The Right Stuff: Appropriate Mathematics for All Students

Promoting the use of materials that engage students in meaningful activities that promote the effective use of technology to support mathematics, further equip students with stronger problem solving and critical thinking skills, and enhance numeracy.

Overview

Students will apply the concepts of

- Linearizing – Students will be able to take data that is exponential in nature and linearize it using the natural logarithm and exponential functions.
- Extrapolation – Students will be able to calculate y-values using x-values beyond the data used to determine the linear model.
- Curve Fitting – Students will be able to find the equation of the line of best fit.
- Algebra – Students will solve for one variable in terms of another.

In addition, students will be able to follow instructions of a technical nature to produce a desired outcome.

Supplies and Materials

- 8.1 Student Worksheet
- Either 8.3 Excel file, 8.4 TI-Nspire™ file, or a handheld that will create a scatter plot and find a model for the data
- The video demonstrating the absorption and elimination phase may be used to help students understand those phases (8.5 Video Model).

Prerequisite Knowledge

Students must be able to copy data from word into Excel or into a handheld, create a scatter plot, work with natural log and exponential functions, identify characteristics of an equation, and find an appropriate algebraic model for data.

Instructional Suggestions

1. Have students discuss the generic drug approval process from the chart provided and the definition of bioequivalence. (For additional information, see: http://www.boomer.org/c/p3/c18/c1802.html)
2. Examine the data and the relationship between time and concentration by using a scatterplot of the data. Discuss what possible equations may fit the model. Could the students model the data using piece wise functions?
3. Observe which data is needed for the elimination phase. Note that is a piece of the original graph. What shape does it take on? Use only this data to convert an exponential model into a linear model. Notice the importance of the equation to calculate the elimination rate constant $\mathbf{k_e}$.
4. Discuss a second method of finding a method of comparison between drugs by creating several new columns of data using previous data and formulas (including linear, natural log and exponential functions) to calculate the absorption rate constant $\mathbf{k_a}$.
5. Use formulas to calculate other values used in the comparison of drugs

Assessment Ideas

Have students create a column of values that contain the first 8 values of the Fibonacci sequence. Second, create a new column based on these values by taking the Natural Log of each of the values in the first column. Third, create a third column by taking the Exponential function of each value in the second column. Finally, create a fourth column that uses the first column and squares each of the values and then add 5.

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Introduction

In this you will examine the idea of bioequivalence from a mathematical perspective.

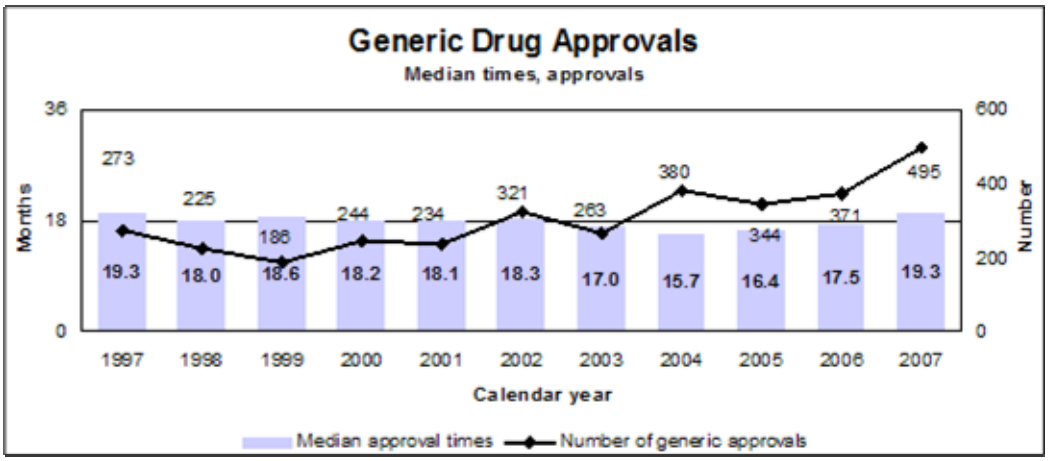
The U S Food and Drug Administration (FDA) defines **bioequivalence** as the following:

> Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions. **Source: www.fda.gov**

Note: Generic drugs save consumers and insurance companies millions of dollars each day. Since the FDA is responsible for approval of all generic drugs, they must insure they are equivalent to name-brand drugs (bioequivalent).

As you can see from the chart on the right, the generic drug approval process can take as long as two years.

Examine the chart. Describe the trend in the number of generic drugs being approved by the FDA and the length of the approval process.



Source: FDA

The number of generic drugs approved is trending upwards while the median approval times fluctuate between 15.7 and 19.3 months.

