CHAPTER **58**

FDA APPROVAL AND REGULATIONS: Truth, Myths, and Misconceptions

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The Food and Drug Administration (FDA) is an agency of the US Department of Health and Human Services. The FDA has been in existence since 1906 with its headquarters in Rockville, MD. The responsibility of the FDA is to protect the nation's public health by regulating and monitoring the safety of drugs, vaccines, medical devices, dietary supplements, food, biological medical products, cosmetics, and veterinary products. Each of these categories has a major subdivision within the FDA to allow precision and focus on regulation and responsibility.

The process of FDA regulation and monitoring of drugs, medical devices, and dietary supplements are each unique and must be explained individually. Although the FDA approval process has many advantages and is very thorough, there are many myths and misconceptions of what a product or drug with the "FDA approval label" really means to both the consumer and the professional prescribing it.

The FDA approval process for drugs is the most stringent subdivision of the FDA. To begin this process, a drug becomes an Investigational New Drug (IND) after preclinical testing in animals. A sponsor must then provide a pharmacologic profile of the drug, an acute toxicity data (done in at least 2 species of animals), and a short term toxicity data (2 weeks to 3 months). This information is then forwarded to one of 9 divisions based on the therapeutic classification of the drug. The FDA then has 30 days to review and approve the IND. Once approval has been achieved, the drug goes through Phase I to Phase III, which includes various human clinical studies. Phase I involves 20-80 patients for 6 months to 1 year of clinical pharmacological study, whereas Phase III involves multicenter, controlled and open trials with 600-1,000 patients and an average of 3 years duration. These phases are designed to establish the safety and efficacy of the drug.

Once a drug has completed Phases I through III, it may now become a New Drug Application (NDA). This should include preclinical and clinical data, manufacturing methods, product quality assurance information, relevant foreign market experience or testing, and all published reports of experience with the drug. This is submitted to 1 of the 9 divisions for review. The average time for FDA approval is 24 months. Once approved, the drug becomes part of Phase IV or post-marketing surveillance. This may be conducted to expand the indications for the drug as well as new doses and safety in patient populations not represented in previous clinical trials. The average time from drug synthesis to FDA approval is 100 months. An example of a wound care product approved as a prescription drug is Regranex (bacaplermin) wound gel.

Within the FDA drug approval process there are some exceptions. An abbreviated new drug application (ANDA) may be submitted for generic products. These products do not require Phases I through III but instead must prove bioequivalence to the brand name. Additional exceptions are intended to increase the accessibility of the experimental drugs to patients. The parallel track method allows drugs to be available after the completion of Phase I trials to patients who are ineligible for enrollment of clinical trials and are unable to benefit from current therapies. This was developed by the US Public Health Service in response to the human immunodeficiency virus. In another option entitled Treatment Investigational New Drugs (IND), the investigator may provide the drug to patients with life-threatening diseases for which there is no satisfactory alternative therapy available. The drug, however, must be in Phase III under investigation in controlled clinical trials.

Additional categories, Individual Investigator INDs and Emergency INDs allow for the release of a drug for use on a single patient basis. Both the FDA and IRB (Institutional Review Board) must approve this decision. An expedited review (Accelerated Approval Process) is designed to get the new drug to the market in a much faster time. This has reduced the time of approval from 9 years to 3 years. This is often done with acquired immunodeficiency disease drugs and may involve the use of Telescoped trials that involve the enrollment of a larger patient population in Phase I and Phase II, thus eliminating the need for Phase III.

Medical devices that receive FDA approval require a much less stringent process than the aforementioned drug

approval process. These devices are placed into Class I to III. Class I devices have low overall risk to the consumer. An example would be latex gloves and the purpose of FDA approval for these devices would be to maintain a high manufacturing quality. Four classes of wound care dressings were reclassified into Class I in 1999 and they include nonresorbable gauze/sponge dressings for external use, hydrophilic wound dressings, occlusive wound dressings, and hydrogel wound dressingss. This classification allows many wound care products to be exempt from any premarket notification procedures or clinical research. Class II devices are considered intermediate risk devices consisting of surgical lasers, and hip and knee prostheses. These devices mostly receive approval by the 510 k mechanism. The 510 k approval process requires demonstrating "substantial equivalence" to a similar device marketed before 1976 and does not require any clinical research. The devices that were approved in 1976 were not subjected to any rigorous tests of clinical effectiveness, thus a newly approved product that is substantially equivalent to a pre-1976 product may have little or no therapeutic value. An example of a wound care dressing placed in this class is Oasis Wound Matrix, Prisma and MediHoney.

