Chapter 15

Regulation of Health Care Technologies

As technologies diffuse from the research laboratory into clinical practice, we frequently encounter a tension between the goal of ensuring that products are fully tested before they are made available to the general public and the desire to make potentially life-saving technologies rapidly available to patients in need. In the United States, the Food and Drug Administration (FDA) is responsible for ensuring that new health technologies made available to patients are safe and effective. The FDA regulates the manufacture, testing and sales of chemical and biological agents and medical devices; its jurisdiction encompasses a range of products that together account for one-fourth of all consumer spending in the US.[1]

In this chapter we will consider the process that the FDA follows in considering whether to approve new drugs and medical devices. We will see that this process has evolved over time—over the last hundred years, the role of the FDA has shifted from a system in which a company could market a drug unless the FDA could prove that it was unsafe to one where drug manufacturers must first obtain permission from the FDA at nearly every step in the testing, production and marketing process.[1] This increasing burden of regulation has occurred largely in response to tragedies which could have been prevented. Yet, we will see that, even today, FDA regulation of dietary supplements is substantially less stringent than that of drugs, sometimes making it difficult for the FDA to act and prevent harm before it occurs.

The distinction is important because more than 50% of Americans use some form of dietary supplements, including vitamins, minerals, amino acids, enzymes, herbs and other botanicals (Figure 15.1).[2] In 2004, Americans spent more than $19 billion on dietary supplements.[3] We have already seen the important health benefits of dietary supplements. At the middle of the 18th century, scurvy killed more

![Figure 15.1: Six out of ten Americans take one or more dietary supplements a day (multi-vitamins, amino acids, weight-loss cures, and herbal tonics). Yet, remarkably little is known about most of them [10].](image)
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British sailors than war; simply supplementing the sailors’ diet with vitamin C prevented scurvy.[3] Adequate dietary folic acid early in pregnancy can prevent neural tube defects in the fetus. Calcium builds strong bones and can prevent osteoporosis;[2, 3] low levels of vitamin B₁₂ may lead to dementia.[3] Yet, unlike drugs and medical devices, the FDA does not review dietary supplements for safety and effectiveness before they are marketed.[4]

The dangers of this approach are illustrated by the recent ban on sales of the dietary supplement ephedra (Figure 15.2), following the death of Steve Bechler, the 23 year old pitcher for the Baltimore Orioles.[2, 3] Bechler died in February, 2003 of heatstroke after taking an over-the-counter product that contained ephedra. When it was sold, ephedra was most popular supplement in US, generating sales of more than $1B/year, and accounting for approximately 10% of the annual sales of the US supplement industry.[3] Nearly 10 years before Bechler’s death, the FDA began to hear reports of the risks associated with ephedra. Yet, in 1999, it was estimated that more than 12 million people in the US were using ephedra.[2] The risks of ephedra use (particularly when used with caffeine), include an increased risk of heat attack, stroke, palpitations, anxiety, psychosis, and death. There is no evidence that ephedra containing supplements are effective except for short term weight loss.[5] Although ephedra products accounted for less than 1% of all dietary supplement sales, a study in 2003 found that they accounted for 64% of all adverse events associated with dietary supplements.[4] The rate of strokes was found to be statistically higher in users taking doses of ephedra above 32 mg a day; many ephedra containing supplement labels recommended that patients take more than 100 mg of ephedra per day.[4] In February of 2003, the FDA sent warning letters to manufacturers of ephedra challenging them to remove unproven claims on their product labels.[2] In February of 2004, the FDA moved to ban sales of ephedra because it posed an unreasonable risk to patient safety. The ban took effect in April of 2004.[5]

In contrast to dietary supplements, the FDA requires that manufacturers provide scientific evidence to indicate that new drugs are both safe and effective before they can be marketed. Generally, data from both pre-clinical and clinical trials are required to gain approval to market a new drug. Pre-clinical testing in cells and animals must be completed to assess potential toxicity before FDA approval for human studies is granted. In order to test a new drug in people, a manufacturer must obtain an Investigational New Drug (IND) approval from the FDA.
In phase I trials, the safety of compound is assessed by administering low doses of the new drug to a small group of healthy volunteers (20-100 volunteers). If successful, then phase II trials to assess the effectiveness of a compound can commence, usually in 100-300 patients who suffer from the condition targeted by the drug.

The final step before seeking FDA approval to market a new drug is to carry out a randomized phase III clinical trial. After conducting phase I, II, and III clinical trials, a manufacturer can file an NDA (New Drug Application) for permission to market the new drug. If the NDA is approved, the manufacturer must still carry out studies to monitor for unanticipated complications of the drug and to study the longer term effects of drug exposure. This is called post-market surveillance. During this period, any adverse effects observed must be reported to the FDA. 

**Figure 15.3** illustrates the current drug development and approval process in the US. The process is expensive, time-consuming and complex. Not many drugs make it through this entire process. For every 5,000-10,000 drugs that enter preclinical testing, on average only ONE makes it to market. It has been estimated that the cost of developing one new drug today ranges from $0.8 billion-$1.7 billion.

