

Key Messages on Product Safety to Consumers Ensuring the Highest Safety Standards for Medicines EFPIA Risk Communication Action Group

Introduction

Medicines play an important role in public health.

The aim of pharmaceutical research and development is to relieve patients from suffering, to improve their quality of life or to prevent them from premature death. Besides the effort to establish the evidence that a medicine provides the benefits expected by patients, the main focus of clinical research is to identify and quantify undesirable effects.

Even though medicines are only approved to be placed on the market if their benefits for patients have been demonstrated, they are unavoidably associated with possible side effects, which may sometimes not be detected before the medicine is widely used. Therefore, also after the approval of a medicine by health authorities, the pharmaceutical industry actively continues to collect and evaluate all available information on possible previously unknown risks to patients and to communicate any such new information to health professionals and consumers. These activities, which involve extensive reporting to authorities is generally known as pharmacovigilance.

Just as not everyone who gets into a car will have an accident, not everyone who takes a medicine will experience side effects. In general, many patients taking a medicine will not suffer any side effects, or will suffer only mild side effects; some may suffer severe side effects. Like car accidents, though, severe side effects are rare in comparison to the number of people exposed - still the possibility of suffering a severe side effect is real. But the likelihood of side effects and their severity from taking a medicine must be weighed against the consequences of a disease or condition for which a medicine is designed to treat. That is why patients, in consultation with their physician, must weigh their personal risk of an untreated disease against the chance of suffering a rare but still possible side effect. As in all human activities and endeavors, taking medicines requires making a tradeoff between benefits and risks.

In an ideal world, a medicine would target only the disease or disorder it's meant to treat and never do anything else; the so called 'magic bullet'. Unfortunately, despite the best efforts of scientists, such a medicine does not yet exist.

All medicines are associated with the risks of possible side effects. New knowledge about those risks is revealed throughout the useful life of a medicine, frequently coming to light only after the medicine is widely used.

1. What does industry do to ensure safe and effective medicines are made available to those who need them?

The pharmaceutical industry is fully committed to its responsibility to protect patient health: monitoring safety occurs before and after a medicine is approved.

- Dedicated professional people in pharmaceutical companies including physicians, scientists and pharmacists are committed to protecting patients by ensuring any new risks associated with medicines are detected as soon as possible and that appropriate action is taken. The increasing use of new scientific methods that anticipate and manage possible risks with medicines, including use of special safety studies before and after a medicine is approved, make the use of medicines safer.⁸ These techniques are known as pharmacovigilance and risk management.
- Risk management is used to ensure that the benefit-risk balance for a medicine remains positive. This can help to reduce delays in approval of needed new treatments and help maintain access to medicines by persons who need them.
- Advances in technology and data accessibility foster the application of the scientific tools of epidemiology and pharmacoepidemiology that facilitate and improve safety monitoring throughout the medicine's useful life.

- Providing transparent and objective safety information, which is easily understood and useful to the patient, is an ongoing commitment by pharmaceutical companies. Both independently and collectively, pharmaceutical companies collaborate with doctors, regulatory authorities and consumers to develop better communication tools to enhance the safe use of medicines. For example, development of easily understandable patient leaflets on safety information, discussion of benefit-risk profiles of medicines on company websites, and involvement of consumer groups to improve their understanding of the benefits and risks of medicines are some of the industry's initiatives to enhance transparency and the quality of safety communication to consumers and patients. Recently, many companies have taken the initiative to describe the results of their clinical trials (positive and negative information) on their corporate websites.
- In summary, through comprehensive "pharmacovigilance" and "risk management," pharmaceutical companies continue to monitor, collect, analyze, and report all safety information associated with the use of its medicines as well as communicate the side effects and safety profile to everybody concerned. These activities continue throughout the entire time that a medicine is being developed and after it has been approved for use in patients

2. *Why are all medicines not safe for everyone? How are risks communicated?*

No medicine – nor any human activity - can ever be described as completely without risk. Safety is not the absence of risk. Regulatory authorities define a medicine as safe when its benefits outweigh risk.

- All medicines have benefits for patient health as well as possible risks. An analysis of the benefit-risk balance takes place in the context of the doctor-patient relationship to determine whether an individual patient may benefit from the use of a medicine.
- When discussing medicine safety it is important to differentiate safety from risk. In life, there is no such thing as "zero risk": nothing is without some risk, including taking medicines. For example, even staying in bed is associated with a risk of acquiring bedsores. Certainly no medicine is completely safe.
- The safety of a medicine is described in terms of its benefit-risk balance. What is considered an acceptable level of risk forms the basis for decisions by regulatory authorities who approve medicines for use, doctors who prescribe medicines and patients who take them. This will often depend on the type of disease being treated e.g. in treating life threatening diseases such as cancer, AIDS and serious infections, side effects of the medicines used are often unpleasant but are accepted because of the desired beneficial effects of the medicine.
- The safety of a medicine also can depend on the ability of the individual to tolerate one medicine versus another similar medicine. Because no two individuals are alike, it is important that, when deciding whether to use a medicine, the benefit-risk balance be assessed for each individual. Biodiversity of humans and each individual's response to medicines ensures that the more medicines we have available to treat a disease the more safely we can treat it.
- In assessing the inherent risk of taking a medicine, it is also important to consider the risks of alternative therapy or no therapy. For example, there has been a significant reduction in AIDS related death due to the availability of new medicines introduced to treat this life threatening condition. Almost 80% (i.e. 80 out of a 100 patients) of a group of AIDS patients starting treatment for this condition were alive two years later despite being unlikely to survive without treatment (i.e. they had a poor prognosis). But 80% of patients with the same poor prognosis and without access to the AIDS medicines were dead after two years. The prognosis is even better if treatment begins earlier. Whilst some patients treated with the AIDS medicines may have experienced side effects, it is clear that treatment significantly prolonged patients' lives⁴. To reiterate the importance of the benefit-risk balance: the risks of taking a medicine must be viewed in the context of the consequences of not taking the medicine.

