Chapter 15 Homework

1. You have developed a new type gold nanoparticle to improve a physician's ability to detect cancer at the earliest possible stages. Many internet based health food stores sell solutions of identical gold nanoparticles to "lift your body's performance, and fight off germs, viruses, bacteria, allergens, pathogens and pollution". Yet, it will be several years before you can begin clinical trials to determine whether this same nanoparticle can improve early cancer detection.

http://alchemistsworkshop.com/_wsn/page8.html

a. Describe the current differences in FDA regulation of this particle when it is used as a dietary supplement vs as a drug.
b. Briefly summarize the history of government regulation of drugs in the US, noting the year of major changes in legislation and the primary changes in regulation associated with these laws.
c. Consider the differences in regulation of drugs and dietary supplements.
d. If I wish to market a new dietary supplement which I claim will improve immune function, am I obligated to provide scientific data to the FDA indicating that it is safe and/or effective before I can sell it?
e. If I wish to market a new drug to treat pancreatic cancer, am I obligated to provide scientific data to the FDA indicating that it is safe and/or effective before I can sell it?
f. The following is an actual internet ad for an herbal supplement. If you were employed by the FDA to monitor and investigate these ads please indicate statements you see that may not follow legal guidelines in the United States. Explain why you chose each of your selections. If you did not identify anything, explain why.

There's a new nutritional supplement available for people suffering from Type 2 diabetes. It's called The Body Rejuvenator, marketed by Lafayette Miracle Solutions. It contains two key ingredients -- green tea extract and cinnamon. The first thing to realize is that nutritional supplements can very successfully control blood sugar in diabetics. Both green tea and cinnamon are well-known to help control blood sugar so that you don't have such wild blood sugar swings (and potentially don't need as much insulin either). Also, there are many other benefits documented from taking both green tea and cinnamon. Green tea is noted for its anti-cancer effects, as well as its ability to aid in weight-loss, which is something that diabetics are typically concerned with.

3. I wish to market a new dietary supplement. Indicate which of the statements in the list below that I am legally allowed to put on the product label. If a statement would not be allowed, indicate why not.

a. Acidophilus, Bifidus & Bulfaricus promote the health of the digestive tract.
b. Black Currant Oil contains essential fatty acids that provide dietary support for normal healthy blood lipids and helps to support the cardiovascular system.
c. SkinAnswer, a glycoalkaloid skin cream, as a treatment for skin cancer.
d. Ephedra-free Total Lean™ helps dieters increase their metabolism and boost their energy.
e. MGN-3, a rice-bran extract, a treatment for HIV, the virus that causes AIDS.
f. ZantrexTM-3 promises 546% more weight loss than the leading ephedra-based diet pill and that's a fact. Here's another fact: Zantrex-3 is way beyond ephedra,

way beyond fat-burners, way beyond everything on the market today. Zantrex-3 is a new category of bifurcated weight loss compounds providing both rapid weight loss and incredible energy combined into a single power-packed Super Pill. New Zantrex-3 is so powerful you won't find it in some Wal-Mart next to some "Flintrock" vitamin for kiddies.

g. BeneFin, which is produced from shark cartilage, as a treatment for cancer.

4. Over the last 100 years, the role of the FDA in regulating drugs has changed significantly. Briefly describe the history of these changes. Contrast changes over time in the history of FDA regulation of medical devices.

5. Read the following article. Explain how, after passing all the safeguards of preclinical testing, phases I-III of clinical trials, and required scrutiny of an FDA panel, problems such as these could occur.

F.D.A. Seeks Reports of Stent Problems
April 23, 2004
By GINA KOLATA

The Food and Drug Administration is actively seeking reports of possible problems with a stent that came on the market last month, saying it has heard of serious medical complications in some cases.

But Dr. Daniel G. Schultz, director of the agency's office of device evaluation, said in a telephone interview on Tuesday that it was too soon to say whether there was a problem with the stent and, if so, what was causing it and what advice to give doctors and patients. The F.D.A. knows of 20 to 25 incidents, Dr. Schultz said, but the reports range from sketchy to highly detailed.

