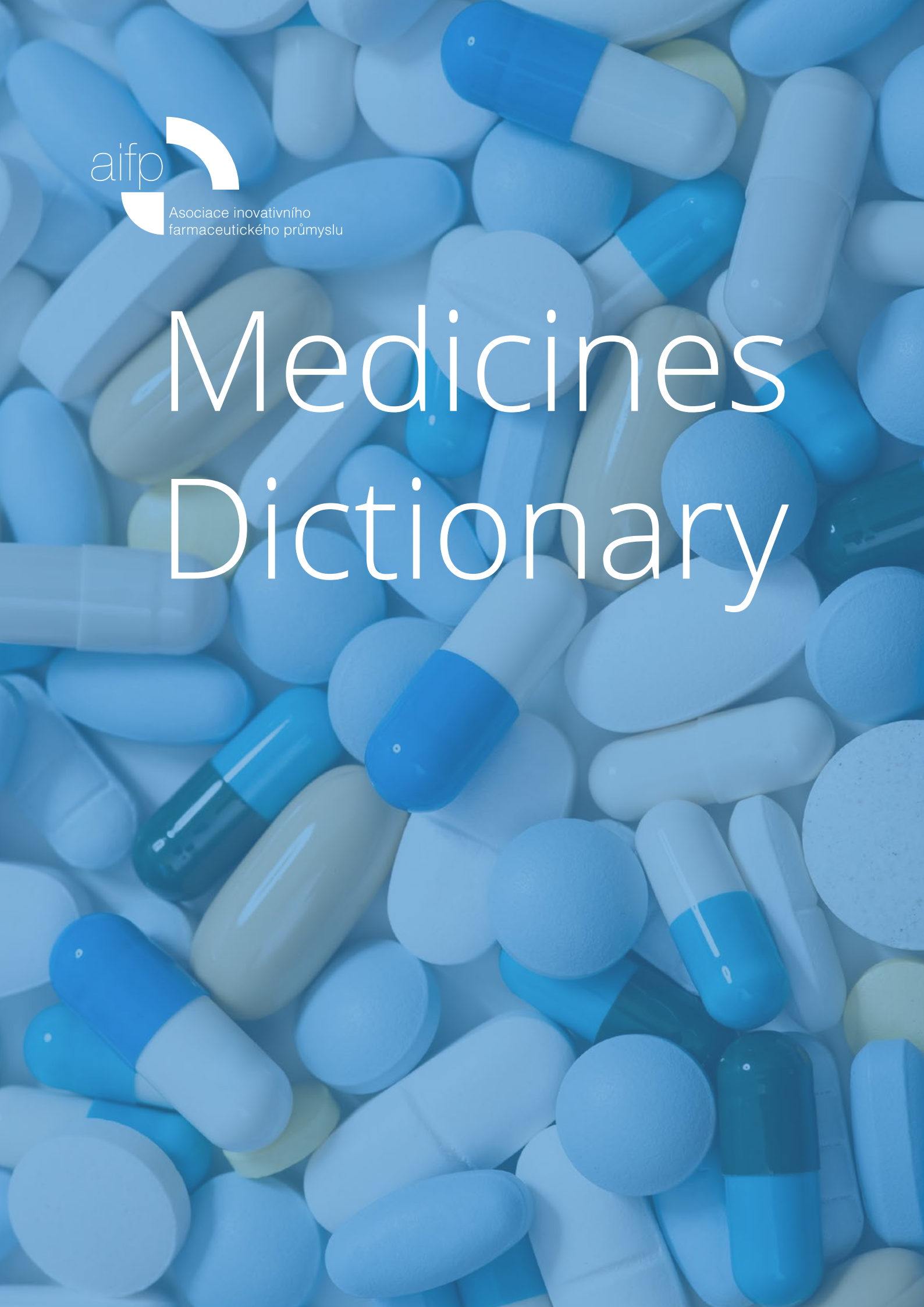

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Asociace inovativního farmaceutického průmyslu

Medicines Dictionary

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Foreword

Mgr. et Mgr. Adam Vojtěch, MHA, Minister of Health

Health is one of the fundamental premises for a happy and creative life of every person. Therefore, one of the issues that people pay the most attention to is what healthcare in the CR – for us and our family members – shall look like. Healthcare belongs among the most monitored public matters. The debate about how to set up different parameters of the healthcare system practically never stops.

We all certainly wish for high-quality healthcare, enough personnel in healthcare facilities and healthcare evenly available around the entire Czech Republic. At the same time, the system must be stable and sustainable in the long run in terms of revenues and expenses.

The drug policy represents one of the key areas of healthcare. The state effectively regulates healthcare in a way so that drugs would always be affordable and available everywhere. The state also performs a thorough drug control to make sure that the drugs used in healthcare are not only safe but also of high quality. And it is this activity that day in, day out helps to improve our healthcare and to provide the best possible services to patients.

In order to achieve good results, we must have full knowledge of the individual important parameters of the healthcare system and used terms. This is why I would like to recommend this glossary to everybody who wants to understand one of the main pillars of our healthcare – the drug policy.

Mgr. Jakub Dvořáček, MHA, AIFP Executive Director

The Medicines Policy is a highly regulated environment and not always it is easy to understand. One of the topical social topics tackles the issue of how to provide the best possible treatment for all patients while the budgetary expenditure is sustainable. Therefore, this brochure is dedicated to everybody who is interested in the healthcare system and is looking for relevant information. This manual will certainly facilitate your understanding of matters concerning medicines.

The Association of Innovative Pharmaceutical Industry has long been striving for the education of patients as well as the general public. Therefore, we support initiatives focused on improving healthcare and exchanging experience among professionals. We believe that this *Medicines Dictionary* will be useful to the general public.

Basic Terminology

Medicinal Product

The Act on Pharmaceuticals defines a medicinal product as **a substance or a combination of substances with curative or preventive characteristics**, which may be used to recover, modify or affect the physiological functions by way of a pharmacological, immunological or metabolic effect, or to determine the diagnosis.

It does not matter whether we use the term medicinal product, drug or medicine. They all mean the same.

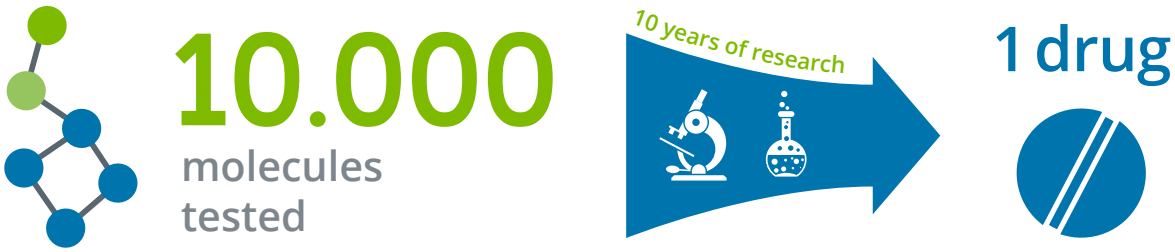
The medicinal product **does not contain only the active substance**. In addition, it also contains excipients, bonding substances, colorants etc., which, for instance, help to keep the tablet together in order to ensure the active substance is released at the right moment and at the right place, or to make sure the color and taste are as least unpleasant as possible for the patient. These substances may have other functions but in principle they do not influence the effect of the medicinal product.

Original and Generic Medicinal Products

Original Medicinal Product

An original medicinal product (sometimes also called the **"reference medicinal product"**) means the first medicine with a new active substance not contained in any other medicinal preparation so far, which has obtained marketing authorization.

The active substance as well as the manufacturing process (know-how), if relevant, is patent protected. The original medicinal product that has successfully received marketing authorization is then granted a protection period, during which no one is permitted to market copies of such a product. It gives the manufacturer the opportunity to recover the cost invested in the development through selling the new marketed drug.

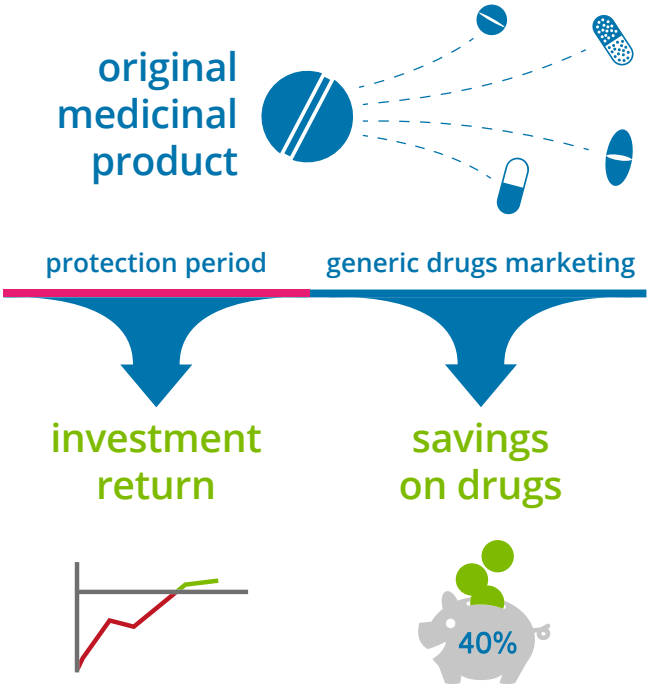


Do you know *that many years of research, development and testing preceded the marketing authorization of an original medicine? At the beginning there were about **10,000 substances** that were subject to a detailed study in order to check if they have any curative potential at all. As the years of scientific research, analyzing and testing went by, many of them proved not to be sufficiently effective, with too many severe adverse effects or otherwise not suitable to advance to the human testing stage (so called clinical trial). Statistics say that out of **10,000 molecules, at the end just one may be really successful** to the point to pass all these tests necessary to be marketed as a new medicinal product. All that after about 10 years of painstaking work by teams of scientists and doctors. Therefore, it should not surprise us that the entire development, funded mostly by private companies, often costs more than a billion or two billion dollars.*

Generic Medicinal Product (Generic Drug)

The term generic drug is used to denote a **legal copy of the original medicinal product**. Upon the expiration of the protection period for which only the original drug has been marketed, generic drugs enter the market very fast. These drugs contain the **same active substance** in the same dosage form (e.g. tablets or injections). Generic drugs may contain different excipients. The marketing of a generic drug is not preceded by any complicated research.

