UNIVERSIDADE DA BEIRA INTERIOR
Ciências da Saúde

Antiviral Therapy for Influenza

Experiência Profissionalizante na vertente de Farmácia Comunitária, Hospitalar e Investigação

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Relatório para obtenção do Grau de Mestre em
Ciências Farmacêuticas
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Resumo

Atualmente, os serviços farmacêuticos hospitalares representam uma importante estrutura global dos cuidados de saúde, com competências específicas, também designadas "actividades de farmácia hospitalar": garantir a terapia dos pacientes, qualidade, eficácia e segurança dos medicamentos, a integração de equipas de cuidados de saúde e promover tanto a investigação científica como ações de ensino. Portanto, a presença de farmacêuticos em ambientes hospitalares é essencial, a fim de garantir a aplicação e o acompanhamento da política do medicamento. Os serviços farmacêuticos hospitalares são dotados de autonomia técnica e científica, reportando para os Órgãos de Gestão Hospitalar, que são responsáveis pela gestão geral.

Hoje em dia, a farmácia comunitária é reconhecida mundialmente como uma instituição de saúde de interesse público que deve garantir a continuidade dos cuidados dos pacientes. As várias farmácias comunitárias distribuídas a nível nacional e internacional funcionam como postos de saúde avançados que contribuem para melhorar a qualidade de vida da população. Os objetivos devem ser claramente definidos, cujo objetivo central é a dispensa de medicamentos de uma forma que possa minimizar os riscos associados à sua utilização e permitir a avaliação dos seus resultados clínicos, a fim de reduzir a elevada morbidade e mortalidade relacionada com a medicação. Por conseguinte, esta morbidade e mortalidade também implicam grandes danos sociais e económicos para a sociedade em geral.

Este sector da saúde tem evoluído ao longo do tempo e tem sofrido grandes alterações a nível legislativo relacionadas com os atuais desafios, o que tornou a farmácia comunitária um espaço onde, para além da dispensa e preparação de medicamentos, também são fornecidos serviços e cuidados de saúde. Assim, os farmacêuticos devem concentrar-se e ser responsáveis pelas necessidades e cuidados do paciente e da comunidade, um conceito designado por Cuidados Farmacêuticos. Este conceito inclui um conjunto de processos clínicos como dispensa, indicação, avaliação terapêutica, educação para a saúde e farmacovigilância relacionadas com uma preocupação principal, que é o uso racional dos medicamentos. O farmacêutico deve integrar e articular todos os serviços, funções e responsabilidades, centrados no paciente com o objetivo de melhorar os resultados clínicos obtidos com o uso de medicamentos e também estar alerta para problemas como a contrafação de medicamentos e efeitos iatrogénicos.

Atualmente, os resultados de saúde são condicionados pela estrutura da unidade de saúde, o que, portanto, deve garantir a existência de um corpo farmacêutico dotado de habilidades próprias, sistemas informáticos para gerir a medicação e informação dos pacientes, e também fontes de informação avançadas relacionadas com a medicação.

Muitas das patologias epidémicas passam pela farmácia comunitária antes de serem avaliadas a nível hospitalar e o seu seguimento faz-se também muitas vezes a nível da farmácia comunitária em simultâneo com o centro de saúde. A gripe ou influenza é um paradigma neste aspecto. É considerada como uma das mais comuns doenças infeciosas agudas que afeta milhões de pessoas a cada ano em todo o mundo. Esta infeção viral aguda, que tem a capacidade de se espalhar facilmente de uma pessoa para outra, representa um importante problema de saúde pública com elevado peso sobre as comunidades em vários aspetos. Os vírus da Influenza têm vindo a circular desde há muitos anos em todo o mundo causando surtos epidémicos sazonais, geralmente associados a altas taxas de morbilidade e taxas de mortalidade consideráveis e, ocasionalmente surtos pandémicos

A vacinação é considerada a principal estratégia de prevenção da doença. Os medicamentos antivirais, de acordo com a literatura, são eficazes para a prevenção e o tratamento da gripe. Atualmente, duas classes de medicamentos antivirais são aprovados para o tratamento: a) adamantanos (ou inibidores de M2) e b) inibidores da neuraminidase. No entanto, para além dos aspetos benéficos relacionados com a medicação antiviral, especial atenção deve ser dada para os efeitos adversos desses medicamentos, a fim de assegurar a saúde e bem-estar dos pacientes.

Palavras-chave

Farmácia Hospitalar; Serviços Farmacêuticos; Farmácia Comunitária; Farmacêutico; Influenza; Antivirais.

Abstract

Currently, the hospital pharmaceutical services represent an important structure of the global health care, with particular competences, also designated “activities of hospital pharmacy”: ensure patients therapy, quality, effectiveness and safety of drugs, integrate health care teams and promote both scientific investigation and teaching actions. Therefore, presence of pharmacists is essential in hospital settings in order to ensure the implementation and monitoring of the drug policy. The hospital pharmaceutical services are endowed of technical and scientific autonomy, reporting to the Hospital Management Bodies which are responsible for the general management.

Nowadays, the Community Pharmacy is globally recognized as a health institution of public interest.
This health sector has evolved over time and has suffer major changes at the legislative level related with the arising challenges, which made the community pharmacy a space where, beyond the dispensation and preparation of medication, are also provided health services and cares. Therefore, the pharmacists must focus and be responsible by the care needs of the patient and the community, a concept designated by Pharmaceutical Cares. The pharmacist must integrate and articulate all the services, functions and responsibilities, imperatively centered on the patient with the objective of improve the clinical results obtained with the medication use and also alert to problems like counterfeiting and medication iatrogenic effects.

Many of the epidemic diseases go through the community pharmacy before being assessed in hospital settings and the follow-up is often made simultaneously within the community pharmacy and the health center. The flu or influenza is a paradigm in this regard. It is a common acute infectious diseases that affects millions of individuals each year all over the world. This acute viral infection, which has the ability to spread easily from one person to another, represents a major public health problem with a high burden on communities in several aspects. Influenza has been circulating for many years worldwide causing seasonal epidemic outbreaks, usually associated with high morbidity rates and considerable mortality rates, and occasionally pandemic outbreaks.
Vaccination is considered the main strategy for prevention of disease. Antiviral medications, according to literature, are effective for the prevention and treatment of influenza. Currently, two classes of antiviral medications are approved for treatment: a) adamantanes (or M2 inhibitors) and b) neuraminidase inhibitors (NAIs). However, beyond the beneficial aspects related with antiviral medication, special attention must be regarded towards the adverse effects of these drugs in order to ensure the health and well-being of the patients.

Keywords

Hospital Pharmacy; Pharmaceutical Services; Community Pharmacy; Pharmacist; Influenza; Antivirals.

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Chapter 1 – Hospital Pharmacy

The report which is presented hereafter reflects all the main activities developed during the internship in the hospital pharmaceutical services, along with the general knowledge withdrawn from this particular professional experience. Several aspects related to the different areas of this hospital section will be discussed with special emphasis to the responsibilities and functions of a hospital pharmacist. Before the contents presentation, a special "thanks" to all the persons involved in this traineeship period must be left here, and highlight the opportunity given which represents a great chance to improve the knowledge regarding the role of a pharmacist in a hospital setting – a valuable experience that can be used in the future.

The internship lasted for two months, between the first day of September and the twenty fifth day of October making a total of 320h, and took place in Guarda in Hospital Sousa Martins. The hospital, which belongs to a Local Health Unit along with the hospital of Seia and several health centers and extensions, has a capacity of internment rounding the 250 patients.

During the traineeship it was provided the opportunity to experience the activities performed by the different areas of the hospital pharmaceutical services applying the theoretical and practical knowledge acquired over the years from the pharmaceutical sciences course.

Table 1.1 and 1.2 - Work scheme – summary of activities in the Hospital Pharmacy

	Week 1	Week 2	Week 3	Week 4
Responsible Pharmacist	Dr. Jorge Aperta	Drª. Célia Bidarra	Drª. Conceição Quinaz	Drª. Anabela Canotilho
Areas/ Services	Storehouse (The hospital medication. Adaptation to the services)	Medicines (A and B); Cerebral Vascular Accident Unit; Psychiatry; Operating Block; Day Hospital	Primary care; Urgency; Pharmacotechnics ; Repackaging.	General ambulatory area; Emergency and Reanimation Medical Car; Cardiology intensive care unit; Narcotic drugs + psychotropic + benzodiazepines
Main activities	Direct observation and contact with the different drugs, pharmaceutical products and medical devices present in the storehouse and other particular storing rooms. Perception of the general organization and storage conditions. Discussion with the responsible pharmacist regarding the main aspects related with this area.	Transcription and conference of the prescriptions. Attendance to the medical visit. Dislocation to the services. Medication conference.	Production of manipulated products. Contact with the distribution made for the health centers. Practical analysis of the several aspects related with the different type of vaccines. Medication conference.	Customer service with dispensation of medication and relevant related information. Practical analysis of the several and complex aspects related to the products with special circuit, namely benzodiazepines, psychotropic and narcotic drugs.

	Week 5	Week 6	Week 7	Week 8
Responsible Pharmacist	Drª. Cristina Dinis	Drª. Isabel Silva	Drª. Beatriz Juanes	Dr. Jorge Aperta
Areas/ Services	Provision (acquisition; reception; and storage); Pulmonology; Outpatient appointments; Medical gases	Orthopedics; Plyvalente Intensive Care Unit; Pediatrics + Pediatric Emergency; Distribution	Surgery; Cardiology; Gynecology; Obstetrics; Ophthalmology; Otorhinolaryngologist ; Blood products	Full integration in the Hospital Pharmaceutical Services
Main activities	Transcription and conference of the prescriptions. Attendance to the medical visit. Dislocation to the services. Medication conference. Practical analysis of general product management with special emphasis to the acquisition process. Instruction about the general procedures related with products requiring special authorization.	Transcription and conference of the prescriptions. Attendance to the medical visit. Dislocation to the services. Medication conference.	Transcription and conference of the prescriptions. Dislocation to the services. Medication conference. Practical analysis of the several and complex aspects related to the products with special circuit, namely blood products.	Full integration with performance of several functions related with the different areas. Accompaniment of certain processes not performed earlier. Theme presentation

1.1 Organization and management of the pharmaceutical services

The hospital pharmaceutical services consist of several areas both related to the different functional aspects in charge as common divisions found in other working infrastructures. The main areas are: the associated area of management and logistics responsible for the selection, acquisition, reception, storage, distribution of the pharmaceutical products and also stock management; the outpatient/ambulatory area especially responsible for the dispensation of 100% reimbursed medication; the pharmacotechnic area responsible for the production of sterile and non-sterile manipulated products; and the area associated with the preparation of the single/individual unit dose. The other common areas consist of the main entrance and different access doors for the professionals, a parcel reception area with a specific door access, storehouse, bathrooms, locker rooms, an area that can be used to take meals and rest during a break in order to gather strengths to have a good work performance, a meeting room used to formative sessions and presentation sessions of new products, and a documentation room where all the necessary records are stored.