"We're fairly early in the process" of assessing the reports, Dr. Schultz said. "At this stage, our main goal is to gather more information."

The device's maker, Boston Scientific, says that its stent is safe and is performing excellently and that any problems are extraordinarily rare.

Paul LaViolette, senior vice president at the company, said more than 70,000 of the stents had been used in the United States since the device went on sale in March.

"We have to conclude, and I will say this with a lot of experience, that this product is performing extremely well," Mr. LaViolette said.

But a few cardiologists reported in telephone interviews that they got into trouble after the stent, a small wire tube used to hold open arteries, was slipped into place. Like all stents, Boston Scientific's stent, the Taxus Express2, comes packaged with a deflated balloon inside. A cardiologist threads the stent with its balloon into an artery. When the site of the blockage is reached, the doctor inflates the balloon, pressing the stent against the artery wall. Then the balloon is deflated and the catheter and balloon withdrawn, leaving the stent flush against the artery, holding the vessel open.

Some doctors said the balloon stuck on the stent when they were removing it. Some were able to free the balloon; some were not. Dr. William Campbell, director of the cardiac catheterization laboratory at Borgess Heart Institute in Kalamazoo, Mich., said a patient was rushed into emergency open heart surgery to remove the balloon and stent. Others, like Dr. Alejandro Prieto of Michigan State University, said that the balloon did not deflate and that he had to use a sharp wire to pop it. But then he also punctured the patient's artery.

"Those are serious problems," said Dr. Schultz, who said the F.D.A. had received similar reports.

Dr. Andrew Carter of Providence St. Vincent's Medical Center in Portland, Ore., said that while his medical center had used several hundred taxus stents without incident he was nonetheless

worried.

"I have never had a balloon that did not deflate, or a device entrapment," he said, referring to balloons that got stuck on stents. "You would never expect to see it. Period."

6. In 1937, a drug manufacturer attempted to modify sulfanilimide, an antibiotic for streptococcal infections, so that it was easier for children to take. Sulfanilimide had been used safely as a pill for years; however, most children can't swallow pills. A company in Tennessee found they could dissolve drug in ethylene glycol (antifreeze). The company tested their new solution for flavor, appearance, fragrance, but NOT for toxicity. They proceeded to ship it all over the country. Within weeks, many children had died.

a. Was this legal at the time?
b. How and when were federal laws reformed to prevent this from happening in the future?

7. Suppose we wish to track the progress of a promising new drug through all stages of development and testing.

a. How long does it typically take for a promising new drug to go from the research lab to the market in the United States?
b. Describe the phases of study researchers must go through to develop a new drug before it can be marketed. For those phases of study which involve giving the drug to patients, give the typical number of patients involved and the goals of the clinical trial.
c. What fraction of promising drug candidates actually make it to the market?
d. What is the cost of developing a new drug today in the US?
e. Recently, several drugs to treat arthritis were withdrawn from the market or given a black box warning. Why were the problems with these drugs not discovered until after the FDA had approved their sale?

8. Contrast the role of the NIH and industry in providing funding to support medical research in the United States.

9. Read the article below and answer the following questions:

Experiment: Closed-Heart Surgery

Associated Press 16:30 PM Apr, 01, 2006

Dr. Samuel Lichtenstein cut a 2-inch hole between an elderly man's ribs. Peering inside, he poked a pencil-sized wire up into the chest, piercing the bottom of the man's heart. Within minutes, Bud Boyer would have a new heart valve -- without having his chest cracked open. Call it closed-heart surgery. "I consider it some kind of magic," said Boyer, who left the Vancouver, British Columbia, hospital a day later and was almost fully recovered in just two weeks.

In Michigan, Dr. William O'Neill slipped an artificial valve through an even tinier opening. He pushed the valve up a patient's leg artery until it lodged in just the right spot in the still-beating heart.

The dramatic experiments, in a few hospitals in the United States, Canada and Europe, are designed to find easier ways to replace diseased heart valves that threaten the lives of tens of thousands of people every year. The experiments are starting with the aortic valve that is the heart's key doorway to the body.