Nevertheless, all medicinal products, including generic drugs, have to receive marketing authorization from the respective medicines agency. However, for generic drugs it is required to submit far less extensive documentation than for an original medicinal product. In principle, the most important is to prove that they have the same characteristics as the original, thus the same effect, including the speed of its onset and length of this effect, etc.



Do you know *that a generic medicinal product is launched into the market at a price that is on average by 20 to 40% lower than the price of the original product?* ***Therefore, generic drugs produce savings for patients as well as for health insurance companies*** *that contribute to the payments for medicines to their insured.*

Examples

The active substance, **acetylsalicylic acid**, is one of the oldest substances in modern history used in medicine. We all are well familiar with it. We use it when we have a fever and pains, e.g. for flu. For more than 100 years, a still popular original medicinal product produced by a German pharmaceutical company containing this active substance has been in the market. However, over time, hundreds of generic copies have entered the market. These copies are just as popular with patients in the Czech Republic.

The same applies to the active substance called **ibuprofen**, which was discovered more than 50 years ago and it is most frequently used to suppress pain. It also has an anti-inflammatory effect. In addition to the original product, there is a good deal of popular generic drugs.

Classification of Products based on a Dispensing Method

Medicines on Prescription

A medical prescription means either prescription or request form. However, most of us are familiar only with the prescription that we receive from our doctor to take to the pharmacy. The prescription is given to medicines that, in order to determine the diagnosis or specifying the use, require a doctor's supervision. There may be all sorts of reasons for that. The most frequent and simple reason is to allow the doctor, after the diagnosis has been determined, to monitor whether the treatment process is right, to see whether there are any adverse or unexpected effects or to observe whether the patient takes the medicine as required.

The decision about whether the medicine is available to patients only when prescribed by a doctor is made by each country's medicines agency (in the Czech Republic, it is the State Institute for Drug Control [Státní ústav pro kontrolu léčiv, SÚKL]). These medicines agencies primarily consider

scientific documentation and data about the safety and efficacy of the respective medicine.

If there are not sufficient safety data available, they will always prefer the option with prescription in order to be able to monitor the patient. Nevertheless, if it is the patient who will pay for the medicinal product, then it does not matter which doctor prescribes the medicine. Any doctor, for instance also a general practitioner, may prescribe the patient any medicine requiring prescription. Thus, they take the responsibility. However, it is a different story if the medicine is partially paid for by the health insurance company and the patient does not pay the full price for the medicine. We will come back to it in the following chapters.

Starting 1 January 2018, doctors must issue prescriptions in electronic form only. It is the so-called e-prescription. Only in some exceptional cases, especially if there is no access to the centralized e-prescription storage (e.g. the Internet is not working), a doctor may issue a classical "paper" prescription. The year 2018 is a transitional year without sanctions for issuing a paper prescription instead of an electronic one. It is prohibited to issue e-prescriptions for medicines containing narcotic or psychotropic substances.

Once a doctor prescribes a medicine in a device connected to the Internet, the central e-prescription storage will send him an identification code of the e-prescription. The doctor can send this identification code to the patient by e-mail or SMS, through an application in his/her mobile phone or tablet or hand it over on paper.

When dispensing the medicine, the pharmacist will upload the identification code provided by the patient and the central e-prescription storage will give the pharmacist information about the medicine, its strength and package size, the number of prescribed packaging and dosage. The pharmacist will inform the central e-prescription storage about the dispensing of the medicine.

Shortly after the launch of e-prescriptions, other functions related to e-prescriptions should be put into operation, in particular the patient's medicine record that will allow the treating doctor, the dispensing pharmacist and the patient himself/herself to check the safety of treatment in particular with respect to taking medicines that contain the same active substance or adversely interact with each other.

There is also a special regime with "restricted prescription." This type is intended for highly sensitive cases when it is advisable that the medicine is prescribed only by specialists who have experience with the disease, for which the medicine holds marketing authorization.

Medicines dispensed based on the restricted prescription may pose an increased risk for the patient if used incorrectly or abused. Therefore, the supervision of the respective specialist is required or the medicine has to be administered by the respective specialist in a hospital. Currently, there are several medicines of this type. For instance, they include the so-called abortion pill (several products with this effect holding marketing authorization) and medical cannabis.

Over-the-counter Medicines

If the medicine has been marketed for several years and has met other conditions, it may be reclassified as available without prescription. It is always necessary that the assessment by clinical practice is positive in terms of the effect and primarily the safety of this medicine. The medicine must hold a marketing authorization **for such diseases** that patients are able to diagnose themselves and that **do not have to be treated under a regular doctor's supervision**. As soon as the medicine is classified as over-the-counter, it is suitable for self-treatment and the appropriate level of expert guidance is guaranteed by a pharmacist. The patient should also read the information given in the package leaflet inserted in every box. A consultation with a doctor is thus not required. This category includes the vast majority of medicines for non-serious diseases, such as **flu** or **cold**.

Glossary

Rx (sometimes also "Rp") – medicinal product available solely on prescription.

OTC ("over-the-counter") – medicine that is available without prescription.

However, within this category there is a special regime of **„restricted medicinal products available without prescription"**. These include medicinal products requiring consultation with a pharmacist upon dispensing of a limited amount at one time. Products containing pseudoephedrine, such as Modafen, Paralen Plus, etc. are a typical example. Unfortunately, these products are abused by drug addicts and thus the purchased amount is limited to the amount sufficient to about a one-week treatment.

Do you know *that SÚKL runs the so-called Database of Pharmaceuticals, where you can find the most current and complete information about medicinal products? The database is accessible to the public and contains information about all medicinal products holding a marketing authorization in the Czech Republic. The information is updated daily.*

Before and After Entering the Market

Clinical Trial

The research phase and positive results of tests with animals or cell cultures is followed by testing the active substance on patients. A **clinical trial** follows a predefined approved plan of several stages, from healthy individuals to ill patients for whom the medicine is developed. The objective of a clinical trial is to demonstrate the safety and tolerability of the medicine and verify its curative effects and behavior in human organisms. Its aim is also to find out any adverse effects.

In **phase I** the active substance is tested on healthy volunteers to determine whether it is safe for a human organism and the doses tolerated by the organism. Low doses are administered at first. Gradually they are increased to find the maximum tolerable dose. No research on healthy volunteers is done if administering the substance to a healthy person is highly inappropriate (e.g. cytostatics).

Phase II already tests the drug on patients. With a small number of patients, the curative effects are demonstrated and only if a good efficiency is shown that prevails the risk of adverse effects, it is possible to proceed with the next phase.

In **phase III** the drug efficacy and other data in terms of dosing and safety are tested on hundreds to thousands of patients. Based on the results of this phase, an application for a marketing authorization is submitted.

Phase IV is conducted after the marketing authorization has been received. This phase focuses on monitoring adverse effects of long-term use in patients and data about possible interactions with other medicines.

Among others, the clinical trial results in defining the use of this medicine (specific indication and a patient population) and setting the most favorable dosing for the patient with the minimum risk of adverse effects.

Proposals for clinical trials to be conducted in the Czech Republic are independently of each other reviewed by the State Institute for Drug Control and an ethics committee. In order to initiate the study, it is necessary to obtain the approval by the State Institute for Drug Control as well as the ethics committee. The review is primarily focused on assessing the patient risk and benefit ratio, scientific rationale for conducting the respective clinical trial as well as study design in order to ensure it generates objective and quality data and information. The ethics committees are predominantly focused on ensuring the protection and safeguarding the rights of enrolled patients or healthy volunteers and they review the ethical aspects of conducting the given study.

382 clinical trials approved in 2015

mostly trying medicines for diseases

- oncological
- cardiovascular
- neurological

Do you know *that the most frequently conducted clinical trials in the Czech Republic include phase III international (involving several countries) and multicenter (involving several hospitals) trials? In recent years the clinical trials mostly focused on oncological, cardiovascular and neurological diseases. In 2015, 382 clinical trials were approved in the Czech Republic, and at the moment more than one thousand clinical trials in various phases are being conducted here. In 2015, pharmaceutical companies paid more than 1.75 billion CZK for clinical trials.*

Each clinical trial engages three important participants – a **sponsor** that is a company or institution (most frequently a pharmaceutical company developing the product) and is responsible for initiating and managing as well as financing the trial, an **investigator** who is a doctor responsible for conducting the clinical trial and a **trial subject** who is a person on whom the active substance is tested.

Either a healthy volunteer or a patient is the trial subject. **Healthy volunteers** are used for pharmacokinetic studies (simply said to test what is happening with a medicine in a body), bioequivalence studies with generic drugs and vaccine studies. When a new medicine is tested, it is usually necessary to conduct dozens of studies in **hundreds of patients** (this rule, however, cannot be observed if it concerns a disease with low incidence in the population; in such a case the medicine may receive a marketing authorization based on data collected from a lower number of patients.

Each patient and each healthy volunteer signs an **informed consent**, confirming their willingness to take part in the clinical trial after having been informed about all aspects. The participation in a clinical trial is not just an opportunity to use a newly developed medicine that is not available otherwise but also the necessity to accept responsibility and duties related to the participation in a clinical trial. The consent to take part in a clinical trial may be withdrawn at any time. It is important to realize that a clinical trial is conducted while the medicine is being developed, which means there is a lack of information about its effects. It is not unusual that during the study it is determined that the treatment benefit is below expectations and as a result the clinical trial is stopped.

In most cases, clinical trials of new medicines are conducted as randomized and double-blind. Randomization means random assignment of trial subjects to groups; either to a group receiving the tested medicine, or to a control group. The control group may receive either a placebo (inactive substance modified to look like the same as the medicine) or a medicine that is compared to the tested medicine. This is done if a placebo administration instead of the active substance could harm the patient. The purpose of randomization is to mitigate bias and to increase the validity of the collected data. The procedure of double-blinding is also used to collect objective data; neither the study doctor, nor the trial subject, knows in which group they were assigned to.