The location of the hospital pharmaceutical services respects the general "Hospital Pharmacy Manual" guidelines as implantation of all areas and storehouses in the same floor, the outpatient/ambulatory area near the circuit that patients commonly use with an extern access and proximity with vertical circulation systems as elevators. [1]

Currently, human resources are the essential foundation to a quality management and the pharmacists need to pay a special and careful attention towards the management area due to the importance and preponderance of the economic resources involved in the Hospital global management. The pharmacists responsible must feel comfortable dealing with the aspects associated with this particular area and should have continuous formation in order to improve their skills. [2]

The management area, and all the related procedures, is well established in the pharmacy structure of the Hospital providing the necessary resources (medications, pharmaceutical products and medical devices) to the different services of the hospital. In addition, good standards of communication and interaction between the pharmacists and the administrative services are necessary, especially for the selection and acquisition of products, due to the elevated importance of the economic factor and the balance needed between the costs of the different hospital services as mentioned above.

1.1.1 Management/Provision

This area represents one of the most important sections of the hospital pharmaceutical services due to the necessity of available and safe medications for all patients, as for the balance between these available medications and the economic budget. Human resources

responsible for this area consist of: Pharmacist; Diagnostic technician; operational assistant; and administrative technicians who represent the provision service.

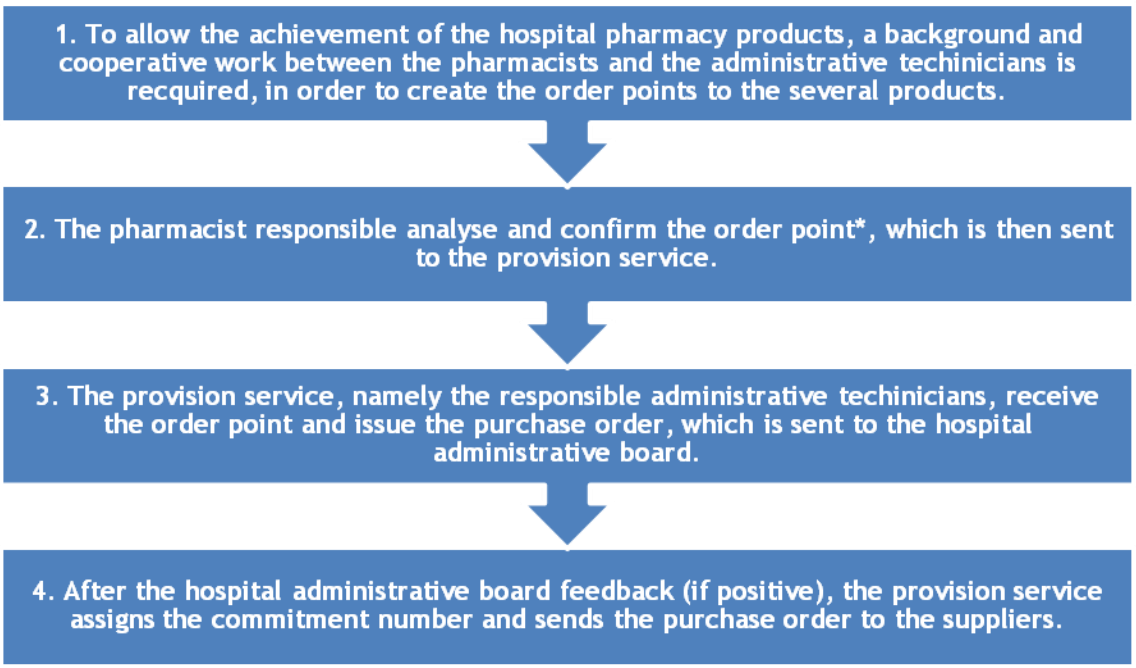

Fig. 1.1 – Process of products requisition.
*the order point is generated informatically through a complex process associated with the logistic sector.

The order point represents the starting element of the general process related to the management area. Beyond the complex aspects associated with the generation of the order point, emphasis must be given to the type of drug acquiring: drugs commonly used and with regular consumption are associated with easier methods of consumption forecasts; drugs commonly used but with irregular consumption need a more specific analysis associated with previous and tendency consumption; drugs used for rare diseases, as seen in the outpatient/ambulatory area, which are associated with the number of treated cases; drugs with over restricted legislation, as benzodiazepines, psychotropic and narcotic drugs, which are associated with strong rastreability need special attention regarding updated consumption information; and new or newly introduced drugs that require a particular cooperative process with other entities as clinical services.

The pharmacist related to the management area, namely acquisition, reception and storage, is responsible for performing several functions: stocks management; elaboration of consumption forecasts; integration in drugs, medical devices and other pharmaceutical products review committees; co-elaboration of the purchase order; acquisition of low consumption and/or sporadic use drugs and also drugs requiring special use authorization; acquisition and reception of drugs containing narcotic and psychotropic substances;

supervision of the drugs, medical devices and other pharmaceutical products reception; control of the legally required technical documentation (narcotic drugs, plasma-derived products and others); and control of the drugs, medical devices and other pharmaceutical products expiration date record. [2]

1.1.2 Systems and acquisition criteria

The selection of medications is based upon the Hospital National Formulary and the therapeutic necessities of the hospital patients. The drugs that should be included in the Hospital National Drug Form should be suggested by the Therapeutic and Pharmacy Commission in which the pharmacist has an active role. [1]

The available budget is one of the most important factors associated with the acquisition of medications implying a selection of the more pharmacoeconomic advantageous medications and, at the same time, ensuring the development of an updated and effective therapeutic arsenal.

The acquisition process requires a previous detailed analysis of the consumption of each drug for the last 6 months, of the actual stock and possible fluctuations related to a particular service or pathology, in order to try to predict the consumption that will have in the future. The amount of products that will be acquired is also related to stock management, more specifically the ABC and XYZ analysis, which provides integrated information regarding the cost and consumption of medications. (This complex process of analysis was only observed in the informatics system without any personal process performed) In addition, particular features as supplier constraints and the space which a particular product occupies are also analyzed. Usually, each product has a predefined order point.

The acquisition can be made by different ways: centralized public tender through a "provision catalog" available from a platform of the Health Ministry – "SPMS"; limited public tender; and by direct negotiation with laboratories or local suppliers as community pharmacies when the amount needed is too low or in urgent situations.

The process is mainly performed on an informatic base: the administrative technicians have a platform, which allows the connection between the buyer and the provider, and are responsible for the requisition generation; after the pharmacist and the hospital administration approvals the administrative technicians adjudicate the proposal; after the providers answer the final report is elaborated.

From the personal infield experience, two aspects stood out: it represents an important procedure that requires constant monitoring by the individuals in charge; and the importance of a good pattern of communication between the professionals of the hospital pharmaceutical services, especially the pharmacists who daily deal with the medications for the different hospital services at their responsibility, and between the professionals of the different hospital services. The administrative technicians also perform an important role helping the

pharmacist with the bureaucratic aspect and, therefore, good communications standards improve the process leaving the pharmacist free to perform other activities.

1.1.3 Reception and conference of the received products

The reception process is the responsibility of the diagnostic and therapeutic technicians in coordination with the administrative technicians (provision section). This process can occur several times during the morning and afternoon of the same day, and consists of: first, the delivery note, brought by the supplier, is attached to the order point by the administrative technician; secondly the diagnostic and therapeutic technician performs registration of the order and the associated product; thirdly and finally, the product is stored.
In the meantime, during the reception process, a quantitative, qualitative, technical and administrative conference is performed to assess if all is correct with the order (such as expiration date and the analysis report accompanying the plasma derived products and chemicals for instance). [2] It should be noted that the pharmacist validates the reception of plasma derived products in order to ensure the required quality of these specific products. If no problem is detected, the registration of the quantity, expiration date and lot of the product is made and then stored according to the internal organization. The delivery note original is kept by the administrative technicians in order to allow the payment by the financial services.

1.1.4 Storage

The storehouse is considered “the core” of the hospital pharmaceutical services and contains the majority of the medications present in the hospital facilities, which therefore must ensure the necessary conditions as space, security, temperature and absence of direct sunlight. [1] [2] However, medication is also stored in the area associated with the preparation of the single/individual unit dose as in different hospital services, provided by the hospital pharmacy, to be used as a backup in particular situations. The hospital is also responsible for providing medication to a number of health centers which have their own storehouses. The internal organization of the storehouse may vary from hospital pharmacy to hospital pharmacy, but usually is made according to different areas as noted: general (where the generic medications are stored); diagnostic products; otorhino and ophthalmic products; plasma expanders; birth control devices; popes and milk; solvents; enteral nutrition; patch material, creams and ointments; oncology products, antidotes and special permission products (stored in a cabinet); psychotropic and narcotic drugs (stored in a specific cabinet with double lock); benzodiazepines (stored in a specific cabinet with lock); cytotoxic (stored near an emergency kit); high volume injection products (stored in an appropriate particular space with access conditions to the pallet trucks); disinfectants; raw material; flammable products (stored in a particular space equipped with smoke detector and ventilation system);

parenteral nutrition; products to be provided in the ambulatory; and products that require refrigeration (stored in fridges and refrigeration cabinets as vaccines and human plasma, respectively). [1] [2] Specifically, human plasma requires storing temperatures between the -28ºC and -42ºC, which are permanently ensured by the professionals.

The disposal of drugs and other products is made by alphabetical order of international common denomination. The storage conditions are very important and in order to avoid problems with expiration date of products, the rule of "first expire first out" is used. The pharmacist attached to the management area is responsible for the control of the expiration date, and in articulation with the administrative services takes actions regarding the products with short expiration date. The quantitative audit is permanently made as the integrity checking of all the drugs, pharmaceutical products and medical devices, whose amount values are updated by the pharmacist in the informatics application related to the general management area.