Do the current regulations governing approval for new drugs effectively balance protection from risk associated with potentially unsafe new drugs against gaining access to potentially effective new drugs? Are the fundamentally different approaches to the current regulation of drugs and dietary supplements appropriate? To help answer these important questions, it is helpful to examine the history of how the FDA regulates drugs, dietary supplements and medical devices.

In contrast to the current complex regulatory process for drugs,
On our second day at SOS, we incorporated a sex-ed lesson into our presentation. We explained a bit about the female and male reproductive systems using anatomy cartoon visuals that we found online. The kids were very curious and asked many many questions. We inevitably had to deal with much giggling during our session, which I guess is normal. I remember having sex-education taught to me in 5th grade and thinking it was the funniest thing in the world.

We also focused on answering questions that came up the day before during our Snowball Activity. At the beginning of the activity we asked everyone to write down any question they had about health, HIV/AIDS, sex, etc. that they would normally be embarrassed to ask their teachers or ask in front of their peers. The purpose of this activity was to decrease the stigma associated with HIV...and just to answer any questions they had in a friendly and non-judgmental environment. After everyone was done writing their questions, we split them up into two teams and had them crumple up the pieces of paper they had written on into ‘snowballs.’ At the count of three, we had a huge snowball fight! This part was fun – the kids got really into this and were screaming and laughing. We felt that it was important to answer the questions that the kids had on this day since we came across many reoccurring questions on HIV/AIDS such as:

- What is the difference between HIV and AIDS?
- How does HIV attack the body?
- What are ARVs?
- What is a white blood cell?
- Can HIV be cured?

And we came across other serious questions such as:

- If a girl is living with her brother and gets raped by him, what will happen?
- What is love?
- We were told at school that condoms are not 100% safe. Why are they not and what are we supposed to do?

Later in the session, we played a version of Jeopardy asking the kids different questions covering the topics of immunity, Global AIDS, Prevention/Transmission, and Treatment. The kids participated well in this game and seemed to enjoy it very much. We found quickly that the kids knew too much for the questions we had made up for our game! They were answering almost all of them correctly.
in the early 1900s, the manufacture and marketing of drugs was much less closely regulated. In the early 1900s, the patent-medicine business accounted for more newspaper ads (Figure 15.4) than any other kind of product, a situation that is eerily similar to today’s widespread internet advertising for dietary supplements.[3] At the time, many supplements contained substantial amounts of alcohol; others were even laced with cocaine, caffeine, opium and morphine.[3] Manufacturers were not required to disclose the contents of patent medicines on the product label.

Largely in reaction to the sickening conditions of the meatpacking industry described in The Jungle by Upton Sinclair (Figure 15.5), Congress passed the Pure Food and Drug Act in 1906.[7] This law permitted the newly formed Bureau of Chemistry, precursor to the FDA, to ensure that labels on foods and drugs contained no false or misleading advertising; in addition, labels were required to contain accurate levels of 11 dangerous ingredients including alcohol, heroin and cocaine.[7]

While the Food and Drug Act provided some protection for consumers, it did not require that companies obtain approval before marketing new drugs. The FDA could act only after harm had occurred. In the early 1930s, sulfanilamide was used as an antibiotic to treat streptococcal infections. It had been used safely as a pill for years; to help make the drug easier to use for children who have difficulty swallowing pills, Massengill, a Tennessee company found they could dissolve the drug in diethylene glycol (antifreeze).[7, 8] They tested their formulation for flavor, appearance, and fragrance, but not for toxicity.[3] At the time, safety tests were not required by law.[8] The new product was called Elixir Sulfanilamide; it was shipped all over the country, and within weeks, more than 100 people were dead, most children.[7] After taking Elixir Sulfanilamide, they experienced severe abdominal pain, nausea, vomiting, and convulsions. [3] One woman who lost a child to the tragedy wrote to President Franklin Delano Roosevelt:

“Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane.”[3]

In reaction to the tragedy, in 1938, Congress passed the Food, Drug and Cosmetic Act (FD&C Act).[3, 7, 8] The FD&C Act gave the FDA the authority it needed to regulate such products before they came on the market. It required that companies test new drugs for safety before marketing. Companies were required to submit test results to the FDA.

Figure 15.4: Lydia Pinkham’s Vegetable Compound was an example of a patent-medicine advertised in the newspaper. Pinkham’s compound was advertised as “a positive cure for all those painful complaints and weaknesses so common to our female population”. In 1914, the American Medical Association analyzed Pinkham’s compound and found it to contain 20% pure alcohol and 80% pure vegetable extracts [10].

Figure 15.5: Upton Sinclair on the cover of Time Magazine. http://i.timeinc.net/time/magazine/archive/covers/1934/1101341022_400.jpg
Regulation of Technologies in a New Drug Application (NDA).