The doctors are motivated to take part in a clinical trial as they have the opportunity to get a new medicine for their patients free of charge and to familiarize themselves with new treatment options for the respective disease; the motivation in patients lies in the opportunity to be treated with the most modern medicines several years before they become a part of regular medical practice, often at times when the existing medication does not offer sufficient efficacy.

In 2015, a total of 6,812 new patients were included in clinical trials. Overall, more than 26,000 patients participate in clinical trials. It has been estimated that the patients participating in clinical trials help to save up to 625 million CZK.

Marketing Authorization

If the new medication successfully passes the phase III clinical trials, all the testing results may be submitted for a marketing authorization by the medicines authority. The main objective of the marketing authorization is to minimize foreseeable risks related to introducing the medicine into the market. The **quality, efficacy and safety** of the medicine are always reviewed, along with a positive ratio of risks and benefits. Although the authorization and post-authorization processes continuously develop as a result of scientific progress, the rules for approving medicines are uniform across all European countries. The authorization procedure may be implemented in several different ways.

Centralized Authorization

The assessment is conducted by the European Medicines Agency (**EMA**) and the authorization granted by the European Commission is valid in **all EU Member States**, Norway and Iceland. This procedure is mandatory for biotechnology manufactured products, new active substances for AIDS, diabetes, oncological, neurodegenerative, autoimmune and viral disease indications and for rare disease treatment products concerning only a very limited number of patients.

Other types of authorization are processed by the medicines authority of the respective country. In the Czech Republic it is the State Institute for Drug Control (**SÚKL**).

Mutual Recognition Procedure (MRP) Authorization

The mutual recognition procedure is designed for the authorization of a medicine that has already received the authorization in one member state. This state is called the "reference state". The reference state prepares an assessment report that includes information submitted post authorization. The authorities in other member states where the medicine seeks authorization review the assessment report and decide whether or not they recognize the authorization.

Decentralized Procedure (DCP) Authorization

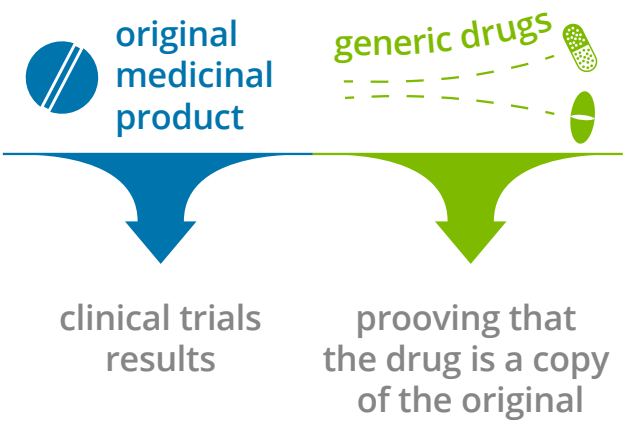
The decentralized authorization is intended for a medicine that has not received the authorization in any country and is supposed to receive authorization for several countries. The authorization applicant chooses the "reference state" that will prepare the assessment report with a positive or negative authorization opinion and the other countries assess the report and decide whether or not they agree with it.

National authorization is only possible for a medicine that has not received authorization in the EU. It is valid for only one country (e.g. Czech Republic). This type of authorization is applied less and less.

As already mentioned above, the requirements for medicine authorization are the same across all EU member states. The principal requirements include evidence of the medicine nature, the individual manufacturing steps, quality control measures imposed on the raw materials as well as final product; it is necessary to prove that the medicine meets stability testing criteria and that the manufacturing follows standards guaranteeing its quality (i.e. good manufacturing practices). Nevertheless, the requirements for presented data and authorization documentation differ, depending on the type of medicine:

Original medicine authorization – to be approved it is necessary to submit results of tests and clinical trials conducted over several years, objective of which was to collect enough information about the use of the medicine in order to assess the risk / benefit ratio.

Generic medicine authorization – to be approved it is not required to submit results of pharmacological and toxicological tests or clinical studies. Instead evidence is required proving that the



generic medicine is a “copy” of the original; a so-called bioequivalence study demonstrates that the same amount of the active substance gets into the blood circulation as for the original medicine and that excretion from the body is also similar, which proves that the respective medicine affects the body in the same way as the original.

In addition to the most common types of authorization, there are authorization procedures for **traditional herbal preparations, homeopathic remedies and long-term used medicines with well-established curative uses** with specific requirements modified for these categories.

Biologics

Biologics are the most modern and the fastest developing group of medicines. Contrary to classic medicines made based on a chemical synthesis, biologics are made from living organisms (cells), into which specific genetic information stored in DNA is inserted. The natural processes in the host cell create diversity thanks to the spatial shape of molecules. The structure of biologics cannot be exactly defined. They are big molecules of protein or polypeptides that are further modified during the extraction, purification, drug form creation and storing of biologics.

After the patent protection of original biologics expires, it is possible to market legal copies of these medicines, so-called biosimilars. Biosimilars are biological medicinal products that are only similar to original biologics. They can never be totally identical since the biological origin and the production method are always unique.

Biosimilars should not be referred to as biogenerics; they are naturally diverse because they are a product of living organisms and therefore, it is impossible to exactly define their structure.

Because of their effect on the immune system, they cannot be replaced with an original biologic without a doctor’s evaluation and without medical reasons for such replacement. Contrary to classic generics, the efficacy and safety of biosimilars must be documented by pre-clinical and clinical trials comparing biosimilars with original biologics and assessed in authorization proceedings.

The main advantage of biologics is their ability to target a specific place in the body (e.g. a cancer cell). Thanks to this, it is possible to target treatment, to achieve better therapeutic effects and to reduce the probability of side effects. In comparison to classic treatment, biological treatment is more expensive because the development of biologics is costly.

The authorization process also defines the dispensing regime (whether the medicine requires a prescription or whether it may be sold as OTC) and generates documents providing the public with information about the medicinal product. **The Summary of Product Characteristics** (SPC) is intended for professionals (doctors and pharmacists). SPC is a rather extensive document that includes all essential information related to the use of the medicine, its dosing, indications, interactions, adverse effects, pharmacological and pharmacokinetic characteristics as well as the information about the marketing authorization holder. Patients are provided with the so-called

patient information leaflet (PIL), which clearly gives information about the medicine important for the patient. The patient information leaflet is inserted in every medicine package and patients are advised to read it carefully prior to the first use of the medicine (and once again, if needed).

Upon completion of the authorization process, an authorization decision is issued, based on which the holder (usually manufacturer) may **launch the respective medicine into the market**. The medicine is continuously monitored and the so called post-authorization monitoring observes the adverse effects, interactions, clarifies the storage conditions, adds new indications, etc., in order to fulfil the primary purpose, i.e. that the medicines legally available in the Czech Republic have adequate quality, efficacy and safety.

The authorized medicine may thus be freely marketed but with the subsequent procedures patients would have to pay themselves for the medicinal products on prescription as well as for OTCs. With some medicines that cost a few tens or hundreds of crowns, it would not be a problem. However, for the vast majority this would be a real problem. Not only with medicines that cost thousands of crowns or more but even easily with medicines for several hundreds if they are used for chronic diseases and it is expected that the patient will have to use them for many months or years.

If that is the case, there is a possibility that the patient may be reimbursed for the medicine by the health insurance company. Nevertheless, it is not at all easy to arrange it. Not every medicine may be covered by health insurance, not every patient qualifies for the reimbursement and not all doctors may prescribe such a medicine. But look at it one by one...

Which medicines may receive a contribution by a health insurance company?

The laws stipulate that the **medicinal products** that **do not require a prescription** (the OTCs), **may not be paid for from public health insurance**. There are only a few exceptions. Therefore, patients do not receive any contribution for OTCs from health insurance companies – the patients themselves have to pay for them. Such medicines may be launched into the market immediately after their authorization. The price is independently set by the manufacturer. Likewise, distributors and pharmacies selling these medicines may charge any commercial mark-up. **The price is only subject to market competition**.

The medicines requiring a prescription are not automatically paid by the insurance companies. Even in this category there are cases where the law does not permit the health insurance to pay for these.

The reason is that the **health insurance may not be used to pay**, for instance, for **supportive** and **supplementary medicinal products**. The law, however, imposes a number of restrictions. Pursuant to the law, health insurance companies do not contribute, for instance, to **contraception**, **potency enhancers**, and others.

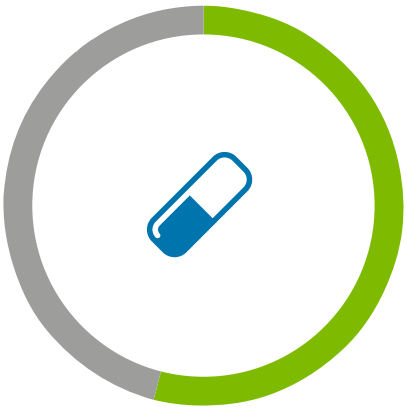
If the medicinal product is not classified in a category excluding health insurance reimbursement, the manufacturer may file an application for its partial or full reimbursement. It is the SÚKL that initiates administration proceedings to make the decision about the amount of reimbursement and its conditions.

Price and Reimbursement Regulation

Formally, it is currently **fully up to the manufacturer** whether they decide to apply for their medicine to be fully or **partially reimbursed from public health insurance**. The manufacturer of the medicine does not have to apply for reimbursement, even if the medicine would otherwise qualify for reimbursement as per the law. They can market the medicine right after having received the authorization. However, patients would then pay the full price at the pharmacy. The final price would thus have to cover not only the price for which the manufacturer supplied the medicine into the market, but also commercial mark-ups of distributors and pharmacies. In addition, neither of these price components would be regulated. The price would be established freely.