The principal reason for the relatively low price of generic medicines is competition increases among producers when drugs are no longer protected by patents. Companies incur fewer costs in creating the generic drug, and are therefore able to maintain profitability at a lower cost to consumers. Generic manufacturers do not incur the cost of drug discovery and instead are able to reverse-engineer known drug compounds to allow them to manufacture bioequivalent versions. Although generic manufacturers do not bear the burden of proving the safety and efficacy of the drugs through clinical trials since these trials have already been conducted by the brand name company, they must still do clinical trials to show that the rate and extent of availability are equivalent to the name-brand drug.

This activity will lead you to calculate two of the factors that the FDA uses to define bioequivalence.

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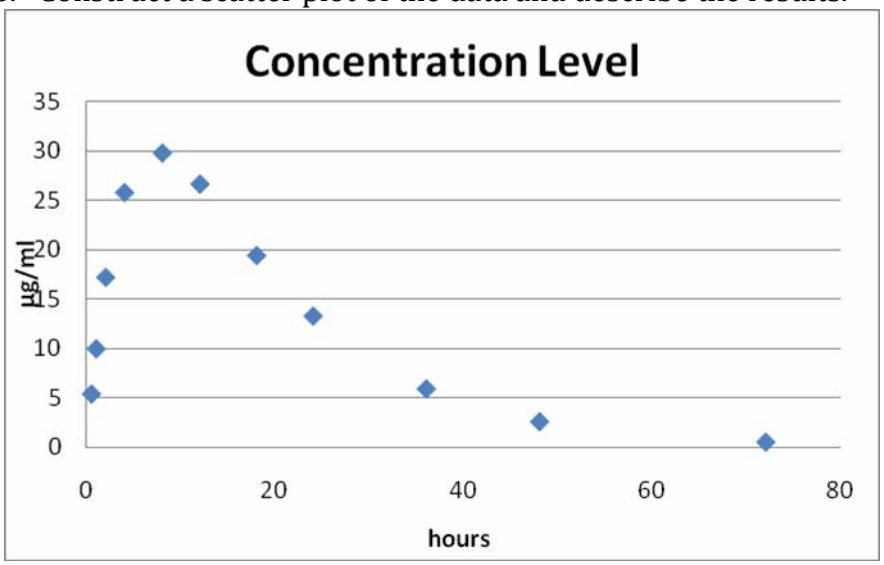
Directions

There are several factors that determine whether a drug is equivalent to a name-brand drug. We cannot go into all of those factors here for lack of time and because of the degree of statistics required.

The data to the right shows the Plasma Concentration (µg/ml) of a drug over time (hours) after an initial dose of 500 mg is given intravenously. A microgram (µg) is one-millionth of a gram. In the hospital setting, it may be abbreviated as mcg.

6. Construct a scatter plot of the data and describe the results.



This graph shows the drug profile clearly. The dose is taken intravenously at time 0. The plasma concentration level begins to increase immediately as the drug is "mixed" in the plasma (the liquid portion of your blood). The concentration level reaches a maximum at a fairly fast rate and then begins to be eliminated at a much slower rate.

You may want to show the video, 8.5 Video Model to demonstrate how the concentration of the medicine might change over time. The video shows a beaker with fresh water running into it. Red food dye clearly shows the concentration (color) changing over time..

Time	Concentration
0.5	5.36
1	9.95
2	17.18
4	25.78
8	29.78
12	26.63
18	19.4
24	13.26
36	5.88
48	2.56
72	0.49

Source: www.inchem.org

Two drugs that are bioequivalent will have a very similar profile.

This activity will look at constants that are calculated to show how similar the two drugs behave in the body.

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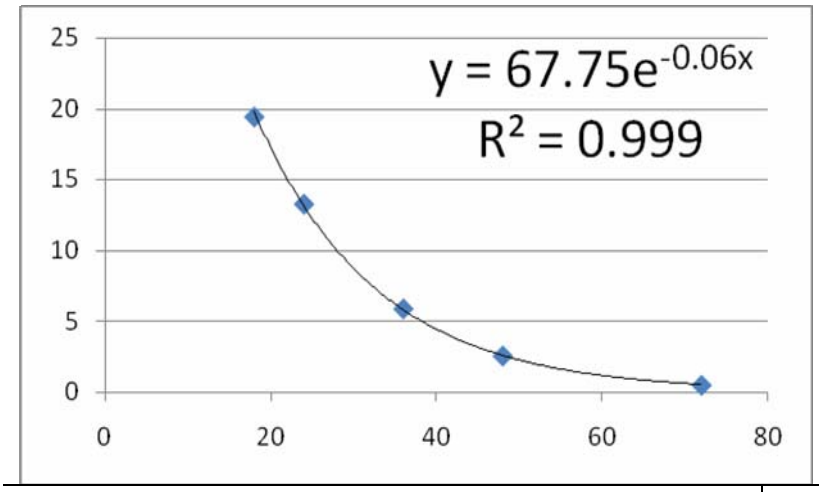
There are two components of this drug profile we'll examine: the absorption phase and the elimination phase (the time when the data becomes exponential in nature). The two data sets that represent those phases are shown in the two tables to the right.