The general storehouse is also equipped with devices that register temperature and humidity, who are permanently controlled. The devices associated with the products kept in cooling conditions deserve a special attention in order to avoid minimal temperature and/or humidity changes, capable of disrupting the integrity of the products (these changes can be caused by several simple events as leaving a door of a fridge barely closed or a power failure). Therefore, these particular devices are connected to the computers and other instruments like mobile phones of the pharmacists sounding an alarm when a problem with temperature and/or humidity is detected.

1.1.5 Management of medical gases

The majority of the hospital services are equipped with a channeled gas distribution system which is related to an outdoor central structure with a particular control system. However, in some services and in occasional situations the supply of these gases is made by the hospital pharmacy, in which the pharmacist is responsible for the general management. Usually, two types of gas containers are provided: the small containers are usually used in special situations when the patients need to move through the different hospital services in order to perform some medical exams; and the big containers are used by the hospital services which are not equipped with the channeled gas distribution system.

The acquisition criteria are identical to the other products where aspects like consumption records and information arising from the communication with the other healthcare professionals are analyzed and considered. The pharmacist must also pay special attention to aspects such as manufacturing license of the provider and market introduction authorization of the respective product. In the reception it is essential to check each product analysis certificate along with the integrity and identification of the containers. The storage is made in controlled tanks and the containers are stored in a particular locked, isolated and ventilated outdoor structure adjacent to the hospital pharmaceutical services. The medical

gases follow a traditional distribution and by replacement of leveled stocks. The health centers associated with the hospital also require medical gases containers, which are ordered by the pharmacist of the hospital pharmaceutical services and the delivery is made directly by the company provider. The quality control of the distribution by the general network must be performed periodically. The containers are also permanently controlled in order to ensure the quality of the products.
The safety data sheet of the medical gases must be available in order to avoid problems and ensure the correct handling of the equipment. All the records are controlled and stored by the pharmacist in articulation with the administrative technicians.

1.1.6 Products requiring special authorization

In some cases the doctor of a determined service, after the Service Director approval, may require the utilization of a product which does not have market introduction authorization in Portugal and therefore is not included in the therapeutic arsenal of the hospital pharmacy. The acquisition request needs the pharmacy and therapeutics committee approval. After its elaboration is subject to the INFARMED by the pharmaceutical services in order to be authorized the order and utilization of the product.
Usually the administrative technician gathers the necessary documentation to initiate the process and the pharmacist related with provision participates and provides some guidance. The role of the pharmacist in this area is to ensure the conformity of the submitted documentation and provide the necessary clinical justifications.
To initiate the process, the Service Director of the requesting service must present the clinical justification with correct identification of several elements: therapeutic indication of the product and dosage; therapeutic strategy; alternative therapeutic listing existing in the market which presents not to be appropriate to the situation; and scientific substantiation of the product utilization. Then, it is made the request to the laboratory of the market introduction authorization certificate in home country, the respective summary of product characteristics in Portuguese and English and information of administrative nature. After the process elaboration, it is send to INFARMED where the special authorizations are analyzed. When the special authorization is granted, the pharmaceutical services receive the document, usually, by fax.

1.2 Distribution

The distribution of drugs, pharmaceutical products and medical devices represents the most common and visible aspect related to the hospital pharmaceutical service. The pharmacists, in collaboration with the different clinical services, are responsible for implementation of policies and procedures leading to a therapeutic rationalization, for both inpatients and

outpatients. Therefore, the main objective is to provide the right drug in the right quantity and quality for each patient and every patient of the hospital in order to fulfill the medical prescription, through use of correct circuits and methodology. [1]

The type of distribution is mainly established according to the need and consumption of products, but also to the specific situations associated with the hospital service (ex: chemotherapy cycles in the Day Hospital and intensive care units). Hereupon, the use of the medicine, namely the prescription and the administration, is associated with different healthcare professionals of the hospital with whom the pharmacist must collaborate directly and therefore perform two main activities: attendance of the medical visit and visit the ward units (both topics discussed hereinafter). Despite the more valuable and useful information that arise from the medical visit, the presence in ward units is also important in order to establish a good interaction with the staff and mainly the head nurses, that can add more information to the pharmacist with the final objective of determine the best type of distribution. There is different distribution systems associated with the different hospital services, although the daily individual distribution in unit dose represents the main system distribution and constitutes a legal imperative since the publication in "Diário da República" of the joint order of the health minister assistant state secretaries and the health offices, of December 31 of 1991. [1] [2] Several years of experience and reflection continue to demonstrate that this type of distribution remains the most effective and safe.

The general distribution process usually begins with a medical prescription or a request made by the clinical services. Whereas the requests are mostly generated informatically, the prescriptions are handwritten which sometimes arises doubts when the pharmacist is reviewing and making the transcription to electronic form. In order to clarify those doubts, the pharmacist can resort the prescriber or the "cardex" (a file elaborated by the ward unit which contains all the information related with each patient therapy), reinforcing the importance of good communication standards.

The pharmacist is responsible for the approval of the requests, usually made through computer, and conference of the products released to the services. The validation and transcription of the medical prescriptions is made taking into account the doses, administration route and frequency, and other important aspects as drug interactions, therapeutic duplication and features associated with specific products such as antibiotics of mandatory justification. [2]

Fig. 1.2 – General procedure related with the distribution area.

Before the products distribution is always performed a double conference with direct observation of the content in order to detect possible errors as drug switch or wrong amount.
Usually, each inpatient facility has a cabinet with a restrict composition of products adapted to its characteristics, which is defined and controlled by the pharmacist in collaboration with the director or head nurse of each service. The timetables for the replacement of the cabinets as for the collection of the medical prescriptions are established with the clinical services. Outside the timetables established, only urgent therapy is provided.
The delivery of the requests and most of the medication to the hospital services is made by the operational assistants, which also perform a direct inspection and control of the amount and expiration date of the products present in the service cabinets. The circuits of distribution to the different hospital services are well established, with a particular door access in the hospital pharmacy that allows the exit of the trolleys containing the products and the entry of the empty trolleys, which are cleaned and disinfected in a specific room near the door access and separated from the work area (fulfilling the "clean an dirty" circuit). [1]
The **traditional distribution** is usually made weekly and allows hospital services to have a central stock, which may be used as needed. The amount of products required may change according to specific situations associated with hospital services, and is from the responsibility of the pharmacist to control and analyze these request fluctuations.
The **distribution by replacement of leveled stocks** is a type of distribution related with a small number of services. This type of distribution is related to services with a regular use of products, allowing the definition of levels.
The **customized distribution** is usually related to specific services with a small number of patients well identified that require a good articulation between the pharmacist and the designated services staff. The main example is the Oncologic Service Unit where is performed

the chemotherapy and the periodicity of the products distribution is established between the pharmacist and the service nurses, according to the treatment cycles schedule.

The **daily individual distribution in unit dose**, as previously stated, represents the main system of distribution and is usually made for a period of 24h with exception of weekends when must cover the period of three days. If possible, the medication must be separated according to the doses taken throughout the day in order to avoid medication exchange. The equipment used in the hospital pharmacy consists of structures that hold a number of cassettes which contain each patient medication, and therefore must be identified with the patient name, inpatient service and number of bed. In this particular distribution system it is also required the identification of several aspects in each single drug package: generic name; dosage; expiration date; and fabrication bath. When these aspects were not indicated, the diagnostic and therapeutic technicians are responsible of making several labels in order to attach to the single drug packages.

This type of distribution provides several benefits, as noted from this experience: increases the safety on the medicine circuit as the medication is daily prepared for each patient; allows a better knowledge and control of each patient pharmacoterapeutic profile; decreases the interaction risks; avoids waists; decreases the time spent in medication preparation by the nurses; and allows each patient an easier therapy cost assignment. [1] [2]

The pharmacist responsible for the general distribution area is also responsible for the implementation of specific procedures in order to improve the quality of the service. One strategy used in the hospital pharmacy is the registration in internal documents of the type of errors occurred during the process of distribution, which are then analyzed and divulgated to make the personnel aware of the aspects that should improve.

1.3 Ambulatory area and products subject to special control

The hospital pharmaceutical services possess an ambulatory area which emerged from the necessity to ensure the surveillance and control of particular chronic diseases and some therapies prescribed by specific health care facilities, and also to face emergency situations like the supply of some products when the community pharmacies can`t ensure it. The surveillance and control acquire a special importance in this area due to the pathologies characteristics, the potential toxic load of the drugs used and also the elevated economic value associated with the treatment. [1] [2]

The physical structure designated for this area must be easily accessible, have a waiting space, a well illuminated service area with proper humidity and temperature conditions in order to ensure the well-being of the patient and the health professional, and must be equipped with structures to the proper storage of the products ensuring the conditions needed (ex: products which must be kept in the cold). [1] [2] The products dispensed to fulfill the necessities of the patients must be properly packed and indentified and the delivery must

be performed by the pharmacist in order to provide information and advices to ensure the correct use of the medication and also increase the therapy adherence. The information provided to the patient must be held confidentially and in some cases a specific designated area must be used with that purpose. The confidentiality in this area represents an important aspect due to the stigma and discomfort that some patients have regarding their pathologies.

The pharmacist related to this area must be responsible for: the distribution, information and control of all the drugs dispensed through this regime; the organization of a control system with the patient's pharmacotherapeutic profile; the elaboration of dispense and prescription processing procedures according to the regulations and boards guidelines to the different groups of drugs. Infarmed is responsible for the publication of the products list to hospital dispense in ambulatory, which must be consulted by the pharmacist.

Many of the products dispensed in the ambulatory area are used for the hospitalized patients and are usually administered by the health professionals. In these situations the pharmacist has the opportunity to provide information to the health professionals regarding some treatment aspects in order to promote the correct use of the medication. The patients attending outpatient appointments and the emergency room can get the medication prescribed for free in the ambulatory area of the hospital pharmaceutical services. Particular drugs of some pharmacotherapeutic groups and subgroups used for the treatment of certain serious pathologies are 100% reimbursed under the current legislation, defined by the decree law nº 118/92. [2] [3]

The main pathologies affecting the patients who usually address to this section of the hospital pharmaceutical services, among others, are: rheumatoid arthritis; multiple sclerosis; prostate cancer; Crohn`s disease; hepatitis B and C; chronic renal failure (pre-dialysis); psoriasis; and benign prostatic hyperplasia. The treatment of the pathologies is associated with high monetary values which represent a major problem to the majority of the patients. Therefore, the patients covered by the National Health Service or ADSE beneficiaries can acquire these legislated products related with a particular pathology without any financial burden. [2]

A different case is the dispensation of products not covered by legislation. With the Administrative Council authorization, drugs for patients with chronic diseases belonging to 100% reimbursed therapeutic groups, when prescribed in the hospital outpatient appointments, may be freely provided.

