The pharmaceutical industry is undeniably the most profitable sector of the chemical and allied products industries. Yet bringing a drug to market is a complex, time-consuming, and expensive process. Billions of dollars are spent each year on the discovery and development of new drugs. It is estimated that pharmaceutical companies spend an average $125 million on the development of each new drug. The US Food and Drug Administration (FDA) estimates it takes an average of 8.5 years to study and test a new drug before its use by the general population is approved. Often a new drug or compound is sought with a specific treatment or disease state in mind, such as acquired immunodeficiency syndrome or cancer. Not infrequently, new drugs are serendipitous discoveries.

The rules and regulations by which the FDA governs and supervises new drug development are outlined in Title 21 of the Code of Federal Regulations. The Code of Federal Regulations essentially divides drug research into 2 phases: the preclinical and clinical phases. The preclinical phase involves laboratory and animal testing, and the clinical phase incorporates drug testing in humans.

Laboratory and animal testing

A pharmaceutical company begins research on a new chemical or drug with animal and in vitro studies, often referred to as the preclinical phase. The purpose of these preclinical studies is to determine a basic pharmacological profile of the drug and to decide the feasibility of continued research and development. Further animal toxicology studies then are conducted.

The preclinical stages are composed of 4 elements:

1. Clinical pharmacokinetics
   - The body’s response to the drug is examined: absorption, distribution, metabolism, and excretion.

2. Pharmacokinetic analysis
   - Events that occur at the cellular and molecular levels are examined. Parameters are obtained, such as dose–drug plasma concentration relationships and biologic half-life.

3. Pharmacodynamic effects
   - The mechanism of action is determined, allowing precision at manipulating the cellular function in focus. Pharmacologic and therapeutic effects are estimated.

4. Toxicology studies
   - Short- and long-term toxic side effects are ascertained along with the drug’s safety at different doses.
   - Carcinogenicity, mutagenicity, and teratogenicity are determined.
   - Monitoring parameters needed for human studies are established.

In animal testing, 2 or more species, a rodent (mouse, rat, or guinea pig) and a nonrodent (cat, dog, or rabbit) are commonly used, since a drug’s effect on one species may be different from its effect on another. Although the FDA does not directly dictate this early laboratory and animal testing, it does have specific guidelines on the types of results that are expected should human testing be requested. Drug companies endeavor to use as few animals as possible and to ensure humane and appropriate care. This preclinical phase typically takes from 1 to 3 years to complete; the average is 18 months.

Once acceptable results are obtained from the tox-
Ecology studies and the drug is determined to be potentially safe and effective in humans, the drug company submits an Investigational New Drug application (IND) to the FDA for permission to try the drug in humans. The IND requires specific information about the drug, including its chemical composition, pharmacologic nature, and the results of animal and preclinical tests. The IND also requires a complete protocol and method for the initial human clinical studies. IND regulations further include institutional review board approval for clinical trials. Until all requested information is submitted to the FDA under the IND, a company is forbidden to ship the drug to any clinical investigator within, or even outside, the United States.5

After submitting the original IND, the drug company is required to wait 30 days before human trials can be initiated.5 This offers the FDA a period to express questions or concerns about the safety of the drug. And if there are questions or concerns, the FDA is obligated to communicate them within the 30 days. Once the IND is approved and human trials begin, the FDA requires annual progress reports from the investigators. The reports are designed to summarize the status of the studies and inform the FDA of any changes and unexpected developments.

There are 2 types of INDs: commercial and noncommercial. A commercial IND authorizes the drug company to collect the safety and effectiveness data required for a New Drug Application (NDA), which, if approved by the FDA, allows the drug to be marketed. A noncommercial IND permits the drug company or sponsor to use the drug in research or early clinical trials for the sole purpose of advancing scientific and medical knowledge.2

Table. Clinical trial phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>20-100</td>
<td>~500</td>
<td>Several hundred to several thousand</td>
<td>Several hundred to several thousand</td>
</tr>
<tr>
<td>Length</td>
<td>Several months</td>
<td>Several months to 2 y</td>
<td>1-4 years</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Purpose</td>
<td>Safety</td>
<td>Safety and effectiveness</td>
<td>Safety, effectiveness, and dosages</td>
<td>Evaluation under normal use by the public</td>
</tr>
<tr>
<td>Percentage of drugs that pass</td>
<td>70</td>
<td>33</td>
<td>25-30</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Related information</td>
<td>Healthy volunteers recruited</td>
<td>Participants have disease or condition</td>
<td>Drug’s ability to cure is validated</td>
<td>Postmarketing surveillance</td>
</tr>
<tr>
<td></td>
<td>Subclinical dose administered</td>
<td>Control groups introduced</td>
<td>FDA approval usually obtained</td>
<td>Drug’s long-term effect realized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum and effective dose is determined</td>
<td>Findings among populations not well-represented in preapproval phases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A, open trials</td>
<td>2B, double-blind trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA = US Food and Drug Administration