In reality, the manufacturers are motivated to apply for the reimbursement of their medicine. Why? Because they would not be competitive otherwise. The medicines without any alternative (generic copies) would not be at risk of being replaced with other medicines by the patients, but its price would most probably be so high that they would not be able to afford them. To generate higher sales, the manufacturer tries to have the patient pay as less as possible and to transfer most of the price to the health insurance company. The situation of medicines with an alternative is even more striking. If their competitors have contracted a reimbursement from the health insurance, it is essential to make sure the new medicine is also covered by the health insurance, otherwise the patients would logically ask for the medicine that is reimbursed.

Therefore, there are many reasons why the manufacturer must submit the application for reimbursement of their medicine from public health insurance. However, there is another condition to be taken into account. If the medicine is supposed to be fully or partially covered from public health insurance, the law requires that the medicine should be subject to price regulation – at all levels – manufacturer, distributors and pharmacies. It means that no entity in the supply chain may set their own price; the price is subject to some restrictions.



Regulations and processes governing the price policy at all levels of the distribution channel (from manufacturers to distributors and pharmacies) are called the **price regulation**. Regulations and processes governing the reimbursement policy based on public health insurance, including the amounts to be reimbursed and the applicable conditions, under which the medicine will be reimbursed, are called the **reimbursement regulation**. Price and reimbursement regulations are partially blended. Both types of regulation are regulated by a joint act, they use similar mechanisms and are implemented through a similar administrative process. Nevertheless, their particulars are independent as they consequently apply to different regulated entities.

Logically, the **price regulation** applies to suppliers of medicines and regulates the procedure of limiting the prices, for which the medicine will be sold. On the other hand, the **reimbursement regulation** is far more complex. It does not apply to suppliers of medicines but it establishes a statutory right of the patient to receive reimbursed medicine if it complies with the reimbursement conditions. At the same time, its mechanisms affect a number of relationships, not only between the patient and his/her health insurance company, but also between the health insurance company and the prescribing doctor or healthcare provider, or between the health insurance company and the manufacturer of the medicine or dispensing pharmacy.

Price Regulation

The price regulation of medicines applies independently to two groups of entities – manufacturers, and distributors and pharmacies. Therefore, we talk about two components of this regulation – **price regulation imposed on the manufacturer and price regulation imposed on distributors and pharmacies** (i.e. regulation of commercial markup). Both components are based on a slightly different principle but they are linked.

Manufacturer's Price

The manufacturer's price is regulated in the form of a maximum price, which is done by SÚKL in an administrative proceeding, or in the form of notifying a maximum price, which is set by the manufacturer. Such a price is subsequently notified to SÚKL. Thus, there are two methods of regulation. The decision which one to use is up the Ministry of Health that issues a decision on price.

Prices in the Czech Republic are not fixed, there are merely limit prices, i.e. they set a limit for the manufacturer of the medicinal product. This applies both to the maximum price as well as to the notified price. The price may not be exceeded but it is possible to supply the medicinal product to the market for a lower price.

The notified price by default regulates such medicinal products that are exposed to sufficient competition within the respective group of medicinal products. A typical example is the situation when generic medicines enter the market after the protection period for the original medicine has expired. When several medicines in the same group are established on the market, it is assumed that the market is sufficiently regulated by the competition. Therefore, the Ministry of Health reclassifies such groups of medicines to be subject to a less strict form of price regulation. Sometimes this process is called **price deregulation**.

Glossary

Price (also called final price or price for end customer) – value of a medicinal product, consisting of a price requested by the manufacturer, which is the price for marketing the product, and a fee (mark-up) for the distributor and pharmacy.

Reimbursement – a portion of the price (or even full price) of the medicinal product, which is covered by the health insurance company from the principal fund of public health insurance.

Supplementary payment – difference between the price and reimbursement for the medicine, which is paid by the patient at the time the medicine is dispensed; if the health insurance company covers the full price of the medicine (reimbursement equals the price), then there is no supplementary payment.

Manufacturer's price (sometimes also called ex-factory price) – the price set by the pharmaceutical company marketing the product.

Commercial mark-up – price set by the distributor that delivers the medicine from the manufacturer to the pharmacy, and the price set by the pharmacy that dispenses the medicine to the patient.

Do you know *that approximately half of the reimbursed medicines in the Czech Republic are regulated only through the notified price method?*

Manufacturer's maximum price

The manufacturer's maximum price is set by SÚKL in administrative proceedings pursuant to the Act on Public Health Insurance. The price of a medicinal product is usually set based on the prices of the respective medicinal product in the countries of the so-called reference basket. The reference basket, including the countries where SÚKL collects the prices of the assessed medicine, is enumerated by law. The reference basket includes all EU countries, except Bulgaria, Czech Republic, Estonia, Luxembourg, Germany, Austria, Romania, Cyprus and Malta. Out of 28 EU countries, ten are excluded. There are several reasons for excluding these countries. As far as the Czech Republic is concerned, it is logical since the maximum Czech price may not be set based on a Czech price; SÚKL would run in a circle. As far as the rest of the countries are concerned, most of the time they are excluded since they do not apply a price regulation, or the price sources (database of pharmaceuticals in the respective country) are not public or the market of the respective country is in principle incomparable to the Czech market.

The **maximum price is set as an average of the three lowest prices of the respective medicine in the countries included in the reference basket**. It means that SÚKL will look for the price of an assessed medicine in all 18 countries of the reference basket where the medicine is marketed. Then they will pick the three lowest prices, calculate their average and this number will be used to set the maximum price after launching this medicine into the Czech market.

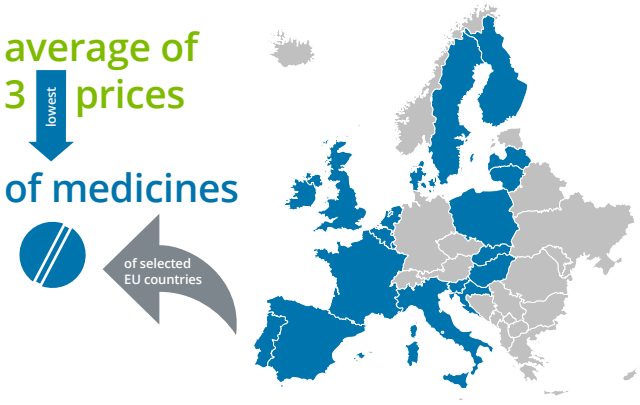
If the medicine is not available even in three countries of the reference basket, its price may be set upon a contract between the manufacturer and the health insurance company. Such a contract is by law called an **agreement on the highest price (AHP)**.

If an agreement with the health insurance companies is not reached, then there is a last option how to set the maximum price – **based on the price of the therapeutically closest comparable product**. This option does not set the maximum price based on the price of the same medicinal product (as when using the countries in the reference basket) but it searches for another medicine that would be therapeutically the closest. Therapeutically the closest medicine is logically the one containing

Glossary

Maximum manufacturer's price – regulation imposed on the manufacturer in the form of setting the maximum price that the manufacturer may not exceed when marketing the medicine to the market; it is set in administrative proceedings, is calculated based on a mechanism specifically described by law and the final decision is made by SÚKL.

Notified manufacturer's price – self-regulation of the manufacturer that may set the price independently based on the market environment; this price is then notified to SÚKL. Subsequently, the manufacturer may not market the medicine for a price higher than the notified price. The manufacturer may increase the price but first it needs to be notified to SÚKL and this may be done only once per calendar quarter.



the same active substance, with the same dosage form (tablet, capsule or solution for injection, etc.), strength (amount of active substance in one tablet or one capsule) and size of packaging (number of tablets or other units of the dosage form).

Primarily, the price is set based on the lowest price of the therapeutically closest comparable product in the Czech Republic. If there is no such product in the Czech Republic, then based on the lowest price of the therapeutically closest product in the reference basket countries.

If no medicine complying with all qualitative criteria is found, the individual criteria are dropped. Therefore, it is not necessary to look for a product with the same packaging size as well as for the product of the same strength; if such a product is not found, a different dosage form would be acceptable as well; in the end even a different, as similar as possible active substance (classified within the same anatomic therapeutic chemical category) would be acceptable.

The procedure for medicinal products that are similar is simpler and shorter. A **similar medicinal product** is e.g. a generic or biosimilar. If a generic drug wants to be included in the public health insurance system and does not request the maximum price or higher reimbursement and broader reimbursement conditions than the original drug, its maximum price and reimbursement will be set within 30 days.

This is to facilitate the inclusion of competitive medicinal products in the reimbursement system since it is competition that helps to reduce prices and reimbursements and, as a result, **health insurance and patients save money**. This is why, the law stipulates that the maximum price and reimbursement of the first similar medicinal product in the reference group is reduced, as compared to the already covered original medicinal product, by 40% in case of a generic drug and by 30% in case of a biosimilar.

Applicable legislation – Act No. 48/1997 Coll., on public health insurance, as amended.

Maximum commercial mark-up

We already know how the maximum manufacturer's price is set. However, this is not the price for which the medicine is available in the pharmacy, or the price paid by the health insurance company (or price to be split between the patient and the health insurance company). **The commercial mark-up still needs to be added to the manufacturer's price.** The commercial mark-up size is also regulated in the form of maximum price that may be added to the manufacturer's price. It is called **a maximum commercial mark-up**. The commercial mark-up is to cover the cost of business and is the **same for all entities participating in the sale of medicinal products**, i.e. distributors and pharmacies. The distributor must inform the pharmacy about which part of the joint commercial mark-up has already been used, and the pharmacy may not exceed the maximum commercial mark-up when setting the retail price for patients.

The maximum commercial mark-up is set in the price regulation issued by the Ministry of Health. The price regulation sets not only the commercial mark-up, expressed as a percentage of the manufacturer's price, but also its calculation method.

Glossary

Price regulation by the Ministry of Health – a legal regulation issued by the Ministry of Health that contains, for instance, the definition of the price regulation basic terms, the method of regulation using maximum price or material price regulation, and the setting of maximum commercial markup.

Price decision – a legal regulation issued by the Ministry of Health that contains a list of active substances, which in a specified dosage form are subject to the regulation only through the notified price.