Beyond these particular drugs, the dispensation of medication in this area only takes place when: the product is not available in the local market and the patient must present a proof, namely a stamp(s), confirming the nonexistence by the community pharmacies; is dispensed cytotoxic for animals; is dispensed cream with 5-fluorouracil; are dispensed products to homes and day centers.

The general process consists of: first, the pharmacist checks and validates the prescription; secondly, prepares and confers the medication which is going to be delivered to the patient; thirdly, the pharmacist provides the medication along with information regarding important aspects related with it; and finally, the informatics registration is made.

The prescription must contain several important elements: patient name and beneficiary number; identification of the prescriber with signature; indication of the place where it was issued and date; and the drug designation by international common denomination, dosage, pharmaceutical form and number of unities to dispense. The pharmacist carefully analyses the prescription also regarding its pharmaceutical and pharmacological aspects, suitability to the individual (drug selection, administration form and dosage), interactions, contraindications and amount prescribed. [2] Usually, the treatment duration or the date of the next appointment are indicated and represents important information since the delivery of products in this area is made in individual dose. In situations of prolonged treatment it is dispensed medication for one month of treatment, and sometimes in particular cases the medication can be provided for two or three months of treatment. The patients which have several prescriptions may opt to leave them in the hospital pharmaceutical services. The pharmacist files the prescriptions and in time informs the patient about the expiration date and the products that still may acquire.

The information provided to the patient by the pharmacist must include not only the basic recommendations regarding the storage, administration form, dosage and possible adverse reactions and but also the reference to the importance and, sometimes, the value of the treatment in order to promote the adherence and minimize wastes.

To finish the dispensation of the products, the pharmacist records the type of product, amount and lot dispensed, signs and dates in the front of the prescription, and then the patient records the type of product lifted, signs and dates on the back of the prescription. This way the pharmacist ensures an extra control of the process.

The record of each episode is performed informatically in order to possess the patient's profiles updated and ready to be consulted and also to perform the general management of the hospital pharmacy products. The patients profile allows the access by the health professionals to individual information, namely the patient name, process number, beneficiary number, address, telephone contact, consultations with the respective date, prescriber, pharmacist responsible for the dispensation, the products dispensed and date of dispensation, and the identification of the cost and the statute or administrative council authorization under which is made the dispensation process. It is important to highlight that the data confidentiality is ensured. [2]

All the billable prescriptions are sent to the respective health regional administration, in this case of North, or to the Health System Central Administration depending on the situation. This process is from the responsibility of the pharmacist in articulation with the administrative technicians.

Psychotropic and Narcotic drugs

According to the ordinance 981/98, from June 8th, the circuit of these drugs involving the requisition and dispense between the services and the hospital pharmacy must be performed

in specific forms. [1] [2] [4] The forms are composed by the original which is kept in the hospital pharmacy and the duplicate that is addressed to the service.
The hospital pharmaceutical services of Guarda possess two identical forms with different color in order to improve the circuit and avoid problems as mixture or others.
In some services there is a defined stock of these particular drugs according to the necessity. Therefore, the requisition and distribution works as replacement of these stocks present in the services. The drugs must be stored in a cabinet with double lock.
The dispense of psychotropic and narcotic drugs is only made if the form is properly filled with the name of the requesting service and the drug name, pharmaceutical formulation and amount. After the requisition validation, the form is signed by the pharmacist responsible for the dispensation and the professional responsible for the reception of the medication. The date of dispensation and reception also must be indicated.
After the utilization of the drugs by the services, the duplicate is delivered to the pharmaceutical services with the patient identification, the discrimination of the dosage administered and the respective date and also the signature of the professional responsible. Then, the pharmacist performs the informatics registration in order to possess the files updated and to periodically send the *General Map of Narcotic and Psychotropic drugs* to the Infarmed properly approved by the competent authority.
When the drugs are not totally used, the responsible professional registers in the form the dosage and justification of the non utilization. The drug is delivered attached to the form.
The stocks present in the different services are usually controlled by the pharmacists associated with each service.
The decree law n.º 15/93, from January 22nd, regulates the utilization of psychotropic and narcotic drugs. [1] [5]

Benzodiazepines

The benzodiazepines also possess a special circuit in the hospital set similar to the psychotropic and narcotic drugs.
The form used is the annex X which also has an original and a duplicate. After the requisition validation, the form must be properly filled to allow the dispensation of the products. The aspects required are the service identification and designation of the drug name, pharmaceutical form, dosage and amount. The form must be signed and dated by the providing pharmacist and the professional responsible for the lifting. The original is addressed to the services and duplicate remains in the hospital pharmacy. After the utilization, the original is sent to pharmaceutical services in order to conclude the process with the registration and storage of the necessary documentation.
The acquisition of these particular products (benzodiazepines, psychotropic and narcotic drugs) by the hospital pharmaceutical services is also related with specific bureaucracy and

processes. One of the aspects stated was the acquisition process of the benzodiazepines in which it is filled the annex VII to send to the laboratory.

Blood products

The identification and registration of the blood products used in the treatment of certain diseases represents a very important aspect regarding this type of medication. This way, it is easier to identify a causal relationship between its administration and the appearance of transmissible blood infections. The bath and expiration date must be properly identified and registered.

In order to make the requisition and distribution registration, there is a specific form (Model nº1804) which has mandatory spaces that need to be filled before the product dispensation. The frame A is filled with the prescriber and patient identification and frame B is filled with the designated blood product and the clinical justification. After the prescription validation by the pharmacist, frame C is filled to complete the distribution registration. The person in charge related with the requesting service that receives the product signs and records the lifting date. The form has two sheets, one addressed to hospital pharmacy and the other to requesting service.

Before the product dispensation, the pharmacist labels each blood product unit with the identification of the patient which is intended, in order to ensure the administration of the right product to the right patient.

At the end of the process, the pharmacist makes the imputation of the blood product dispensed whose number is registered in the sheet form addressed to the hospital pharmacy and files the document. The sheet form addressed to the service goes along with the product.

When the blood products dispensed are not totally administered due to situations like the sooner end of treatment, these must be returned to the hospital pharmacy. The unused blood products must be returned within 24h and during the time that remains in the service must be kept in proper storage conditions. The devolution is registered in frame D of the service sheet form and must contain the date and signature of the person responsible for its administration. Next, the pharmacist makes the return record where are indicated the number of the devolution record and the amount of product units returned.

The pharmacist is responsible for the blood products circuit closure and therefore, at the end of treatment, must visit the requesting service and verify several aspects in the sheet form addressed to service, namely the frame D: administration date; blood product name, dosage, amount administered; lot and source laboratory; signature and identification number of the person who administered.

The legislation regarding the requisition, distribution and administration of blood products is present in the joint order nº 1051/2000, from September 14th. The acquisition is regulated by the Health Minister Dispatch nº 5/95, from January 25th. [1]

1.4 Pharmacotechnics - Production and inspection

Currently, the hospital pharmacy is related to the preparation of pharmaceutical formulations normally used for the treatment of individual and specific patients, but also in a larger scale for the treatment of potential patients. These pharmaceutical formulations are important as they are not available in any other place and need to be prepared by the pharmacist. In this context, special attention must be regarded to the several actions performed, from the labeling to the aseptic manipulations, in order to produce safe and effective pharmaceutical formulations for every patient. To accomplish this purpose it is essential the definition of responsibilities, procedures, processes and resources allowing the implementation of a quality management system. [1] [2]

In the hospital pharmacy of Guarda, this area is responsible for the preparation of manipulated products for internal and external use and drug repackaging. These operations are from the responsibility of the pharmacists and require specific facilities, equipment and human resources. The standards and procedures differ in each operation but all must be allied with good practices in order to achieve a quality product. The concept of clean area represents a particular important aspect related to this area and several parameters must be respected: smooth and waterproof exposed surfaces, also without joints, in order to minimize the release and accumulation of particles and/or microorganisms; places of hard cleaning, cupboards and unnecessary equipment must be avoided; the false ceilings must be tight in order to avoid space contamination through them. [1] [2]

During the traineeship it was given the opportunity to prepare several **manipulated products** with the ultimate control of the pharmacist related to this area.

The operation of these non sterile formulas preparation is related with several aspects. First, the acquisition of raw materials must be made according to the specifications related to the purpose which are going to be used and the Portuguese or European pharmacopoeia requirements. At reception, beyond the normal control measures as careful observation of the containers integrity, the pharmacist must pay special attention to the certificates of analysis that come with each product in order to ensure the quality of the products received. The storage is performed in a particular division separated from the other products with controlled temperature, light and humidity. The packaging and closing material (containers, stoppers, etc) is subjected to the same quality control standards of raw materials: must only be received when properly packed and transported; and stored in controlled conditions in order to avoid contamination.

In the hospital pharmaceutical services there is a specific area, the pharmacotechnic laboratory, used for the preparation of the manipulated products which must ensure the necessary conditions. The equipment must be kept cleaned, dry and protected of any contamination when is not being utilized. The preparation of the products is made by the pharmacists gifted with adequate formation and experience, which also must keep high

hygiene and cleaning standards and report any health problem that can cause errors or introduce some contaminants types. [1] [2] The preparation process is performed after the reception and validation by the pharmacist of a medical prescription or a hospital service request. Usually the medical prescriptions or the hospital service requests are able to be scheduled, in which the pharmacist prepares and delivers the manipulated product(s) in a specific date, or are urgent and prepared readily as possible according to the requisition. The manipulated products requests are registered in a document which discriminates the date of preparation, identification of the manipulated product, dosage, patient name and age, the delivery date and a field to the identification of the person who performs the reception. Sometimes the requisitions of the manipulated products are handwritten, as stated during the traineeship, which can be difficult to understand and some experience in this field is advantageous.

The pharmacist responsible for the preparation of the pharmaceutical formulation ensures that the workplace conditions are suitable: available equipment and raw materials in perfect conditions; and the necessary documentation related to the preparation.