Testing drugs in humans

Clinical human trials are allowed to begin after IND approval. These trials are divided into 4 sequential phases, which are simply labeled phases 1, 2, 3, and 4 (Table).1 Some of the phases may overlap temporarily, and some of the trials may be involved in more than 1 phase. Phase 1 studies initiate the use of the drug in humans. The subjects are healthy volunteers, not patients, and usually are male. For ethical reasons, women of childbearing age are banned from participating in phase 1 and phase 2 trials, simply to protect a fetus from exposure to an experimental chemical. Some investigators will enroll women who cannot conceive so as to have adequate representation of women in their findings.

Typically, 20 to 100 subjects are enrolled in phase 1,
and a large percentage of them are college students. Volunteers often are recruited by using newspaper, radio, or television ads or by posting notices on bulletin boards. Phase 1 investigations take place in a local hospital, medical school, or other appropriate facility out of which the pharmaceutical company can operate.

Before drug administration, a thorough physical examination, including complete blood and urine analyses and an electrocardiogram, is performed on each participant. The primary concern of phase 1 is safety. Not infrequently, the first study involves only 1 dose of the new drug for the purpose of monitoring the pharmacokinetics in humans: absorption, distribution, metabolism, and excretion. This initial dose usually is no more than 10% of the dose determined to have no effect in the preclinical animal trials. And during this initial dosing, the volunteers are kept within the investigation facility under close medical supervision and monitoring, as they are during incremental dose increases. Phase 1 generally lasts several months, yet it is estimated that only about 70% of the drugs for which INDs are submitted to the FDA will successfully complete phase 1 and move to phase 2 trials.

In phase 2 studies, investigators give the drug to patients who have the particular condition or disease the drug is intended to treat. While safety is still a concern, the primary purpose of phase 2 studies is to assess effectiveness. Control groups are introduced at this point.

There are phase 2A and phase 2B studies. The phase 2A trials are open trials, meaning that the responsible physicians, and often the patients, know whether the experimental drug, an older drug already approved and known to be effective, or a placebo is being given. Phase 2A studies are clinical pharmacology studies intended to determine the minimum effective dose and effective dose range. Phase 2B trials often interface with phase 3 trials in that they both are intended to verify efficacy at these specified doses. Phase 2B studies are double-blinded studies, meaning that neither physicians nor patients know whether the new drug or the placebo is being dispensed.

While the subjects participating in phase 1 studies are healthy volunteers, phase 2 subjects are selected from a fairly restricted population. They typically are chosen from patient volunteers who have the condition or disease under investigation, but who are relatively free of coexisting illnesses or disorders. The number of patients enrolled in phase 2 usually is around 500, with 300 to 350 receiving the investigational drug and the remainder a placebo.

Phase 2 lasts several months to 2 years, yet only about 33% of clinical drug trials successfully complete this phase to proceed to phase 3. The results of the phase 2 studies are put through exhaustive statistical analyses to warrant advancement to the extremely expensive phase 3 trials. Phase 3 is intended to validate the new drug’s creation and its ability to cure or treat an ailment. The climactic FDA approval of a new drug is typically obtained with the phase 3 trial.

Successful phase 2 studies lead to the initiation of phase 3 trials. The purpose of phase 3 is to validate the statistical results of phase 2 and to further assess safety, dosage, and effectiveness of the drug in a targeted population. Phase 3 engages well-controlled clinical trials, involves several hundred to several thousand patients, and lasts 1 to 4 years. About 25% to 30% of the original drugs for which INDs are submitted will complete phase 3, and only 20% of this remainder will ultimately be approved for public marketing.

The drug approval process

At the completion of phase 3, companies prepare an NDA. An NDA is “an application requesting FDA approval to market a new drug for human use in interstate commerce.” The purpose of an NDA is to paint a thorough picture of the drug, from its chemical structure to the results of its phase 3 trials. It includes specific technical information and scientific data such as:

1. A description of the chemical and physical composition of the drug.
2. An explanation of the methods, facilities, and controls used to manufacture, process, and package the drug and how the drug will be shipped and stored in bulk supply.
3. Actual samples of the drug with examples of labeling and package inserts.
4. Proof that neither the manufacturing process nor the drug itself is harmful to the environment.
5. A description of the pharmacologic actions and toxicologic effects of the drug, including effects on reproduction and the unborn fetus.
6. A briefing of the data from all preclinical animal studies and clinical human trials, with a comparison of the results and statistical evaluations.
7. A summary of the benefits and risks and convincing evidence that, as long as the drug is used as prescribed, the benefits outweigh the risks.

