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THE REGULATION OF PHARMACEUTICALS AND MEDICAL DEVICES

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Introduction

The “Legal Regulation of Pharmaceuticals and Medical Devices” course aims to allow students to understand the basic regulatory framework of medicinal products and medical devices, with the regulation of medicinal products having a more dominant position due to the larger scope of legal regulation. The concept of the course for the students is to acquire basic hard-knowledge related to key aspects of the legal regulation and learn what the sources of the legal regulation are and what legal regulation applies. As external guests will be hosted, the students will benefit from presenting their questions with leaders of the respective fields and in addition learn more about the particular functions the guests perform in the pharmaceutical industry.

General Introduction to Pharmaceuticals and Medical Devices Market

Learning outcomes

The topic aims at providing the students with a basic understanding of the regulatory framework of the pharmaceuticals and medical devices markets. The main focus is in the area of the definition of a pharmaceutical product with basic division into Rx and OTC products; and medical device with basic distinctions necessary for understanding the applicable type of regulation.

The students should understand the key activities related to pharmaceuticals and medical devices, i.e., manufacturing, distribution, and dispensing, are subject to strict legal regulation. Students should be able to understand where the source of legal regulation is found what are medicinal products and medical devices.

I. The Pharmaceutical Market

The pharmaceutical market is one of the largest and most important markets in the world. World-wide, it is estimated that the pharmaceutical market is valued at approx. 1.250 billion U.S. dollars at the end of 2019.[1] Given the fact that pharmaceuticals are a key component in our healthcare, it is only logical that the regulatory framework of pharmaceuticals is one of the most complex, in comparison to other subjects of legal regulation.

The pharmaceutical market involves various subjects that deal with pharmaceuticals: (i) manufacturers, (ii) distributors, (iii) dispensers, (iv) healthcare professionals, (v) sick funds, and (vi) end user-patients. This chapter will focus, in more detail, on the first three categories.

a. Medicinal Products

The regulatory framework of medicinal products consists of the EU legal regulation, which consists of both directives and regulations, as well as the national legal regulation, which consists of statutes, decrees of the Ministry of Health, and guidelines of the State Institute for Drug Control (*SUKL*). In addition, there are self-regulation rules included in various codes of ethics for manufacturers of innovative as well as generic medicinal products. The following is a general overview of applicable legal regulations, which include basic rules on how to handle pharmaceutical products: (i) the Regulation on Authorization of Medicinal Products (Regulation (EC) 726/2004); (ii) Clinical Trials Regulation (Regulation (EU) 536/2014); (iii) Falsified Medicines Regulation (Regulation (EU) 2016/161); (iv) Community Code relating to medicinal products for human use (Directive 2001/83/EC) – which also includes the regulation of advertisement of pharmaceuticals; (v) Act No. 378/2007 Sb., on Pharmaceuticals; (vi) Act No. 48/1997 Sb., on Public Health Insurance; (vii) Act No. 372/2011 Sb., on Health Services; (viii) Act No. 40/1995 Sb., on the Regulation of Advertising; (ix) Decree No. 229/2008 Sb., on Manufacture and Distribution of Pharmaceuticals; (x) decrees governing good manufacturing, distribution,

[1] https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/

clinical, laboratory practice; and (xi) the Association of Innovative Pharmaceutical Industry's and the Czech Association of Pharmaceutical Companies' Code of Ethics.

Most of the regulatory framework, at the statutory level, is based on Act No. 378/2007 Sb., on Pharmaceuticals, as amended (*Act on Pharmaceuticals*). A pharmaceutical product means **a substance or combination of substances**:

a. which is / are presented as having therapeutic or preventive properties in the case of human or animal diseases; or
b. which may be used or administered to humans or to animals with a view to restoring, correcting, or modifying the physiological functions by means of a pharmacological, immunological, or metabolic effect or with a view to making a medical diagnosis.

The Act on Pharmaceuticals further includes specific matters, which are considered medicinal products, for example, these include: (i) pharmaceuticals intended for use or administration to humans; (ii) pharmaceuticals intended for use or administration to animals (veterinary products); (iii) immunological pharmaceuticals (e.g., vaccines, serums, etc.); (iv) homeopathic products; (v) blood derivatives (i.e., industrially prepared pharmaceuticals derived from human blood or human plasma); (vi) transfusion products (i.e., human blood and its constituents processed for administration to humans by means of a transfusion intended for the treatment or preventing of a disease), etc.

As pointed out above, pharmaceuticals are medicinal products for humans as well as animals. For the purposes of this handbook, we will consider the medicinal products only as medicinal products for humans.

Medicinal products are further divided on the basis of their nature of availability to the general public: (i) so called Over-the-Counter (*OTC*) medicinal products, which may be dispensed without any prescription and (ii) prescription-only medicinal products (also known under the abbreviation *Rx*), which can be dispensed only if a physician issues a prescription for a patient. This division has an impact on both the dispensation of such products as well as on reimbursement from public health insurance, price regulation, and advertising, where Rx medicinal products are usually much more regulated.

b. Manufacturing and Manufacturers

In terms of manufacturing, there needs to be a distinction made between innovative medicinal products and generic medicinal products.

The innovative pharmaceuticals are medicinal products which are original, i.e., there is an original research which results in a pharmaceutical product which has never been used on the general public. The registration process requires submission of the results of conducted clinical trials, which are to be carried out in several stages, aiming to obtain sufficient information for the intended use of the pharmaceutical in order to assess the benefit-risk balance.

On the other hand, the generics registration process does not require results from pharmacological and toxicological tests or from clinical trials. The manufacturer of a generic medicinal product must prove that the generic medicinal product is "bioequivalent" to the original pharmaceutical, i.e., the same amount of active substance gets in the bloodstream and the exclusion from the organism is the same and therefore the generic acts in the body in the same way as the original medicinal product does.

The manufacturing process is, nonetheless, heavily regulated both on the EU as well as national level. Manufacturers need to maintain the highest level of security of the process as well as the quality of the process. This is ensured by so-called standard operating procedures, which need to be prepared, observed, and reviewed regularly for compliance with rules in them.

c. Distribution and Distributors

Distribution is a category of activities which include, as stipulated in Article 5(5) of the Act on Pharmaceuticals, all activities consisting of procurement, storage, delivery, including intra-EU supply of medicines and exports to countries other than EU member states, and other related commercial transfers, regardless of whether such activity is carried out for any consideration or free of charge. Distribution is not considered to be: dispensing of pharmaceuticals; sales of selected pharmaceuticals and their use in the provision of health services; distribution of transfusion products by transfusion service facilities; or import of medicinal products from third countries (this activity is considered as manufacturing). It is important to understand whether certain conduct falls under the definition of distribution because, if it does, it will be subject to the regulation of distribution activities. Moreover, distribution activities are reserved for distributors and therefore only an entity, which obtained distribution license can conduct such activities.

The role of the distributor is to work in cooperation with (i) manufacturers, (ii) other distributors, (iii) pharmacies, and (iv) other persons authorized to dispense pharmaceuticals to the public or use pharmaceuticals in the provision of healthcare services.

The majority of the Czech market is covered by a few large distribution companies, such as Phoenix, ViaPharma, and Alliance Healthcare. However, there are more than a hundred of distribution licenses issued by the SUKL as various manufacturers (which outsource their distribution activities to key distributors) and pharmacies are involved in the trade with pharmaceuticals, even if volumes of sales are low.

Given the fact that innovative medicinal products often do not have competition, their manufacturers are in a dominant market position which triggers various competition law obligations, which must be carefully observed.

d. Dispensing and Dispensers

The dispensing of medicinal products, depending on their OTC or Rx status, is reserved only for a defined selection of subjects. These include: (i) pharmacists in pharmacies, (ii) pharmaceutical assistants in pharmacies, and only in relation to OTC medicinal products, and (iii) physicians, pharmacists or other healthcare professionals of a blood center authorized to conduct this activity.

In general, dispensing medicinal products requires obtaining a license from the SUKL. The primary requirement is meeting the technical and material equipment requirements (size of the space, instruments necessary for the normal operation of pharmacies, etc.) and ensuring that qualified staff are employed and they follow the rules of good pharmaceutical practice.

II. Medical Devices Market

The medical devices market is very large given the fact that various items meet the international understanding of a medical device. There are more than 500,000 different types of medical devices available: (i) diverse materials used for medical interventions (dressing material, syringes, needles, etc.); (ii) medical devices available upon prescription (glucometers, wheelchairs, hearing aids etc.); (iii) active implantable medical devices (pacemakers, etc.); (iv) in vitro diagnostic medical devices (devices for examining blood, urine, etc.); or (v) large medical instruments (X-ray, CT, etc.). All of the above can be included in the group of medical devices. Given the broad understanding, also software may be considered a medical device.

Similarly to the pharmaceuticals market, the medical devices market involves various subjects that deal with pharmaceuticals: (i) manufacturers, (ii) distributors, (iii) healthcare professionals, (iv) sick funds, and (v) end user-patients.

a. Medical Devices

The regulatory framework of medical devices consists of the EU legal regulation, which consists of both directives and regulations, as well as of the national legal regulation, which consists of statutes, decrees of the Ministry of Health, and guidelines of the SUKL.
In addition, there are self-regulation rules included in various codes of ethics for manufacturers of medical devices, both in-vitro as well as classical medical devices.
The following is a general overview of applicable legal regulations, which include the basic rules on how to handle medical devices: (i) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC ("MDR"); (ii) Act No. 89/2021 Sb., on Medical Devices ("Act on medical devices"); (iii) Act No. 268/2014 Sb., on In Vitro Diagnostic Medical Devices; (iv) Act No. 40/1995 Sb., on the Regulation of Advertising - which also includes the regulation of advertisement of medical devices and in vitro diagnostic medical devices; and (v) the MedTech Code of Ethical Business Practice.
The reimbursement is governed by Act No. 48/1997 Sb., on Public Health Insurance.

In order to assess the scope of applicable rules, there needs to be a definition of a medical device, which is stipulated in Article 2(1) of the MDR

> "'*medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*
>
> *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
>
> *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
>
> *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*

providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

devices for the control or support of conception;

products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point."

This definition is a key aspect in the assessment between the application of pharmaceuticals or medical devices legal regulation.

Similarly to pharmaceuticals, medical devices are further divided to (i) prescription medical devices and (ii) freely available medical devices.

Also, there is a distinction on the basis of security requirements regarding handling the medical devices and based on the specific hazard class, there are more or less stringent regulatory rules for handling and availability of the medical devices for each class (I, IIa, IIb, III).

The classification criteria of the medical devices depend on: (i) duration of contact with the patient (temporary, short/long term); (ii) invasiveness (non-invasive devices, invasive, invasive surgical implants); (iii) operation mode (non-active devices, active therapeutic and diagnostic devices); and (iv) anatomical site on which the device is affecting (in particular the central circulatory system and central nervous system).

b. Notification of Medical Devices

In order for the medical device to be placed on the market, it needs to be notified to a regulatory authority.

Registration of medical devices is regulated by the MDR, which introduces the European database on medical devices ("Eudamed"). However, according to the transitional provision of Article 74(5) of Act on Medical Devices, until the medical device module of the Eudamed is fully functional, medical devices shall be registered in accordance with the relevant provisions of Act No. 268/2014 Sb., in the version in force before the effective date of Act No. 89/2021 Sb.

Therefore, the process of notification is currently regulated particularly by Article 31 et seq. of Act No. 268/2014 Sb., in the version in force before 26 May 2021. The process of notification is electronic, and it is managed in a registry of medical devices. The notification requirements include, in particular, the complete name of medical devices, designation, intended purpose, categorization of the medical device, whether or not clinical trial was performed (where necessary), when the medical device was introduced to the market, validation, a manual in the Czech language (unless not required due to the low-risk of use of the medical device), and details of involvement of the notified person.

The notification obligation is due within 15 days of the date of the placement of the medical device on the market. Based on the electronic submission, the SUKL issues a decision on the notification and enters the medical device into the Registry of Medical Devices. The notification is valid for 5 years and may be repeatedly extended.