This area has a particular documentacional set which contains several important documents mainly associated with raw materials and the manipulated products produced (beyond the common and important references as: Portuguese Pharmaceutics Form; Portuguese Pharmacopoeia; Pharmaceutical Tecnology – Calouste Gulbenkian Foundation; Good Hospital Pharmacy Practices; and others). The raw materials are usually followed by the analytical bulletin, whereas the manipulated products possess its safety sheets. The pharmacist uses the internal preparation sheets, which contains the procedural scheme, as possible guidance and for registration of the manipulated products. The registration must contain detailed information regarding the raw materials used and reference to the service or patient which is intended. These preparation sheets are essential in order to clarify possible problems related with the formulation, which discriminate the raw materials and equipment used enabling a deep analysis to identify the possible cause of the problem. More specifically, the identification of the raw materials lot is important to connect the possible problematic raw material with the responsible provider. The records of the procedures and the developed programs related to the control and calibration of all the equipment are also analyzed and archived. The balances used for the raw materials weighing must be periodically checked and calibrated by an external entity accredited by the Portuguese Institute of Quality. [1] [2]

The pharmacist is responsible for the validation of several steps throughout and in the end of the preparation process: validation of the raw materials identification and quantities; validation of the calculations; verification tests such as the organoleptic properties; and the final validation of the manipulated product with the signature and dating of the preparation sheet which authorizes its use. A very important aspect related to the final product is the labeling which is elaborated by the pharmacist and must contain the identification of: the pharmaceutical services and contact; the pharmaceutical form, international common

denomination, dosage, quantity, route of administration and storage conditions; the preparation date and expiration date assigned; the patient name.
The delivery of the manipulated product is made in the ambulatory area by the pharmacist who can ultimately provide additional information.

The Pharmacotechnics area also includes the **repackaging of solid oral drugs** (tablets and capsules), which represents a important operation in the way that makes available the use of particular necessary individual doses as ¼ or ½ of the tablets usually commercialized by the industry and whose drugs are provided in multipacks. The drugs are only fractionated when the properties, namely the pharmacokinetic properties, are not affected. The process is performed in a particular space which ensures the isolation and other necessary conditions. The person in charge of the repackaging process must follow the hygiene and safety rules as the utilization of gloves mask and head cover. [1] [2] The general process is controlled and verified by the pharmacist who is responsible for its registration. The registration form must contain information as the repackaging date, name and signature of the person who performed the operation, quantity of product repackaged and remaining, label sample, expiration date and name and signature of the pharmacist responsible for the operation verification.
These drugs must be properly packed in order to ensure the conservation and maintenance of specific parameters as tightness, mechanic protection and light and air protection and also ensure that can be used safely, quickly and cosily. [1] [2] For this purpose in the pharmacy is used an automated repackaging equipment of solid oral drugs which also makes the process faster and more efficient. This equipment also performs the labeling of the units doses which ensures the identification of the repackaged product. The information present in the label consists of the generic name, dosage, lot, expiration date and identification of the service, and is introduced informatically in a computer associated with the equipment. The expiration date represents a particular aspect which must be properly attributed taking into account the drug initial validity period, and for this purpose a scheme is fixed in the work space to provide instructions.
Before the execution of the process, certain aspects must be regarded: the equipment must be clean and functional (it must be cleaned before and after its utilization); the workbench must contain only the drug intended to be repackaged in order to avoid errors and cross contamination.
The final product validation is from the responsibility of the pharmacist and includes the verification of the repackaged product sleeves and the label elements. The nonconformities also are registered in order to control and manage the necessary quality criteria. The packed products usually are used for the unit dose preparation of the daily individual distribution reducing the time dispended by the nurses in the medication preparation and the contamination risks, or ambulatory dispensation.

Products like **disinfectants and antiseptics** are provided to the several hospital sections by the hospital pharmaceutical services and the general management is made by the pharmacist, from the acquisition of the products and services requests validation to the distribution. In some occasions the pharmacist is also responsible for the preparation of these products usually used to ensure the cleaning and hygiene conditions of the hospital facilities and equipment.

The area related to the production of pharmaceutical products represents one of the most distinguishable and notorious feature of the pharmacist profession, in which the pharmacist assumes an important and essential role. It is an area that is closely related to the art and ingenuity of this particular profession which must be preserved and performed with high professionalism.

1.5 Information and Documentation

The information related to drugs is a typical pharmaceutical feature and pharmacists have always been a source of information providing advices about the medications use in order to achieve a correct and safe therapy. However, due to some conditions, as the elevated number of new drugs, the therapy complexity and the elevated number of publications in this area, pharmacists need to have several and updated sources of information which also must have a wide range allowing the coverage of all hospital specialties. Internet represents the main source of global information which pharmacists can use to access the most updated original documentation published in scientific journals, catalogs and WHO publications, or through systems that index and allows the quick access to the primary sources. Other medications information services as contact with INFARMED for legal aspects associated with a specific drug, medical departments of the pharmaceutical industry for specific data regarding certain medications or other extra-hospital institutions possessing a vaster scientific documentation, can also be used to withdraw important and reliable information. Finally, updated textbooks also represent a compilation of selected and evaluated information, which should be the first to be consulted when dealing with a problem as they can provide more objective and confirmed information. [1] [2] Some of the textbooks consulted during the traineeship were: “Martindale, The Extra Pharmacopeia”; “Handbook on Injectable Drugs, Trissel L.”; “Drug Interactions, Stockley”. Therefore, these available sources of information must be used by the pharmacists with the gold of promoting the safe, effective and economic use of drugs, medical devices and pharmaceutical products. A major aspect also related with this topic is the continuous formation that the pharmacist must have. Therefore, he must attend several formation sessions in order to improve and expand the knowledge related with the general health.

As stated through this report, the pharmacist represents a valuable source of information which is sought in several situations from the simple contact by phone or fax by patients and

health professionals regarding different therapeutic aspects to provide indications face to face. When the information is provided face to face it can be given in an active or passive form: the active form involves the direct dialogue with the concerned individual; the passive form involves the providing of pamphlets and leaflets with the respective information and indications written or presented through allusive figures or schemes. [2] The main occasions in which the pharmacist provides information face to face is in the ambulatory area, in the medical visit and when goes to the infirmaries of the different services. However, the ambulatory is the most important area in which the pharmacist usually contacts directly with the patients who are going to use the medication. In these cases the information given must be short, simple and objective and at the same time must cover all the essential aspects.
All the documentation related to the drugs, pharmaceutical products and medical devices, from the acquisition to the distribution, represents a valuable amount of vital information in order to access the quality of the general management. Therefore, most of these documents are kept in the hospital pharmacy in a collection room for a period of 5 years with particular exceptions as the documentation related with blood products which must be stored for longer periods (50 years).

1.6 Pharmacovigilance and Technical committees

The intervention of the pharmacist as a health professional also includes the notification of possible medical adverse reactions. Therefore the pharmacist must always assume a vigilant posture in all the areas of the hospital and especially in the hospital pharmaceutical services, notifying these events in a specific form available on the INFARMED site. The contribution to the prevention and detection of these adverse reactions can include the screening of precipitating factors as excessive prolongation of certain therapies, and the awareness of the prescriber to its monitoring when the patient profile or/and the pharmacological characteristics requests it. The form is sent to the INFARMED National Center of Pharmacovigilance and a copy is sent to the Pharmacy and Therapeutics Commission. [1] [2]
Beyond all the functions performed by the pharmacist, this also integrates some decision-making Committees as the Pharmacy and Therapeutics Commission and the Ethics Committee.

1.7 Other activities

During the traineeship, I had the opportunity to contribute to the elaboration of certain research projects like the work related with the consumption of enteric nutrition in this particular Local Care Unit and also attend some formation sessions related to new products and more specific sessions like the Neurology clinical session regarding encephalitis. Again, a

special emphasis must be given to this formation sessions which contribute to the improvement of the skills associated with this particular health care profession.

1.8 Bibliography

2. Hospital Pharmacy Manual, Executive Board of the Hospital Pharmacy, Ministry of Health, march 2005.

3. Good Hospital Pharmacy Practices, Specialty School Board in Hospital Pharmacy, Pharmaceutical Order, 1999.

4. Decree law nº 118/92.

5. Ordinance 981/98 from June 8th.

6. Decree law n.º 15/93 from January 22nd.

Chapter 2 – Community Pharmacy

The report which is presented hereafter reflects all the main activities developed during the internship in the community pharmacy "Taborda", along with the general knowledge withdrawn from this particular professional experience, where the special contact with the population allows the application of the skills and abilities acquired through the years of curricular formation. Several aspects related to the different areas of this health sector will be discussed with special emphasis to the responsibilities and functions of a pharmacist affected to this sector. Before the contents presentation, a special "thanks" to all the persons involved in this traineeship period must be left here, and highlight the opportunity given which represents a great chance to improve the knowledge regarding the role of a pharmacist in a community pharmacy setting – a valuable experience that can be used in the future.

The internship lasted for three months, between the month of November and the month of February making a total of 480h, and took place in Fundão in Pharmacy Taborda. The community pharmacy is located in the centre of Fundão and the technical director is the pharmacist Ana Cristina Veiga Almiro e Castro which is responsible for the general management.

During the traineeship it was provided the opportunity to experience the several activities performed in the different areas of the community pharmacy applying the theoretical and practical knowledge acquired over the years from the pharmaceutical sciences course.

2.1 Organization of the Community Pharmacy

The community pharmacy is one of the gateways in the Health System due to its accessibility to the population, and is designated as a space characterized by the provision of differentiated technical and scientific health cares which intend to always serve the community with the highest quality. In this sector are performed activities directed to the medication and to the patient, and therefore the pharmacist needs appropriate facilities, equipments and sources of information in order to perform these activities. [1]

The human resources of the pharmacy are composed by:

- 3 pharmacists: Ana Cristina Veiga Almiro e Castro (technical director); Ana Rita Leitão; and Carina dos Santos.
- 6 pharmacy technicians: Marisa Cruz; Maria de Fátima Rodrigues; Márcio José Gonçalves; Jorge Alberto Pires; Luís Nunes Silva; and Luís Miguel Almeida
- 1 cleaning assistant: Elizabete Gomes.

The several functions and responsibilities of the entire working team are clearly defined in the internal procedures of the pharmacy. The work schedules are also properly defined with the collaboration of all the professionals. It is important to emphasize the spirit of cooperation and mutual help between the professionals of the pharmacy, especially in common tasks, which contributes to a better internal functioning. Consequently, this work dynamics ensures the providing of quality pharmaceutical services.

