Drug Approval: The Long and Bumpy Road to Market

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Author's disclosures of potential conflict of interest are found at the end of this article.

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Novel pharmacologic agents for symptom management continue to emerge and provide options to improve quality of life in patients with cancer; however, bringing novel pharmacologic agents to the bedside can be a lengthy and arduous process. Once a new agent is available, many questions often arise. What is its role in the symptom management armamentarium? Why does the agent take so long to get to market? How much is the novel agent going to cost, and will insurance companies pay for the new drug? Just how does a molecule that begins on a bench become approved for market?

Fentanyl nasal spray (Lazanda) is a novel agent for breakthrough cancer pain (BTCP) management that was discussed by Joan Schey in the first part of this issue's *Translating Research Into Practice* feature (see page 402). This commentary provides a behind-the-scenes look at what it takes to "translate pharmaceutical research into practice," using fentanyl nasal spray as an example. Table 1 includes an overview of the US Food and Drug Administration (FDA) steps to drug review.

Table 1. The FDA Steps to Drug Review

1. Preclinical (animal) testing
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase I studies (typically involve 20 to 80 people)
4. Phase II studies (typically involve 100 to about 300 people)
5. Phase III studies (typically involve several hundred to about 3,000 people)
6. The pre-NDA period, just before an NDA is submitted, which is a common time for the FDA and drug sponsors to meet
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or issue a complete response letter.

Note. FDA = US Food and Drug Administration; NDA = new drug application.

From Research Bench to Investigational Drug

The FDA's Center for Drug Evaluation and Research (CDER) has the responsibility to ensure that approved pharmacologic agents are safe and effective. Data must be submitted by the drug's sponsor to the CDER in a series of tests (FDA, 2009).

Under most circumstances, drug development begins in the laboratory or "bench" setting using nonhuman subjects. When the sponsor determines that sufficient data have been attained from the bench research, the drug's sponsor (usually the manufacturer) meets with the FDA to discuss submission of an Investigational New Drug (IND) application to the CDER. Once the IND is in place, clinical trials in humans can begin (FDA, 2009).

Because fentanyl had already been approved for pain control, the FDA did not require bench research for the approval of intranasal fentanyl. Instead, human clinical trials that focused on the intranasal delivery of fentanyl were required. Trials began on intranasal delivery of fentanyl in the 1990s (Striebel, Wessel, & Rieger, 1993; Zeppetella, 2000), but the journey for the FDA approval of Archimedes Pharma's fentanyl nasal spray began in 2005 when Archimedes Pharma acquired PecSys, the pectin-based technology mentioned in Joan Schey's article that allows for efficacious, rapid, and consistent delivery of fentanyl. Archimedes Pharma filed an IND with the CDER, and clinical trials for fentanyl nasal spray began in 2007 (Archimedes Pharma, 2011).

SEE PAGE 371

Use your smartphone to access the FDA's guide to the drug development and approval process.

Clinical Trials

The FDA requires three phases of clinical trials to be employed prior to the approval of pharmaceutical agents. Phase I trials test the drug with a small group of patients (approximately 20 to 80) to evaluate safety, dosage, and side effects. Phase II trials involve a slightly larger group of patients (approximately 100 to 300) to evaluate efficacy and further safety. Phase III trials involve large groups of patients (approximately 1,000 to 3,000) to confirm efficacy, monitor side effects, and gather additional information about

the safety of the drug (National Institutes of Health, 2007). Depending on the pharmaceutical agent, the FDA can require placebo-controlled trials. For example, the FDA required a placebo-controlled trial for the approval of fentanyl nasal spray, but rescue medications were allowed within the trial to ensure patient comfort (Portenoy, Burton, Gabrail, & Taylor, 2010). Occasionally, drugs may be approved based solely on phase II data in an expedited review process, although the gold standard remains the phase III randomized trial. Phase IV trials are conducted as part of the postmarketing effort to obtain further information on a newly approved agent as well as to collect safety data.

Three global phase III clinical trials were submitted to the FDA for the approval of fentanyl nasal spray: one placebo-controlled trial, one active comparator trial, and one long-term safety trial. Patients from the first and second trial were also enrolled in the long-term open-label trial. The global trials included over 500 patients from 13 countries and involved over 100,000 episodes of BTCP (Archimedes Pharma, 2011).

New Drug Application

Once the drug manufacturer concludes that evidence demonstrating the drug's safety and efficacy is sufficient to meet FDA requirements, the drug's sponsor will submit a New Drug Application (NDA) to the FDA, requesting that the new drug be approved for market in the United States. After receipt of the NDA, the FDA has 60 days to determine whether the file will be reviewed. The FDA can refuse the NDA if essential studies are missing. The NDA must contain the following elements:

- Manufacturing specifications
- Stability
- Bioavailability
- Method of analysis on each of the dosage forms
- Packaging and labeling for the prescriber
- Packaging and labeling for the consumer
- Results of the toxicologic studies not included in the IND

Upon receipt of the NDA, the FDA's CDER scientists (physicians, chemists, statisticians, microbiologists, pharmacologists, and other experts) conduct a thorough and often lengthy review of the submitted data to determine safety and efficacy of the drug. While drugs are always accompanied by side effects, the benefits of the drug must clearly outweigh the side effects. Not all drugs proceed down the same path. Some may be accelerated for approval if they provide treatment for life-threatening conditions that lack satisfactory treatment (FDA, 2009).

Barriers can occur along the road to approval. Failure to demonstrate drug efficacy or unexpected safety concerns are common reasons for FDA denial of approval. Other reasons for delay include the need for additional studies and clinical data, substandard manufacturing practices, and an inability to meet supply in the marketplace once the drug is approved. The FDA inspects manufacturing facilities prior to approval (FDA, 2009).

Once the NDA is filed, the drug is in the patent development phase. For fentanyl nasal spray, approval was sought in both European and US markets. Archimedes Pharma submitted data to the European Medicines Agency—the European equivalent to the US FDA—in early 2009. Data in the form of a NDA were submitted to the FDA later in 2009. Fentanyl nasal spray was approved in Europe as PecFent in mid-2010, and on the US market as Lazanda in June 2011.

Labeling

Once an investigational agent is approved, there may be considerable lag time before the drug is on the shelf and available for patient use. Labeling and the package insert must be negotiated, and provider and patient education materials cannot be developed until the labeling is final. Lazanda was available for patient use in October 2011, approximately 4 months after drug approval (Archimedes Pharma, 2011).

Drug approval of pharmaceutical agents in the United States can be a lengthy process. The steps to approval for fentanyl nasal spray began in 2005, with eventual approval in 2011: a more than 6-year course of action. The FDA, through its stringent requirements, strives to ensure safety and efficacy of every product on the US market. The lengthy process has not been without criticism, however, and some studies have even begun to evaluate differences and outcomes between the US and European approval processes (Trotta, Leufkens, Schellens, Laing, & Tafuri, 2011).

Conclusions

Advanced practitioners (APs) in oncology are on the forefront of symptom management, as they are often the first to prescribe novel symptom management strategies such as fentanyl nasal spray. Advanced practitioners should understand the process of drug approval in order to appreciate the safety and efficacy of each newly approved agent, and to provide patients with this information as requested. Understanding the process helps APs and patients to be aware of the considerable time and resources that go into drug approval in the United States, which contributes to the higher costs of novel agents. But above all, enhanced quality of life and relief of pain are the desired outcomes, and APs must continue to prescribe the best individualized treatment available based on efficacy, side-effect profile, and cost of therapy, to advocate for each patient's access to care.

DISCLOSURE

The author has no conflicts of interest to disclose.

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