In addition to the notification of medical devices, generally, distributors and persons servicing medical devices are obliged to submit notification of their activities as well to the SUKL according to the Act on medical devices. The registration obligations of manufacturers, authorised representatives, and importers are unified by the MDR across EU member states, with data being entered directly into the Eudamed.

c. Distribution of Medical Devices

The distribution of a medical device is regulated by the MDR. A distributor is defined in Article 2(34) of the MDR as any natural or legal person in the supply chain, other than the manufacturer or the importer, that makes a device available on the market, up until the point of putting into service.

d. Sale of Medical Devices

Unless a medical device is reserved for use under supervision of a doctor or paid by the public health insurance system, medical devices may be sold in regular stores without further restrictions.

However, all medical devices, with certain exceptions, must bear a CE mark, i.e., official confirmation that the medical device conforms with health, safety, and environmental protection standards for products sold within the European Economic Area.

Specific conditions for storage, packaging, transport, distribution, and dispensation may apply, please find more details in chapter on distribution.

III. Questions

Are you able to define what a medical device and a pharmaceutical product is and what are the differences between them?
What are the sources of legal regulation pertaining to medical devices and pharmaceutical products?
What is the difference between original and generic medicinal products?
Can you define what activity would fall under the distribution of a medicinal product and why is it important?
Do you think software can be a medical device? Why?

Clinical Trials

Learning outcomes

This seminar is focused on clinical trials and aims to allow students to understand why regulation takes place and what the key principles are. Additionally, the seminar is focused on the identification of stakeholders and their role in a clinical trial.

The students should be able to understand the framework of local regulatory requirements to start a clinical trial.

I. Clinical Trials

Clinical trials are among the most important parts of research and development of new medicinal products. Clinical trials consist of verification and demonstration of the effectiveness and safety of potential medicinal products that have emerged from detailed testing in the laboratory conditions. The clinical trials are carried out before the marketing authorization is approved, i.e., before the placement of the new medicinal product on the market. A clinical trial is a part of research and development activities of both medicinal products as well as medical devices.

A clinical trial is basically a research project process, where at different stages, various medical assumptions related to use of medicinal products are verified by observing reactions of patients to the medicinal product. The path of each pharmaceutical starts in laboratories, then continues with animal tests, and after thorough research, the medicinal products that have proven to be sufficiently safe and effective start to be tested in clinical trials involving patients or healthy volunteers.

Developing new pharmaceuticals is a long, complex, and risky process with no guarantee of success. The costs for a clinical trial world-wide are usually in the levels of billions of USD and the process takes several years. Therefore, clinical trials must follow very strict rules and follow a predetermined schedule, the so-called protocol, which allows them to be controlled, verifiable, and serve as a solid base for the registration of medicinal products or medical devices.

Clinical trials involve a broad group of people, who must maintain the validity of the scientific aspects, and tend to involve patients, workers to monitor progress and compliance, and deal with administrative aspects, such as concluding clinical trial agreements.

II. Regulations of Clinical Trials

The regulation of a clinical trial is a relatively new area of law (dates to the 50's of the 20th century), which emerged as a rection to involuntary tests performed on people during the second world war. As a reaction to these atrocities, many countries joined the Council for International Organizations of Medical Science. Subsequently, as the clinical trials developed, the International Conference on Harmonisation was established, which introduced the "ICH E6 Good clinical practice", which addresses good clinical practices, and an international ethical and scientific quality standard for designing, conducting, recording, and reporting.

There are 14 basic principles, which govern modern clinical trials:

(i) Ethical conduct - Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. The three basic ethical principles, namely respect for persons, beneficence, and justice, are of equal importance and permeate all other Handbook for Good Clinical Research Practice (GCP) Guidance for Implementation principles enumerated below.[2]

(ii) Protocol - Research involving humans should be scientifically justified and described in a clear, detailed protocol.[3]

(iii) Risk Identification - Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.[4]

(iv) Benefit-Risk Assessment - Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the research subjects.[5]

(v) Review by Independent Ethics Committee/ Independent Review Board - Research involving humans should receive an independent ethics committee review board approval / favourable opinion prior to initiation. [6]

(vi) Protocol Compliance - Research in humans should be conducted in compliance with the approved protocol. Once the ethics committee gives its approval/favourable decision on the protocol, it is essential that the trial be conducted in compliance with that protocol so that the decision on the ethical acceptability of the trial remains valid. [7]

(vii) Informed Consent - Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the approval of a legally authorized representative should be obtained in accordance with applicable law. [8]

(viii) Continuing Review/Ongoing Benefit-Risk Assessment - Research involving humans should be continued only if the benefit-risk profile remains favourable.[9] The position of monitors who observe the conduction of the trial as well as the principal investigator is therefore crucial. The termination of a clinical trial is often the outcome

2 World Health Organization, *Handbook for Good Clinical Research Practice (GCP) Guidance for Implementation* p. 21 (available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf).
[3] *Id*. at 27.
[4] *Id*. at 35.
[5] *Id*. at 42
[6] *Id*. at 48.
[7] *Id*. at 54.
[8] *Id*. at 59.
[9] *Id*. at 72.

of clinical trial without the medicinal substance being subject to registration simply because its results are not good enough.

(ix) Investigator Qualifications - Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf. [10]

(x) Staff Qualifications - Each individual involved in conducting a trial should be qualified by education, training, and experience to perform their respective task(s) and currently licensed to do so, where required. [11]

(xi) Records - All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.[12] Given that some medicinal substances have long-term effects, it might be necessary to work with clinical trial records even after several years post registration.

(xii) Confidentiality and Privacy - The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). [13]

(xiii) Good Manufacturing Practice - Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.[14]

(xiv) Quality Systems – Systems and procedures, which guarantee the process flow ensuring quality of the clinical trial is a key aspect of every clinical trial. These methods are often updated to ensure the best current standard of practice.[15]

a. Participation in a Clinical Trial

According to the Act on Pharmaceuticals, the following categories of patients are forbidden from participating on the clinical trials: (i) persons deprived of legal capacity or whose legal capacity is limited, persons whose informed consent cannot be obtained due to their state of health, persons who are not citizens of the Czech Republic, or persons under 18; (ii) pregnant women or breastfeeding women; and (iii) dependant persons, i.e., persons in custody or serving a custodial sentence, or persons to whom health services are provided without their consent (conducting a clinical trial on those persons is permissible only if it is expected to provide a preventive or curative benefit to those persons).

b. Conditions Which Must be Fulfilled to Carry out the Clinical Trial

Clinical trial can be carried out only if: (i) the foreseeable risks and difficulties for the trial subjects are balanced by the expected benefits for the subjects as well as for other potential patients; (ii) the trial subject or their legal representative had the opportunity to understand the objectives, risks, and difficulties of the clinical trial as well as the conditions under which the clinical trial is to take place and have been informed of their right to withdraw from the clinical trial at any time; (iii) the rights of the trial subject to physical

[10] *Id*. at 82.
[11] *Id*. at 87.
[12] *Id*. at 92.
[13] *Id*. at 103.
[14] *Id*. at 110.
[15] *Id*. at 115.

and mental integrity, to privacy, and to the protection of data about their person are ensured in accordance with special legal regulations; (iv) the trial subject or their legal representative gave written consent after being informed of the nature, significance, implications, and risks of the clinical trial; (v) the trial subject may withdraw from the trial by revoking their informed consent without any consequential harm caused to them; (vi) the liability insurance of the person conducting the trial and the contracting authority has been entered into prior to the commencement of the clinical trial, the insurance provides compensation in the event of the death of the trial subject or in the event of damage to the health of the trial subject as a result of the clinical trial; the sponsor is obliged to ensure the conclusion of such insurance.

c. Minors and Adults Legally Incapable of Giving Informed Consent

Clinical trials can be conducted on minors or adults legally incapable of giving informed consent only upon fulfilment of set legal conditions such as (i) the informed consent of the parents or another legal guardian was obtained; (ii) the minor has received, from the examiner or their designee, information on the clinical trial, its risks and benefits at a level appropriate to the minor's ability to understand; and (iii) no incentive or financial amount is provided other than compensation etc.

III. Ethical Committee

The ethical committee is an independent body composed of both health professionals and persons without formal medical education. The ethical committee must consist of, at least, one person without medical education and one person who is not an employee of the health service provider who conducts the trial. The ethical committee's responsibility is to protect and ensure the rights, safety, and health of patients (e.g., by expressing an opinion on the clinical trial protocol), the suitability of investigators and facilities, methods, and documents used to inform the patients of the evaluation and to obtain their informed consent. The health service provider or the Ministry of Health are authorized to establish an ethical committee.

IV. Launch of the Clinical Trial

A clinical trial may be initiated by the sponsor only if the ethical committee has issued an affirmative opinion and the SUKL has authorized the initiation of such clinical trial or has not refused a clinical trial where applicable.

a. Assessment of the Application

If the application for authorization of a clinical trial or the notification of a clinical trial is submitted and is considered complete, the SUKL will assess it within 60 or, in certain cases, 90 days since it notified the sponsor of its completeness.

b. Commencement of the Clinical Trial

If the SUKL issues an affirmative authorization, the sponsor may carry out the clinical trial. The sponsor is obliged to immediately inform the SUKL and the Ethical Committee about the commencement of the clinical trial. The authorization of a clinical trial expires if the clinical trial does not start within 12 months of the authorization.

The sponsor is entitled to contractually ensure the fulfilment of part of its obligations related to the clinical trial by another person; the sponsor's responsibility for the accuracy and completeness of the clinical trial data is not affected.

The sponsor provides free medicinal products and any devices used during the trial. If the sponsor is an examiner, a health services provider, a university, or the state through its organizational unit, and the evaluated medicinal products are registered in the Czech Republic, the evaluated medicinal products do not have to be provided free of charge.

V. Process and Termination of the Clinical Trial

Throughout the whole process, the sponsor maintains a protocol. After the clinical trial commences, the protocol can only be adjusted via amendments. In the event of significant changes, the sponsor notifies the SUKL or requests the consent of the ethical committee.

If a new fact arises in connection with the conduct of a clinical trial or the development of the medicinal product and, such fact may affect the safety of the trial subjects, the sponsor and the examiner shall take immediate measures to protect the trial subjects from imminent danger. Moreover, the sponsor regularly, however, at least once a year, evaluates and updates the set of information for the examiner.

The sponsor notifies the SUKL and the relevant ethical committees within 90 days upon the termination of the clinical trial that the clinical trial has been terminated. If the clinical trial is terminated prematurely, the period is reduced to 15 days; in that case, the sponsor shall state the reasons for the early termination. The documentation on the clinical trial, with the exception of the documentation pursuant to a special legal regulation, must be kept by the sponsor or the examiner for at least 5 years from the completion of the clinical trial.

VI. Questions

Related questions:

Who conducts clinical trials?
How long do clinical trials last and how much do they cost?
What are the patients' role in clinical trials?
How are the clinical trials regulated?

Distribution

Learning outcomes

This seminar provides a basic overview of applicable regulatory framework.
As distribution of medicinal products is subject to a very detailed regulation in comparison to distribution of medical devices, emphasis is made on medicinal products.

Students should understand what medicinal products can be distributed, what are the key requirements for a distribution license and what are key distributors obligations. Emphasis is put on reporting obligations which serve a basis for regulatory action related to the availability of medicinal products.

I. Regulations of Distribution of Medicinal Products

The area of distribution of medicinal products in the Czech Republic is regulated by the following regulations: (i) Articles 75 to 78 of the Act on Pharmaceuticals; (ii) Articles 35 to 41, 42, and 45 of the Decree no. 229/2008 Sb., Decree on Production and Distribution of Medicinal Products; (iii) Compilation of Community Procedures on Inspections and Exchange of Information No. EMA/572454/2014; (iv) Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use No. 2013/C 343/01; (v) Guidelines of 19 March 2015 on Principles of Good Distribution Practice of Active Substances for Medicinal Products for Human Use 2015/C 95/01; and (vi) the SUKL Guidelines DIS-13 and DIS-15.

