Builder) to get a sense of the relationship. You will fit different models to the data within this graph to decide what is the most appropriate regression model to use. You'll then fit that model using the Fit Y by X platform to produce a more detailed analysis and evaluate model assumptions. You will use this model to try to decide what temperature setting achieves the target API. A similar set of analyses will be done on a second response variable – Impurities. You will also be asked to critique the experiment, identify other data that would be useful in this investigation, and any ideas you have for recommendations and next steps for the engineering team to take.

1. Create a scatterplot of API vs Temperature. Comment on the general nature of the relationship.

> *Instructions:* *Graph > Graph Builder. Place 'API' on the Y axis, and 'Temperature' on the X. Note: The target of 350 +/- 2.5 has been added as the specification limits to the column properties, with the option to be shown on graphs as reference lines. This can be changed by right-clicking on the column and choosing Column Properties > Spec Limits.*

2. Fit a simple linear regression model to these data. Interpret the Equation, F-Test and the R^2 value. Describe what part of the relationship this model is (and isn't) describing.

> *Instructions:* *Select the Line of Fit icon in the tool palette.* 
> *Select to display the R^2 , Equation, and F-Test from the Line of Fit controls on the left.*

3. Fit a quadratic linear regression model to these data. Interpret the F-Test and the R^2 value. Describe what part of the relationship this model is (and is not) describing.

> *Instructions:* *Under the Line of Fit controls on the left, choose Quadratic under the Degree menu drop.*

4. Fit a cubic linear regression model to these data. Interpret the F-Test and the R^2 value. Is this model better at describing the relationship than the quadratic? Justify your answer with numerical evidence.

> *Instructions:* *Under the Line of Fit controls on the left, choose Cubic under the Degree menu drop.*

5. Add a prediction interval for the model that best fits the data to the graph. Interpret both the Confidence Interval and Prediction Interval now shown the graph comparing them to the Target API of 350 +/-2.5 mg/mL.

> *Instructions:* *Select Prediction in the Line of Fit controls on the left.*

6. Create both a quadratic and cubic regression model to these data using the Fit Y by X modeling platform. Compare the results between the two models. Find another metric that provides numerical evidence (that you didn't use in Exercise 4) that justifies which of the two models (quadratic or cubic) you believe is best to use.

> *Instructions:* *Analyze > Fit Y by X. Choose the variable 'API' for the Y and 'Temperature' for X. From the top red triangle in the report, select Fit Polynomial > 2, quadratic. Then again for Fit Polynomial > 3,*

7. Perform model diagnostics on your chosen model to evaluate the assumption of constant variance and normality of the residuals. Are there any cause for concern about the assumptions?

> *Instructions:* *Under the red triangle next to the chosen model, select Plot Residuals.*

8. Is there a temperature setting that achieves the API target of 350 mg/mL? If not, what temperature achieves the closest? Interpret both the Confidence Interval and Prediction Interval at this temperature?

> *Instructions:* *Under the red triangle next to the chosen model, select Profiler. From the Profiler red triangle, add the Prediction Interval.*

9. Augment the scatterplot created in Exercises 1-5 by indicating the day each of the experimental runs were performed? Is there anything revealed causing concern about this experiment and thus the model you've chosen to describe the relationship between 'Temperature' and 'API'?

> *Instructions: Return to the Scatterplot, and place the 'Day' variable in the color role.*

10. Do you believe trying other temperatures not used in the experiment would be the next best approach to try to achieve API to target? If so, which temperatures levels would you recommend? If not, why?

11. Critique the experimental protocol that the team followed. Do you have ideas for alternative approaches the experiment could have been conducted? Why would this approach be better than what was done?

12. Perform the same analyses on the 'Impurities' outcome variable with the goal of creating a model that best describes the relationship between 'Temperature' and 'Impurities', identifying if the target of < 0.1% can be achieved, evaluating if there is a difference between the two days of the experiment, and describing any other insights uncovered.

13. What other data could be useful to have and/or collect in future experiments to help achieve target objectives? Provide some recommendations and next steps the engineering team should take.