At this point in time, companies could test drugs in patients without approval from the FDA. It took yet another tragedy to change this provision. In the 1960s, the William Merrell company hoped to market the drug thalidomide in the US. It submitted an NDA to the FDA to market the drug.[8, 9] However, an FDA medical officer, Frances Kelsey (Figure 15.6), refused to approve the NDA because of insufficient data regarding the safety of the drug. Even though the drug was never approved to be marketed in the US, the company distributed over two million tablets in the US for investigational use, which was not regulated by the FDA at that time. By 1962, it became clear that thalidomide caused severe birth defects, and the FDA quickly acted to seize the supply of thalidomide that had been distributed.

In response to this averted tragedy, President Kennedy signed the Drug Amendments Act into law in 1962. The new law required that FDA be provided with full details of planned clinical investigations of new drugs, requiring previous animal testing before initiating human clinical trials. In addition, it required that manufacturers prove new drugs to be both safe and effective before marketing them. The FDA was given control of all prescription drug advertising; previously this had been regulated by the Federal Trade Commission.

While the FDA is also charged with regulating food safety, up until the 1960s, the line between foods and drugs was fairly clear and it was usually straightforward to determine whether a new product should be regulated as a food or a drug. However, over the past few decades, the line dividing foods and drugs has become increasingly less clear.[3] For example, in the 1970s, several government commissions issued recommendations encouraging Americans to alter their diets if they wanted to have longer, healthier lives.[3] We have seen that changes in diet can reduce a patient’s risk of developing heart disease, diabetes, and cancer. In 1984, Kellogg’s, together with the National Cancer Institute, launched a marketing campaign for All-Bran cereal that illustrated how a low-fat, high-fiber diet might reduce risk of certain cancers.[3]

Over this same period, the popularity of dietary supplements increased dramatically. Between 1990 and 1997, the use of herbal remedies increased almost four-fold in the US.[10] In 1994, after intense lobbying from the dietary supplement industry, Congress passed the Dietary Supplement Health Education Act (DSHEA). DSHEA permitted supplement manufacturers to make statements about the role of their products in health without FDA approval, provided that they could substantiate the claims with scientific evidence and that they included a dis-

Figure 15.6: Frances Kelsey received the President’s Distinguished Federal Civilian Service Award in 1962, from President John F. Kennedy; she was the second woman ever to receive the award [3, 16]. Her actions at the FDA are credited with preventing thousands of birth defects in the United States.

Research in Alternative Medicine:
The National Center for Complementary and Alternative Medicine (NCCAM) is branch of the NIH which oversees scientific research on complementary and alternative medicine (CAM).
The mission of NCCAM is to rigorously and scientifically explore complementary and alternative healing practices, to train complementary and alternative medicine researchers, and to disseminate accurate information to the public and professionals.
http://nccam.nih.gov/
Challenges of Health Technology Regulation in Developing Countries

Many developing countries struggle with the challenges of effectively regulating foods, drugs and medical devices [20, 21]. As commerce becomes increasingly global, these challenges are a concern for patients and consumers everywhere. The recent deaths of more than 100 people in Panama due to cold medicines and antihistamines containing diethylene glycol are eerily reminiscent of the 1938 Elixir Sulfanilamide tragedy in the United States [21].

The Panamanian tragedy resulted when the government of Panama manufactured cold medicines and antihistamine syrups with what it believed was pharmaceutical grade glycerin imported from Barcelona. On its way to Panama, the solvent passed through three trading companies on three continents, originating in China. Unfortunately, the barrels of solvent sent to Panama did not contain pharmaceutical grade glycerin, which costs about $1,815/ton; instead the Chinese manufacturer had substituted the less expensive solvent diethylene glycol which is similar in appearance to glycerin, but costs only $725-845/ton. The company was not certified to make pharmaceutical grade ingredients, and falsely certified the purity of the solvent. After Panamanian children began to die as a result of taking the cough syrup, Panama asked the CDC to test the medicine and found that it contained the poison diethylene glycol. The map below shows the original source of the solvent in China, and tracks its shipment and labeling as it made its way to Panama.

As a result of the tragedy, the FDA has now recommended that all glycerin shipments be tested for diethylene glycol. More recently, in 2007 the FDA issued a consumer advisory warning people to discard all toothpaste made in China after federal officials discovered toothpaste containing diethylene glycol in Miami, Los Angeles, and Puerto Rico [20]. Diethylene glycol was not listed as an ingredient on the label of the tainted toothpaste, but was discovered after FDA officials began to test Chinese made toothpaste following similar discoveries in toothpaste shipped from China to Latin America.
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claimer that the statements had not been evaluated by the FDA.[7] Unlike drug manufacturers, companies selling supplements are not required to prove products are effective or even safe before marketing them. Table 15.1 outlines the types of claims which can be made regarding dietary supplements under DSHEA, and whether FDA review of supporting data and approval are required.[10] Manufacturers are not permitted to make claims linking their product to a specific disease without FDA review. For example, without FDA review, manufacturers CANNOT say that a product reduces cholesterol but they CAN say it maintains healthy cholesterol levels if they have evidence to support this. They CANNOT say that echinacea cures disease, but with evidence CAN say it has natural antibiotic activities and is considered an excellent herb for infections of all kinds.[3]