The general structure of the pharmacy ensures the accessibility to all the patients including children, elderly and disabled citizen through an access ramp. The entrance intended to the patients is situated at street level with a front door that only opens with the individual presence, protecting the patients from the direct contact with the exterior. The external appearance of the pharmacy is an important feature and the pharmacist is responsible for ensuring that is characteristic, professional and easily visible and identifiable. [1] Above the entrance and also covering the main show window there is a sign with the identification of the pharmacy, "FARMÀCIA TABORDA", and also an electronic symbol with the "green cross" which can provide additional information like the temperature and the available pharmacy services, and is illuminated during the night. Next to the entrance there is also an outer plate with the identification of the technical director. The show windows are elaborated professionally with exposition of specific products and provide information to the patients about the business hours, the identification of the municipal pharmacies who are in permanent service regime, and also information about the health services provided including the respective prices. The facade is permanently cleaned according to the established cleaning service and presents good conservation conditions.
The interior space addressed to the customer service is professional and allows an effective communication between the individuals. The environment is calm and adequately illuminated and ventilated in order to provide the optimal conditions to the patient and the communication process. This space is also equipped with chairs to accommodate the patients while they are waiting and also a variety of products exposed in shelves and exhibitors according to the legislation. The working surfaces, cabinets and shelving are made of suitable material, smooth and washable, with the hygiene and cleaning following the standards of the cleaning service like is made in the exterior. [1] There are visible signs indicating the smoking ban, and similar to the exterior there is an inner plate with the identification of the technical director and the owner above the service counters. The counters are separated by a slight physic structure, usually a screen and other equipment used for the customer service, and two of the five counters are single, in order to preserve the privacy of the patient. The counters must not include objects which may difficult the communication and visualization between the health attendant and the patient. [1] The pharmacists, pharmacy technicians and collaborators are properly identified with a card containing the name and professional title. In this space there are also a variety of products exposed in order to allow the visualization and verification by the patient. However, the products subjected to medical

prescription are stored in other spaces with access only to the professionals. The disposition of the products in this space, starting in the entrance door and following from the left to the right there are: perfumes; hygiene products like toothbrushes and dental floss; Cosmetic products, mainly related with hair; behind the service counters are exposed the most required products not subjected to medical prescription like syrups, analgesics and others; Natural products like food supplements; products related with childcare like bottles, nursing nipples, milky products, skin products and others; veterinary products like collars, disinfectants and others; a small section of products used to clean the respiratory airways like seawater; and a variety of cosmetic products disposed in different sections according to the brand, including creams and oils to the hair, face and body, and also beauty products mainly intended for women. This space is also equipped with exhibitors which contain particular products like comfortable work shoes intended for professionals related with health industry and other official entities who work in health institutions and other products like canes and insoles to accommodate the movement of the patients.

In the interior space addressed to the customer there are three access structures: one structure leads to the lockers area and more ahead to the **laboratory**; the other structure leads to the **workspace of the pharmacy professionals** and the main **storehouse**; and the last structure leads to a **consulting room**, where are provided and performed other pharmaceutical services allowing a private and confidential dialogue, and more ahead the technical director office. Only the last structure is intended for the patients in order to address the consulting room, whereas professionals related with the health industry may also use this structure to access the technical director office.

The laboratory surfaces are made of suitable material (marble) and smooth, and the equipment used to measure some parameters and prepare the manipulated products are in conditions of use being permanently checked. [1] The pharmacy professionals workspace contains several documentation related with the different processes performed in the pharmacy like recipes processing and informative guidelines about the products commercialized, and also related with the recommendations and standards present in the current legislation. This space also contains the necessary equipment to perform the many and complex procedures beyond the dispensation process made during the customer service, like computers with internet connection, devices for the barcode reading and telephones. The consulting room is physically separated from the other areas, ventilated and, as far as possible, free from noise and disturbances which can affect the communication between the professional and the patient, in order to establish a good environment for the providing of differentiated services. [1] The general structure of the pharmacy is also composed by a larger storehouse and a meeting room intended for specific meetings and formation courses, situated on the floor above the pharmacy with an outside access and an interior access through the technical director office. The meeting room is also equipped with a coffee machine to accommodate the pharmacy professionals and several documentation related with the products and services provided by the pharmacy.

The pharmacy structure also includes equipment related to an important topic which is security. The security system implanted ensures the safety and protection of the patients, pharmacists, pharmacy technicians, collaborators, medication and equipment present in the pharmacy, especially during the night service. The night service is done through an attendance wicket protecting the integrity of the professionals and the pharmacy. Inside the pharmacy there are several surveillance cameras with image recording, and also a respective sign indicating that the public is being filmed. Other specific protective structures consist of: urgent call device; protection systems against intrusion and theft; signs advertising the patients and professionals regarding slippery floor or places in maintenance, in order to avoid accidents; alarm system against fire and extinguishers; and output flags. [1]

The technical director is responsible for ensuring that the pharmacy possesses all the equipment necessary for its activity, in good working conditions, complying with the required performance, with a maintenance plan approved and followed, and in specific situations with a calibration and control plan, and also adapted to the products prepared and dispensed in the pharmacy. The documentation associated with the equipment and the several processes performed in the pharmacy like laboratory material (scales, glassware, and others), pharmacopoeias, forms and official documentation is conform the current legislation and the respective standards. The pharmacy professionals, mostly the pharmacists, along with pharmacy technical director ensure the preservation of the equipment and the elaboration of the necessary documentation.

The informatics equipments and the automated analytical systems present in the pharmacy are kept in good environmental and operational conditions, respecting a methodology which allows avoiding loss of information, in case of accident or informatics failure, through an easy and fast data recovery, namely through an effective system of backup copies. The environmental and operational conditions are ensured by having these equipments in places and environments according to the manufacturers' recommendations, performing preventive maintenance, safeguarding unauthorized intervention, ensuring power supply and preserving them from exposition to informatics viruses. These informatics equipments are also responsible for ensuring the protection and integrity of the information related with the entrance, processing, storage and transmission, with different access levels defined. However, the pharmacy possesses a contingency plan by inoperability of the informatics systems which allows the provision of the basic services. The informatics programs for clinical use are designed, implemented and validated in order to avoid errors and respect the data`s confidentiality, documented and suitable for the use, used by collaborators with proper formation, and validated and audited periodically, especially after any change, file restoration, breakdown or data recovery. [1] The software implemented in the community pharmacy for the processing and registration is "Sifarma 2000". This program contains all the

several and different aspects related with the operations developed in the pharmacy allowing a quality management and a uniform basis of work for all the professionals. The program is easy to use and also allows the customization and, in particular situations, the creation of necessary documents. The total or partial access to the program is made by an access pass with proper identification by the system of the individual accessing, preventing the unauthorized access and modification of data.

2.2 Drugs and other health products

The community pharmacy is a place where we can find a huge amount of medication and other pharmaceutical products normally used for the prevention and treatment of several diseases. Therefore, it is essential to have a quality general management, namely a stock management, in order to possess the enough amounts of necessary products to provide.
The products available to be dispensed in the pharmacy are: medication subjected to medical prescription; medication not subjected to medical prescription; manipulated products; veterinary products; nutrition products; phytotherapeutic products; hygiene and cosmetic products; orthopedic products; medical devices; childcare products; and others.

2.3 Information and Scientific Documentation

The community pharmacy professionals, mostly the pharmacists, are constantly placed in a position where they have to provide important, correct, safe and effective information. Therefore, the pharmacy and the professionals must have several sources of information regarding the products and the services provided, as for other general health aspects, in order to be informed at a scientific, ethical and legal level and assume a level of competence appropriate to an efficient service providing. [1] The permanent evolution in the health area also represents a major concern associated with the information given to the several individuals about the vast therapeutic arsenal and services. Therefore, it is essential to have bibliographical sources continuously updated and organized. Nowadays, with the technological development, practical digital sources of information are used with clinical purposes.

In the process of products dispensation, the professional must mandatorily dispose of physical or electronic access to sources of information related with indication, contraindications, interactions, dosage, utilization precautions and others. The pharmacy has in is library all the official and required books like: the Portuguese Pharmacopoeia; the Galenic Formulary; and the Therapeutic Records. Other physical bibliographical sources consist of: Summaries of products characteristics; documents with information related with nutrition products;

documents with information related with veterinary products and animal characteristics; documents with information related with natural products; documents with information related with cosmetics and hygiene products; and other particular documents with specific information. Currently, due to the facility, celerity and security associated with digital sources of information, the computers with internet connection assume a special importance and utility, being preferentially used. The most important digital sources consulted are: INFARMED; Infomed; and others. The program installed in the pharmacy also allows the consultation of many information of interest.

The main responsibility of the pharmacists and health professionals is the patient`s, and the general citizen`s, health and well-being, providing the right to a quality, effective and safe treatment. The counseling about the medication`s rational use and the monitoring of the patients represent very important aspects related with the gold of ensuring the top quality of the services provided, respecting the principles stated in the ethics` code. [1] In order to improve the knowledge and the quality of the information provided, the pharmacy health professionals, mostly the pharmacists, attend several formation courses related with different health topics. These formation courses can take place in the pharmacy being organized and managed by the technical director, or can take place in several other locations with the registrations being available through the internet and, usually, with a limited number of participants. Some of the formation courses can even be made through the internet without any physical displacement, having only to proceed to the online registration and download the associated documents. The completion of these formation courses improves the knowledge, attitudes and skills related with the functions of the pharmacy professionals. However, for the pharmacists, the continuing formation is a professional obligation and must include the attendance to courses of scientific and technical formation, symposiums, conferences and professional and scientific meetings, beyond pharmacy internal clinical sessions and the reading of relevant publications. If possible, the pharmacists also must attend audit courses in order to apply the knowledge acquired in the evaluation of the own pharmacy professional activities. [1] All the professional activities with curricular relevance are registered in order to each pharmacist possess a permanently updated resume (*curriculum vitae*). During the trainneship/internship I attended a formation course which took place in the meeting room related with veterinary products.

2.4 Provision and Storage

The general management of the pharmacy is from the responsibility of the technical director who, thereby, is the person in charge of the products buying decision and stock management. The provision is one of the most important functions related with this structure due to the

necessity of owning the essential products available and the equilibrium between the cost of the products obtained and the cost of the products dispensed, in order to provide sustainability conditions. The informatics program installed in the pharmacy is the platform where is carried out the several procedures related with the provision area, like the elaboration of the orders, reception of the products and registration of the products` movements. However, this is a complex area which also requires an extensive office work in order to evaluate and select the best product suppliers. The pharmacy can perform orders to wholesale distribution warehouses or acquire the products directly from the laboratories. Normally, each pharmacy has a main daily supplier which offers the best order conditions, delivery, payment and products` devolution. Usually, the products are obtained through orders to wholesale distribution warehouses which allows the order of suitable amounts regarding the stock levels established, have a wide variety of products and also allows the delivery of orders several times daily, ensuring the pharmacy necessities related with the work dynamic. The direct order to laboratories is especially performed when the pharmacy wants to make an acquisition aplenty, the products of laboratories are not available in the daily suppliers or when a product is sold out in the providing warehouses. [1] These laboratories present some advantages like offer of special price conditions when a product is acquired aplenty, supply of formation actions about the products and according to order`s dimension the provision of exhibitors and samples, in order to show the product to the patient more easily.