II. Medicinal Products Which Can be Distributed

The following categories of medicinal products may be distributed in the area of the Czech Republic: (i) medicinal products registered in accordance with the Act on Pharmaceuticals or (ii) medicinal products not registered in accordance with the Act on Pharmaceuticals if they are registered in accordance with European Union law by the competent authority of another Member State; however, these medicinal products may not be placed on the market in the Czech Republic, with the exception of deliveries to pharmacies that have a certificate for delivery abroad, their distribution is permitted under the specific treatment programs etc.

Medicinal products, which are not registered and do not fall under a specific import regime (e.g. specific use of medicinal product or individual import) cannot be distributed in the Czech Republic. This is mainly because the key reason for defining distribution rules is to ensure safety of the medicinal products. As unregistered medicinal products did not undergo a scrutiny from the European Medicines Agency or the SUKL, it is not assumed safe to distribute and further use such medicinal products.

III. Distribution Authorisations

An applicant is issued a distribution authorisation if it meets the requirements set by the Act on Pharmaceuticals. Among others, the applicant needs to prove (i) it has the appropriate and adequate premises, installations, and equipment to ensure the proper storage and distribution of medicinal products; (ii) it has ensured the services of persons who meet the conditions set out in the Act on Pharmaceuticals and the services of a

qualified person who is responsible for ensuring that medicinal products, or medicinal substances and excipients according to the scope of the distribution authorisation are distributed in accordance the Act on Pharmaceuticals, etc.

IV. Basic Obligations of the Distributor

The rights and obligations of the distributor are defined in Articles 77 and 76(3) of the Act on Pharmaceuticals. A basic overview of responsibilities is as follows: (i) to subscribe medicinal products only from other distributors or from medicinal products manufacturers or to subscribe products imported by the manufacturers; (ii) to distribute medicinal products only to authorized persons according to Article 77(1)(c) of the Act on Pharmaceuticals; (iii) to ensure an effective system for withdrawing medicinal products from circulation; (iv) to keep records of its activities for 5 years; (v) to keep records to a sufficient extent in accordance with the requirements of the law; (vi) to follow the rules of good distribution practice; (vii) to ensure the supply of medicinal products for human use to operators authorized to dispense medicinal products in quantities and time intervals corresponding to the needs of patients in the Czech Republic; (viii) to provide documentation tracking the distribution of the medicinal product (containing data on the medicinal product, supplier or customer and time data on distribution), if the customer is a pharmacy operator and a holder of a distribution authorisation, to provide relevant data whether it took the supply of medicines as a pharmacy or as a distributor; (ix) to cooperate with the staff of the authorities authorized to carry out inspections; (x) to regularly provide the SUKL with complete and correct data on the supply of medicinal products for human use; (xi) to request the SUKL in advance to change the distribution authorisation in the case of intended changes compared to the conditions under which the authorisation was issued; (xii) to verify the legitimacy of its suppliers and customers (permits, authorizations) and to inspect whether the intermediary is registered in accordance with legal regulations; and (xiii) to verify whether the received medicinal products are not counterfeit, namely by checking the protective elements on the outer packaging according to EC Regulation 2016/161.

V. Risk Management

Quality risk management is a systematic process of evaluating, controlling, communicating, and reviewing all risk factors that could have an impact on the quality of medicinal products. It can be used proactively and retroactively. The management of risks related to the quality of medicinal products should ensure that the risk assessment is based on scientific knowledge, experience with this procedure and, ultimately, contributes to ensuring the quality, efficacy, and safety of the medicinal products distributed.

VI. Distributors' Register

The SUKL establishes and manages a publicly accessible register of distributors, the purpose of which is to register persons authorized to provide mediation of medicinal products for human use. The SUKL shall publish the content of the register of intermediaries on its website.

VII. Other Information

The SUKL collects information from marketing authorization holders, distributors, and pharmacies on the volume of medicinal products on the market in the Czech Republic and on the volume of medicinal products dispensed and used in the provision of health services. The SUKL processes and evaluates this information in order to ensure sufficient coverage by medicinal products. If, on the basis of the evaluation of the gathered information, the SUKL concludes that the current stock of the medicinal product does not adequately cover the current needs of patients in the Czech Republic and a shortage of this medicinal product (i.e., insufficient coverage of current patient needs in the Czech Republic) has a direct impact on the protection of the health of the population and a significant impact on the provision of health services, the SUKL communicates this information to the Ministry of Health. If the Ministry of Health concludes there is a shortage of certain medicinal product, it places such product on the list of medicinal products that the distributors are required to report to the SUKL if being distributed abroad.

In order for the SUKL and the Ministry of Health to have sufficient information about the availability of medicinal products on the market, there are various reporting obligations of the stakeholders. The reporting obligation pertains to (i) distributors authorised to distribute medicinal products in the Czech Republic, (ii) local manufacturers or importers of medicinal products outside of the EU, and (iii) distributors executing deliveries of medicinal products in the Czech Republic on the basis of a distribution authorisation issued by the concerned authority of another EU member state.

The reports must be submitted monthly and must be provided to the SUKL no later than the 10th day of the month following the relevant calendar month for which the report is being made. The reporting is made in relation to each individual warehouse separately and it must be distinguished between reporting delivery or return of medicinal products. The reports must be submitted regardless of the fact that no actual distribution occurred during the relevant month.

The reporting relates to registered medicinal products including promotional samples and specific cases of supply of non-authorised medicinal products, e.g., medicinal products supplied under specific therapeutic program. In specific cases, it may also include the supply of pharmaceuticals abroad (outside of the Czech Republic).

The reports are submitted via an electronic interface of the SUKL. The report varies depending on the type of recipient of the medicinal products. However, in general, the reported data include for example, the following items: medicinal product movement type (delivery or return of pharmaceuticals), client type, the SUKL code and name of the pharmaceuticals, price, quantity, batch, marketing authorisation holder.

Reporting is a crucial basis for regulatory authorities making decisions related to availability of medicinal products on the Czech market. The data also serves as a base for *de lege ferenda* plans of the regulatory bodies. In particular, data on availability is an important argument for the introduction of various emergency supply schemes related to medicinal products which are not usually available on the market or are subject to temporary outages. However, such schemes may be introduced only under the framework of statutory regulation and there a legislation change is needed. Although there are discussions on the unavailability of medicinal products taking place for the past several

years, there is no complex emergency supply scheme in place. It is particularly important in situations where the supply of medicinal products from outside of the EU is endangered due to restrictions of logistics and national actions related to limitation of export of medicinal products in the countries where such medicinal products are being manufactured.

VIII. Distribution of Medical Devices

Given the fact that the majority of medical devices do not present a significant risk to human health compared to medicinal products, the conditions for distribution are significantly less comprehensive and complicated.

Distribution of medical devices is governed by the MDR, in particular its Article 14, and the partially by the Act on medical devices. The key principle of the regulation of distribution is that it may be carried out by a notified distributor, unless specific exemptions under Article 23(1) of the Act on Medical Devices apply, i.e., the distribution only relates to risk class I medical devices or the distributor only supplies medical devices to a user who is not a health services provider.

In accordance with Article 14(2) of the MDR, before making a device available on the market, distributors shall verify that all of the following requirements are met: (i) the device has been CE marked and that the EU declaration of conformity of the device has been drawn up; (ii) the device is accompanied by the information to be supplied by the manufacturer in accordance with the MDR; (iii) for imported devices, the importer has complied with the requirements set out in the MDR; (iv) that, where applicable, a UDI (Unique Device Identification) has been assigned by the manufacturer.

The MDR also imposes other obligations on distributors, such as the obligation to ensure that, while the device is under their responsibility, storage or transport conditions comply with the conditions set by the manufacturer.

IX. Questions:

Can a non-registered medicinal product be distributed?
What does a distributor need to fulfil to distribute medicinal products?
Is distribution of medicinal products and medical devices similar?
Where is the legal regulation of distribution of medicinal products?

Reimbursement of Pharmaceuticals

Learning outcomes

This seminar provides students with an overview of the free healthcare concept in the Czech Republic in relation to pharmaceuticals, medical devices, and healthcare services with the focus on understanding how reimbursement practically works so citizens can enjoy free pharmaceuticals and medical devices.

The students should understand the basic requirements of the process of reimbursement for medical devices and pharmaceuticals.

I. Free Access To Healthcare

Free access to healthcare is guaranteed by the Charter of Fundamental Rights and Freedoms (Chapter 4, Article 31) under which "*Everybody has the right to protection of their health.* ***Citizens are entitled under public insurance to free medical care and to medical aids*** *under conditions set by law*". Medical care means health services while medical aids mean pharmaceuticals or medical devices. The government is obliged to ensure free access to healthcare for citizens based on the system of public insurance.

a. Free Access to Healthcare vs. Regulatory Fees

In 2008, a system of regulatory fees was introduced in order to regulate the overuse of patient visits of health services providers. Fees for certain health services were set at CZK 30 (approx. EUR 1.20) for a medical examination and medical prescription (repealed by legislation), CZK 60 (approx. EUR 2.40) for one day of on-board hospital care (repealed by the Constitutional Court[16]) and CZK 90 (approx. EUR 3.60) for an emergency service provided. According to statistics, the number of prescriptions of pharmaceuticals decreased by 40% after the introduction of regulatory fees.

In 2014, the regulatory fee for on-board hospital care was repealed by the decision of the Constitutional Court[17] due to its increase from CZK 60 to CZK 100. The court ruled that it conflicts with the right to a free access to healthcare as provided by the Charter of Fundamental Rights and Freedoms. Such a regulatory fee would restrict access of a certain group of persons to healthcare (economically weaker groups of persons).

In 2015, the regulatory fee for medical examinations and medical prescriptions was repealed by the legislature (initiated by the politicians).

[16] Decision of the Constitutional Court of the Czech Republic Pl. ÚS 1/08 of 20 May 2008, available at http://nalus.usoud.cz/Search/GetText.aspx?sz=Pl-1-08_1.
[17] Decision of the Constitutional Court of the Czech Republic Pl. ÚS 36/11 of 20 June 2013, available at https://www.usoud.cz/fileadmin/user_upload/Tiskova_mluvci/Pl__US_36-11_nadstandard-_konecne_zneni_oprav-3.pdf.

II. Public Health Insurance in the Czech Republic

Pharmaceuticals, medical devices, and health services are either reimbursed a) fully by the insurance company; b) partly by the insurance company and partly paid by a patient; or c) fully paid by the patient.

In the case of partial reimbursement of the medicinal product by the insurance company patients pay a co-payment which is set as the difference between the price for which the medicinal product is provided to the final consumer and the amount of the reimbursement. The amount of the co-payment is determined by the SUKL.

a. Medicinal Products

Each medicinal product intended to be reimbursed from public health insurance is subject to (i) "price" regulation (maximum price / matter-of-fact price AND mark-ups); (ii) "amount of reimbursement" regulation (i.e., reimbursement by the insurance company); and, potentially, (iii) "reimbursement conditions" regulation (e.g., prescription and indication restrictions or use in the provision of health care in specialized workplaces).

If a SUKL decision determines the amount of reimbursement and the conditions of this reimbursement, health insurance companies are obliged to reimburse the medicinal product in accordance with such decision.

Mark-ups applied in the distribution chain are governed by the Price Regulation of the Ministry of Health. Thus, the final price of a medicinal product may vary from one pharmacy to another because of the pricing policy of each participant in the distribution chain.

b. Medical Devices

The system of reimbursement of medical devices has recently been amended. The amendment follows the decision of the Czech Constitutional Court from 2017[18], according to which, the original rules on reimbursement of medical devices stipulating that medical devices are reimbursed from public health insurance in the least economically demanding version, as identified by the market research carried out by a health insurance company, are non-transparent and non-reviewable.

Under the new rules, only medical devices included in any of the reimbursement groups listed directly in the Act on Public Health Insurance would be reimbursed from public health insurance in the amount and under the terms laid down therein.

Medical devices are included into reimbursement groups or groups of essentially interchangeable medical devices (i.e., even narrower groups including medical devices which, by their specific functional characteristics and their intended purpose of use, are aimed in the same way at treating the health condition of patients with the same indication) on the basis of a notification to the SUKL.