Do the majority of supplement retailers follow these rules? A recent study published in the Journal of the American Medical Association reviewed information presented about the eight most widely used herbal supplements found using the five most popular internet search engines.[10] More than 80% of retail sites contained statements that made health-related claims (Table 15.2); more than half claimed to treat, prevent, diagnose or cure specific diseases even though these disease-related claims had not been reviewed by the FDA as required.[10] In addition, half of the sites with health-related claims omitted the required disclaimer that the statements had not been evaluated by the FDA.[10]

Under DSHEA, there are almost no standards that regulate how dietary supplement pills are made, and they are not required to be tested once they are made.[3] DHSEA also places the burden of proving that a supplement is mislabeled on the FDA.[7] In response to the ban on ephedra, Congress has considered, but not passed, several bills that would modify 1994 law so that many unregulated botanical supplements would be

<table>
<thead>
<tr>
<th>Type of Claim</th>
<th>Definition</th>
<th>FDA Preapproval Required</th>
<th>Acceptable Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>Approved claims of relationships between a nutrient and a disease or condition, provided certain other components to the claim are included</td>
<td>Yes</td>
<td><em>A diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life</em>[17] <em>Healthful diets with adequate folate may reduce a woman’s risk of having a child with a brain or spinal cord defect</em>[16]</td>
</tr>
<tr>
<td>Nutrient content</td>
<td>Descriptions of the relative amounts of a nutrient in a product, as per specific FDA regulations</td>
<td>Yes</td>
<td>Low in sodium, fat free</td>
</tr>
<tr>
<td>Structure or function</td>
<td>Role of a nutrient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient acts to maintain such structure, provided that such statements are not disease claims</td>
<td>No</td>
<td>Saw palmetto supports prostate function Echinacea helps to maintain immune function</td>
</tr>
</tbody>
</table>

Echinacea is one of the most commonly used cold remedies in US. A recent clinical was carried out to determine whether echinacea could reduce the duration of the common cold. In a placebo controlled trial involving 400 children with common colds over 4 months, researchers found that the placebo worked just as well, and that children taking echinacea were more likely to develop a rash than those receiving placebo [10].
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Sample Disease-Related Claims from Dietary Supplement Web Sites: From [9]

**Gingko Biloba**

“Its effects in improving circulation also contribute to its use for impotency and peripheral vascular insufficiency...Gingko treats depression, headaches, memory loss and ringing in the ears (tinnitus). It is also recommended for Alzheimer’s, asthma, eczema, heart and kidney disorders.”

**St. John’s Wort**

“St. John’s Wort is effective in the treatment of mild to moderate depression...recent studies have shown that it could have a potent anti-viral effect against enveloped viruses.”

**Echinacea**

“Because it has natural antibiotic actions, Echinacea is considered an excellent herb for infections of all kinds. In addition, it works to boost lymphatic cleansing of the blood, enhances the immune system and has cortisone like properties which contribute to its anti-inflammatory action. It is recommend for stubborn viral infections, yeast infections and for arthritic conditions.”

**Ginseng**

Q: “(I have) high blood pressure (170/90). Will American Ginseng lower blood pressure, and if so, how much should one take and how long before results show?”

A: “While American Ginseng will help, we have combination product that will do a much better job. Look at product #1960 American Ginseng/Garlic/Tien Chi. This is a great product.”

“It is potentially beneficial for AIDS, radiotherapy, and chemotherapy patients, as it reduces the side effects of toxic drugs by increasing red and white blood cell counts. Dang Shen is given for breast cancer, asthma, diabetes, heart palpitations, memory or appetite loss and insomnia.”

**Saw Palmetto**

“The lipophilic extract of the saw palmetto (ser repens) berries is the most widely used herbal preventive and therapeutic agent for benign prostatic hypertrophy (BPH).”

**Kava Kava**

“It is a valuable urinary antiseptic, helping to counter urinary infections and to settle an irritable bladder...Kava kava’s analgesic and cleansing diuretic effect often makes it beneficial for treating rheumatic and arthritic problems such as gout.”

**Valerian Root**

“The herb valerian is most effective in treating a wide range of stress conditions such as irritability, depression, fear, anxiety, nervous exhaustion, hysteria, delusions, and nervous tension...The herb is useful for treating shingles, sciatica, neuralgia, multiple sclerosis and epilepsy.”

**Table 15.2:** Illegal health-related claims about dietary supplements are commonly found on retail websites.

How does the regulation of medical devices compare with that of drugs and dietary supplements? The FDA did not regulate medical devices before 1938. Similar to drugs, after the Food, Drug and Cosmetic Act was passed in 1938, the FDA could only challenge the sale of medical devices it believed were unsafe and could only remove them from the market after patient injuries had occurred as a result of their use.

