Homework Assignment 10: Due at the beginning of class 3/1/02

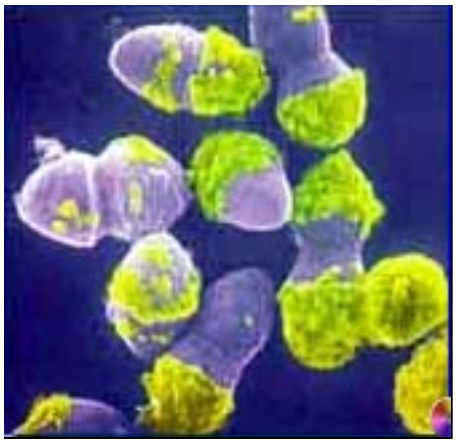

Figure 1: A scanning electron micrograph showing the bacterium *Enterococcus faecium*. Bacteria of the genus *Enterococcus* are a leading cause of hospital-acquired infections. (Note that the colors are false and were added digitally to enhance the detail in the electron micrograph.)

According to the Centers for Disease Control and Prevention[1], every year approximately nine million people contract a serious bacterial infection while in undergoing treatment in a hospital[2]. Every year there are approximately 80,000 deaths in hospitals and nursing homes as a result of bacterial infections[3].

The bacteria of the genus *Enterococcus* are leading cause of hospital-acquired infections (see Figure 1[4]). Bacteria such as *Enterococcus faecium* can cause serious infections of the blood, heart, urinary tract and central nervous system[5]. In previous decades, standard medical practice was to prescribe a powerful antibiotic (such as vancomycin, see Figure 2[6]) to patients who had developed a serious bacterial infection. However, in recent years[7] many strains of dangerous bacteria have become resistant to antibiotics. Nowadays even the most potent antibiotic drugs are practically useless against the new strains of "super bugs" (such as *Enterococus faecium*) that infect patients in hospitals and nursing homes[8]. As Dr. Leon Smith of the St. Michael's Medical Center commented (somewhat anthropomorphically):

> "The bacteria are brilliant, absolutely brilliant. They can change. They know how to fight back. They were here billions of years ago before we were, and they will be here after we are gone."

In April of 2000, the FDA gave approval for use of an entirely new kind of synthetic antibiotic called oxazolidiones (see Figure 4[9]). Oxazolidinones are the first new class of synthetic antibacterial agents introduced since the discovery of quinolones more

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[1] Source: http://www.cdc.gov
[2] Source: CNN. "FDA approves first in a long-awaited new class of antibiotics." April 18, 2000.
[3] Source: Centers for Disease Control and Prevention. http://www.cdc.gov
[4] Image source: http://www.lnl.gov/
[5] Source: M. Friedlander. (2000) "Single day effort reveals genes of dangerous enterococcus bacteria." *Science Beat*, **2**(3): 3.
[6] Image source: http://www.lilly.se/produckter/vancocin/
[7] Due in part to rampant over-prescription of antibiotics by physicians. As physicians prescribed powerful antibiotics on a widespread basis, the phenomena of *artificial selection* favored those mutant strains of dangerous bacteria that were naturally resistant to the agents used in antibiotic drugs.
[8] Source: CNN. "FDA approves first in a long-awaited new class of antibiotics." April 18, 2000.
[9] Image source: http://www.pubs.acs.org/

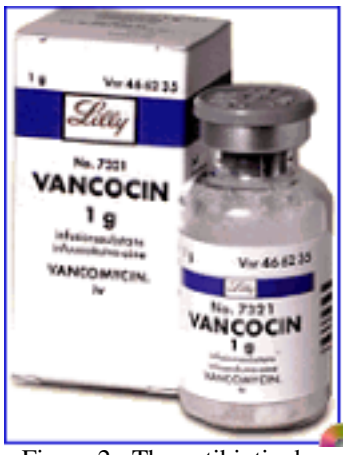

Figure 2: The antibiotic drug Vancocin manufactured by Lilly Pharmaceuticals. The antibiotic compound in this drug is vancomycin.

than 30 years ago[10]. The first of these new synthetic antibiotics was released in April of 2000 by the Pharmacia Corporation under the trade-name Zyvox™ (see Figure 3[11]). In clinical trials[12], Zyvox™ was able to significantly inhibit the growth of vancomycin-resistant strains of *Enterococcus faecium* (in addition to significantly inhibiting the growth of other dangerous, antibiotic-resistant bacteria).

Zyvox™ is available in both tablet (for oral dosage) and liquid (for intravenous injection) forms. For many drugs, intravenous injection is the dosage method of choice in a hospital, as there are trained personnel present who can safely administer the drug. However, many patients prefer an oral dose as this does not involve a painful injection.

Generally speaking, oral administration of a medicine is not as effective in delivering the drug to the patient as an intravenous injection. Some of the reasons for this include[13]:

- The drug may be destroyed by stomach acid or digestive enzymes.
- The drug may combine with chemicals from food in the stomach (chelation) to form an insoluble compound that cannot be absorbed into the blood stream.
- Some drug molecules are so polar (i.e. carry high electrical charges in certain parts of the molecule) that they cannot cross cellular membranes and thus cannot cross the stomach lining.

Figure 3: The synthetic antibiotic Zyvox (in tablet form).

