Determination of the benefit-harm balance is important in the regulatory approval process. The Food and Drug Administration (FDA) decides which medications can be legally marketed to the American public while upholding its Mission Statement, which states that “the FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices...”

Another type of benefit-harm balance is determined for individual patients by their physicians. The factors involved in this assessment are discussed in Chapter 2.

**How objective is this assessment?**

In Chapter 3, we discussed the regulatory requirements for medication approval. Generally, this means the benefits of a new medication should outweigh the potential harm. This decision is somewhat subjective, since there is no objective formula that can give us the absolute truth about a medication. In fact, government agencies like the FDA and the European Medicines Agency (EMEA) have reached different conclusions on medication approval based on the same documentation.

**What factors are considered?**

All medications have positive and negative effects. The positives, as discussed in Chapter 47, may relate to alleviation of symptoms, reduced risk of disease complications or extending one’s lifespan. The negatives include treatment-induced symptoms, serious complications or events, birth defects, adverse drug interactions, unwanted environmental effects and, in the worst cases, death.

Many factors are considered in the determination of benefit-harm balance. How important is the beneficial effect? Will it contribute to prolonged survival for cancer patients or to stop a runny nose? What is the likelihood of benefit? Is the risk of a bone fracture reduced by one case per 10 patients treated for 5 years or just one in 100 treated for 5 years?

For patients with serious diseases, it may be important to factor in and accept adverse drug effects if it improves the patient’s condition or prolongs their life. Another consideration is prognosis if no treatment is initiated. Will treatment alter the prognosis? For most medical conditions, we are fortunate to
Chapter 46 - How is the benefit-harm balance determined?
have treatment alternatives, and it is reasonable to compare a new medication to these alternatives and their favorable and unfavorable treatment effects. Does the new drug add value to existing treatments? Remember that new medications are not necessarily better than older ones. Treatment alternatives are not always represented by other medications (for example, surgery and radiation therapy for patients with prostate cancer).

**What are the dilemmas for the regulators?**

A major dilemma for regulators is incomplete documentation of favorable and unfavorable effects. Participants in clinical trials leading up to regulatory approval meet very specific qualifications and often differ from future drug users (see Chapter 47). In addition, the number of patients and the duration of trials conducted to gain approval for new medications are limited. As a result, more than half of all new medications are reported to have at least one serious adverse effect only after they have been FDA-approved and available to the public. For example, rosiglitazone (Avandia), a medication for Type 2 diabetes, had no known major safety problem when it was approved. Subsequently, it was shown to double the risk of heart failure and bone fractures (women only), to increase the risk of heart attacks by approximately 40 percent and, in rare cases, to cause eye complications that could lead to blindness. The lesson is that safety information is incomplete for adverse effects that are uncommon, unexpected, or do not appear until after long-term use in clinical practice.

Another dilemma is assigning a number to treatment effect. Percentages are easily understood but can vary depending on treatment length. If an adverse reaction occurs at a rate of 2 percent, it would be critically important to know if the risk is 2 percent during the first week, first month or first year. Since adverse effects tend to increase over time, a 2 percent risk in one week may be 10 percent to 20 percent in one year.

An attractive way of determining the benefit-harm balance is to estimate benefit and harm during the same treatment period. For example, celecoxib (Celebrex) reduced the risk of colorectal cancer from 3.1 to 1.5 per 1,000 patients treated for three years. Thus, the net benefit was 1.6 per 1,000 patients treated for three years. However, over the same period, it increased the risk of cardiovascular events from 14.6 to 27.3 per 1,000 patients, for a harm of 12.7. Therefore, the risk of cardiovascular events with celecoxib is about eight times higher than the benefit of lower colorectal cancer (12.7 divided by 1.6).

**What is the current strategy?**

Unfortunately, raising the current standards for drug approval would be problematic. It would delay introduction of new drugs, increase drug
development costs and probably reduce the pharmaceutical industry’s interest in developing new and potent medications. Thus, the regulatory approval of a new drug carries uncertain risks. Since 1992, 20 new drugs have been withdrawn from the U.S. market due to serious adverse effects, some of which were known at the time of approval.

The current system for weighing benefit vs. harm during the regulatory process is unlikely to change. All relevant parties -- the pharmaceutical industry, the regulators, physicians and patients -- need to be alerted to possible and previously unknown adverse effects, particularly in the first years after drug approval. Suspected and confirmed problems should be reported to the FDA so action can be taken to update or strengthen label warnings or, if necessary, withdraw the drug from the market. This monitoring is essential through the life cycle of a medication.

Key messages

✓ Assessment of benefit-harm balance by regulatory agencies is subjective when weighing potential benefits and harms.
✓ The evaluation is influenced by many factors: disease severity, alternative treatments, type and magnitude of benefits, and the likelihood of harmful effects.
✓ At the time of initial drug approval, its safety information is incomplete.