The different orders are performed by the technical director in collaboration with the other professionals, mainly the pharmacists, who provide important information regarding the movement of the products and stock management. The pharmacy informatics` program also provides a diversity of information related with the movements of the products, by consulting the products sheet, like consumption rates, amount of products in stock, availability of the products by the suppliers and others, providing a support to the elaboration of the orders. Each product has a minimum and maximum quantities defined in the program according to a previous analysis of its rotation and average monthly output, and the amounts of products requested in the orders are usually made according to those defined levels. These guidance limits can also be changed in several situations in order to get the ideal stock: when the professionals verify an increased demand of a particular product; in seasonal changes when a specific type of products is mostly dispensed; the payment terms to the suppliers; the advertising emphasis given to certain products; and the prescribing habits of the region clinicians. [1] After the elaboration of the order, the technical director determines the purchasing requirements and ensures the registration of the purchase information with an essential level of detail. Usually the elaboration of the orders is performed during the end of the afternoon and the delivery of the three daily orders is performed respectively during the morning, lunch time and end of the afternoon, but in particular situations it can be elaborated a punctual and necessary order.

The acquisition of the orders is usually made by the pharmacy professionals ensuring that the products or services ordered are in conform to the specified purchase requirements, the pharmacy quality requirements and the legal requirements. The products are usually delivered in bathtubs properly identified and accompanied by the respective delivery note and invoice containing several parameters such as: supplier`s identification; the document`s number; the total cost of the order to the pharmacy; the individualized description of the products shipped; the amount requested and sent of each product; the "IVA" that each product is subjected; and when applicable the selling price to the public of the products possessing a variable profit margin. After the verification, the professional signs the delivery note and makes the registration of the order in the program, which allows the association with the request made informatically and consequently a control of the products requested and received. The products of each order are individually checked and registered in order to give input in the pharmacy stock. During the products registration is also verified and recorded the lot and expiration date in order to ensure traceability and integrity, respectively. [1] When the registration is concluded, it is necessary to put etiquettes in all the products without an established fixed price. The etiquettes are issued in proper equipment with the name of the product, the price, the "IVA" which is subjected and the respective bar code. The collocation of the etiquettes must not cover any important information related with the product. After this process the products are properly stored. The pharmacy professionals ensure that no product is used with a pending acceptance process.

The psychotropic and narcotic drugs represent a type of products in which the pharmacist develops a more interventional function. Since these products are related with specific aspects like the particular cost and mostly, the serious adverse reactions that can cause, the pharmacist ensures the control of all the products` movements and the proper storage and dispensation. [1] These products are ordered along with the others but with a physical separation and with special support information by the pharmacists. The reception of the products must be registered and signed by two members of the team and one of them is the pharmacist. The storage is made in a particular cabinet in the main storehouse area. The dispensation of the products is made under the control of the pharmacists following all the legal aspects and demands associated. According to the law nº 11/2012 from march 8th, the narcotic drugs can`t be prescribed along with other medication in the same prescription. [2] However, it can be prescribed until four different products, in a total of four packages by prescription (two packages of a product, and four packages in the cases of individual packages). The pharmacist is responsible for the preparation, elaboration and emission of the entries and exits lists. The sending and record of the documents related with the control of these particular products is made under the current legislation.

All the areas of the pharmacy ensure the several storage conditions associated with the different products commercialized. Conditions like illumination, temperature, humidity and ventilation of the storage areas are taken in consideration and properly managed, respecting the specific demands of the drugs, other pharmaceutical products, chemicals, raw materials and packaging materials. [1] The different storage areas are equipped with particular devices situated in specific places, which allows the monitoring of these parameters. These devices are permanently checked and the data recorded.

The storehouse is considered the central core of the pharmacy and is properly organized in order to allow an easy and rapid access to the products. The main storehouse is the one near the pharmacy professionals` workspace which contains the majority of the medication dispensed daily. It is composed by two major structures with sliding drawers, cabinets with several shelves and a fridge intended to store the products that require conservation in cold. The two major structures contain different products: one is used to store syrups, internal and external use solutions, ointments, creams and gels, drops and eye ointments, suppositories, wallets/sachets and injectables; the other is used to store the most important drugs, tablets and capsules (including drugs in general, generic and homeopathic pharmaceutical products), which represent a big slice of the economic factor associated with the general management of the pharmacy, ampoules, natural products which include the phytotherapeutic and food supplements, injection needles, glucose strips and hygiene and cosmetic products. The cabinets are used to store drugs and products of veterinary use, bandage material, medical devices, some hygiene products including cosmetics and dermopharmaceutical products, and a particular space intended to store the psychotropic and narcotic drugs.

Many of the products, mostly hygiene and cosmetics, are exposed harmoniously in the interior space destined to the customer service where the necessary conditions for the proper storage are ensured, making use of devices who register the temperature and humidity. These devices are permanently checked and the pharmacist is responsible for the registration of the designated parameters in specific sheets, which are after archived.
Beyond the structures previously indicated, the pharmacy also possesses a big storehouse above the general infrastructure which contains all the products commercialized that are not able to be stored in the pharmacy.

In all the structures the storage of the products is made according to the international common denomination and the dosage, with the brand products always following the generic products. The only exceptions are the natural products section in which the products are stored by the brand name, and the cosmetic and hygiene products usually stored in the general brand section.

Monthly, it is performed the control of the products` expiration date, mostly by the pharmacy technicians. The pharmacy professional consults the program and obtains a list of products in stock with an expiration date in the following three months. Then, it is performed the control of the products in order to dispense the specific products which can be used with a safe margin before the expiration date, or perform the removal request.

2.5 Products dispensation and Counselling

The dispensation of products is the hallmark of the community pharmacy, and is designated as the professional act in which the pharmacist, after the situation general evaluation, provides the products to the patients according to the medical prescription, or in self-medication regimen or pharmaceutical indication. During the dispensation, the pharmacist assesses the medication, in order to identify and solve problems related with the medication, protecting the patient of possible negative results of the products. This process is always accompanied by the provision of all the essential information for the medication correct use. [1]

The general dispensation process consists of: reception of the prescription and verification of the aspects proving the validity and authenticity; pharmacotherapeutic evaluation of the prescription or indication/self-medication by the pharmacist; intervention to solve the possible problem related with medication identified; delivery of the product prescribed, indicated or in self-medication; clinical information provided orally or/and written ensuring that the patient receives and understands it in order to withdraw the maximum benefit from the treatment; revision of the medication use process; offer of other pharmaceutical services; and documentation of the professional activity. This process requires human and physical resources and, when necessary, exist a private dialogue without interruptions in order to perform a safe and efficient dispensation.

The reception of prescriptions and verification is made taking the following measures: identification of the patient, prescriber and entity responsible for the payment; verification of the prescription authenticity and expiration date; interpretation of the treatment type and the prescriber intentions; identification of the product and confirmation of the pharmcaceutical form, dosage, presentation, administration method and treatment duration. [1] When the prescription is not possible to be dispensed, the professional must help the patient solving the problem. This step may not be performed when the patient addresses the pharmacy in order to obtain a service or product which does not require prescription.

The pharmacotherapeutic evaluation of the prescription is made taking into consideration: the necessity of the product; adequacy to the patient (contraindications, interactions, allergies, intolerances, and others); adequacy of the dosage (frequency of administration and treatment duration); and the patient/system conditions to administrate the product (legal,

social and economic aspects). When necessary, the pharmacist may contact the prescriber in order to solve possible problems related with the medication detected or in particular situations when is necessary more essential information. The identified problems related with the medication and the way they were solved, is properly registered. To perform the evaluation, the pharmacist may use the following sources of information: questions to the patient or the prescriber; bibliographical sources accessible in the pharmacy; or external sources, namely drug information centers, competent authorities and the pharmaceutical industry.

The pharmacist owns professional competence to select products similar to those prescribed, having the same qualitative and quantitative composition in active principles, same pharmaceutical form, same dosage and, when appropriate, the same bioequivalence properly documented. This selection is only made with the patient`s consent and the final decision belongs to the patient. In order to perform a quality and safe selection the pharmacist has also access to proper and precise information related with the quality and bioequivalence of the products. However, according to the current legislation, namely the law nº 11/2012 from march 8th and ordinance nº 137-A/2012 from may 11th, the prescriber has the authority to decide if authorizes or not the dispensation of a generic product instead of the product prescribed. [2] [3] The current legislation determines that the prescription is made by the international common denomination of the active principle, pharmaceutical form, dosage and presentation, with certain exceptions to the prescription by the brand name: absence of brand medication or similar generic products; technical justification included in the prescription by the prescriber; medication with narrow therapeutic index; suspect of intolerance or adverse reaction to a product with the same active substance, but identified by other commercial denomination; medication destined to ensure the continuity of a treatment with a duration higher than 28 days. [1] These exceptions must be written informatically in a proper writing field of the prescription. The legislation also forces the pharmacy to possess in stock at least three products of each homogenous group among the five cheapest products, and during the dispensation the patient is informed about the cheapest product which he can acquire.

When the products are being dispensed, the professional ensures the product stability conditions, check the condition of the package and also verify the expiration date promoting the quality of the products provided. After the registration of the products associated with the proper prescriptions, also processed in the program, the patient signs the back of the prescriptions to confirm the products acquisition, not forgetting the financial burden.

During the registration process and after, the pharmacist provides all the necessary information to a correct, safe and effective use of the medication according to the particular needs associated with each patient. Beyond the oral communication, advices and other

information, this aspect is reinforced by writing or with proper support material. Many patients request the professional to write specific indications in the products packages. The contraindications, interactions and possible side effects are usually explained. Finally, the professional must see if the patient has any doubts about the precautions associated with the medication use like the way it must be taken, the treatment duration and any special precautions.
Following the provision of the necessary information, if appropriate, the professional offers other pharmaceutical services that the pharmacy can provide like the monitoring of the biochemical and/or physiological parameters.