The need for a less invasive alternative is great and growing. Already, about 50,000 people in the U.S. have open-heart surgery every year to replace the aortic valve. Surgeons saw the breastbone in half, stop the heart, cut out the old valve and sew in a new one. Even the best patients spend a week in the hospital and require two months or three months to recuperate. Thousands more are turned away, deemed too ill to

survive that operation and out of options. Demand is poised to skyrocket as the baby boomers gray; the aortic valve is particularly vulnerable to rusting shut with age. The new experiments are a radical departure from that proven, if arduous, surgery.

The artificial valves do not even look like valves, squished inside metal cages until they are wedged into place. Barely 150 of any type have been implanted worldwide, most in the last year. It is unclear if they will work as well as traditional valve replacements, which last decades.

For now, the only patients who qualify for these valves are too sick to be good candidates for regular valve replacement.

Some deaths during the earliest attempts at implanting the devices forced doctors to come up with safer techniques. Clinical trials apparently are back on track, and even the most skeptical cardiologists and heart surgeons are watching how these pioneers fare. The hope is that one day, replacing a heart valve could become almost an overnight procedure.

“There's lots of technical challenges that need to be overcome," said Dr. Robert Bonow, a valve specialist at Northwestern University, who is monitoring the research for the American Heart Association. "Most of us do think this is the future," he said.

O'Neill's first successful patient in March celebrated the one-year anniversary of his through-the-leg implant. "I call it a new birthday," chuckled Fred Grande, 78, a Richmond, Michigan, car collector who took one of his beloved models for a fast spin less than a week after the procedure.

"That's the home run we want to hit with all the patients," said O'Neill, cardiology chief at William Beaumont Hospital in Royal Oak, Michigan.

"It's gratifying" to watch people once deemed beyond help bounce back, added Dr. Jeffrey Moses of New York-Presbyterian Hospital/Columbia University, who with O'Neill is leading the U.S. study. One of Moses' first patients is playing golf at age 92.

The heart has four valves -- one-way swinging doors that open and close with each heartbeat to ensure blood flows in the right direction. More than 5 million Americans have moderate to severe valve disease, where at least one valve does not work properly, usually the aortic or mitral valves. Worldwide, roughly 225,000 valves are surgically replaced every year.

Topping that list is the aortic valve. It can become so narrowed and stiff that patients' hearts wear out trying harder and harder to push oxygen-rich blood out to the rest of the body. Calcium deposits accumulate on its tender leaflets. Touch one chipped out of a patient and it feels almost like a rock.

With minimally invasive valve replacement, doctors do not remove that diseased valve. Instead, they prop it open and wedge an artificial one into that rigid doorway.

"It's ironic. You use the disease process to actually help hold your valve in place," said Lichtenstein, of St. Paul's Hospital in Vancouver, who helped create the between-the-ribs method.

Edwards LifeSciences in Irvine, California, the biggest maker of artificial heart valves, and Paris-based CoreValve are testing versions of a collapsible valve made of animal tissue that is folded inside a stent, a mesh-like scaffolding similar to those used to help unclog heart arteries.

The difference is how doctors get the new valve to the right spot, pop open its metal casing and make it stick.

The U.S. studies thread the Edwards valve through a leg artery up to the heart, known as "percutaneous valve replacement." Unlike with open-heart surgery, doctors do not stop the patient's heart. So the trickiest part is keeping regular blood flow from washing away the new valve before it is implanted.

Once the device is almost in place, doctors speed the heartbeat until normal pumping pauses for mere seconds -- and quickly push the new valve inside the old one. Inflating a balloon widens the metal stent to the size of a quarter, lodging it into place and unfolding the new valve inside, which immediately funnels the resuming blood flow.

So far, 19 Americans have been implanted this way, plus more than 80 other people worldwide, most of them in France by the procedure's inventor, Dr. Alain Cribier, and in Vancouver by Lichtenstein's colleague, Dr. John Webb.

Fourteen people in Canada, Germany and Austria have received the Edwards valve through the ribs. That is a more direct route to the heart for patients whose leg arteries are too clogged to try the other experiment. Doctors make a tiny hole in the bottom of the heart muscle so the new valve can enter. Then they use the same balloon technique to wedge it inside the old valve.