We have seen the rapid innovations in medical technology that occurred throughout the 1960s; in the field of cardiology alone, the heart lung machine, prosthetic heart valves and many other technologies first came into use. The FDA initially tried to regulate many medical devices as drugs. After a number of catastrophic failures of life sustaining medical devices in the 1970s, including some types of heart valves and pacemakers, there was broad recognition that different rules were needed to regulate devices.[11]
In 1976, Congress passed the Device Amendments to FD&C Act. These amendments recognized that no single regulatory policy would work for all devices. The rules for regulating the manufacturing and sales of a tongue depressor should be different from those which are applied to an artificial heart.

The 1976 Amendments recognized three classes of medical devices. Class I devices pose the least risk to patient; they are not life sustaining, and encompass about 30% of medical devices including devices such as X-ray film, tongue depressors, and stethoscopes. The FDA requires that manufacturers use a process called Good Manufacturing Practices when making some Class I devices (stethoscopes, but not tongue depressors); essentially this entails keeping extensive records about the source of suppliers for all parts of the device. Class II devices are not life sustaining, but must meet performance standards. Class II devices make up about 60% of medical devices and include things like blood pressure monitors, and catheter guide wires. Class III devices are for use in supporting or sustaining human life, and they pose the greatest risk to patient. About 10% of medical devices are considered to be class III devices, including stents, heart valves, and LVADs. These devices face the most stringent approval process.[1, 11, 12]

Manufacturers must show that a new device is both safe and effective and receive approval from the FDA prior to marketing the device. [1, 11, 12] Because medical devices were not formally regulated until 1976, there are two paths to obtain approval to market a new device.

**Premarket Notification Process (510K):** The 510K is the approval path for new class I or II devices which are considered to be substantially equivalent to a device already on the market prior to 1976. The manufacturer notifies the FDA 90 days prior to when they plan to market the new device through a 510K application. In order to be considered substantially equivalent, a new device must have the same indications for use, and be no more risky and no less effective than a pre-1976 device.[1]

**Premarket Approval Application (PMAA):** The PMAA is the approval path for all new class III devices, as well as the path for class I or II devices that have no pre-1976 equivalent. Manufacturers submit a PMAA and provide the FDA with full reports of studies to show the safety and efficacy of the new device. All investigational studies must have been carried out with prior FDA approval under an IDE.[1]

**Investigational Device Exemption (IDE):** An IDE is required for clinical trials using an investigational device which will be used in a way that could pose a significant risk to study participants. [11, 12] An IDE application includes a complete description of
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**History of Regulations:** The history of regulating drugs in the US, is the repeating story of misfortune, disaster, and tragedy—leading to reforms in drug regulation

1906: Pure Food and Drug Act
Drug labels could not contain any statement regarding therapeutic effect which is false and/or fraudulent. The FDA could act only after drugs were marketed [6]. To prevent marketing of an ineffective drug, it was not enough to show that product did not work; the government had to show that seller knew the claims it made were false [6].

1938: Food, Drug and Cosmetic Act
Marked the beginning of era in which it is illegal to market a new drug without FDA approval. New drugs could not be marketed without first notifying the FDA and allowing agency time to assess safety. The seller’s belief regarding product’s value was no longer relevant. The central issue became does the product really work [6]?

1962: Drug Amendments to FD&C Act
Converted pre-market notification system into pre-market approval system where the FDA must review evidence of drug safety and effectiveness. Required that evidence of safety and efficacy come from well-controlled investigations by qualified experts. The FDA has the authority to prevent harm before it occurs [6].

1976: Device amendments to FD&C Act
Devices are assigned to one of three classes. Based on the class of the device, the FDA may require pre-market approval or simply provide oversight of the manufacturing process and device labeling [6].

1994: Dietary Supplement Health & Education Act
Deregulated the dietary supplement industry. Manufacturers are not required to notify the FDA before they market supplements and they are not required to test safety or efficacy. Manufacturers are allowed to make health related claims without FDA review if: they are supported by scientific evidence, they do not mention a specific disease, and are accompanied by a disclaimer that indicates statements have not been evaluated by the FDA [9, 10].

In order to provide an incentive for companies to develop devices for rare conditions, the FDA provides a third path for device approval. If a device is designed to treat or diagnose a condition that affects fewer than 4,000 patients/year, would not otherwise be available without exemption, and no comparable device is available, companies can apply for approval under a humanitarian use exemption. To obtain approval, the manufacturer must show that patients will not be exposed to unreasonable or significant risk of injury or illness by device.

In the device approval process, the FDA considers the device and its intended use together. After the manufacturer submits a request for marketing approval, the FDA convenes an advisory panel to act on the request. The advisory panel includes physicians and scientists with expertise in the field of use relevant to the device. In addition, the panel includes two non-voting members: one consumer representative and one industry representative. Although the FDA is not required to follow the recommendations of panel, it usually does.[12]

Once a device is approved for use, a Medical Device Reporting System is used to detect device related problems in a timely manner. Clinicians are required to report serious injuries or deaths that may have been caused by or related to a medical device within 10 days.