An NDA has the potential of incorporating literally thousands of pages of reports and documents. It is scrutinized by members of a special FDA review team made up of experts in the fields of chemistry, medicine, pharmacology, pharmacokinetics, statistics, and microbiology.

The review process is lengthy. The mean review
time for an NDA, and subsequent approval of a new drug, was 32.2 months in the early 1980s. During the last several years, the FDA has been aggressive about reducing this review time, which now averages 24 months. For obvious reasons, drugs that prove to have potential benefit for treating life-threatening or severely debilitating diseases warrant an expedited review. The FDA recognizes this and assigns review priority based on a classification system of (1) chemical type and (2) treatment potential. Chemical type classes are as follows:

1. **New molecular entity, or NME**: drug that has never been marketed in the United States. This also is referred to as a new chemical entity, or NCE, in some literature.
2. **New derivative**: A drug that is derived from a “parent” drug already on the market.
3. **New formulation**: A new dosage form or formulation derived from a drug already on the market.
4. **New combination**: A combination of 2 or more drugs that are already on the market, the combination of which has not been marketed as 1 product.
5. **Already marketed drug product, but a new manufacturer**: An already marketed drug duplicated by another chemical company.
6. **Already marketed drug product, but a new use**: A different company proposes a new use for a drug already on the market.

There are 2 treatment potential classifications:

1. **Priority review drug (P)**: A drug that claims a new indication or indication derived from a drug already on the market.
2. **Standard review drug(s)**: A drug that allegedly offers therapeutic qualities similar to drugs already on the market.

The FDA is required to report an initial evaluation of the NDA within 6 months. With this initial evaluation, the FDA determines whether to accept the NDA, reject it, or declare it incomplete. If the NDA is declared incomplete, it usually is because the FDA requests further data or has unanswered questions regarding the data. If the NDA is judged acceptable, the FDA expert review committees continue to analyze the NDA, and the sponsoring drug company continues to submit any new evidence or data obtained from further phase 3 studies.

The final evaluation and ultimate decision whether to approve the new drug are basically determined by 2 cardinal questions:

1. **Do the results of the well-controlled studies provide evidence that substantiates the effectiveness of the drug?**
2. **Do the results support an acceptable benefit-to-risk ratio?** In other words, do the benefits outweigh the risks so long as the drug is used as prescribed?

Once the review and evaluation of the NDA are complete, the FDA replies in writing to the applying pharmaceutical company with 1 of 3 possible responses: (1) approved; (2) approvable, if certain minor changes are made; or (3) not approvable, owing to major reasons or problems. If the latter is the ruling, the applying company can completely withdraw the application, make the recommended adjustments and reapply, or request a hearing. In general, about 75% of all the NDAs submitted are approved by the FDA. As soon as the NDA is approved, the manufacturer can begin production and distribution to get the new drug onto the market for public use.

**Postmarketing surveillance**

FDA approval is granted once adequate safety and effectiveness information is proven. Yet this information is limited by the fact that it is obtained before drug approval, under relatively controlled conditions, in a relatively limited population. The premarking studies involve several thousand people, of whom some have the disease state of concern yet are generally free of concomitant disease. And as a rule, women, young children, and elderly people make up little, if any, portion of the premarking trial population. Needless to say, an adverse reaction that was not identified in preapproval studies might surface once the drug is used by the general public. For example, an untoward reaction might occur in only 1 in 5,000 or 1 in 10,000. If there were only 3,000 or 4,000 participants enrolled in the premarking trials, the reaction conceivably could never appear until the drug is released for marketing. This sheds light on why the FDA’s accountability does not end once a new drug is approved and why postmarketing surveillance is so vital.

Postmarketing surveillance refers to the process of obtaining “information on drug experience after a drug is approved for use by the general population…(through)…ad hoc and formal studies and monitoring systems….” These studies are instituted to assess the 3 most outstanding postmarketing concerns. First, the nature of the drug is explored more closely, with an intimate focus on the incidence and severity of adverse reactions. Second, the drug’s long-term effects on morbidity and mortality are ascertained. And third, the consequence of use in populations not well represented in premarking studies, for example, pediatrics and geriatrics, is clarified.