Based on such notification, the SUKL updates the list of medical devices that may be subject to full or partial reimbursement from public health insurance. The SUKL would review the fulfilment of legal requirements for the inclusion of specific medical devices in

[18] Decision of the Constitutional Court of the Czech Republic Pl. ÚS 3/15 of 30 May 2017, available at https://nalus.usoud.cz/Search/ResultDetail.aspx?id=97740&pos=1&cnt=1&typ=result.

the reimbursement group only ex post if it is concluded that such legal conditions have not been fulfilled.

c. Health Services

Healthcare services are reimbursed from the health insurance by the respective health insurance company to which a patient is contracted to. Health services are reimbursed only if the health service provider is contracted to patient's health insurance company, otherwise the patient must pay for the procedure by themselves. Healthcare service providers, that wish to have the health services reimbursed from public health insurance, must conclude a framework agreement on the provision and reimbursement of the reimbursed health services with the health insurance companies. The reimbursement of health services is regulated by government tariffs applicable for the relevant year, unless otherwise agreed between the health insurance company and the health services provider.

Reimbursement tariffs are set by the Ministry of Health through a point scheme, under which each medical procedure is assigned a point value by the relevant national authorities, subject to periodic revisions to such point values as practices and techniques evolve. Payments for medical procedures are made by health insurance companies on behalf of patients who receive such procedures.

d. Inpatient Care

There are no differences between the pricing of pharmaceutical products delivered to patients "in the community" and the pricing of pharmaceutical products delivered to patients in hospitals in the Czech Republic. When providing inpatient care, the health insurance company fully reimburses (i) medicinal products; (ii) individually prepared medicinal products; (iii) radiopharmaceuticals and transfusion products; (iv) medical devices; and (v) pharmaceuticals for advanced therapies, tissues, and cells that are less economically challenging depending on the extent and severity of the illness.

III. Pricing and Reimbursement of Pharmaceuticals

e. Legal Background

EU

Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (Transparency Directive).

CZ

Act No. 48/1997 Sb., on Public Health Insurance; Price Regulation of the Ministry of Health 1/2019/FAR; and implementing decrees of the Ministry of Health.

The Public Health Insurance Act stipulates the types of pharmaceutical products that the health insurance company reimburses. The Czech regulatory authorities are the SUKL, as the primary competent authority, and the Czech Ministry of Health which also participates in regulating the price of pharmaceutical products.

The process of setting the maximum price and reimbursement price was significantly amended in 2008, in connection with the implementation of the Transparency Directive. Previously, the reimbursement of medicinal products was set by the Ministry of Health

while the maximum price was set by the Ministry of Finance. The process was often criticized for being non-transparent and lacking control by superior administrative body. As of 1 January 2008, the SUKL took over this agenda and is now responsible for price regulation and setting reimbursement prices of medicinal products.

According to Article 6(1) of the Transparency Directive

> *Member States shall ensure that a **decision on an application** submitted, in accordance with the requirements laid down in the Member State concerned, by the holder of a marketing authorization **to include a medicinal product in the list of medicinal products covered by the health insurance systems is adopted and communicated** to the applicant within 90 days of its receipt.*

According to Article 6(2) of the Transparency Directive

> ***Any decision** not to include a medicinal product in the list of products covered by the health insurance system **shall contain a statement of reasons based upon objective and verifiable criteria**, including, if appropriate, any expert opinions or recommendations on which the decision is based. In addition, the applicant **shall be informed of the remedies available to him under the laws in force and of the time limits allowed for applying** for such remedies.*

IV. Reimbursement of Pharmaceuticals

When setting the reimbursement amount and conditions, the SUKL evaluates a pharmaceutical in terms of (i) its therapeutic efficacy and safety; (ii) the gravity of the illness that the pharmaceutical product treats; (iii) its cost-effectiveness and impact of its use on health insurance funds; (iv) public interest; (v) the suitability of route of administration, drug form, strength, and packaging size; (vi) the usual dosage; (vii) the necessary treatment duration; (viii) the level of cooperation of the person to whom the pharmaceutical product is administered; (ix) its substitutability with other pharmaceutical products reimbursed from health insurance and the comparison of the price and reimbursement of such pharmaceutical product with the price of the evaluated pharmaceutical product; and (x) the recommended procedures of professional institutions and professionals, always in terms of cost-effectiveness and the impact on health insurance funds.

When setting the amount and conditions of the reimbursement of a pharmaceutical, the SUKL includes it in a reference group, i.e., a group of pharmaceutical products that, in general: (i) are therapeutically interchangeable; (ii) have similar or close efficacy and safety; and (iii) have similar clinical uses.

The Ministry of Health issues a decree on the list of reference groups. The decree determines about 200 groups of pharmaceutical products based on therapeutic indications. The reimbursement price is set according to the EU's lowest price of a medicinal product within a reference group (reference product). In general, the cheapest out of a defined group of pharmaceutical products (in most cases a locally manufactured one) is fully reimbursed.

a. Specific Reimbursement of Generics

The original pharmaceuticals are more expensive than generics. The reason for this is that the original pharmaceuticals are subject to a costly process of development and clinical trials prior to registration. Generic pharmaceuticals are only subject to this process to a very limited extent before registration.

It is clear, therefore, that more financial means is necessary to register the original pharmaceutical product, but this will then be reflected in the selling price of such pharmaceutical product.

The SUKL reduces the reimbursement amount by 32% for a product registered as generic under the Act on Pharmaceuticals, provided there is only one similar product within the reimbursement system which was not registered as a generic pharmaceutical; or by 15% for a product not registered as generic under the Act on Pharmaceuticals if there is only one similar product within the reimbursement system which is not registered as a generic medicinal product. The reimbursement of the first similar product in the reference group reduces the base reimbursement identical for the whole reference group by the same percentage.

V. Pricing of Pharmaceuticals

According to the Price Regulation, pharmaceutical products that the health insurance company reimburses are subject to (i) the regulation of the maximum price of a pharmaceutical product; (ii) the regulation of a matter-of-fact price (if applicable); and (iii) the regulation of maximum distribution margin, i.e., the maximum margin which a distributor may add on top of the price that an entity launching the product on the market in the Czech Republic charges.

The maximum price of the originator means the highest possible price for which a manufacturer, importer, or market authorisation holder (i.e., an originator) can place a pharmaceutical on the Czech market. It is set by the SUKL for pharmaceuticals reimbursed from public health insurance. The maximum price of the originator is not set for pharmaceuticals not covered by public health insurance. The maximum price of the originator then forms the basis for calculating the selling price for which patients buy pharmaceuticals in a pharmacy. The selling price of the pharmaceutical is composed of the originator's price, business mark-up, and VAT.

The ex-factory price of a certain medicinal product is set as the average of the 3 lowest ex-factory prices of this medicinal product found in the reference basket (reference basket states – all EU countries except for Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Germany, Greece, Luxembourg, Malta, and Romania). If the reference basket lowest price is extremely low (more than 20% lower than the average of 2 other lowest prices of the same product) then the price is set as the average of the 2 other lowest prices of the reference product. If the product (with the exception of highly innovative pharmaceuticals) is not on the market in at least three reference basket states, the agreed price of the medicinal product can be used in the evaluation. If none of the above-mentioned procedures are applicable, the price is set as the maximum ex-factory price of the closest therapeutically comparable medicinal product available in the Czech Republic or in the reference basket countries.

VI. Pricing and Reimbursement Procedure

The requirements for accepting the application for setting the maximum price and/or reimbursement (meaning both reimbursement price and conditions of reimbursement) differ for the applicant of generic and original medicinal products.

The application for the reimbursement of a generic or biosimilar product is simpler than the application for the reimbursement of the original product. In case of an original product or in case of a new indication, it is, among other things, necessary to submit (i) data from clinical trials; (ii) cost effectiveness analyses; and (iii) budget impact analyses.

The pricing and reimbursement procedure is run as an administrative proceeding with fixed terms and conditions where the company (in connection with both original and generic medicinal product) has to apply (fill the form) and the decision is made within 75 days in case of an application only for price or only for reimbursement (165 respectively for joint application for price and reimbursement). Since 2012, a special type of short 30-days procedure is available for generic and biosimilar products. The appeal authority against decisions made by the SUKL is the Ministry of Health.

VII. Special Cases

a. Innovative Pharmaceuticals

Different rules apply regarding a health insurance company's reimbursement of highly innovative pharmaceutical products. In compliance with the Public Health Insurance Act, the SUKL decides on the amount and conditions of a temporary reimbursement of a highly innovative pharmaceutical product in respect of which there is insufficient information on its cost effectiveness or the results of therapy during its use in clinical practice. The amount and conditions of the reimbursement are stipulated for a 24-month period and may be renewed for a further 12 months.

b. Pharmaceuticals Not Registered in the Czech Republic

The SUKL may decide on the amount and conditions of reimbursement of pharmaceutical products that are not registered in the Czech Republic. It may issue this decision if the use of the unauthorized pharmaceutical product was approved within a specific therapeutic program according to the Act on Pharmaceuticals. The SUKL determines the reimbursement of the unauthorized pharmaceutical product if its use is sufficiently substantiated lege artis (by expertise) and it is the only method of treatment, or if its use is cost-effective in comparison with the treatment available and shall do so for the duration of the specific therapeutic program.

c. Off-Label Use of Pharmaceuticals

The SUKL may decide on the reimbursement of a registered pharmaceutical product for off-label use in cases where use of that product is sufficiently justified by the current state of knowledge and the use of the pharmaceutical product is the only option of therapy or the use is cost-effective in comparison with the available therapy.

VIII. Questions:

Does every citizen in the Czech Republic have access to healthcare?
Which regulatory norms apply to the legal regulation of reimbursement?
Is the price of reimbursed medicinal products regulated?
Are medical devices subject to reimbursement? If yes, describe the process.
Is off-label use subject to reimbursement?

Advertising and Marketing

Learning outcomes

This complex topic is connected with various other topics within the course of the Legal Regulation of Pharmaceuticals and Medical Devices. Therefore, this seminar should serve to provide knowledge of rules for advertising of pharmaceuticals and medical devices and for understanding the implications if advertising is connected with other activities in the life science industry (e.g., patient finding and interacting with HCPs).

The students should understand the basic statutory rules related to advertising of pharmaceuticals and medical devices and the differences between advertising aimed at the general public and healthcare professionals.

I. Advertising of Pharmaceuticals

The pharmaceutical industry is subject to rigorous legal regulation. Therefore, the advertising of pharmaceutical products is also subject to various legal rules with the aim to restrict communication to the general public with respect to Rx medicinal products. The communication to the general public with respect to OTC medicinal products is not restricted, however, there are specific rules defining what the advertising should include. The purpose of the legal regulation is to protect the general public from receiving advertising regarding a product which they cannot understand given the lack of their medical education.

II. Regulatory Framework

The regulatory framework for the advertising of medicinal products consists of Act No. 40/1995 Sb., on Regulation of Advertising, Act on Pharmaceuticals, and Act No. 89/2012 Sb., Civil Code. In addition, some specific rules may be found in Act No. 480/2004 Sb., on Certain Services of Information Society; Act No. 634/1992 Sb., on Protection of Consumer; Act No. 40/2009 Sb., Criminal Code; and Act No. 231/2001 Sb., on Radio and Television Broadcasting.

III. Basic Terms

The term "*Advertising*" means any announcement, demonstration, or other presentation, circulated primarily through communication media, intended to support economic activity; in particular, consumption or sale of goods, construction or lease of real estate, sale or use of rights or obligations, provision of services, or promotion of a trademark. Specifically, in relation to pharmaceuticals, the term includes any information, persuasion, or incentive provided in order to support the prescription, supply, sale, dispensing, or consumption of pharmaceuticals, in the form of, namely: (i) visits by sales representatives; (ii) supply of free samples of pharmaceuticals; (iii) a gift, consumers' lottery or offer of any benefit or financial or another reward; (iv) the sponsoring of promotional meetings attended by healthcare professionals; and (v) the sponsoring of scientific congresses attended by healthcare professionals and reimbursement of travel and accommodation costs related to their participation.