In this homework assignment, you will use the methods that clinical researchers employ to determine how much of a drug will be available to a patient who takes the drug orally, as compared to a patient who takes the drug via an intravenous injection. This quantity is called the *absolute oral bioavailability* (or simply the bioavailability) of the drug.

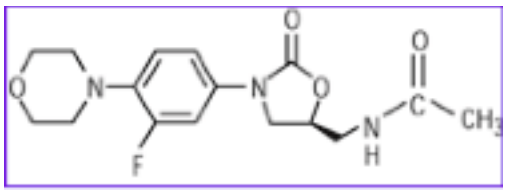

Figure 4: Chemical structure of the active antibiotic ingredient of Zyvox.

[10] Source: S. Katzman. (2001) "Targeted combichem for antibiotics." *Modern Drug Discovery*, **4**(8): 15.

[11] Image source: http://www.zyvox.com/

[12] Source: ZYVOX™ Full Prescription Information Pamphlet, January 2002.

[13] Source: http://www.usask.ca/medicine/pharmacology/Fri08SEP.pdf

1. Figure 5[14] gives the plasma concentration curves for patients who took Zyvox™ orally and intravenously. When they are attempting to determine the bioavailability of a drug, clinical researchers calculate the area under the plasma concentration curve (AUC) for the drug. Draw a collection of rectangles on the plasma concentration and use them to calculate the area under the curve for a patient who took Zyvox™ orally. The width of each of your rectangles should be 30 minutes.

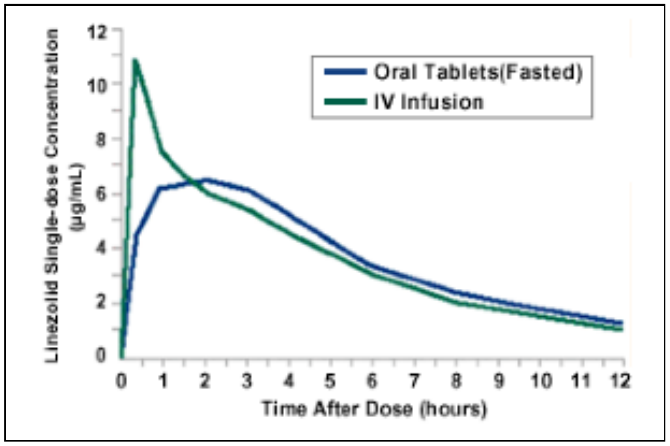

Figure 5: Plasma concentration curves for patients receiving Zyvox™ orally and intravenously.

NOTE: You should download the Appendix to this homework and use that to draw the rectangles on the plasma concentration curve. Hand in the diagram (showing your rectangles) that you used as well as the calculations that you performed to calculate the AUC.

2. The plasma concentration curve for a patient who received Zyvox™ orally is quite well approximated by the function[15]:

$$P(T) = 0.024238 \cdot T^3 - 0.58732 \cdot T^2 + 3.5477795 \cdot T + 0.5$$

where T = number of hours since Zyvox™ was administered and $P(T)$ = plasma concentration in µg/ml. If you were going to estimate the area under the curve defined by $P(T)$ between $T = 0$ and $T = 12$ using 100 rectangles, how wide would each rectangle have to be? Use your calculator to approximate the area under the curve defined by $P(T)$ between $T = 0$ and $T = 12$ using 100 rectangles.

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[14] Image source: http://www.zyvox.com/

[15] This equation was obtained by reading values off the plasma concentration curve and running cubic regression on a graphing calculator.

3. Draw a collection of rectangles on the plasma concentration curve and use them to calculate the area under the curve for a patient who took Zyvox™ intravenously. The width of each of your rectangles should be 30 minutes.

NOTE: You should use the Appendix to this homework assignment to draw the rectangles and use them to calculate the AUC. Hand in the diagram your used (showing the rectangles) as well as your calculation of the AUC.

4. The plasma concentration curve for a patient who received Zyvox™ intravenously is quite well approximated by the function[16]:

$$C(T) = 9.4 \cdot (0.85)^T$$

where T = number of hours since Zyvox™ was administered and $C(T)$ = plasma concentration in μg/ml. If you were going to estimate the area under the curve defined by $C(T)$ between $T = 0$ and $T = 12$ using 500 rectangles, how wide would each rectangle have to be? Use your calculator to approximate the area under the curve defined by $C(T)$ between $T = 0$ and $T = 12$ using 500 rectangles.

5. According to Pharmacia Corporation (the company that manufactures Zyvox™) the drug has 100% bioavailability[17]. In terms of a mathematical formula, the bioavailability of a drug could be expressed as:

$$Bioavailability = \frac{AUC_{ORAL}}{AUC_{INTRAVENOUS}} \cdot 100\%$$

where AUC_{ORAL} is the area under the plasma concentration curve for a patient who received an oral dose of the drug and $AUC_{INTRAVENOUS}$ is the area under the plasma concentration curve for a patient who received the drug intravenously. Does your analysis support Pharmacia Corporation's claims? Briefly explain your reasoning.

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[16] This equation was obtained by reading data points from the plasma concentration curve and running exponential regression on a graphing calculator.

[17] Source: ZYVOX™ Full Prescription Information Pamphlet, January 2002.