3. *How do new medicines become available?*

The process for approving medicines and assessing their safety is highly regulated. Regulators and pharmaceutical companies work together for many years to study the safety of medicines and ensure their safe use.

- Regulatory authorities in your country approve all medicines for use.
- Medicines research and development is a complex and strictly controlled process, which continues for many years. Pharmaceutical products are tested extensively in animal and other non-human (pre-clinical) studies before being given to humans in clinical trials. Experimental clinical (i.e., human) trials are then performed in a highly rigorous and regulated manner. This rigorous process of pre-clinical and clinical testing demonstrates efficacy (i.e. that the medicine works) as well as safety and eliminates many medicines with unacceptable benefit-risk profiles. After many years of research, there is a considerable amount of information that is provided to regulatory authorities, often together with data from other countries in which the medicine is already available for public use.
- Research, for both efficacy and safety, may take up to 10-15 years and involve many hundreds or thousands of patients. Safety information will be collected on all patients taking part in a clinical trial to test the medicine before it is approved. Pharmaceutical companies take on average 12 to 15 years and invest about a billion euros to develop each new drug. In biopharmaceuticals, while the number of new medicines has been increasing steadily, clinical development times have doubled since 1982 to an average of 68 months (well over 5 years).^{2,1,8}
- After several years of thorough research all the efficacy and safety information collected is used to assess whether or not the safety of a medicine is acceptable to allow approval by a regulatory authority. Regulatory authorities then review the available data and decide if an acceptable benefit-risk profile has been demonstrated within the disease or diseases that the medicine is to be used. This evaluation is done to the strictest of standards and a medicine will only be approved if the benefits of the medicine for a particular disease outweigh its risks.
- If these conditions are met, information about appropriate use of the medicine is developed in conjunction with the pharmaceutical company to provide doctors, pharmacists and other healthcare practitioners as well as patients with a summary of important benefit-risk data, including dosing information, indications for use, and other information.
- During the process of drug development companies regularly inform both doctors taking part in the clinical trials and regulatory authorities of any new emerging safety information.

4. Once approved by regulatory authorities, why do some medicines have greater risks than benefits for certain patients?

Despite rigorous research in thousands of patients, not all side effects of medicines can be predicted at the time of regulatory approval. Waiting to discover every side effect of each medicine before it is approved for use would mean that patients are deprived of valuable new medicines and many would suffer needlessly.

- In most cases, when a new medicine is approved, almost everything known about its safety in humans at that time is typically based on the responses of several thousand people who took it during clinical trials. While medicines are studied extensively, it does not mean that all risks with any medicine are known at the time of approval.
- Despite the scientific strengths of the pre-marketing development and approval processes, it cannot be assured that all risks are known. Instead, it is likely that unknown risks come to light only after medicine approval. Nevertheless, based on the information available at the time of approval, the benefits of a pharmaceutical product, when used as directed, are believed to outweigh the known risks in populations like those studied prior to approval. Clinical trials, combined with data from pre-clinical studies, are the accepted approach to demonstrating efficacy and safety prior to marketing. However, even though clinical trials are the best tools available to identify the benefits and risks of a medicine, it is important to note that they have limitations; for example, for ethical reasons, children or pregnant women, or very sick patients, may not be included in clinical trials.
- In addition there are important safety questions that cannot be answered by conventional clinical trials¹²:
 - Many common side effects can be identified on the basis of the numbers of patients studied in clinical trials before a medicine is approved, but to detect rare side effects it is necessary to study the use of the medicine in much larger patient populations⁶.
 - To detect a side effect which occurs rarely in 1 of 10,000 treated patients, one would need a clinical trial of at least 30,000 patients. Conducting clinical trials of

this size is not usually feasible before approval¹¹ and it would delay access of important new medicines to patients who need them.

- Industry recognizes that it is most important to have strong monitoring methods in place to ensure that new risks are identified and communicated as quickly as possible.

5. *How do the risks of taking medicines compare with other activities in life?*

Side effects of medicines can be placed in the context of the risks that are taken in every day life; while some less frequent events are severe or fatal, the majority of medicine side effects that occur are transient and not serious.

- Patients should discuss benefits and possible side effects with their physicians^{5, 11}.
- Many, but not all, side effects of medicines may be anticipated and therefore managed by taking the appropriate dose and by identifying patients who may be at higher risk.
- Side effects can occur with any medicine. The risk of incurring them, however, often can be less than risks that are accepted in every day life, like driving in a car or taking an airplane flight.
- What is the chance that a side effect will occur? ⁵

Perhaps surprisingly, it is not always possible to answer this question accurately. If a side effect is common or fairly common, then good information about its frequency is likely to be available. However, a rare side effect may have only affected a few users and it may be quite uncertain how often it really occurs. A guide to what is meant by common and rare in this context is given in the following table:

Description	Chance of being affected	Equivalent to
Very common	more than 1 in 10	One person in a family
Common	between 1 in 100 and 1 in 10	One person in a street
Uncommon	between 1 in 1,000 and 1 in 100	One person in a village
Rare	between 1 in 10,000 and 1 in 1,000	One person in a small town
Very rare	less than 1 in 10,000	One person in a large town

- Placing risks into context allows informed decision making by both physicians and patients. In other words, those who need medicines must consider the risks of not taking the medicines.
- Decision-making about the appropriate use of medicines must be a partnership between doctors and their patients⁵.

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