AHP – agreement on the highest price between the health insurance company and manufacturer of the medicinal product concluded in public interest; the manufacturer may not exceed the agreed price when supplying the product to the Czech market.

If the maximum manufacturer's price is CZK 500, but the manufacturer markets the medicine for CZK 400, the percentage of the maximum commercial mark-up is not calculated on CZK 500 but on the actually charged CZK 400. The commercial mark-ups of the individual distributors are added up plus the pharmacy's mark-up is added as well. The total amount charged by the distribution chain and the pharmacy together may not exceed the maximum commercial mark-up.

The percentage rate of the maximum commercial mark-up is based on the degressive principle, i.e., as the manufacturer's price increases, the maximum permitted commercial mark-up to be split up between the distributors and the pharmacy decreases. The amount obtained based on the percentage rate is to be increased by the so called extra payment, i.e. by a maximum fixed amount corresponding to the range as per the base amount (see table below).

The amount of maximum commercial mark-up is currently as follows.

Range	Base from (CZK)	Base to (CZK)	Rate	Extra payment (CZK)
1	0,00	150,00	37 %	0,00
2	150,01	300,00	33 %	6,00
3	300,01	500,00	24 %	33,00
4	500,01	1 000,00	20 %	53,00
5	1 000,01	2 500,00	17 %	83,00
6	2 500,01	5 000,00	14 %	158,00
7	5 000,01	10 000,00	6 %	558,00
8	10 000,01	9 999 999,00	4 %	758,00

The table shows that if the manufacturer markets the medicine for the actual (not maximum) price of CZK 100 (excl. VAT), then distributors with the pharmacy may add a maximum of CZK 37 (excl. VAT) (37% out of CZK 100). VAT is added to the result (VAT imposed on medicines is currently at 10%) and the resulting price charged by the pharmacy thus may not exceed CZK 150.70.

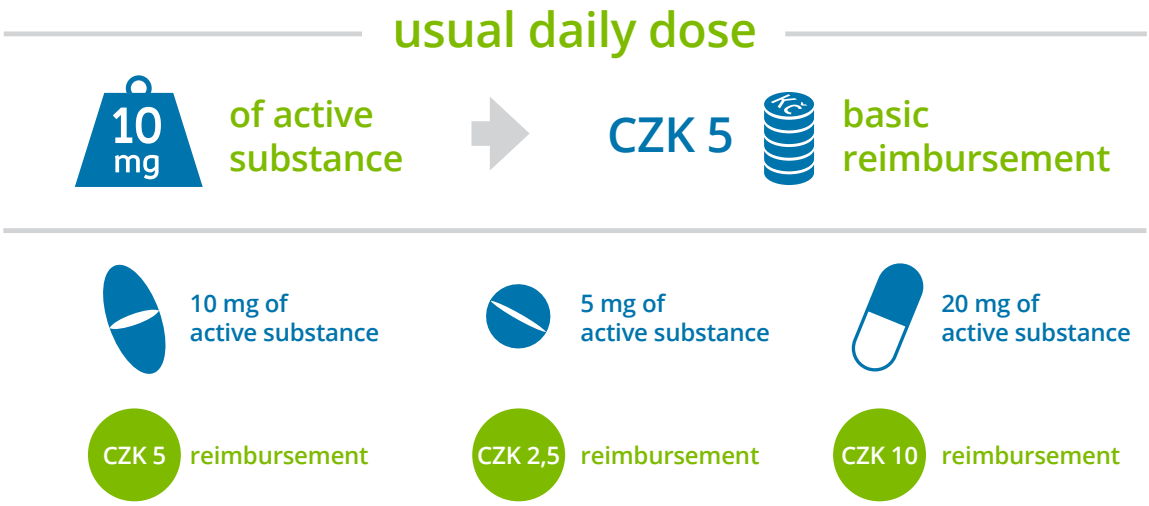
However, nobody except for the distribution chain knows the actual price, at which the manufacturers market the medicine. Only the manufacturer's maximum price or notified price is known; and we are able to add the maximum commercial mark-up to it. This gives each patient the opportunity to check what the theoretical maximum final price in the pharmacy would be, if consisted of the maximum manufacturer's price and maximum commercial mark-up and VAT.

It is mandatory for SÚKL to publish the maximum prices and notified prices on their website. Each patient can check whether the price of the medicinal product in the pharmacy corresponded to the maximum price set for the end customer that is to be calculated as a sum of the maximum manufacturer's price (or notified price), maximum commercial mark-up and VAT. If the actual price of the medicinal product exceeds the price calculated in this manner, it does not automatically mean that the manufacturer, or distributor and/ or pharmacy breached the law. A situation called a clearance sale should be taken into account.

If the maximum manufacturer's price is reduced after the medicine has been marketed (SÚKL adopts a new decision reducing the maximum price), then it is not necessary to respond immediately and reprice the product. The act on prices establishes the option to clear the remaining product for the original price within a maximum of 3 months since the maximum price was reduced. Therefore, the publicly available database will show a new lower maximum price but for three months it is possible for the market to sell the already purchased medicine for the original higher price.

Glossary

List of reimbursed medicinal products and foods for special medicinal purposes (MP/FSMP) – a list published by SÚKL, stipulating, among others, the maximum manufacturer's price, maximum final price of the medicine, amount of reimbursement for the medicine covered by public health insurance and the amount of supplementary payment for the medicine that is included in the patient's supplementary payment protection limit.



Reimbursement Regulation

Once again, **it is SÚKL that makes the decision** in the administrative proceedings. When it comes to innovative medicines these are very complicated and long administrative proceedings, covering a complex assessment of the medicine in terms of its future status in clinical practice, its efficacy and safety compared to other already reimbursed medicines, its degree of benefit generated and other qualitative and quantitative parameters.

The reimbursement for the medicinal product is set based on the so called **basic reimbursement for the reference group**. The reference group means a group of principally therapeutically interchangeable medicinal products with similar or close efficacy and safety and similar clinical use. The list of reference groups is stipulated in the Decree on the **List of Reference Groups**, published by the Ministry of Health.

The reimbursement for the reference group is set at the level of basic reimbursement. Basic reimbursement is a reimbursement for one usual daily therapeutic dose. The **reimbursement regulation** in the Czech Republic lies on the principle of the same reimbursement for the same effect, which means if several active substances are therapeutically interchangeable, the reimbursement

should be set based on the usual daily therapeutic dose level, at which they would have the same effect. In terms of the public health insurance resource it should not matter which specific active substance is given to the patient; the reimbursement for the same effect should be the same. In addition to mutual therapeutic interchangeability of the respective active substances, the administrative proceedings ascertain the dose, at which the respective active substances have the same effect in a day of therapy.

The basic reimbursement for one day of therapy is determined based on the so called **external price reference**, thus based on the prices of medicinal products in any EU country. The basic reimbursement is set as per the lowest manufacturer's price for a usual daily therapeutic dose.

The State Institute for Drug Control sets the basic reimbursement based on the **daily cost for comparably effective and cost-effective therapy**, if lower than the reimbursement calculated using the external price reference.

Furthermore, the law allows to set the basic reimbursement using the price stipulated in the **agreement on the highest price** or the **agreement on reimbursement**, if lower than the basic reimbursement calculated using the external price reference or cost of comparably effective therapy.

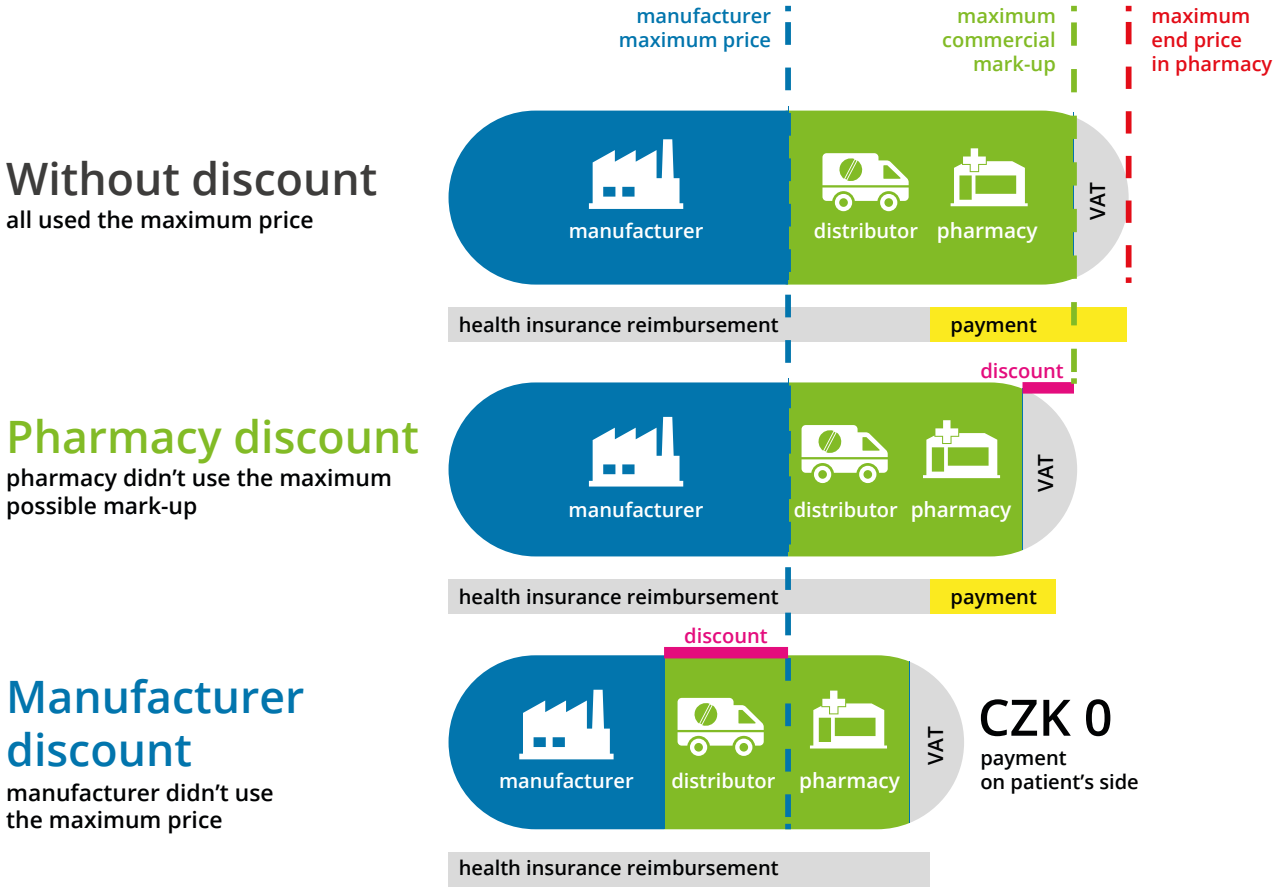
The basic reimbursement is used to calculate the reimbursement of the individual medicinal products, using coefficients stipulated in the implementing decree to the Act on Public Health Insurance.