The FDA requires post-marketing surveillance for both new devices and drugs. In 2004-2005, two new drugs were removed from the market due to side effects identified after they had been approved for use. The case of the selective non-steroidal anti-inflammatory drugs, Celebrex, Bextra and Vioxx, provides
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Recently Approved Devices:

Information about newly approved medical devices can be found on the FDA’s website.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/MDA/mda-list.cfm?list=1

For example, on October 24, 2003, the agency approved a new type of coronary artery stent, the NIRflex Stent System, to treat coronary artery atherosclerosis. A summary of the action and the evidence of the safety and efficacy of the device can be found at:

http://www.fda.gov/cdrh/mda/docs/p020040.html

The approval letter from the FDA specifies the conditions of the approval, and a copy of the letter can be found at:

http://www.fda.gov/cdrh/PDF2/P020040a.pdf

Vioxx was manufactured by Merck, and was introduced in 1999 as an alternative to the available non-selective, non-steroidal, anti-inflammatory drugs (NSAIDs) for treatment of osteoarthritis related pain. At the time, the existing non-selective NSAIDs were effective in treating this pain, but these drugs produced gastrointestinal side effects such as ulcers. These existing non-specific NSAIDs inhibited two types of COX enzymes; it was thought that inhibition of COX 2 was responsible for the anti-inflammatory effect (and pain reduction), while inhibition of COX 1 caused the gastrointestinal side effects. Vioxx selectively inhibited COX 2, so it
Grassroots Soccer Week: July 19, 2007

Sophie           Lesotho

We have been collaborating with an organization called Grassroots Soccer, which mixes HIV education with sports activities. A coordinator for Grassroots Soccer in Lesotho, Refiloe, helped us all of last week to conduct the different activities with the children. One of the best games was ‘HIV Dodge.’ The activity clearly shows the role of the immune system, how HIV attacks it, and how ARVs attack HIV. It is a dodgeball-like game where all of the people standing around the human in a circle act as germs to attack the human in the middle with a dodgeball. The human cannot move, but the immune system acts as a defense to prevent the human from getting hit. The children then count how many times the human is hit. In the next round, HIV comes in and holds the hands of the immune system behind his/her back. The human is hit many more times than when HIV was absent. In the final round, ARVs come in and hold HIV’s hands behind his/her back and the human is once again protected against the attack of germs.

All of the games were cleverly thought out and fun to participate in. What bothered me though was that the kids didn’t seem to remember the messages as much as they did the games themselves. This somewhat surprised me because I had the notion the games would always work to drive in the educational messages. Unfortunately, this does not always seem to be the case. Overall however, the kids participated well in the activities and I hope that the activities helped to increase their understanding of HIV concepts.

At the end of the week, we gave the kids post-test evaluations to see how much they learned during the weeks we have spent with them (we gave them pre-test evaluations during our first session). I also interviewed some of the children on what they have learned about HIV/AIDS, what their favorite activities were, and also what their aspirations are for the future. We will continue working with the SOS children over the next 2 weeks that we are here, but we will be reiterating what we have already taught them - except this time, their role will be to teach others. We are having the kids perform and put together ‘Immunity Skits’ that illustrate the role of the immune system, how HIV affects it, and how ARVs work (much like the dodgeball game except using acting). We will record these skits on the video camera and hopefully show this tape in the clinic waiting room and in schools back in Houston.
was thought that it would relieve pain without gastrointestinal side effects.\[18\] Vioxx received approval from the FDA in 1999, and sales grew rapidly.\[18\]

A 1996 study sponsored by Merck showed that COX 2 inhibition could also precipitate the formation of thrombus in the vascular endothelium \[18\], which suggested that the drug might have cardiovascular side effects. Despite the biological plausibility of this hypothesis, none of the clinical studies that were part of the 1998 NDA for Vioxx were designed to evaluate cardiovascular risk associated with the drug.\[17\]

Subsequent to its initial approval, a large study of 8,000 patients was carried out to expand the possible indications for use of Vioxx.\[17, 18\] In late 1999, the DSMB monitoring the study noted a 79% greater risk of cardiovascular death or serious cardiovascular event for those taking Vioxx.\[18\] The board recommended that the study continue, but that a plan to monitor adverse cardiac events be developed. A number of the members of the DSMB had consulting relationships with Merck, and it is unclear whether this potential conflict of interest influenced their recommendation.\[17\] When data from the study were finally published, the study authors used different stopping dates for the cardiovascular adverse events than they did for the primary study outcome. This highly irregular procedure was not described in the methods section of the paper. More importantly, it had the effect of underestimating the risk of cardiovascular adverse events.\[17\] In 2002, the FDA required that the Vioxx label be changed to indicate that physicians should exercise caution in prescribing Vioxx for patients with a history of ischemic heart disease.\[18\]

Another large study in 2004 reported that Vioxx was associated with increased cardiovascular risk, but only after 18 months of use.\[17\] Subsequently, the study authors, who included five Merck employees and other authors who had received consulting fees from Merck, noted that their study contained flaws in the statistical analysis which understated the risk of cardiovascular side effects.\[17\]

Not long afterwards, two other randomized studies noted the increased cardiovascular risk of Vioxx \[18\], causing the FDA to issue a cautionary note warning of the risk of cardiovascular events associated with the drug, and requiring a black box warning to be added to the drug label. Subsequently, Vioxx was voluntarily withdrawn from the market by Merck \[17\], but only after more than 80 million patients had taken the drug \[18\].