On the other hand, the legal regulation provides examples of what is not considered advertising, e.g., advertising of a company's reputation in general, rather than drawing attention to a certain or identifiable pharmaceutical product; information on human health or disease, unless it contains any reference (even a hidden reference) to a human medicinal product; sales catalogues and pricelists, unless they include a description of the medicinal product's characteristics; or non-promotional correspondence and related materials used to respond to an individual inquiry regarding a particular medicine.

There are several subjects that are liable for particular advertising, i.e., an *advertiser* who has ordered an advertisement from another person; an *advertising processor* who has processed the advertisement either for itself or for another legal or natural entity; and a *disseminator of advertising* who publicly disseminates the advertisement.

IV. Supervision of Advertising

Advertising is supervised by the SUKL, which is the regulatory authority in the area of advertising medicinal products, with the exception, however, of advertising on radio and television, which is supervised by the Council for Radio and Television Broadcasting. The rules on advertising, which are stipulated by the Code of Ethics of Association of Innovative Pharmaceutical Industry (*AIFP*) are supervised by the AIFP's Ethics Committee, and the rules on advertising, which are stipulated by the Code of Ethics of Czech Association of Pharmaceutical Companies (*CAPC*) are supervised by the CAPC's Ethics Committee.

V. Advertising Aimed at the General Public

Advertising aimed at the general public is, by law, restricted to OTC medicinal products, with the exception for vaccination campaigns specifically approved by the Ministry of Healthcare of the Czech Republic. However, under certain conditions, items such as educational brochures for patients regarding Rx medicinal products are allowed provided no promotional claims are allowed in such brochure and there is a need for additional information, which is medically justified.

Information on human health or disease, unless it contains any reference (even a hidden reference) to a human medicinal product, are not considered advertising and thus disease awareness campaigns not containing any direct or indirect reference to any medicinal product aimed at the general public should be, in general, allowed.

The advertising of Rx pharmaceuticals, with respect to the general public, is forbidden. In this respect, the following is also prohibited: (i) provision of free samples of pharmaceuticals; (ii) comparative advertising; and (iii) advertising that, e.g.,: (a) creates the impression that consultation with a physician is not necessary; (b) indicates guaranteed effects or lack of any side effects; (c) indicates that the use of a medicinal product will improve the health of a person who uses it; (d) indicates that failure to use a medicinal product may adversely affect the health status of persons; or (e) indicates in an inappropriate, excessive, or misleading manner the possibility of healing.

Generally, the advertising of OTC medicinal products must (i) include the name of the medicinal product as it appears in the marketing authorization; (ii) contain the information necessary for the proper use of the medicinal product; and (iii) include a clear invitation to read the product information leaflet carefully.

VI. Advertising Aimed at HCPs

Rx pharmaceuticals may be advertised only to HCPs, i.e., persons authorized to prescribe or dispense such products, such as physicians and pharmacists. In the past, the SUKL, and subsequently the Municipal Court in Prague in the case against Walmark – file no. 8 As 204/2014[19], ruled that legal entities (e.g., pharmacies) can also be considered healthcare professionals. However, this opinion is not widely accepted, and it remains unclear if this legal interpretation would be enforced by the SUKL in the future.

The advertising of Rx pharmaceuticals may be carried out only through information channels dedicated mainly to healthcare professionals. The advertising must include (i) accurate, current, and verifiable information; (ii) basic information according to the summary of product characteristics (SPC), including the date of approval or latest revision; (iii) information about the manner of dispensing the product according to the registration decision; and (iv) information about the reimbursement status of the product under the public health insurance system. The information channels may include, for example, periodicals for healthcare professionals, professional literature; websites dedicated only to healthcare professionals having double-click verification for HCPs.

The Act on Pharmaceuticals considers hospitality and entertainment, as well as gifts, provided to HCPs as advertising and thus stipulates several rules related to such activities. Hospitality is legally permissible if it is commensurate with the nature of the meeting, secondary to the main purpose of the meeting (i.e., scientific or business) and extended only to HCPs (i.e., not to their spouses or social partners). The entertainment of HCPs is prohibited and therefore HCPs may not be provided with tickets to theatre or sport events as part of sponsorship, hospitality, or entertainment.

Gifts or other benefits can be promised or provided to individual HCP in connection with the advertising of human pharmaceuticals only if the gift or other benefit is of a small nominal value and it is related to the HCP's expert activities. According to a resolution of the SUKL (ÚST-16), "*small nominal value*" means CZK 1,500, including all gifts provided to an individual HCP in a particular calendar year. The SUKL also mentions the criterion of influencing a professional's judgment. The AIFP Code of Conduct allows that only literature and medical utility items may be provided to HCPs.

VII. Content of Advertising of Rx Medicinal Products

The advertising of a medicinal product for human use must support its rational use without exaggerating its properties. All information contained in the advertisement (and thus information taken from professional publications or from the professional press) must be supported by the SPC. The advertisement **may contain additional claims, provided that these statements confirm or refine the SPC data and are compatible with them and do not distort them.**

[19] Decision of the Municipal Court in Prague 8 As 204/2014 of 10 September 2015, available at http://www.nssoud.cz/files/SOUDNI_VYKON/2014/0204_8As__1400058_20150914135222_prevedeno.pdf

VIII. Reminder Advertising

A specific type of advertising is the so-called reminder advertising. If the advertisement of a pharmaceutical product is intended to serve as a reminder of such product, it must not include information other than (i) the brand name of the product approved in the marketing authorization; OR (ii) its International Non-proprietary Name (INN); AND/OR a trademark.

A reminder advertising is allowed to be aimed at healthcare professionals with respect to Rx medicinal products and OTC medicinal products, as well as to the general public with respect to OTC medicinal products.

IX. Samples

In the course of advertising medicinal products, free samples may be provided to persons authorized to prescribe medicinal products on the basis of their written and dated request. The samples may be provided in the form of the smallest registered package with label "*sample - not for sale*". The samples should be provided exceptionally in limited amounts per calendar year, the SUKL recommends samples for treatment of 5 patients per year, for 3 months of their treatment. Samples are regular pharmaceuticals and may be distributed only by distributors or sales representatives authorized by the marketing authorization holders. Samples may not be provided based on request by an institution. Samples may not be distributed to the general public and may not contain narcotic or psychotropic substances.

X. Advertising of Medical Devices

Previously, the advertising of medical devices was not subject to specific legal regulation. Only the general rules applied. A new regulatory framework regarding advertising of medical devices was enacted, in connection with the introduction of the MDR, which became effective on 26 May 2021.

A new legal framework for the advertising of medical devices came into force on 26 May 2021. Newly**, the advertising of medical devices and in vitro diagnostic medical devices are regulated alike as the advertising of human medicinal products.**

The definition of advertising for medical devices and in vitro diagnostic medical devices is similar in extent to the definition of advertising for medicinal products for humans, therefore applies to **any provision of information about the product in order to increase its sales**. Exceptions shall be the information provided in response to specific questions or accompanying documentation of a non-promotional nature, as well as catalogs without a description of the medical device and general information on diseases without reference to a medical device or an in vitro diagnostic medical device, as in the case of medicinal products for humans.

The subject of any advertising can be only medical devices, that can be in accordance with the MDR placed on the market and in vitro diagnostic medical devices, that can be in accordance with legislation placed on the market, but there is an exception for placing and presenting non-approved devices at trade fairs.

XI. Advertising Intended for the General Public

The subject of the advertising intended to the general public may not be a medical device and an in vitro diagnostic medical device, **which is intended solely for use by healthcare professionals; and further, on medical devices available only by prescription**. Furthermore, these medical devices and in vitro diagnostic medical devices are prohibited to be provided to the general public in the form of **samples.**

The law contains relatively **detailed rules on how advertising for medical devices and in vitro diagnostic medical devices must be formulated for the general public** (for example, must contain: the trade name of a medical device and in vitro diagnostic medical device, the intended purpose of a medical device and in vitro diagnostic medical device, and many others, **and at the same time, it stipulates what advertising cannot contain** (for example, give the impression that consultation with a doctor, medical intervention, or treatment is not necessary, especially by offering a diagnosis or offering treatment at a distance, to point out in an inappropriate, exaggerated, or in a misleading way to the possibility of recovery and many others.

Advertising Aimed at Professionals

Advertising aimed at professionals in the field of medical devices and in vitro diagnostic medical devices applies similar rules as in the case of medicinal products for humans. The important aspect here is the expertise of the communication and suitability of the medium (aimed primarily at professionals). The regulation copies the regulation of sponsorship restrictions and gift restrictions to a negligible value and relation to the performed activity.

The provision of samples is possible in the amount necessary to test the medical device and in vitro diagnostic medical device in accordance with the intended purpose of use. Thus, the provided sample of a medical device and in vitro diagnostic medical device must be visibly marked with the words "*Not for sale*" or "*Free sample*".

Advertising for a Health Targeting Product

Another novelty that the amendment brought, is the concept of a **health targeting product.** Advertising is newly regulated also for this product. The definition of a health targeting product is relatively vague definition and will be specified in subsequent practice. Advertising for any health targeting product that is neither a medicinal product, nor a medical device, nor an in vitro diagnostic medical device, nor a food for special medical purposes, which suggests that the product is a medicinal product, or a medical device, or an in vitro diagnostic medical device, or a food for special medical purposes, shall be prohibited.

Furthermore, advertising for such a product *shall not imply that the use of the product will improve or preserve the health condition of the user, imply that the non-use of the product may adversely affect the health condition of persons, or recommend the product with reference to the recommendations of scientists, health professionals, or persons who are not one of these, but which, due to their actual or assumed social status, could encourage the use of the product.*

XII. Questions

Related questions:

What constitutes advertising?
What is reminder advertising?
What obligatory information must advertising focused on the general public include in relation to OTC products?
What is the source of regulation of advertising?
Which authority is the supervision of compliance with advertising rules?

Relations with HCPs

Learning outcomes

Interactions with HCPs are crucial for the life science industry both in terms of advertising as well as development. Since the HCPs have some powers given by the state, e.g., prescription, and they are instrumental to the provision of healthcare services, this seminar will focus the types of interactions and key aspects of the selected types.

The students will discuss the role of HCPs and their potential conflict of interest in interacting with the life science industry.

I. Relations with HCPs

The life science industry is specific in the necessity of research and development and the involvement of physicians (HCPs) in these activities. Given the fact that such physicians may prescribe products of their partners (life science companies), there is a potential conflict of interest which is resolved by various rules and principles.

There are two types of interactions between the life science industry and HCPs – (i) interactions which are considered as advertising where the HCPs are passive recipients of performance from the life science industry and (ii) interactions where the HCP is in a position of a vendor of the life science industry and actively provides services, e.g., as a member of an advisory board, speaker, or investigator in a clinical trial, etc.

The governing principle of interactions between the life science industry and HCPs is that the advertising interactions must adhere to strict statutory and self-regulatory rules and that any services must be of fair market value and there must a legitimate need for such service.

While there is no specific legal regulation focused just on interactions with HCPs, the regulation comes from (i) the Act on Advertising and (ii) self-regulation (the AIFP Code of Practice and the MedTech Code of Conduct).

II. Education of HCPs and Support of Meetings

The education of HCPs is often provided as a sponsorship of a healthcare professional or an organizer of a meeting. A life science company may provide sponsorship to the organizer of a seminar, scientific congress or symposium (i.e., scientific meeting), or a meeting attended by healthcare professionals organized in order to support the prescription, sale, supply, or consumption of human pharmaceuticals (i.e., promotional meeting). It is also lawful to reimburse healthcare professionals for costs incurred as a result of attending scientific events in relation to transport, accommodation, and registration fees.

The support of HCPs education is considered advertising and it is therefore in the scope of the Act on Advertising. The definition of an HCP under the Act on Advertising recognizes a group of people who may be subject of advertising related to Rx medicinal products, medical devices, or in vitro diagnostic medical devices. Therefore, the support of education

related to Rx medicinal products, medical devices, or in vitro diagnostic medical devices is limited only to HCPs.