Glossary

Reference group – a group of principally therapeutically interchangeable medicinal products with similar or close efficacy and safety and similar clinical use.

Basic reimbursement – a reimbursement identical across the whole reference group for a usual daily therapeutic dose.

Usual daily therapeutic dose (UDTD) – amount of the active substance per day for a regular patient; it is used to compare the efficacy for the same indication within a group of medicinal products.



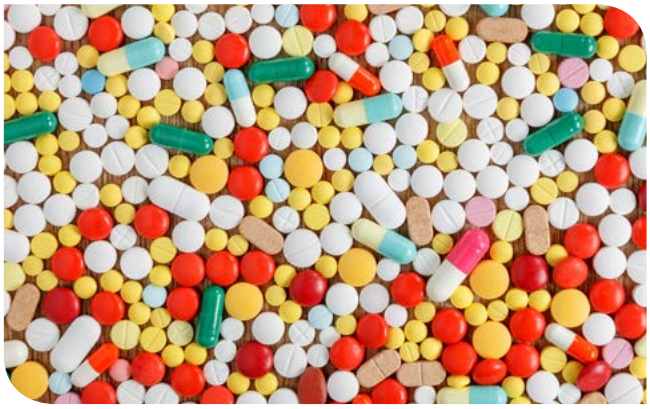
The State Institute for Drug Control may stipulate conditions applicable to the reimbursement of medicinal products, if required in terms of expert aspects or safety aspects related to the treatment, or if necessary to guarantee efficient and economical utilization of medicinal products.

There are two main types of reimbursement conditions, **prescription and indication restrictions**. The prescription restriction defines which doctor with specialized competence may prescribe the medicinal product to be reimbursed using public health insurance resources. The reimbursement decision may stipulate that the medicinal product can only be prescribed by a specified doctor or another doctor authorized to prescribe the medicinal product by the specified doctor.

Simultaneously, the State Institute for Drug Control may specify the **indication restriction**, i.e. define the group of patients or conditions, for which the medicinal product will be reimbursed from public health insurance funds. The indication and prescription restrictions applicable to the respective medicinal products are set forth in the **List of reimbursed medicinal products/foods for special medicinal purposes** or in **auxiliary codebooks** published on the **State Institute for Drug Control website**.

As part of each proceedings aimed to set or change the basic reimbursement in a group of principally therapeutically interchangeable medicinal products, the State Institute for Drug Control must examine whether a full reimbursement (i.e. no supplementary payment by a patient needed) is guaranteed for at least one medicinal product across the group of products falling under the active substance category stipulated in **Appendix 2 to the Act on Public Health Insurance**. Appendix 2 to the Act on Public Health Insurance currently includes 195 groups of active substances. These are the groups, in which the law requires to have a fully reimbursed medicinal product.

Not all groups of medicinal products are included in any of the groups listed in Appendix 2. Therefore, the publicly proclaimed opinion that each reference group must include at least one fully reimbursed product is not true. Therefore, the State Institute for Drug Control must first establish whether the given reference group is included in a group in Appendix 2. If not, the Institute is not obliged to



guarantee full reimbursement of the medicinal product in the discussed group. If the reference group falls under an Appendix 2 group, the State Institute for Drug Control must examine whether a full reimbursement of at least one medicinal product is guaranteed.

If a full reimbursement is guaranteed, there is no need to adjust the calculated basic reimbursement. If a full reimbursement for at least one medicinal product in the Appendix 2 group is not guaranteed, the State Institute for Drug Control is obliged to adjust the basic reimbursement so that the least expensive medicinal product is fully reimbursed for. In such a case, the basic reimbursement is then set based on the price of such a medicinal product in the Czech Republic.

Glossary

Appendix 2 – an appendix to the Act on Public Health Insurance stipulating the groups of medicinal products with at least one medicinal product to be fully reimbursed for.

Full reimbursement of medicinal product – obligation to guarantee a fully reimbursed medicinal product in the group of medicinal products falling under the Appendix 2; this obligation does not apply to every group of therapeutically interchangeable medicinal products (reference group).

Supplementary Payment

The difference between the price for the medicinal product and the reimbursement from public health insurance is paid by the patient in the form of a **supplementary payment**. Considering the fact that the price for the medicinal product is not fixed, the supplementary payment may differ from pharmacy to pharmacy.

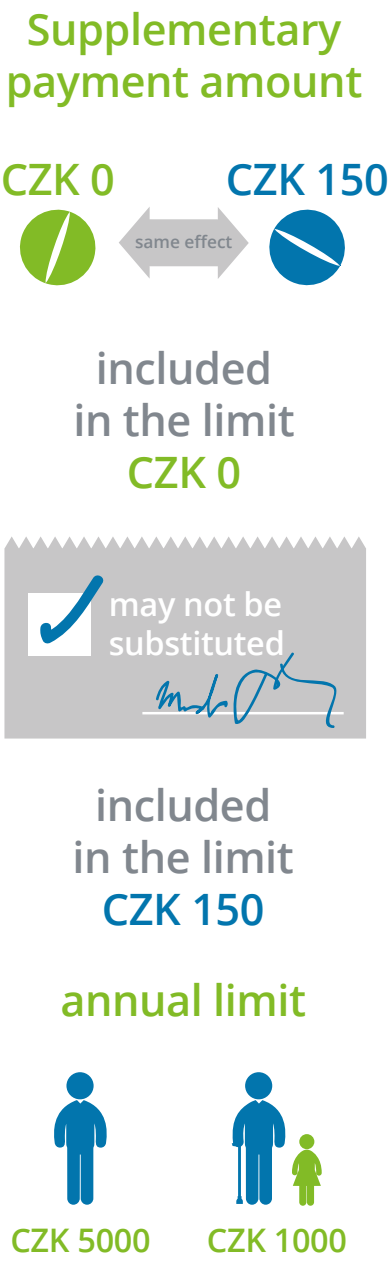
The Act on Public Health Insurance protects patients from high supplementary payments with the so called **supplementary payment protection limit**. The supplementary payment for a medicine in the amount of the lowest supplementary payment for a medicine containing the same active substance with the same method of administration as the dispensed medicinal product is added up under the protection limit. Therefore, if there is at least one medicinal product containing the same active substance with the same method of administration as the dispensed medicinal product fully reimbursed by the health insurance company, the eligible supplementary payment to be included to the protection limit is CZK 0, regardless of the actual supplementary payment paid by the patient.

There is an exception to this - if the prescribing doctor notes on the prescription that the prescribed product may not be substituted. In such a case, the actual supplementary payment in the full amount is added to the protection limit. The amount of the eligible supplementary payment for each reimbursed medicinal product may be found in the **List of reimbursed medicinal products/foods for special medicinal purposes**. The supplementary payments for medicinal products containing active substances for supportive and supplementary treatment are not eligible to be included in the protection limit; except for patients older than 65. **The list of active substances used in supportive and supplementary treatment is set forth in the Decree issued by the Ministry of Health of the Czech Republic. The protection limit is CZK 5,000 per year. Starting 1 January 2018, the protection limit for individuals under 18 and over 65 years of age was reduced to CZK 1,000 and for individuals over 70 years of age to CZK 500.**

It is not necessary to personally monitor whether the protection limit for supplementary payments for medicinal products has been exceeded; this is done by the health insurance companies as per the law. The health insurance company is obliged to refund the amount over the limit to their insured within 60 days of the end of the quarter in which the limit was exceeded.

Glossary

Eligible supplementary payment – a supplementary payment that can be included in the protection limit as the lowest supplementary payment against a medicinal product containing the same active substance and administered the say way and the dispensed medicinal product.



Highly Innovative Medicinal Products

Highly innovative medicinal products are such medicinal products that **are used to treat serious diseases and are considerably more effective as compared to current treatment or considerably reduce the death rate or have significantly less serious side effects**, due to which patients had to interrupt their treatment. Highly innovative medicinal products are also medicines that **have no alternative** covered by health insurance.

These innovative medicinal products, about which we do not have yet enough data to go through the standard process of setting reimbursement from health insurance, can obtained so-called temporary reimbursement (for three years at the maximum). This should provide enough time to gather more information about their effectiveness so that they could receive permanent reimbursement.

Innovative medicinal products often save, prolong or improve the patient's life. Treatment with innovative medicinal products is very expensive and is provided only in specialized health care centers that have a contract for such treatment with a health insurance company.

In 2016, health insurance's cost of these medicinal products provided in health care centers amounted to CZK 15.18 billion. The number of patients treated with innovative medicinal products went up by almost 50% between 2010 and 2015. However, funds spent on this treatment cannot be deemed as consumption only. It is also an investment because such treatment helps not only to prolong life but also to prevent or postpone disability, which means that patients can keep working (if treatment is provided on time, patients remain active while before they became disabled; the survival time has been prolonged for decades).

Exceptional Health Insurance Reimbursement Method

In special situations when patients **as a result of their medical condition** may not be treated with medicines reimbursed from the health insurance, an exceptional reimbursement method applies as per **Section 16** (of the Act on Public Health Insurance). It means that if all options of reimbursed treatment of the specific patient has been exhausted, and the non-reimbursed medicine is the **only treatment option**, the examining doctor engaged by the health insurance company may approve that the insurance company will pay for such a medicine.