Talks have begun with the Food and Drug Administration about opening a similar U.S. study later this year.

CoreValve's slightly different valve is being tested in Europe and Canada. It, too, is threaded up the leg artery. But it is made of pig tissue instead of horse tissue and has a self-expanding stent that requires no balloon. Doctors remove a sheath covering it and the stent's metal alloy, warmed by the body, widens until it lodges tight against the old, rocky valve. More than 45 have been implanted; CoreValve hopes to begin a U.S. study next year. Lead researcher Dr. Eberhard Grube of The Heart Center in Siegburg, Germany, expects within months to begin testing a newer version small enough to thread through an artery at the collarbone, another more direct route to the heart.

The experiments come with some significant risks. Edwards temporarily halted the U.S. study last year after four of the first seven U.S. patients died. Initially, doctors threaded the valve up a leg vein, not an artery, a route that required tortuous turns inside the heart and sometimes damaged a second valve, O'Neill said. Twelve people have been implanted since the study restarted in December using the artery route considered easier and safer. All but one have survived and are faring well, researchers say.

O'Neill and Moses -- plus doctors at a third hospital, the Cleveland Clinic -- have government permission to implant eight additional patients in the U.S. pilot study, which will be expanded if it goes well. CoreValve's first four patients died as doctors struggled to develop and learn the through-the-artery technique, Grube said. For doctors, pushing the large valve through tiny, twisting arteries -- against regular blood flow and guided by X-rays -- is laborious. Occasionally, they are not able to wedge it into position. Because they are squeezing a round valve into an irregular-shaped opening, there is a risk that the new valve will leak blood backward into the heart, also problematic.

But once researchers master how to get the valve into place safely, the question becomes how much recipients benefit. Do these very ill patients live longer than expected? If not, does quality of life improve enough to warrant the procedure anyway?

Three of French inventor Cribier's original patients have lived 2 1/2 years so far, with a "return to normal life and no sign of heart failure," he said. Eleven others have lived a year and counting. CoreValve reports five patients faring well a year later. Aside from those who did not survive the implantation, others have died from their advanced illnesses even though their new valve was working.

It is the cases of astounding successes -- Grande and Boyer, for example -- that have other heart specialists taking note, Northwestern's Bonow said.

"Patients have to know what they're getting into," he said. Many of the seriously ill are willing to chance the experimental procedure because "they're so debilitated and ... there have been some good examples of patients who have gotten better." The bigger challenge, Bonow added, is whether to expand the studies to include less sick patients who could survive open-heart valve replacement but want to avoid its rigors. Already, there are such patients clamoring to be included. That is a difficult decision because even 80- and 90-year-olds successfully can have regular valve replacement. When performed by the most skilled surgeons, risk of death from the operation is about 2 percent -- but in less experienced hands, it can reach 15 percent, Bonow said.

Just as using a balloon to unclog heart arteries is sometimes done on patients who would fare better with bypass surgery, researchers eventually will have to ask if patients would accept a less-than-perfect aortic valve if they could skip surgery's pain and risks, said Dr. Michael Mack of Medical City Hospital in Dallas. "There is a trade-off, and how you make that trade-off is a totally gray area," he said.

But Vancouver's Boyer, who had two previous open-heart surgeries for clogged arteries, said avoiding that kind of pain is not a trivial issue for patients. "They're doing something to the field of medicine that's going to make life a hell of a lot easier to people who've got that problem," said a grateful Boyer,

describing how he could finally breathe easy after the through-the-ribs valve implant. "I think I'll have a bunch of other parts go bad before I have a problem with this."

a. Discuss the factors which are likely to affect the diffusion of this technology. Do these factors always benefit the patient?
b. Why do you think the sample sizes are so low for the studies reported here? Consider what we learned in Chapter 12 about the trials of the Abiocor artificial heart. What factors do you think the FDA considers in decisions regarding the clinical trials reported here?

10. Consider a new implantable device that does not have any reasonably similar products already in the market.

a. What class of device would the FDA consider this product?
b. Would this device need a 501(k) or PMA approval process?
c. Based on your answer to part b, describe the remaining steps needed to carry this product through to the market?