III. Market Research and Non-Intervention Study

In their capacity as service providers, HCPs often participate in market research. Such research is used for the life science industry to obtain information which then improve their commercial activities. Such market research is not a specifically regulated activity provided it does not fulfil the criteria of a non-intervention post-registration study (*NIS*) under Article 3a(2) of the Act on Pharmaceuticals. An NIS is a study where a medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of a patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicinal product is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods must be used for the analysis of collected data. Therefore, should any market research consist of a prescription of a medicinal product, it would be subject to the regulation of an NIS in the Act on Pharmaceuticals and as such it would need to be reported to the SUKL.

IV. Speakership and Advisory Board

The other most common type of interaction between the life science industry and the HCPs in their capacity as service providers are speakerships and participation at the advisory boards.

Speakership engagement entails the interaction of an HCP in a capacity as a speaker at an event. Such speaker usually prepares a presentation related to their area of expertise. The key element which needs to be addressed is that the entity, which engaged such speaker, will usually be liable for the content of such presentation. Therefore, it needs to be certain that such presentation, as it will be considered advertising, does not include off-label recommendations and it complies with all necessary aspects of an advertising material. Thus, it is quite common that life science companies reserve the right to review such presentations and request changes where necessary to mitigate any potential non-compliance.

V. Contractual Relationships

As standard practice, interactions between HCPs and industry are recorded in contractual documents. Such documents provide an overview of the applicable rules, which the contractual parties (i) wish to impose upon themselves but also (ii) rules which apply anyway but the contractual parties wish to summarize in an agreement for ease of reference.

While there is no specific legal regulation of contracts between HCPs and life science industry companies, from a practical point of view, the key areas to focus on in a contract are, depending on the nature of interaction, intellectual property, transparency, anti-bribery warranties, and safeguards ensuring that if the interaction does not take place, the HCP will return the funds or support which they have been provided with.

VI. Questions

Related questions:

Which particular subjects include the term “healthcare professional”?
What is a benefit for a person if they are considered a healthcare professional?
What is a key source for regulation of relations with healthcare professionals?
What would you put into a contract for sponsorship of HCPs attendance of an educational meeting, what wording would you use?

Compliance

Learning Outcomes

Compliance is a relatively new area of the life science industry, which ensures that all commercial activities meet the legal and ethical standard of a given life science company. The students should be able to identify potential areas that may be important for an international life science corporation and articulate a compliance program for such company.

I. Compliance

Given the fact that the life science industry is subject to some of the most rigorous legal regulation, compliance plays a key role in this industry. Specifically, in the life science industry, there is a significant role of self-regulation associations (EFPIA or MedTech associations), which define their own rules, which are stricter than those stipulated in statutory regulation. The key principle of such rules is to avoid regulation from the government and adhere to the regulation, which is prepared by professionals with the knowledge of the specifics of the industry.

II. Compliance Programs

Compliance as a concept is carried out via compliance programs, which define basic rules, processes, and oversight. Such rules are stipulated in so-called Standard Operating Procedures (*SOP*), which define processes, responsibilities, and potential sanctions. From a legal perspective, the SOP should be implemented as internal regulations of employers to ensure that they are binding on employees and potential non-compliance could be sanctioned by termination of employment. Financial sanctions on employees are very limited and in the corporate environment very unusual.

The governing principles of compliance programs are:

(i) correctness – this is based on the requirement that all external communication, particularly health claims, must be valid, exact, documentable, complete, balanced, and may not generate misleading outcomes;

(ii) independence of prescription – given the potential conflict of interest of a HCP who would interact with life science industry, there must be safeguards guaranteeing that any interaction will be free from any potential measure, which can influence prescription, e.g., any link between prescription and financial funds for rendered services;

(iii) written form – it is highly recommended to ensure that any internal decision or external action is well documented, including stipulating involved individuals and approvers of a given activity, any legal interaction between a life science company and an HCP should be documented in a written signed agreement;

(iv) selection by qualification – engagement of a particular HCP as a service provider should be subject to careful selection and consideration of qualification of such an HCP to avoid any potential concern related to the legitimacy of the services provided by such an HCP;

(v) fair market value – it is necessary to ensure that any payment to an HCP will be in line with the fair market value of the services of such an HCP; this is achieved through sophisticated fair market value calculators which are developed to reflect what is a fair remuneration for services of a given HCP (it considers experience of the healthcare professional as well as the nature of the services which are to be provided);

(vi) genuine need – engagement of an HCP should be based on a genuine need for services of such an HCP, i.e., a life science company should be able to demonstrate how it benefits from services provided by the HCP;

(vii) benefit of the public from grants – any gifts or grants should follow improvement of education, research and development, or healthcare and should not primarily serve as a benefit provided to a particular healthcare professional;

(viii) documentation of payments – all payments must be duly documented as it is also a requirement under good accounting principles; and

(ix) due diligence – to avoid any unnecessary risks arising out of engagement or cooperation of a partner, which may have public record of non-compliance, it is very common and recommendable to ensure that there is a due diligence process in place, which ensures that only reputable partners are engaged and any risk to a life science company is thus limited in this respect.

In general, compliance programs have been historically inspired by the US Foreign Corrupt Practices Act (*FCPA*), which, when simplified, requires US-based companies to introduce mechanisms to identify, report, and rectify any conduct that could be incorrect in nature. The sanctions for non-compliance are very often imposed in the tens of millions of USD and there is an individual criminal liability of the responsible managers (including liability of the managers, which did not conduct the corrupt practices but ignored them). For more information see https://www.sec.gov/spotlight/fcpa/fcpa-cases.shtml.

In the Czech Republic, the compliance programs are often inspired by the guidelines of the Prosecutor General's Office on application of Article 8(5) of Act No. 418/2011 Sb., on the Criminal Liability of Legal Entities and Proceedings Against Them. These guidelines indirectly provide instructions to legal entities how to fulfil their exculpatory compliance programs to avoid criminal liability.

Any efficient compliance program should be accompanied with measures on continuous observance and review. Therefore, it is more and more common that companies have introduced a special role of compliance officer whose purpose is to implement, enforce, improve the compliance program of the company.

III. Questions

Related questions:

Why is compliance important in the pharma industry?
What are the key principles of compliance programs in the Czech legal environment?
Look up several codes of ethics of key international life science companies and describe what they have in common.

Ethical Regulation of the Pharmaceutical Industry Learning outcomes

This seminar will focus on the role of self-regulation in the life science industry with a specific focus on the Code of Practice of the Association of Innovative Pharmaceutical Industry (AIFP), which is the cornerstone of self-regulation of the pharma sector.

Students should understand the key rules and the important role of the AIFP in the pharma sector.

I. Supervision of Advertising in the Pharmaceutical Industry

The main authorities supervising advertising on the pharmaceutical market are the SUKL (except for by means of TV and radio), Council for Radio and Television Broadcasting (TV and radio), and other self-regulatory institutions such as CAFF, AIFP, MFE, EFPIA, or other professional chambers which are governed by the codes of conduct of pharma associations.

II. Main Associations in the Pharmaceutical Industry

The main associations operating in the pharmaceutical industry are AIFP – Association of Innovative Pharmaceutical Industry[20], currently made up of 35 pharma companies, CAFF – Czech Association of Pharmaceutical Companies, currently made up of 18 pharma companies, AVEL – Association of Wholesalers of Pharmaceuticals whose members are 3 main wholesalers of pharmaceuticals, and the SVOPL – Association of Manufacturers of OTC Pharmaceuticals with 11 pharma companies. Each of the abovementioned associations has issued its own code of conduct to regulate the conduct of its members. However, the AIFP, as the association connecting the most important and largest pharmaceutical companies, plays a crucial role in the pharmaceutical sector and its regulation.

III. AIFP Basic Facts

The AIFP was established in 1993 as a non-profit organization, funded by its member companies. Currently, the AIFP has 35 members - pharma companies. The AIFP itself is member of the EFPIA (EU level).

The AIFP acts as a neutral platform for expert groups composed of representatives of member companies, and its goal is to strengthen the principles of ethics and transparency in the Czech pharmaceutical industry.

a. Self-Regulation of the Pharmaceutical Industry

Given that the legal system introduces only minimum requirements to ethical regulation, more detailed ethical rules were established, among others, on (i) the regulation of gifts (limited and in future eliminated); (ii) sponsoring (congress venues); (iii) non-interventional studies (reviewed by the director of AIFP); (iv) number of samples provided (4 x 2); (v) transparency of relationships with HCPs or health care organisations ("HCOs"), etc.

[20] https://www.aifp.cz/cs/

The industry associations, such as the AIFP, increase the ethical standards of their members and thus also influence other market participants, mostly due to the detailed knowledge of the environment, mutual supervision, influence of American companies, and European associations. Self-regulation plays a key role in the pharmaceutical industry and allows deep self-cultivation of the industry without extreme measures being taken from the side of the state.

The AIFP itself has long been committed to cultivating Czech healthcare in the area of ethics. It seeks to strengthen the principles of transparency of relationships between pharmaceutical companies and other stakeholders through various projects such as (i) adoption of a Code of Conduct which covers the promotion of Rx pharmaceuticals to HCPs; (ii) adoption of a Disclosure Code, i.e., "Code on Disclosure of Transfers of Value From Pharmaceutical Companies to HCPs and HCOs", which covers the transparency of relationships with HCPs / HCOs; and lastly (iii) adoption of a Patient Code, i.e., "Code of Practice on Relationships Between the Pharmaceutical Industry And Patient Organizations" (PO), according to which (a) the cooperation with POs must be based on a written contract clearly indicating the purpose and amount of the financial aid / exact description of non-financial aid, etc., (b) exclusive cooperation only with a sole PO is prohibited, and (c) each AIFP Member must publish a list of cooperating POs together with a monetary value / description of non-monetary performance.

These three codes (i.e., Code of Conduct, Disclosure Code, and Patient Code) have been recently consolidated into one AIFP Code of Practice, that has become effective on 1 January 2021.

b. AIFP Code of Conduct

The AIFP Code of Conduct covers the promotion to and advertising aimed at HCPs connected with Rx pharmaceuticals. According to the AIFP Code of Conduct, "*Promotion*", "*Promotional*", or "*Promotional claim*" mean any statement made by a member of the AIFP or its representative, whether verbal or written, which conveys the positive attributes of a product, which extend beyond a simple non-qualitative or quantitative description of the therapeutic category or approved indication for the purpose of encouraging the usage of such product. It includes statements concerning efficacy, rate of adverse reactions or other cautionary aspects of the product, and comparative information. The AIFP Code of Conduct is supervised by an ethics committee consisting of 11 - 13 members, who are elected for a two-year term. The AIFP Code of Conduct regulates among others:

i. Methods of Promotion

The Code of Conduct covers all methods of promotion such as oral and written promotional activities and communications, journal and direct mail advertising, activities of medical sales representatives, internet, and other electronic communications, as well as the use of audio-visual systems such as films, video recordings, data storage services, and the provision of samples, gifts, and hospitality etc.

ii. False and Misleading Claims

According to the Code of Conduct, the provided information about products must be valid and accurate, must not mislead, and must not be able to cause deceptive imagination.

All artwork (for example, graphs, illustrations, photographs etc.) taken from published studies must clearly indicate the precise source(s) of the artwork and must be faithfully reproduced. Moreover, the artwork included in promotion must not mislead about the nature of a pharmaceutical.