It is a rather complex process in terms of administration; the treating physician needs to submit a request, specify the treatment the patient has already received and give reasons why the requested medicine is the only treatment option for this patient. Most often it concerns medicines that are new and the reimbursement from the health insurance has not been set yet, or medicines that are to be used to treat a condition that is not included in the marketing authorization, but at the same time there is a scientific rationale for this medicine to be used for the specific patient in a situation when another therapy is not effective or may not be given to the patient for medical reasons. In some cases, this applies to a situation when the medicine is covered by the health insurance only for a certain period of time, but the specific patient could benefit from an extended treatment. However, this must be approved by an examining doctor. The insurance company examining doctor thus always has to assess the justification of the request to see whether it is really a situation with no alternative treatment option; then they can approve the request. If the application is rejected, they need to provide the reasons for such rejection.

The reason for approving such an application for reimbursement must always be, as mentioned above, the patient's medical condition. Other reasons, such as the patient's financial situation, their requirement or rejection of treatment, may not be addressed using public health insurance funds.

Reimbursement Notice

The so-called Reimbursement Notice, which stipulates the principles of regulation of all health care segments on a yearly basis, is an important part of the public health insurance system. The notice sets the rules for calculating different limits of reimbursement from health insurance for each specialization, e.g. general practitioners, ambulance specialists, dentists, hospital care and laboratories.

The notice specifies how the limits for medicinal products prescribed by individual doctors or provided as part of health care are calculated. It also specifies the limit costs of each diagnostic group of medicinal products provided in specialized health care centers.

If a doctor, hospital or specialized health care center exceeds the limit specified in the notice, the health insurance company will not reimburse such care or will reimburse it in part only. However, if the health care facility and the health insurance company agree on the rules of health care reimbursement and sign a contract, such a contract will have priority over the rules of the Reimbursement Notice so that a specific situation, to which the rules in the notice do not apply, could be evaluated on a one-by-one basis.

Availability of Medicines for Patients

Although more than 56 thousand codes (packaging types) of medicines have received market authorization in the Czech Republic, in reality less than 15% of this total number is actually marketed. Perhaps each of us has faced the situation when the medicine requested in the pharmacy was not available. If this applies to a medicine, to which generic drugs (copies with the same active substance) exist, its unavailability is usually not a big problem since the patient may be given the generic drug; they will "only" have to get used to a different name and appearance of the medicine used. Nevertheless, the situation is quite different if it concerns a medicine, to which there is no generic drug. The patient has to go back to his/her doctor to find another alternative - a medicine with another active substance - which may but may not agree with the patient just like the original medicine.

There is a number of reasons for medicine unavailability in Czech pharmacies. The most common include problems with the manufacturing of the medicine, which most of the time only results in a temporary deficit in supplies. An appropriate solution is based on the duration of such deficit, seriousness of the disease treated with this medicine and a number of patients who really need it.

Legal regulations governing pharmaceuticals stipulate that only authorized medicines with verified safety and efficacy may be used to provide medical care in the Czech Republic. Simultaneously, these regulations introduce certain instruments for situations when the authorized medicine is not available and may not be substituted with another authorized medicine.

If a short-term unavailability is expected or if it applies to a medicine for only a small number of patients, the solution may be to individually import an unauthorized medicine from abroad. Such medicine is then prescribed by the treating physician and the prescription says "Unauthorized medicinal product". The imported medicine must be authorized in another country - usually it is imported from any of the neighboring countries (e.g. Germany, Slovakia). The problem may arise if such a medicine is not covered by the health insurance company in the Czech Republic - either the patient needs to pay for it or it is possible to apply for the special reimbursement if the conditions of Section 16 are met (see chapter Exceptional Reimbursement Method).

If the medicine is unavailable for a long period of time, the Ministry of Health announces, in joint effort with SÚKL, a call to submit applications for the so called Specific Treatment Program (STP). Based on the program, the applicant, most commonly the manufacturer or distributor of the medicinal products, may supply the unauthorized medicinal product to the Czech Republic (until the authorized one is available again). Such medicine is dispensed by a pharmacy with "Specific Treatment Program" written on the box. A reimbursement from the health insurance may be set as well.

In recent years we have been increasingly faced with a situation when, despite the manufacturer not having any problems with production (medicines are produced and delivered to the Czech Republic), these medicines are not available in pharmacies. It is caused by "re-exports", which means that the medicine was imported to the Czech Republic and exported back abroad.

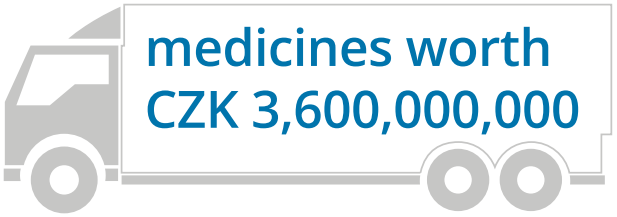
Re-exports

Re-exports concern such medicines, the Czech price of which is lower than the price abroad. If the re-exporter purchases medicines for a lower (officially set) price and is able to sell it for a reasonably higher price, the difference between the prices after deducting the cost related to export is the re-exporter's profit.

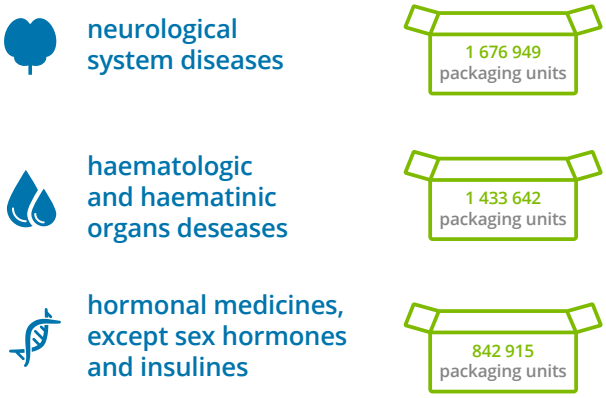
The method of setting the maximum price is described in the respective chapter, including reasons why it is in the Czech Republic's interest to set this price at a reasonably low level in order to ensure financial sustainability of the health insurance system. The reverse side of this success in reducing the maximum prices lies in the risk of re-exports. The higher the difference between our price and the price in any other country (only one is enough), the more attractive this medicine is for the re-exporters. This applies not only to the Czech Republic but to any country - it is a fact that a number of European countries are faced with the problem of re-exports to a various extent.

At a glance the simplest solution seems to be a general ban on exports of medicines to another country. This is, however, not possible since the free trade rule between individual countries is one of the principal pillars of the EU and, under standard circumstances, it also applies to medicines. Another solution could be uniform European prices that would entirely eliminate the reexports. However, this would relieve the pressure to set the lowest price required practically by every country in a situation where it is apparent that the financial strength of the respective healthcare system significantly differs. Thus, if the prices increased without an increase in the reimbursement from the health insurance because the system could not handle such an increase, it could result in a situation with medicines in the market, though unavailable to patients due to high supplementary payments.

The restrictions or ban imposed on export may be imposed on specific medicines, where justified that if re-exported, there would be a lack of these medicines in the market, putting the health of that country's patients at risk. SÚKL reviews information about medicine supplies and consumption and evaluates the risk of insufficient stock of individual medicinal products on the Czech market, taking always into consideration the interchangeability of a specific medicine. The Ministry of Health will place the medicinal products that may not be available on the market on the list of medicinal products, the planned export of which must be reported to SÚKL. If SÚKL decides, based on the mandatory reports of medicine manufacturers, distributors and pharmacies, that the medicinal products on the list of the Ministry of Health may not be available to patients in the Czech Republic due to the export planned in the next three months, the Ministry of Health will restrict or totally ban such export.



most frequently exported medicines



Medicinal Product Advertising

As suggested in the previous chapters, medicines are a commodity regulated by strict rules, starting from early development, through authorization and the entire time they are marketed. The purpose of these regulations is to **protect society's health** (i.e. public health) as well as the health of individuals. Therefore, it should be no surprise that medicinal product advertising is also regulated by rules stipulated by law.

Simply said, advertising means any activity aimed at increasing the sales of goods (in our case medicines). Nevertheless, it is not at all simple to differentiate between the provision of information about treatment options and medicinal product advertising.

The medicinal product advertising is regulated in order to make sure that the **individuals making a decision about the use of medicines** get objective, current and exhaustive information. The previous chapter has explained that upon their authorization the method of dispensing is always defined, which means whether the medicines may be dispensed solely upon prescription or whether they qualify as OTCs. While it is the patient who directly (or upon consulting the doctor or pharmacist) **makes the decision** regarding OTCs that do not need to be supervised by a doctor, it is the doctor who is responsible for prescribing (and subsequent using) prescription-only medicines.

The practical implication of the said rule is that the advertising for **prescription medicines** may only be addressed to **healthcare professionals** (doctors and pharmacists), while the advertising for **OTC medicines** may be addressed to the **general (lay) public**. Let's explain in greater detail the regulation of advertising we are all exposed to, i.e. advertising for OTC medicines.

The law defines two types of requirements - general, applicable to any advertising for medicines (regardless of who the target group is), and special requirements adopted to a target group.

General Requirements:
• Only an **authorized medicine** may be a subject of advertising.
• All information presented in the advertising must **be in line with the summary of the product characteristics** (which is a public document approved during the marketing authorization process). The advertising is obviously usually briefer, but all information presented in the advertising has to be found in the summary of product characteristics.
• Advertising must introduce the medicine **objectively** without exaggerating its characteristics and thus support its **rational use**.

Advertising targeting the general public must comply with a number of special requirements, such as the obligation to state the information that it is a medicine, its name, information about correct use and a reminder to read the package leaflet. Advertising may not suggest that the effects of the medicine are guaranteed, that it does not cause any adverse effects or that it is better or equal to the effects of other treatments. Likewise, the advertising may not reference any recommendations given by scientists, healthcare professionals or people with high social status. It means that if you see or hear an advertising saying "3 out of 4 doctors recommend" or if a famous person recommends a product, you can be almost sure that the product is not a medicine subject to the marketing authorization process, in which its efficacy would be demonstrated, but it falls under a different category of products (most frequently dietary supplements or cosmetics).