Absorption		Elimination	
Time	Conc.	Time	Conc.
0.5	5.36	18	19.4
1	9.95	24	13.26
2	17.18	36	5.88
4	25.78	48	2.56
8	29.78	72	0.49
12	26.63		

7. Create a scatter plot for the elimination phase and determine the equation of best fit.



Discuss the elimination phase by pointing out that the exponential model is often the most appropriate model for growth and decay.

Make mention of the coefficient of x in the exponent since that will be one of the constants we find later.

The concentration during the elimination phase can be modeled with an exponential function. However, in the laboratory, technicians use another method to find the information they need. The data is first linearized by taking the natural logarithm of the concentrations.

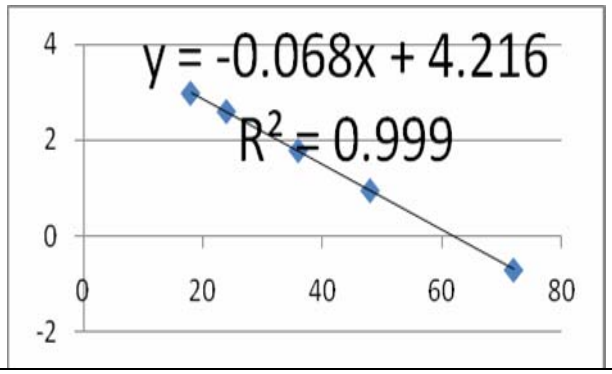
3. Create a third column in the table with the elimination values and graph the time versus the linearized concentration.
   Find the linear model and its slope:

   ln(Conc.) = _____ * Time + _____

The linear model that fits the (time, ln(conc)) data is y = -0.0683x + 4.2

The slope of this line is -0.0683 (units?).

Elimination		
Time	Conc.	Ln(Conc.)
18	19.4	**ln(19.4)=2.965**
24	13.26	**2.585**
36	5.88	**1.772**
48	2.56	**0.940**
72	0.49	**-0.713**



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The elimination rate constant, $\mathbf{k_e}$, is the negative of the slope of this line. This is one of the factors that the FDA uses to test bioequivalence.

4. What is the value of $\mathbf{k_e}$? **$k_e = 0.0683$**

Then the FDA compares the $\mathbf{k_e}$ value of the name brand drug with the value of the generic drug to see if a bioequivalence exists.

Another factor used in testing bioequivalence is the absorption rate constant, $\mathbf{k_a}$. Finding it requires additional computations.

5. Complete the table to the right by extrapolating the line found in (3). That is, use the linear model found in the elimination phase to compute the ln(concentration) for times 0.5, 1, 2, 4, 8, and 12 (numbers smaller than the first data value used to determine the model).

Steps 5 – 8 involve creating new columns from previous data. Students do not necessarily have to fill in the Student Worksheet, but need to have a working copy (eg. Excel) that will have the values for each new column.

Time	Conc.	Extrap: ln(conc)
0.5	*5.36*	4.216-0.0683(time)=4.1817
1	*9.95*	**4.14752**
2	*17.18*	**4.07918**
4	*25.78*	**3.94251**
8	*29.78*	**3.66917**
12	*26.63*	**3.39583**
18	19.4	**2.96527**
24	13.26	**2.58475**
36	5.88	**1.77156**
48	2.56	**0.94001**
72	0.49	**-0.71335**

6. Complete the fourth column of the table by raising the number *e* = 2.71828… [spreadsheets have a built-in function: "=exp(number)"] to the value in the third column to show the modeled concentrations. Remember the third column represents the natural logarithm of the modeled concentration.

   - Accuracy may vary with the number of decimal places used in the calculations.