Examples of false and misleading claims are e.g., (i) citing the results of an excessively favourable (or excessively unfavourable to a comparative product) study in a manner suggesting that those results are typical; (ii) citation of data previously valid but made obsolete or false by the evaluation of new data; (iii) suggestions or representations of uses, dosages, indications, or any other aspect of the SPC not approved by the SUKL or by European Medicines Agency (EMA); (iv) shortening an approved indication (e.g., in a by-line) so as to remove a qualification or limitation to the indication; (v) use of animal or laboratory data to directly support a clinical claim; (vi) presentation of information (e.g., type, size and layout) in such a manner, which, to the casual reader, could produce an incorrect perspective; (vii) shortening the title of graphical representations reproduced from literature altering the original author's meaning; and (viii) use of preliminary results without clear indication of its preliminary nature.

iii. Good Morals

The promotion and the promotional materials (including graphics and other visual presentations) must conform to generally accepted standards of good morals and taste, recognize the professional standing of the recipients, and not be discriminatory, deceptive, or disparaging.

iv. Unqualified Superlatives and New Products

Pharmaceuticals must be presented objectively and without exaggeration. Therefore, unqualified superlatives are forbidden. Claims included in the promotion must not imply that a pharmaceutical or its ingredient are unique or has some special merit, quality, or property unless this can be substantiated. According to the Code of Conduct, the word "*safe*" must never be used to describe a pharmaceutical without proper qualification. It must not be stated that a product has no side effects, toxic hazards, or risks of addiction or dependency. The word "*new*" must not be used to describe any pharmaceutical which has been marketed, or any therapeutic indication which has been generally promoted for more than one year in the Czech Republic.

v. Distinction of Promotional Material

The advertised promotional material must be clearly distinguishable and must not be disguised (not even based on subliminal perception). Any materials sponsored by a member of the AIFP relating to pharmaceuticals and their use (promotional in nature or not), must indicate that it has been sponsored by the respective member. Advertisements in a journal should not

be designed to resemble an editorial matter unless clearly identified as an advertisement.

vi. Product Information – Abridged Product Information

Abridged product information must accurately reflect the full product information; however, it may paraphrase or give more detail to the full product information.

Even if paraphrased, some information must still appear, for example (i) the brand name of the product; (ii) approved indications for use; (iii) contra-indications; (iv) clinically significant warnings; (v) clinically significant adverse events and interactions; (vi) available dosage forms; (vii) registration number; (viii) storage conditions etc.

vii. Reminders

A reminder is designed to remind recipients of the existence of a product. Reminders must not contain any promotional claims and may contain only (i) the brand name of the pharmaceutical approved in the registration decision; OR (ii) its INN; AND (iii) trademark.

It is not allowed to only use reminders in the first 12 months from the first advertising of a new pharmaceutical.

The use of reminders is possible for both HCPs and the general public.

viii. Mailings

Mailings regarding promotion material should only be sent to those categories of HCPs where their need for or interest in such information may be assumed. Requests to be removed from promotional mailing lists must be complied with quickly and can be restored only on a specific request or with written permission.

Exposed mailings (e.g., postcards, envelopes, or wrappers) must not carry information which might be regarded as advertising to the general public or which could be considered unsuitable for the general public.

Items suggesting a requirement for urgent attention are not acceptable for promotional purposes. The use of faxes, e-mails, automated calling systems, text messages, and other is allowed only with prior permission, or upon the request of the recipient. Any mailing must conform to data privacy rules in general.

ix. Medical Representatives

"*Medical Representative*" means a person expressly employed by a company whose main purpose is the promoting of the company's products to HCPs.

The medical representatives' duties are (i) to be familiar with the relevant requirements of the applicable code(s), and all applicable laws and regulations, (ii) to be adequately trained, and (iii) to have sufficient scientific knowledge about the pharmaceuticals they offer. Medical representatives must ensure that the frequency, timing, and duration of visits do not cause an

inconvenience, must not use any bribe or trick to gain an appointment, and must take reasonable steps during an interview to ensure that they do not mislead about their identity or about the company they represent.

x. Product Samples

Product samples can only be supplied to HCPs who are qualified to prescribe such products in order for the HCPs to gain familiarization and acquire experience in dealing with such pharmaceuticals. Previously, each HCP could receive a maximum of 4 samples per year of a particular new pharmaceutical, whereas sampling of a particular pharmaceutical was allowed for only 2 years after the first HCP first requested samples of such pharmaceutical (the "4x2" rule).

The Code of Practice, effective from 1 January 2021 changes this rule and allows sampling of a particular pharmaceutical for 2 years after an HCP first requested samples of such pharmaceutical.

A new pharmaceutical means a pharmaceutical for which a new marketing authorisation has been granted (incl. extension of application for new dosage forms or a new indication) or a new group of prescribing HCPs has been authorized.

Members must have adequate systems of control and accountability for samples which they distribute.

xi. Travel and Meeting Sponsorship

Members of the AIFP may only sponsor events for purely **professional and scientific purposes** (e.g., scientific events and scientific congresses) and all sponsors must be publicly disclosed and mentioned in all documents relating to the events and proceedings.

The sponsorship of HCPs attending events organized by third parties is subject to the following principles: (i) the purpose of the event must only be purely professional and scientific; (ii) the event must be directly related to the HCP's area of expertise; and (iii) members must report every provided sponsorship. Moreover, the sponsorship cannot (i) be extended to spouses or other traveling companions; (ii) be linked to prescribing behaviour; (iii) include the sponsoring of entertainment (e.g., sporting or leisure) events; or (iv) cover longer stays at the venue (arrival at the venue must happen within 24 hours before start of the event and departure must occur within 24 hours after the event finishes).

The following rules apply to member-sponsored events / stand-alone events: (i) hospitality at the venue must be reasonable in level and strictly limited to the main purpose of the event; (ii) members can cover costs for travel, accommodation, meals; (iii) members should avoid using entertainment facilities; (iv) only approved pharmaceuticals can be promoted at these events; (v) hospitality at promotional events cannot be extended to other people than HCPs (family members, etc.); (vi) at least 75% of usual working

hours must be allocated to the scientific program; and (vii) invitation to the event must not be linked to level of prescriptions.

xii. Sponsorship to HCOs

Any other than abovementioned sponsorship must, in general, conform to the standards of ethics. Sponsorships can never be based upon the number of prescriptions. Sponsorship of equipment and other tangible items (e.g., TV sets, printers, PCs, furniture, etc.) are appropriate forms of sponsorship for HCOs only if it (i) is used as a means of diagnosis/evaluation; or (ii) improves medical quality or patients care; and (iii) is not to be used for personal use of an individual HCP.

All forms of sponsorship must be based on a written request by an HCO.

xiii. Market Research

If data of individual patients is not collected and assessed, the activity is considered market research (rather than non-interventional study) which may be considered advertising as well. Promotions must not be presented during market research or research of any type.

Market research is not to be carried out by medical representatives or any other position involved in sales activities unless there is no payment to the physician who is taking part in the research. Payments must be kept to a reasonable level. Members carrying out market research must utilize its results in practice.

xiv. Hospitality Offered to HCPs

Hospitality is legally permissible if it is commensurate with the nature of the meeting, is secondary to the main (i.e., scientific or business) purpose of the meeting and extended only to HCPs.

The hospitality is limited to lunch or dinner and generally includes refreshments (i.e., food and drinks). No travel and accommodation should be provided. The entertainment of HCPs is prohibited (e.g., tickets to theatre, sport, etc.).

xv. Gifts and Inducements

Gifts to HCPs are forbidden!

However, it is permitted to provide informational or educational materials (but must be inexpensive, directly relevant to the practice of medicine or pharmacy, and directly beneficial to the care of patients), for example, disease and treatment brochures, prescription manuals, brochures on treatment regimen, and healthy lifestyle, etc. Items of medical utility aimed directly at the education of HCPs and patient care are also permitted but must be inexpensive and not offset routine business practices of the recipient.

The total value of all informational or educational materials and items of medical utility provided to a single HCP cannot exceed 1,500 CZK per year

(this does not apply to member companies' own marketing / educational materials).

xvi. The Use of Consultants

It is permitted to use HCPs as consultants and advisors, whether in groups or individually, for services such as speaking at and chairing meetings, involvement in medical/scientific studies, clinical trials or training services, participation at advisory board meetings, and participation in market research where such **participation involves remuneration and/or travel**.

The use of consultants may occur under certain conditions, among others: (i) a written agreement must be signed in advance; (ii) a legitimate business need for such services has been identified in advance; (iii) the criteria for selecting consultants are directly related to the identified need and the persons responsible for selecting the consultants have the expertise necessary to evaluate whether the particular HCPs meet those criteria; (iv) number of consultants is reasonable for the business need, etc.

c. AIFP Disclosure Code

Under the Disclosure Code, each AIFP member shall annually document and disclose, transfers of value it makes, directly or indirectly, to or for the benefit of an HCP or HCO. Cooperation between professionals and the industry may create the potential for conflicts of interest. There are efforts to make these relationships more transparent and clearer. In Slovakia, France, and the Netherlands, they even have specific law regarding the transparency of relationships between the pharmaceutical industry and HCPs and HCOs. Transparency is very important because HCPs have a direct impact on costs of healthcare and therefore an interaction with a vendor to the healthcare (life science industry) should be subject to transparency and subsequently public review.

According to the AIFP Disclosure Code, gifts, grants, costs associated with organizing scientific meetings (registration fees, travel, and accommodation costs), and remuneration for services and consultations must be disclosed and be published for at least 3 years. The members have the duty to keep relevant records for at least 5 years from the end of the reporting period.

Information on subjects working with innovative pharmaceutical companies who are the recipients of value or for whose benefit the value is intended (HCPs and HCOs) and HCOs as the organizers of a professional events are to be disclosed on the basis of the Disclosure Code as well as third party company (organizer, agency) hired by the member to organize a professional meeting. Often, the members prefer not to be directly involved in the sponsorship contract and provide their sponsorship to an organizer.

Protection of personal data must be in accordance with the data protection laws (e.g., GDPR) and data subjects must be informed about the processing of their personal data.

a. Conditions for Disclosure Obligation

Direct and indirect payments or other benefits (can be monetary, in kind, etc.) must be connected to the development and sale of exclusively human generic or original Rx pharmaceuticals. An indirect payment is considered to be a situation where payments or benefits are provided on behalf of the member for the benefit of the recipient or are provided through a third party for which the member knows or is able to identify the HCP / HCO that will benefit from the performance provided.

IV. Related questions:

What are the key local associations in the area of pharmaceuticals?
What is the source of self-regulation rules?
Why is transparency a key value in the pharma industry?
Why is there self-regulation in place?

Personal Data Protection with a Focus on Pharmaceuticals and Medical Devices Business Activities

Learning outcomes

This seminar will the use discussion to assess particular life science situations and life science activities from the legal regulation point of view.

The students should understand the key aspects of data protection regulations, who the key subjects are, and what are the basic conditions that need to be met for lawful data processing.

I. Regulatory Framework

Protection of personal data is generally stipulated in Regulation (EU) No. 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (GDPR) and Act No. 110/2019 Sb., on Processing of Personal Data.

The protection of natural persons in relation to the processing of personal data is a fundamental right. Article 8(1) of the Charter of Fundamental Rights of the European Union (the Charter) and Article 16(1) of the Treaty on the Functioning of the European Union (TFEU) provide that everyone has the right to the protection of personal data concerning him or her.

The GDPR works with key terms used throughout the regulation, it is namely: (i) "personal data", which means any information relating to an identified or identifiable natural person ("data subject"); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier, or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural, or social identity of that natural person; (ii) "processing", which means any operation or set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure, or destruction; and (iii) "controller", which means the natural or legal person, public authority, agency, or other body which, alone or jointly with others, determines the purposes and means of processing personal data; where the purposes and means of such processing are determined by Union or Member State law, the controller or the specific criteria for its nomination may be provided for by Union or Member State law, in simple terms, the data controller is key entity with the main liability for compliance of processing of personal data with the GDPR.

II. Personal Data Protection Under GDPR in the Life Science Industry

The GDPR is very important regulation in the life science industry as sensitive personal data of patients, such as details of their health, is being processed in various cases, e.g., clinical trials, patient finding initiatives, patient support programs, case studies presented by speakers, provision of healthcare services, maintaining patient registries, or conducting non-intervention studies, etc. While this is not an extensive overview of applicable obligations under the GDPR, it serves as a source for an overview of regulations applicable to the most common activities of life science companies relating to patients.