In addition, medicine advertising may not exclusively target children under 15 years of age because they are not able to responsibly take medicine without any supervision, and the advertising may not make them seek or take any medicines. The law stipulates several other requirements intended to protect patients and to ensure that information given in the advertising is comprehensible and clear, not misleading or false.

The form of advertising is not regulated. It means that OTCs may be advertised in newspapers, magazines, on TV, radio or the Internet.

When the law sets forth rules and restrictions, there must also be somebody to supervise that they are complied with. It is not possible to solely rely on

the responsibility and consciousness of the entities involved in the pharmaceutical business. It is the State Institute for Drug Control that supervises the compliance of printed and Internet advertising with the advertising rules, while the advertising broadcasted on the radio or TV is supervised by the Council for Radio and Television Broadcasting. Should either of these authorities find out and prove that a certain advertising breaches any legal provisions, then they may impose a fine that often amounts to tens of thousands or hundreds of thousands of Czech Crowns, depending on the severity of the breach.

Do you know *that the only prescription medicines, advertising of which may target the general public, are vaccines? Such advertising, purpose of which is to increase the vaccination coverage of the population, must be carried out as part of a vaccination event approved by the Ministry of Health. It always concerns advertising for optional vaccination that it is up to every individual (of course after consulting a doctor) to decide whether or not they will get vaccinated, e.g. flu vaccination.*

Borderline Products, or not everything sold in a pharmacy is a medicine

In addition to medicines, pharmacies offer other categories of products that are generally called health and beauty products. They include medicines, medical devices, dietary supplements and cosmetic products. Thanks to their characteristics or presentation, some products may fall under several categories. It is useful to know how these categories differ and what we can expect from them in order to make better decisions, based on our needs, while purchasing them.

Medicines

The previous chapter described in quite a detail the regulation applicable to medicines, i.e. the level of supervision and complexity of the process each medicine is subject to before it may be marketed. Very briefly - just to compare with other product categories - we can summarize: if a "box" says medicinal product, it is a medicine that had to go through the process of clinical trials and authorization, part of which its **efficacy and safety** had to be demonstrated, and that all information given on the box and package leaflet corresponds to what had actually been demonstrated for the respective product. It is essential to keep in mind that the entire regulation of pharmaceuticals requires a lot of funds and that the resources invested in the development must be reflected in the price of the medicine. The regulation of other categories is not as demanding.

Dietary Supplements

Dietary supplements are a category most likely considered as medicines with expected curative effect since we often do not carefully read the text on the box. Despite the visual appearance of dietary supplements often being very similar to OTCs, in terms of regulatory requirements these two are very different categories.

The different purpose arises from the definition of a dietary supplement itself. A dietary supplement is a food product, purpose of which is to complement a common diet and that it is a concentrated source of vitamins and minerals or other substances with nutritious or physiological effect; the supplement may contain one substance or a combination of substances. This food product is intended for direct consumption in small measured amounts (usually tablets).

The fact is that dietary supplements do not demonstrate their efficacy, but only harmlessness. The legal regulation stipulates which substances may the dietary supplements contain and which substances are banned. Simultaneously, there is a common European list of so called health claims that may be stated on the dietary supplements (no other claims may be stated on dietary supplements). Only a small number of claims stated on the dietary supplements in the past have been approved; it concerns claims that were actually demonstrated by results of a clinical trial.

The most frequent verbal term in the health claims is "contributes to a normal function" or "condition", which shows that the dietary supplements are not intended to treat the disease condition but are intended to help to sustain a normal condition. Let's use the well-known vitamin C as an example. It has a total of 15 approved health claims, 14 out of which says "contributes" (to a normal function of the immune system, to normal energy metabolism, to normal collagen formation, etc.); the last claim says that it increases iron absorption.

Therefore, dietary supplements may not directly present curative or preventive characteristics. However, in practice we often see that a famous person promotes a product that is a dietary supplement on TV, saying he/she uses this product and that it is "for joints". Then it shows how he/she runs up and down the stairs, etc. A person who watches

such an advertising may often get an impression that the famous person moves like this thanks to the promoted product, even though such information was not given at all. Or the box may provide information about a certain disease and an individual may get the impression that the product is intended for such a disease, although this specific information is not given at all.

The fact that a dietary supplement contains the same or similar substance as a medicine does not mean that it has the same or similar effect on the human body. The destiny of any substance in a body is complicated and exposed to a number of factors, such as the size of the molecule and excipients. That is also why, generic drugs (copies of original medicines) need to prove their bioequivalence (see the respective chapter). Any time we are selecting a suitable product in a pharmacy, we should be aware of what to actually expect from a certain category, considering the requirements that had to be met prior to its marketing.

Dietary supplements play their role if a person, for any reason, lacks vitamins, minerals and nutrients received from food – either due to an increased need or insufficient intake (illness, season, etc.) – then it is necessary to supplement the missing substances. Dietary supplements should not be used as a substitution for a varied diet and they should not be used for a long period of time.

Medical Devices

Medical devises are another category of products often seen in pharmacies. Sometimes they are still denoted with an obsolete term “medical technology devices”, or a simplified term “medical aids.”

Medical devices are a very numerous and heterogeneous group – they include the simplest products, such as cotton wool, dressing or bandage required to comply with only minimum requirements, through more complex products (injections, dioptric contact lenses) up to technologically advanced and complex that they have to meet strict requirements (artificial joints, imagining devices). Additionally, the group includes **in vitro diagnostic medical devices** (IVD) – such as laboratory diagnostic devices (chemistry analyzer), diagnostic tests (pregnancy test, tests for various diseases) and **active implantable medical devices** – such as pacemakers, cochlear implants.

The law defines a medical device as an instrument, device, equipment, software, material or another object that the **manufacturer designed to be used in people** in order to **determine diagnosis**, prevention, **monitoring**, treatment or mitigation of disease or injury or health disability **compensation**, or in order to **examine**, **replace** and/or modify the anatomic structure or physiological process, or for birth control. A medical device **does not generate** any pharmacological, immunological or metabolic effects in a human body or on its surface (its function, however, may be supported by these effects) - this distinguishes medical devices from medicines, since medicines generate these effects.

The so-called **specified purpose of use**, thus the purpose the product is to be used for, is essential for a medical device – for the product to be classified as a medical device, it must comply with either of the purposes stipulated in the definition. It technically means that, in addition to medicines, the medical devices may state the so called **medical purpose**, thus that they treat or compensate for a disability, if relevant. Such a characteristic of a medical device must be demonstrated in a **clinical trial** which is carried out by assessing the safety and efficacy data of an equivalent medical device, if there are reports about using the equivalent medical device in clinical practice. Only if it is a new medical device or a different use of a medical device, is the clinical trial conducted with patients.

Medical devices are divided into **safety classes**. Different classes are subject to a different degree of regulation imposed on the specific medical device. Only a medical device that has been subject to the legally defined evaluation of **conformity of its characteristics with basic requirements** defined by legal regulations (government regulation, directives), carrying the **CE marking**, with a written **declaration of conformity**, accompanied with **information about its safe use** in the Czech language and notified to the State Institute for Drug Control (if this obligation is specified) may be marketed.

Class I

The simplest medical devices – glasses, dressing, stethoscope, wheelchair, syringes without needles, crutches, etc. – the evaluation of conformity with requirements is conducted by the manufacturer alone; all other classes require the evaluation to be done by a notified body that issues a certificate.

Class IIa

Needles, surgical gloves, contact lenses, medical devices implantable to established body orifices to remain in place for a max. 1 month, orthoses and prostheses, hearing aids and other electromechanical devices – sonograph, ECG, etc.

Class IIb

Invasive medical devices – bone screws, moist wound healing devices, dialysis devices, ventilators, infusion pumps, X-ray machines, etc.

Class III

Medical devices containing medicines, medical devices with bovine collagen - such as vessel prostheses, valves, stitches, everything that comes in contact with CNS and central blood circulation, IVD, joint replacements, breast implants, etc.

While most of the medical devices may be recognized at first sight, in some cases their classification into this category or in the medicines category is determined solely by the mechanism of action - i.e. whether the product generates pharmacological, immunological or metabolic effects in the human body. A typical example of a medical device that is historically perceived as a medicine concerns the active so-called animal charcoal used against diarrhea. It is an inert substance that is not absorbed from the intestine but while passing through the intestine it binds bacteria, toxins, gasses and other substances and subsequently it is fully excreted (without generating any of the abovementioned mechanisms of action).

There are also groups of products with characteristics close to several categories of medical technology and only details and small differences determine how the specific product should be classified. For instance, various lozenges used for sore throat and a cold may be both medicines and medical devices. If the lozenges contain an active substance that pharmacologically affects the bacteria causing the infection, or an active substance affecting the mucous membrane cells and thus suppresses the pain, they are classified as authorized medicinal products. On the other hand, if the lozenges contain, for instance, lichen extract which covers the mucous membrane surface and thus protects against dry environment and harmful substances (the mucous membrane is capable of its own recovery under this protective layer), such lozenges are classified as medical devices.

The mechanism of action is usually used to classify products taken orally (swallowed or sucked) but this type of differentiation is also used, for instance, within a group of products used against lice in people. If the product kills the louse as a result of a pharmacological effect on its organism, then the product is classified as a medicinal product and needs to also receive marketing authorization as such. However, if the product affects the louse in a different way, for example, it is made on the basis of silicone oils that cover the louse and this physical mechanism kills it, then it is classified as a medical device.

The fact remains that the regulation of medical devices differs from the regulation of medicines and it allows for a faster, less demanding process prior to launching it into the market. At the point where the medical device has already been marketed, the biggest difference lies in the regulation of advertising. While the advertising for medicines is highly strictly regulated (see the respective chapter), advertising even for the most complex medical devices of class III is only subject to general requirements, just like advertising for any other product.

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