Class III devices are considered the highest risk to the consumer. Examples of Class III devices are implantable devices and those that are life-supporting such as cardiac stents and pacemakers. These devices require a premarket approval (PMA). PMA consists of data on performance from humans, safety information, and data on effectiveness. A premarket approval process takes, on average, about a year and approximately $36 million. On the other hand, 510 k mechanism takes, on average, about 3 months and about $13 million. Dermagraft and Apligraf are the only two wound care products approved by the FDA under Class III and thus received PMA.

Dietary Supplement approval is regulated under yet a different set of regulations. The DSHEA (Dietary Supplement Health and Education Act of 1994) states that the supplement manufacturer is responsible for ensuring that a dietary supplement is safe before marketing it. The manufacturer is also responsible for making sure that their label information is truthful and not misleading. The FDA is only responsible for taking action against any dietary supplement that is deemed unsafe after it reaches the market. The FDA also requires the manufacturer who wishes to market dietary supplements with "new dietary ingredients" to notify them. This must include information by which the manufacturer has concluded that the new dietary ingredients are expected to be safe. There are no regulations on what this information should include.

The FDA does some post-market surveillance that includes monitoring the safety of the supplement. This may include posting adverse effects and general product information. The FDA differentiates the terms "medical food" and "dietary supplement." A medical food provides nutritional support for a specific disease or condition and is intended to be used under a physician's supervision whereas a dietary supplement is intended to support the healthy function of a part of the body. Commonly used products termed "medical food" are Metanx for diabetic neuropathy and Limbrel for anti-inflammatory conditions. An example of a commonly used dietary supplement is glucosamine for cartilage health.

The FDA also regulates human tissue under 21 CFR Parts 1270 and 1271. Examples of human tissue are human bone, skin, tendons, dura mater, and heart valves to name a few. Not included in this category is the transplantation of vascularized human organs such as kidneys, liver, and heart which are overseen by the Health Resources Services Administration. The FDA requires that the establishments marketing human tissue are to test and screen donors, to follow written procedures for the prevention of the spread of communicable disease, and to maintain records. This approval process applies to tissues recovered after May 25, 2005 and is intended to protect the public health and safety while also keeping the regulatory process at a minimum. Examples of commonly used products are Wright Medical Graft Jacket, and bone grafts used intraoperatively.

Although the drug approval process appears to be thorough with a substantial amount of research and clinical data, there are many things that an FDA-approved drug does not entitle. For a new drug to receive FDA approval there is no requirement that the new drug be better than the products already available. The new drug must only be effective and fairly safe. Effective essentially means better than no treatment for a specific entity such as lowering cholesterol or lowering blood pressure. However, these drugs have proven to, at times, increase mortality. Also, the FDA makes no judgment on cost effectiveness for a new device or drug. The FDA would approve a million dollar wound care product if it worked and was relatively safe. The FDA also does not do head to head comparisons of drugs. The FDA would not make a statement that one drug is better than another for lowering cholesterol. Many times, a drug that has been on the market for years is more effective than a newly approved drug. Also, the FDA does not approve every use

to which a medical product might be prescribed. There are many instances in which the doctor prescribes a drug that is off-label from FDA approval.

There are many pressures for FDA approval of drugs and products. A big challenge for the FDA is the speed at which an approval can be achieved. There needs to be a balance between a thorough process in which the public is safe/aware of all possible adverse effects but also that a drug or product with new technology is approved as quickly as possible to potentially save lives. In 1992, Congress passed a law that allowed the FDA to collect user fees from drug companies with the intention to have quick approval of experimental drugs that may offer substantial benefits. These fees, however, have quickly developed to account for half of the FDA's budget for drug evaluation. This includes 12% of the agency's $1.3 billion budget. Naturally, this raises concern by placing more pressure on the FDA to approve a corporate product from a major contributor. Another issue is that of conflict of interest. Many of the members of the agency's drug advisory committees have a direct financial interest in the drug that they are asked to evaluate.

After a drug is approved and available in market, the FDA does some post marketing surveillance to assure continued safety. However, the FDA lacks the financial ability and manpower to effectively have surveillance on these products. The FDA states that the reporting of adverse effects by manufacturers is mandatory, however, late and lack of reporting cases by drug companies have been a major problem. Widespread marketing and exposure of the population to newly improved drugs before some of the serious side effects are known can be very detrimental to the consuming population. One way the FDA regulates adverse effects of a product is to issue a black box warning, which is a type of warning that appears on the package insert for prescription drugs that carry significant risk of serious or life threatening adverse effects. This is the FDA's strongest warning of products remaining on the market. An example of this was in July 2008 when the FDA placed a black box warning on Fluroquinolone antibiotics for possible tendonitis and tendon rupture.

The FDA approval process is something that we as practitioners should be aware of. By understanding the approval process each product and drug undergoes, we can know what the FDA approved label means and how this directly affects our patient's safety.

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