While the continued surveillance of Vioxx did ultimately identify the increased risk and lead to FDA action, the action may have been delayed as a result of conflicts of interest. Because
Merck had billions of dollars at stake, and also paid consulting fees to some of the academic investigators who carried out the clinical studies, published the results, and served on the DSMB of the trials, ethical concerns were raised.[17, 18] In fact, in later reviewing the adverse cardiovascular event data from 18 different clinical trials of Vioxx, investigators showed that the only source of variation in whether Vioxx was judged to be associated with increased risk of myocardial infarction was whether the events in each trial were examined by an independent, external committee or not.[18] As a result, many have recommended reforms to the drug development and regulatory process. For example, it has been suggested that academics engaged in industry-designed studies should have full access to clinical data and that these data should be made accessible to the public.[17]

After Merck withdrew Vioxx from the market, the FDA began a systematic reexamination of the risks associated with both selective and non-selective NSAIDs. In 2005, FDA asked Pfizer to withdraw the selective NSAID Bextra from the market because the overall risk-benefit was judged to be unfavorable.[16] The FDA advisory panel reviewing the data from Bextra voted 17 in favor, 13 against keeping Bextra on the market; but FDA judged that, given the closely split decision, regulatory action

**Figure 15.7:** The costs of developing one new drug have rapidly escalated.

**Figure 15.8:** Despite an increase in R&D spending, the number of applications for new drugs and biologic agents has declined dramatically over the last decade [6].
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should be taken.[13] The advisory committee assessing the risk of Celebrex unanimously recommended that it remain on the market; FDA concurred and recommended labeling changes to highlight the increased cardiovascular risk associated with the drug. Finally, FDA also recommended labeling changes for non-prescription non-selective NSAIDs (e.g. Advil, Motrin) to highlight the potential cardiovascular and gastrointestinal risks associated with these products.

The story of Vioxx illustrates an important challenge in the development of new health technologies. The current development path for new medical products has become increasingly challenging and costly.[6] Just over the last decade, the costs of developing new drugs have escalated rapidly (Figure 15.7) to more than $1.7 billion. In part, late failures of new drugs due to unexpected adverse effects contribute to these increasing product development costs.

The increasing costs of development have been paralleled by increases in health-related research and development (R&D) funding in the United States. Figure 15.8 shows that, over the period 1993-2003, R&D funding increased dramatically, both in the private sector and from the federal government primarily via the National Institutes of Health. Despite this increase in R&D spending, there has been a dramatic decline in the number of new applications submitted to the FDA for approval of new drugs and biological agents over the same time period (Figure 15.8). If the cost and complexity of developing new health technologies continues to increase in a way that outpaces R&D investments, health innovation will likely decline.[6] In the final

National Institutes of Health:
- National Cancer Institute
- National Eye Institute
- National Heart, Lung, & Blood Institute
- National Human Genome Research Institute
- National Institute on Aging
- National Institute on Alcohol Abuse & Alcoholism
- National Institute of Allergy & Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Biomedical Imaging & Bioengineering
- National Institute of Child Health & Human Development
- National Institute on Deafness & Other Communication Disorders
- National Institute of Dental & Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute on Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of General Medical Sciences
- National Institute of Neurological Disorders & Stroke
- National Institute of Nursing Research
- National Library of Medicine
section of this chapter, we examine how health-related research is funded in the US and what actions are being taken to sustain and expand innovation.

**Figure 15.9** provides a detailed picture of who carries out research in the US and who pays for it. In this graph, research is divided into three types: basic research, applied research and development. The graph on the right illustrates that most basic research is carried out in universities and colleges. As we move to applied research and development, we see that most is carried out in private industry. The graph on the left shows who pays for R&D; basic research is largely supported by the federal government, whereas applied research and development is funded primarily by industry.

The federal government funds approximately 36% of all medical research in US. This is mostly funded through the National Institutes of Health which is organized into a number of different disease- and technology-related institutes. In 2006, the annual NIH budget was $28 billion. The NIH budget doubled from 1998-2003, and has been flat through 2007. While the focus of the NIH is on basic research, the contributions to development of new products has been substantial. A US Senate Report in May 2000 examined the role of public funding in the development of the 21 new drugs introduced between 1965 and 1992 which were considered by experts to have had highest therapeutic impact on society. The report found that public funding of research was instrumental in development of 15 of the 21 drugs. Three of these drugs, captopril (Capoten), fluoxetine (Prozac), and acyclovir (Zovirax), had more than $1 billion in sales in 1994 and 1995. Others, including AZT, acyclovir, fluconazole (Diflucan), foscarnet (Foscavir), and ketoconazole (Nizoral), had NIH funding and research to help in clinical trials.