Time	Conc.	Extrap: ln(conc)	Modeled Conc.
0.5	5.36	*4.1817*	exp(4.1818)=65.48
1	9.95	*4.1475*	**63.28**
2	17.18	*4.0792*	**59.1**
4	25.78	*3.9425*	**51.55**
8	29.78	*3.6692*	**39.22**
12	26.63	*3.3958*	**29.84**
18	19.4	2.96527	19.4
24	13.26	2.58475	13.26
36	5.88	1.77156	5.88
48	2.56	0.94001	2.56
72	0.49	-0.71335	0.49

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A number called the "residual" is then found by subtacting the actual concentrations (found in the second column) from the extrapolated concentrations during the absorption phase (found in a fourth column and in italics).

7. Complete the table by finding the residuals.

Time	Conc.	Extrap: ln(conc)	Modeled Conc.	Residuals
0.5	*5.36*	4.18185	*65.48*	65.48-5.36=60.12
1	*9.95*	4.14770	*63.28*	**53.33**
2	*17.18*	4.07940	*59.1*	**41.92**
4	*25.78*	3.94280	*51.55*	**25.77**
8	*29.78*	3.66960	*39.23*	**9.44**
12	*26.63*	3.39640	*29.84*	**3.21**
18	19.4	2.96527	19.400	-
24	13.26	2.58475	13.260	-
36	5.88	1.77156	5.880	-
48	2.56	0.94001	2.560	-
72	0.49	-0.71335	0.490	-

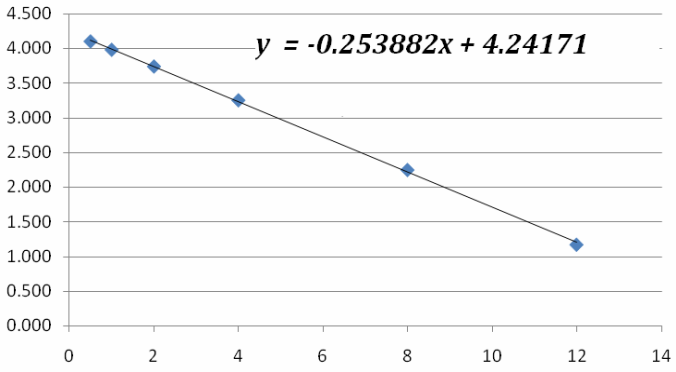
The absorption rate constant, k_a is then found by finding the negative of the slope of the line that fits the time and ln(residual) data during the absorption phase.

8. Complete the table and construct a scatter plot with a line of best fit.

The linear model that fits the (time, ln(residuals)) data is
y = -0.253882x + 4.2142

The slope of this line is -0.254.

Time	Residuals	ln(residuals)
0.5	*60.127*	4.096
1	*53.338*	**3.977**
2	*41.930*	**3.736**
4	*25.783*	**3.250**
8	*9.456*	**2.245**
12	*3.226*	**1.166**



9. What is the absorption rate constant?

k_a =

k_a = 0.254

The FDA compares the k_a (absorption rate) value of the name brand drug with the value of the generic drug to see if a bioequivalence exists.

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Two other values used to compare drugs are the $\mathbf{t_{max}}$ and $\mathbf{C_{max}}$.

$\mathbf{t_{max}}$ is the time it takes for the drug to reach a maximum concentration. This value is independent of the dose.

$\mathbf{C_{max}}$ is the maximum concentration and depends not only on the two rate constants but on the initial dose (**D**), the fraction of the dose that goes into the bloodstream (**F**), and the volume of blood ($\mathbf{V_D}$). Let **D = 500, F = 1** and $\mathbf{V_D}$ **= 10.**

10. Find $\mathbf{t_{max}}$ and $\mathbf{C_{max}}$.

For this drug when taken intravenously, the maximum concentration occurs at t = 7 hours. The times for the two phases are not exactly separated by the time at which the maximum concentration occurs. The elimination phase is purer for t greater than tmax.

$$\mathbf{t_{max}} = \frac{\ln\left(\frac{k_a}{k_e}\right)}{k_a - k_e}$$

$$\mathbf{C_{max}} = \frac{k_a * F * D}{V_D * (k_a - k_e)}\left(e^{(-k_e * t_{max})} - e^{(-k_a * t_{max})}\right)$$

$\mathbf{t_{max}}$ = 7.09

$\mathbf{C_{max}}$ = 30.88

The FDA defines equivalence as between 80% and 100% of a value or between 100% and 125% of the value. Thus tmax (above) could be between 5.7 and 8.9. Cmax could be between 24.7 and 38.6.

As a follow-up or even as an introduction to this activity, try the following activity.

Place a fairly large beaker of clear water under a water source with a drain beneath. Turn the water on so that there is a small, continuous flow. Add some (the amount depends on the size of the beaker and the water flow) red food coloring every 10 seconds for 30 seconds . Allow the water to run for another 90 to 120 seconds showing the elimination phase. (video available)

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