In general, the GDPR requires a *data controller*, typically the life science company, which (i) determines the purposes and means of processing personal data; (ii) identifies the purpose of the processing and legal title, (iii) complies with information obligations towards the data subjects (and/or obtains their consent, if necessary); and (iv) complies with the requirements ensuring the safety of the data processing.

The data controller needs to demonstrate that the processing of a data subject's personal data is lawful and thus fulfils at least one of the requirements under Article 6 of the GDPR: (i) the data subject has given consent to the processing of their personal data for one or more specific purposes; (ii) processing is necessary for the performance of a contract to which the data subject is party to or in order to take steps at the request of the data subject prior to entering into a contract – which typically is the case where the data subject is a party to an agreement such as an agreement on enrolment in a patient support program; (iii) processing is necessary for compliance with a legal obligation to which the controller is subject – which may be the case for clinical trials; (iv) processing is necessary in order to protect the vital interests of the data subject or of another natural person; (v) processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller; (vi) processing is necessary for the purposes of the legitimate interests pursued by the controller or by a third party, except where such interests are overridden by the interests or fundamental rights and freedoms of the data subject which require the protection of personal data, in particular, where the data subject is a child – which will be the case in processing personal data where the data controller provides any kind of benefit and for marketing purposes collects the personal data of data subjects involved in provision of such benefit.

However, where special categories of personal data are being processed, i.e., in cases where personal data regarding racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, and the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health, or data concerning a natural person's sex life or sexual orientation is processed, the data controller may usually practically rely only on legal title under Article 9(2)(a) of the GDPR – free consent of the data subject. This may prove very problematic in cases where, without processing special categories of personal data of data subject, it is impossible to provide a service or conclude an agreement as these reasons are not considered to be legal title for processing special categories of personal data. Consent without which a service cannot be provided, or agreement performed is, by definition, not free. However, since there is no other legal title, consent is generally relied on as the only suitable legal title under Art. 9(2) of the GDPR.

One of the key obligations of a data controller is to fulfil an information obligation towards data subjects under Article 13 of the GDPR. The data subject should be provided with information detailing: (i) the identity and the contact details of the data controller; (ii) the contact details of the data protection officer, where applicable; (iii) the purposes of the processing for which the personal data are intended and also the legal title based on which such personal data is being processed (as it is necessary to ensure that once personal data is processed under a given legal title with specified purpose; the purpose is not changed unless the data subject is informed or consents and the new purpose is covered by an appropriate legal title), as well as the legal basis for the processing; (iv) the legitimate interests pursued by the data controller; (v) the recipients or general categories of recipients of the personal data, if any; (vi) the period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period; (vii) the existence of the right to request access from the controller to personal data and rectification or erasure of personal data or restriction of processing concerning the data subject or to object to processing as well as the right to data portability; (viii) right to withdraw consent if consent is the legal title for processing of personal data; and (ix) the right to lodge a complaint with a supervisory authority.

It is common that a life science company engages a third party to carry out the contemplated activity or outsources the complete project. This, however, does not exempt the life science company from its liability to protect and duly process personal data and comply with applicable statutory obligations. Third parties are considered *data processors* that are liable for processing in the scope of their involvement defined by the data controller.

Ensuring compliance with the GDPR is also key from the financial perspective where the fines, which may be imposed, although in the Czech Republic maximum fines historically have not been imposed, may be up to 10,000,000 EUR, or in the case of an undertaking, up to 2 % of the total worldwide annual turnover of the preceding financial year, whichever is higher. Interestingly, in the Czech Republic, some of the public corporations, such as municipalities not exercising delegated power and education organisations established by municipalities are not subject to fines under the GDPR.

III. Questions

Related questions:

What is the source of data protection rules?
Why is the protection of personal data important in the pharma industry?
Can you name some of the data processing activities, which take place in the pharma industry?
What are legal titles based on which you can process personal data and special personal data?

Patient Support Programs

Learning outcomes

To apply all information gained in the course, the students will design patient finding initiatives (an activity on how to identify new patients) and patient support programs (an activity on how to help patients from the position of a pharmaceutical company). This seminar should allow students to connect all the hard facts they have learned and apply them to practical situations.

The students should describe the need they are addressing, what tools they used, how the legal regulation impacted their initiatives/programs, what contractual documentation will be used and what will be in it. The students should be able to design the initiatives/programs and discuss their weak spots and if they are able to legally achieve their purpose under such initiatives/programs.

I. Patient Support Programs (PSPs)

Patient Support Programs are sets of services designed for selected groups of patients depending on their disease or prescribed treatment. PSPs can also be part of the conditions set by the EMA when registering a medicinal product, but most often it is a voluntary activity of the manufacturer. PSPs pursue legitimate non-promotional goals such as increasing adherence, educating the patient about the disease, or the right ways to apply the medicine and patient's safety.

a) Development and Practice

PSPs were originated in the USA and the extensive concept developed in the USA is not applicable in its entirety in the Czech Republic - including financial assistance to patients who cannot afford treatment (discounts, reimbursement of medicines). PSP arose from pharmacovigilance recommendations and in some countries (e.g., Poland), PSPs are subject to registration, however there is no unified approach to regulation in the EU.

In the Czech Republic, as the SUKL has approved dozens of patient programs focused on a specific group of patients since 2015, the interest of pharmaceutical companies in their implementation is growing (pressure from headquarters, results, market trend). In the Czech Republic, the rules are only general, there is neither an SUKL instruction nor a public opinion.

b) Basic Rules

Basic regulatory framework is set by Act No. 40/1995 Sb., On the Regulation of Advertising. PSPs must have a non-advertising nature in order not to be subject to the rules for advertising of medicinal products. Any information, persuasion, or incentive intended to promote the prescription, supply, sale, distribution, or consumption of medicinal products for human use is considered to be advertising of medicinal products for human use and is thus forbidden in relation with PSPs.

PSPs may not disrupt the patient-physician relationship, determine or change the diagnosis, prescribe treatment or motivate such activities, or interfere with the HCP's independence. In order to avoid the aforementioned, it is not possible to provide financial benefits to an HCP or other medical staff in connection with the implementation of a PSP.

PSPs can be envisioned as a program for patients taking a specific medicine or for all patients within a specified indication (e.g., diabetes) if the nature of the program is strictly non-promotional in all aspects. If there are third parties involved, e.g., nurses, the relevant qualifications must always be met, and the content of the PSP must be considered.

Data protection laws must be observed in the structure of the PSP (designate the controller, processor, conclude the relevant contracts, fulfil other information obligations, etc.).

An integral part of PSPs is pharmacovigilance, i.e., the process of monitoring the use of medicinal products in everyday clinical practice so that it is possible to recognize previously unrecognized side effects or change in the nature of side effects. The goal of pharmacovigilance is an assessment of the risk-benefit balance of medicinal products to decide what action, if necessary, is needed to make medicinal products safer to use, and providing information to healthcare professionals and patients to improve the safe and effective use of medicinal products.

While initiating the PSP, it is important to question the liability between the sponsor, the service provider, the patient, or the healthcare facility in the event of any damage, injury, or breach.

c) Non-promotion Nature

The PSP must have a non-promotional content. Any presentations applied during a PSP may not include advertising, except necessary labelling of materials.

Key Performance Indicators (KPIs), the measurable values that demonstrate how effectively a company is achieving key business objectives, must not be observed during PSPs (this concerns monitoring the increase in sales, volume of prescriptions, etc.);

d) Components of the Patient Program

Significant components of the PSPs are, for example, (i) disease education, treatment, screening; (ii) education on other specifics, such as a demonstration for the application of the drug at home (this concerns applications by injection, operation of the medicine delivery device, safety rules etc.); (iii) support of patient adherence and compliance to the prescribed treatment (reminders, follow-up communication, consultations); (iv) provision of disease related services, etc.

If providing other components as a part of material support, there must always be a link to the application or storage conditions of the medicinal products and the respective components must always be only of reasonable value, i.e., they must not be of an undue benefit to the patient.

Patients may be reimbursed for appropriate reasons, e.g., for adequate transportation to the centre where the medicinal products is administered.

e) Most significant risks

The most significant risks while implementing the PSP are e.g., (i) an assessment of the PSP as advertising to the general public; (ii) assessment of the PSP as a violation of the restriction on providing unjustified benefits to HCPs or other healthcare professionals; (iii) the violation of data protection law rules; (iv) off-label communication or illegal comparative advertising; (v) fulfilment of the definition of a non-interventional study or

market research; (vi) reimbursement of the services that are covered by public health insurance; (vii) failure to respect fair market value standards when providing remuneration for services; (viii) the choice of an HCP/workplaces involved in the PSP is not independent; (ix) unauthorized provision of health services; (x) civil or criminal liability if there is damage/injury while participating in the PSP (both nurse and patient); and (xi) pharmacovigilance.

II. Patients Finding Initiative

The main goal of Patients Finding Initiatives is to actively search for patients within the framework of preventive examinations, especially through the involvement of general practitioners. The initiatives involve raising awareness of a certain disease among patients and HCPs, its early diagnosis with great emphasis on finding affected people among their relatives, early initiation of treatment in order to prevent the deterioration of the course of the disease, detection of disease in the early stages, etc. There are various potential projects to identify patients which could benefit from treatment. The projects vary depending on the specific group of patients that need to be found.

In general, there are three categories of Patients Finding Initiatives – (i) the identification of a patient through a physician, (ii) identification of a patient through their treating institution, and (iii) the identification of a patient through the patient themselves.

The Patients Finding Initiatives use various tools from disease awareness projects on the internet in the form of a website or mobile app, involvement of general practitioners who identify patients with a proclivity to a particular disease or involvement of artificial intelligence, which identifies patients though their medical records in hospitals.

The key element of any Patients Finding Initiative is to protect the rights of the potential patient, particularly the right to have their personal data protected and the right for due healthcare. Therefore, any Patients Finding Initiative needs to introduce adequate safeguards depending on which type of tool is being used.

a) Identification of a Patient through a Physician

In this case, the sponsor of a Patients Finding Initiative needs to contemplate a design of the projects, i.e., whether the physician will proactively identify potential patients via inspection of the patient's medical record of if a physician will review a patient's eligibility for the Patients Finding Initiative during a patient visit. In case the physician accesses the patient's medical records, it is necessary to ensure that there is a valid legal reason for access to the documentation based on Article 65 of the Act on Provision of Healthcare services. In case the physician assesses patient's eligibility for the Patients Finding Initiative during a patient visit, there is no need to access the patient's medical records. However, if a physician is to operate with the data of the patient, requirements of the GDPR need to be met. The physician must either perform their obligations as a data processor and the sponsor should ensure compliance with the GDPR obligations as a data controller or the physician must produce anonymized information, which is not subject to the GDPR regulation.

b) Identification of a Patient through their Treating Institution

In situations where the patient is identified through their treating institution, it is often the case that there is an involvement of IT processing of the institution's database with medical

records. The key aspect that needs to be addressed is that there needs to be a legitimate reason for accessing the medical records. Most often, the institution will rely on an informed consent, which must provide that the medical records may be accessed for research or additional healthcare services. Provided this condition is met, the sponsor or institution in its capacity as a data controller needs to ensure that there is valid legal title for the processing of sensitive personal data as well as regular personal data. Therefore, it is crucial that prior to initiation of such a Patients Finding Initiative, the institution must warrant that it obtained all necessary consents (data processing and informed) and that it is authorized to perform the Patients Finding Initiative.

c) Identification of a Patient through the Patient themselves.

The patient may also be found if they analyse their own health and find indications of a potential disease. In this respect, a sponsor usually creates an information website focused on disease awareness. It is crucial that such websites do not include any advertising content, which would relate to Rx medicinal products. Moreover, the website should not encourage self-treatment but rather recommend finding a relevant physician who would attend to the symptoms of the patient in question. In this scenario, it is unusual for the sponsor to have access to any personal data of patient's and thus, in general, the GDPR would not apply to this scenario.

III. Related activity:

Based on the discussed limitations, design a program based on which you would identify suitable patients with a rare genetic disease or a patient support program.