Does regulatory approval of a medication guarantee its safety?

There are four types of adverse events difficult to detect during the approval process: rare, late or unexpected events, and those that are similar to disease symptoms or complications. Detection of such adverse events requires large and/or long-term studies, which may not be conducted until well after the medication has been marketed, or which may not be conducted at all once a drug is approved by the FDA.

Why are rare adverse events difficult to detect?
The short answer is lack of numbers. When a new medication is approved for marketing, typically just 1,000 to 5,000 patients are exposed to it. As a result, if a medication causes only one serious adverse event for every 5,000 to 10,000 patients being treated, there is a good chance that no such drug-induced event will occur in pre-approval trials prior to marketing the drug. The risk of one in 5,000 patients treated for a year may not sound alarming. If, however, 1 million Americans are treated with the medication, one would expect 200 such events per year, or 2,000 over 10 years.

Rare adverse effects occurring at a rate of one in 1,000 are seldom detected in pre-approval clinical trials. If the true risk of the adverse event is one in 1,000, about 3,000 patients are actually required to detect a single case with high probability (95 percent). A total of 6,500 patients are needed to detect three cases! These numbers illustrate why clinical trials testing investigational medications (i.e., not yet FDA-approved) cannot be relied upon to detect rare adverse events.

Why are late adverse events difficult to detect?
Adverse events may occur at any time after ingesting the first dose of a medication. Many adverse symptoms develop early, but if a medication adversely influences a disease process, it may take years before the event manifests itself. If the medication is carcinogenic, a resultant cancer diagnosis may not be made for at least several years following treatment. If it adversely affects the gradual age-related increase in hardening of the arteries, the complications of heart attacks and strokes may not occur until many years later. Medications leading to decreased bone density may be linked to increased bone
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fractures only after numerous patients undergo treatment for a number of years. Because only a few hundred patients may have been treated for one year or longer, most pre-approval clinical trials are not suitable for detection of late adverse events.

**Why are unexpected adverse events difficult to detect?**

It is difficult to find something that no one is looking for. The critical information may not even be collected during the pre-approval trials. It may take years before there is even a suspicion that an adverse event is drug-induced. There are many examples of adverse events detected after a decade or longer. Phenylpropanolamine, an ingredient in cough medicines, was found to cause brain hemorrhage after decades on the market. Another example was the antiarrhythmic terfenadine (Seldane), now off the market, which interacted with an antibiotic (erythromycin), as well as grapefruit juice, to cause fatal heart rhythm disturbances.

Fen-phen, the combination of fenfluramine and phentermine, became popular for the treatment of obesity. It was later shown to cause heart valve abnormalities. Detection of these valve problems requires a special diagnostic procedure called echocardiography. If there was no anticipation of heart valve abnormalities, there was no good reason to perform costly echocardiograms in the fen-phen trials. In most cases, the real answer can only come after asking the right question and looking for the answer. The typical clinical trial is not a good source for detecting unexpected adverse events.

**Why are some adverse events difficult to attribute to medications?**

Some of the types of events induced by medications may also occur in patients as part of a disease’s natural history and be unrelated to treatment. In these situations, it is difficult to attribute the event to a medication. Patients with serious cardiac arrhythmias (rhythm disturbances) are at a high risk of dying suddenly. In a classic trial of several antiarrhythmic drugs commonly used to treat serious cardiac arrhythmias, the expectation was that these medications would reduce the high risk of sudden death. Surprisingly, the reverse happened – these antiarrhythmic agents increased the risk of sudden death, a risk already known to be caused by the condition itself.

**Does the government regulatory approval process guarantee medication safety?**

For the reasons stated above, regulatory approval is no guarantee that all safety problems linked to a new medication are known at the time of FDA approval. Experience shows that approximately half of all medications eventually cause serious harm not recognized at the time of regulatory approval. Careful
post-market monitoring of safety is essential for all new medications. This monitoring should continue as long as a medication is on the market.

Key messages

✓ Regulatory approval of a new medication is no guarantee that all serious safety problems are known.
✓ Rare, late and unexpected adverse events, as well as those commonly caused by the underlying disease, are often not detected until years after approval.
✓ Post-marketing safety monitoring is essential for all medications.