Postmarketing surveillance studies are included in phase 4 of a drug study. The primary objective of phase
4 is to evaluate the drug under natural conditions in normal public use. Sometimes phase 4 engages uncontrolled studies as opposed to the rigidly controlled studies of the first 3 phases. As discussed, phase 4 trials might detect previously unidentified side effects. Conversely, new indications for the drug also might be discovered. Other types of trials involved in phase 4 are geriatric use trials, cost-effectiveness trials, comparative trials, and quality-of-life studies.4

The reporting of adverse drug reactions, especially those not included in the drug's labeling, is required by the FDA and is an important part of postmarketing surveillance. In 1962, US Congress passed the Drug Amendments to the Food, Drug, and Cosmetic Act, which required drug companies and pharmaceutical manufacturers to immediately report to the FDA any adverse drug events that were determined to be associated with their products.9 The definition of an adverse drug event and the specific requirements for reporting such an event are outlined in the Code of Federal Regulations. More than 30,000 adverse drug events are reported annually to the FDA and drug manufacturers.2

Phase 4 studies are a method of collecting data on postmarketing adverse events. Yet information on new drug reactions is collected primarily from voluntary sources, such as physicians, pharmacists, and nurses, through the FDA's voluntary Medical Products Reporting Program called MedWatch.2,9 Healthcare professionals traditionally have been an effective and reliable source of unforeseen drug reactions. But depending on this source for determining the incidence and rates of reactions is relatively unreliable. The FDA, the World Health Organization, and most industrialized countries have implemented surveillance programs and adverse reaction reporting systems for prompt detection of potentially unsafe and harmful medical products on the market.9 Through such programs, statistical data on adverse reactions associated with a particular drug can be obtained.

Some recent and widely publicized examples of drugs pulled off the market because of postintroduction problems are Rezulin and Raplon. Rezulin (troglitazone), an oral antglycemic drug manufactured and distributed by Parke-Davis, was withdrawn in the early part of 2000 because it was associated with serious and fatal liver failure. Raplon (rapacuronium bromide), an intravenous neuromuscular blocking agent manufactured and distributed by Organon, Inc, was voluntarily withdrawn from market in March 2001 because of its association with serious and fatal bronchospasm.

As you can see, the whole process of getting a drug from the chemist's bench onto a pharmacist's shelf is not easy. On the contrary, it is extensive, expensive, and time-consuming…and rightfully so.

Historic milestones
The FDA, which was formed in 1931, does not create or invent new medicines. Rather it functions to determine whether a new drug, previously tested by a chemical manufacturer in a laboratory, is safe enough to test in humans and, if so, ultimately to determine whether the drug is sufficiently safe and effective to release to the general public. By doing so, the FDA serves as a protector or guardian of public health, welfare, and safety. This responsibility and authority were bestowed on the FDA in 1938 with the Federal Food, Drug, and Cosmetic Act, a revision of the Food and Drugs Act of 1906. Unfortunately, it took the tragic deaths of 107 people, mostly children, in 1937 to prompt the amendment.

The deaths resulted from the marketing of “Elixir Sulfanilamide” by S. E. Massengil, a small company in Tennessee. The elixir contained diethylene glycol, a poisonous solution. At that time the FDA had only the weak legal authority to accuse Massengil of “adulteration and misbranding,” charging a trivial fine of $16,800.1,8 “Elixir” on the label implied the product was alcohol-based. Indeed it was not alcohol-based, and had Massengil merely labeled it a “solution,” no accusation of breaking the law could have been made.1,8 This historic event spawned congressional legislation requiring manufacturers to test investigational new drugs for safety in animals before human use.1

Until the thalidomide disaster of the 1960s, safety was the only concern addressed by the FDA before it would approve a drug for marketing in the United States.7 The FDA had not yet approved thalidomide. It was a sedative marketed in other countries, and its use by pregnant women, mostly in West Germany, resulted in the birth of thousands of deformed babies.5 Like the elixir sulfanilamide tragedy, the thalidomide disaster precipitated dramatic concern for the need for tighter regulation of prescription drugs. In October 1962, Congress passed the Kefauver-Harris Drug Amendment that required manufacturers to submit to the FDA information on how the drug is tested in humans and proof of effectiveness and safety.5,8

Other changes brought about by the Kefauver-Harris Amendment pertained to obtaining informed consent and reporting adverse drug events. The amendment required a remark in the subject's chart declaring that verbal consent had been secured.10 Later, in 1967, the FDA drafted a policy statement that affirmed the consent process and made the informed, written, and signed consent document a requirement.10
Summary
New drug evaluation, approval, and regulation is a serious business that carries with it an awesome responsibility, and so is it in the business of anesthesia. Certified Registered Nurse Anesthetists must possess a strong working knowledge of a vast number of drugs and medical products and also must be continuously aware of the potential for unsuspected adverse reactions associated with such drugs and products. Regardless of the setting or environment in which anesthesia care is provided, it is important to understand the concept of drug regulation and the process of drug approval for the purpose of professional awareness, as well as for patient safety and advocacy.

REFERENCES

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