The NIH carries out internal research and also makes grants to academic and industrial researchers to carry out health related research. In general, the NIH sets research priorities by issuing requests for proposals through one of its institutes. Investigators write a proposal, describing their hypothesis, the significance of the proposed research, any preliminary results they have obtained, their planned research design and methods.
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and the plans to protect any animals or human subjects to be used. The NIH convenes a panel of experts in the field who critique the proposal and provide a numeric score to be used in determining whether the work should be funded. Following the review, the investigator receives both the score and the written comments. Each institute within the NIH then reviews the scores of all submitted proposals and decides which should receive funding. The scores range from a best of 100 and a worst of 500; typically proposals scored in the range of 100-170 are funded. Approximately 10-15% of submitted proposals are funded, although the fraction of funded proposals has been dropping steadily over the last four years because the NIH budget has not kept pace with the number of submitted proposals.

What does the future of biomedical research and technology diffusion hold? Today, many researchers and policy makers are concerned that the converging challenges of flat research budgets and the increasing complexity of new technologies and their regulation will limit our ability to achieve the potential health gains that could result from new basic science knowledge. Both the NIH and the FDA have introduced new programs to address these challenges. Recognizing the increasing time required for new technologies to diffuse from the bench to the bedside, in 2003 the NIH announced a series of new initiatives called the Roadmap to increase the emphasis on translational research. These initiatives are focused on creating new research approaches and teams that can work to speed the transition from the research lab to the clinical environment.[6]

In parallel, to address the challenges associated with the increasingly complicated product development path, the FDA announced the Critical Path Initiative.[6] The goal of this initiative is to develop new scientific and technical methods to improve the predictability and efficiency on the path from laboratory prototype to commercial product.[6] For example, one pharmaceutical company has estimated that drugs which initially appeared promising but later failed due to liver toxicity observed in clinical trials have cost more than $2 billion in the last decade.[6] New predictive biological or computational models to predict liver failure early in the drug development process could have an enormous impact to speed and reduce the cost of drug development. These may include animal or computer methods, or biomarkers to predict risk of future toxicity, or new clinical evaluation techniques. Figure 15.10 illustrates the process of product development, from basic research to FDA approval, and illustrates where improvements in translational research and the critical path can help speed the successful development and diffusion of new health technologies.
I am in love….with a little girl named Lisemelo. She is the most beautiful and sweetest little girl I have ever met in my life. Every time we walk by her home at the SOS orphanage, she is always waiting on the side of the road for us because she knows by now the times that we usually walk by. She just stands there and smiles at you so sweetly. Then, when you run up to her to give her a hug, she opens her arms so wide for you to pick her up (she is a tiny 2-year-old). I wanted to cry today though….instead of walking back to the clinic from the SOS Village, Christina and I were picked up. As we drove by little Lisemelo’s home, she was standing out on the street and she could see us in the car as we approached. I waved to her and her face looked so sad when she realized that there would be no hugs today. I looked out the back car window after we had passed and I could see her walking up closer to the street and looking after our car. I was so sad….oh goodness, what do I do? I am so in love with little Lisemelo! But! I love all of our SOS kids. They are so funny. I caught a recording of them doing a dance-off of sorts in front of the camera today. I was filming while Christina was trying to teach the kids a hip-hop dance that they are learning as part of their Immunology Skit which they will be performing next week. Their awesome personalities shined through so well in this recording. I wish that there was some way to post it up on the blog. As I filmed, all of the kids (from ages 4 all the way up to 16) were laughing and jumping in front of the camera showing off their best moves. They kept pushing each other aside to hog the camera view and were laughing as they tried to steal the spotlight from each other. It is one of the funniest and cutest things I have ever seen. I love our SOS kids…I don’t know what I’m going to do without them.

Christina teaching the SOS kids a dance:
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.

2. Consider the differences in regulation of drugs and dietary supplements.

   a. 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?
   b. 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?
   c. 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.

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.

There's a new nutritional supplement available for people suffering from Type 2 diabetes. It's called Rejuvenator, marketed by Lafayette Miracle Solutions. It contains two key ingredients -- green tea and cinnamon. The first thing to realize is that nutritional supplements can very successfully control sugar in diabetics. Both green tea and cinnamon are well-known to help control blood sugar so the diabetics don't have such wild blood sugar swings (and potentially don't need as much insulin either). Also, there are other benefits documented from taking both green tea and cinnamon. Green tea is noted for its effects, as well as its ability to aid in weight-loss, which is something that diabetics are typically concerned with.
Chapter 15

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.

April 23, 2004
F.D.A. Seeks Reports of Stent Problems
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 sulfanilamide, an antibiotic for streptococcal infections, so that it was easier for children to take. Sulfanilamide 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
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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.

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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."

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?
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[15] Administration USDoFaD. FDA Public Health Advisory: FDA Announces Important Changes and Additional Warning for COX-2 and Non-Selective Non-Steroidal Anti-Inflammatory Drugs
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