The patients` medication is registered informatically through the program installed in the pharmacy along with other aspects related with the patient, ensuring the confidentiality of the data. All the medications dispensed are registered, and are kept updated records of the products prescriptions who demand control like others in which the records are mandatory by law or by the professional agencies demands. [1] The traceability of all the products received and dispensed ensures the safety of the patient. All the professionals interventions performed during the dispensation are also properly registered.

In self-medication situations, usually designated as the establishment of a medication treatment by the patient`s own initiative, the pharmacist guides the patient to the utilization or not of the sought product promoting a self-medication instauration with proper instruction respecting the medication rational use. [1] In order to provide quality guidelines, the pharmacist must possess enough information to correctly evaluate the specific health problem of the patient such as: information about the problem; the symptoms and how long they persist; and the products already taken. When the information is associated with a possible serious pathology, the pharmacist advises the patient to attend a medical consultation. When the problem is considered as a minor pathology (usually designated as not serious health problem, self-limiting, with a short duration and which not present any association with clinical manifestations of other health problems), the pharmacist provides all the necessary information, only dispensing the medication in cases of manifest necessity. [1] The professionals can and must always indicate possible non-pharmacological treatments in order to solve the health problem. Sometimes the pharmacist is also called to make an urgent dispensation, which consist in the evaluation and delivery of medication that a patient needs in urgent conditions. All these situations are registered and only are performed with a previous pharmacotherapeutical profile of the patient.

2.6 Other health care services provided by the Community Pharmacy

Currently, the Community Pharmacy is a space where are provided several other health care services beyond the most recognized and characteristic function, the medication dispensation. These services consist of: determination of biochemical and physiological parameters; administration of vaccines and injectables; and consultations with professionals of different specific areas like nutrition, dermatology, physiotherapy and podiatry. All the services referred are performed in the consulting room which can be easily accessed by the patients through the customer service area. The consulting room is equipped with structures to accommodate the patient during the procedures developed such as chairs, a comfortable surface for a horizontal position and a table. This area is also equipped with a cabinet where are stored the particular documentation and devices associated with the different services provided. The documentation present in the pharmacy is related with the recommendations and guidelines, associated with the parameters determination and vaccines and injectables administration, the records of the essential aspects related with the services, and also bibliographical sources related with the several health areas.

The determination of biochemical and physiological parameters represents an important function which allows indicators` measurement for the evaluation of the patient`s health status. [1] This function is only performed by qualified professionals, mostly pharmacists. The equipment available in the pharmacy allows the determination of: blood sugar; cholesterol; triglycerides; weight, height and body mass index; abdominal girth; and blood pressure. The equipment, namely the digital scale and the specific devices used in the determination of blood sugar, cholesterol and triglycerides, and blood pressure, are properly validated and calibrated periodically. The procedures performed during the parameters determination are executed under the specific recommendations in order to provide a safe and quality service. After the verification and validation of the results presented by the digital devices, the pharmacist is responsible for providing proper information and recommendations regarding the results obtained. The pharmacist ensures that the patient understands the situation and receives the information transmitted. Conditions like privacy and an adequate environment are also permanently ensured. [1]

The administration of vaccines and injectables is also an important function which allows the administration of specific products by qualified professionals in order to avoid possible problems related with the medication. [1] This operation is usually performed in hospital settings, namely by the nurses in admitted patients or in ambulatory patients, and health centers. In the community pharmacy this operation is only performed by qualified pharmacists under the law in force. All the equipment necessary is present in the consulting room like disinfectant products, bandage material, proper containers for the material used,

and the specific utensils used in the administration operation. The administration is correctly performed under the current updated recommendations and guidelines in order to ensure the safety and effectiveness of the medication. The pharmacist is responsible and must be capable of providing information to the patient about the cares to follow related with the different procedures and formulations. The processes of administration are recorded along with the patient`s information.

The consulting room of the pharmacy is also used to provide consultations related with four areas: Nutrition; Physiotherapy; Podology; and Dermatology, more specifically skin and capillary diagnosis. The technical director of the pharmacy contacts and establishes an agreement with specialists of the referred areas in order to determine a work schedule, to provide the services to the patients. The schedule is established and promoted along with the divulgation of the service. The patients which intended to go to the consultations, contact the pharmacy and is scheduled an hour to the specific service. The day before the provision of the services, the patients are informed by phone call and text message in order to confirm the availability of the patient to attend the consultation at the time scheduled. The support documentation associated with this area is ensured by the pharmacists and the technical director.

2.7 Preparation of medication

The preparation of medication includes the elaboration of the requests made by the different homes responsible for the care of old people, and the preparation in small scale of manipulated products. The pharmacists are responsible for all the procedures and documentation associated with the medication preparation.

The requests made by the different homes responsible for the care of old people are elaborated according to the indications provided by the homes` representative individuals. These indications contain specific information about the patient for who the medication is intended, the type of products required (generic or brand) and the amount of each product (one, two or more packages; packages with few or many individual drugs). Usually, all the medication is packed together and provided in a single package and the distribution to the patients is made by the homes` professionals, whereas for particular homes and patients the medication is already packed in individual packages with the proper identification of the patient as required by the institution. The pharmacist is responsible for the procedures related to preparation of medication: elaboration of each patient profile with important information related with the medication provided; collection of the several products and output processing according to the recipes; packing of the products and identification; and delivery of the products with possible supply of important extra information. Usually, each

month a different pharmacy is in charge of providing these products. All the necessary records are performed by the pharmacist and archived in order to allow the posterior invoicing process.
The pharmacy can also prepare and provide personalized medication in particular situations and required by the patient. The preparation of the medication is from the responsibility of the pharmacist and must be prepared for a short period of time in order to ensure: the conservation of the products assuring the integrity, quality, effectiveness and safety; and a more frequent contact with the patient to promote the therapy adhesion. [1]

The preparation of manipulated products is made in a specific area with specific devices and documentation: the laboratory. This area ensures the conditions required to the preparation of these products (illumination, ventilation, temperature and humidity) with particular monitoring devices, similarly to the other pharmacy areas. [1] The equipment of the laboratory consists of: devices for heating specific products; scales, which are periodically checked in terms of maintenance, validation and calibration; glassware as watch glasses, funnels, erlenmeyer flasks, volumetric flasks, precipitation cups, pipettes, beakers and others; and other particular utensils like spatulas and plastic containers, and materials used to make the verification and validation like the pH strips. The pharmacy laboratory is also equipped with a machine called “Unguator” which makes the mix easier, less stressful, time saving and more effective. All the equipment is periodically checked in order to ensure the use conditions. The documentation associated with this area consists of: the bibliographical sources consulted for the preparation; and the records of the manipulated products prepared. The bibliographical sources present in the laboratory are diverse containing the most important references like the Pharmacopoeia, the Portuguese Pharmaceutical Formulary; the Galenic Formulary; the Good Pharmaceutical Practices issued by the Pharmaceutical Order; and the Good Manipulated Products Preparation Practices stipulated by law. All the manipulated products prepared are associated with supporting documentation which contains the record of the lot number, components used and respective lot, preparation procedure, data of the patient and prescriber, quality control, utilization deadlines, conservation conditions and calculation of the respective price according to the current legislation. The identification of the manipulated products with the lot number is important because allows the traceability. [1] These records are performed informatically in specific sheets previously created which are associated to the informatics program installed and used in the pharmacy. The raw materials are usually stored in the original package, but when they need to be transferred to another container, the necessary measures are taken to avoid contamination and the container is properly labeled. All these particular products possess the safety data sheets, the analytical bulletins proving the conformity with the pharmacopoeia requirements, and also the records related with the movements of raw materials used in the manipulated products` preparation.

The process begins with the validation of the request or prescription presented by the patient. Before the preparation and dispensation of the manipulated product, the pharmacist obtains important information regarding different aspects: the health problem for which is going to be used; allergies and/or intolerances; other health problems associated with the patient; the medication that the patient is currently taking; possible difficulties in drug administration; and preferences (solid, liquid pharmaceutical forms; flavor; and others). The prescription is always professionally interpreted based on pharmacotherapeutic and pharmacotechnical aspects with special attention to the pharmaceutical form, non tolerated components and incompatibility between components. [1] The preparation of the manipulated products is made according to the documented procedures present in the prescription and the other several bibliographic sources and follows the standards of manipulation. The semi-finished product is checked to see if satisfies the requirements established in the general monograph of the Portuguese Pharmacopoeia for the respective pharmaceutical form. After the preparation, the final product is controlled ensuring the required properties of the manipulated product like the organoleptic characters and the necessary non-destructive tests according to the Portuguese Pharmacopoeia. The final verification of the product mass or volume must correspond to the quantity or volume prescribed. The results of these verifications are registered in the respective manipulated product preparation sheet. In order to finalize the preparation, the final product is properly packed and labeled according to the current legislation. The label usually contains important information to the patient like the composition of the manipulated product, utilization precautions and expiration date. The expiration date is a specific parameter which must be attributed according to the different components of the final product. Finally, the dispensation is made by the pharmacist who ensures that the patient receives the essential information regarding the most important aspects of the manipulated product.

Summarizing, the laboratory allows the preparation of safe and effective manipulated products, which takes in consideration the specific pathophysiological profile of the patient. All the manipulated products are prepared according to standards and documented procedures like the Good Pharmaceutical Practices and the Good Manipulated Products Preparation Practices. The dispensation is made by the pharmacist along with the supply of necessary information in order to promote the correct use.

This pharmacy area represents one of the most ancient procedures associated with the community pharmacies and also one of the most identifying and distinguishable skills of the pharmacists. However, with the permanent evolving of the pharmaceutical industry and the extreme variety of different products, this area has fallen into disuse with very few manipulated products being prepared.

2.8 Pharmacovigilance and other health activities

The pharmacovigilance is designated as the public health activity which gold is the identification, quantification, evaluation and prevention of the risks associated the commercialized medication use, allowing the following of the possible medication adverse events. [1] The usual procedure associated with this area from the responsibility of the pharmacy professionals, especially the pharmacists, is the identification of medication adverse reactions and notification of these events to the national pharmacovigilance system – INFARMED. When the pharmacist detects a possible adverse reaction related with the medication, he records the event by filling a particular form and sends it with celerity according to the national pharmacovigilance procedures to the health authorities. In the notification of the adverse reaction, the pharmacist includes the following information: description of the adverse reaction (signs and symptoms), as the duration, gravity and evolution; relation between the signs and symptoms with the medication use; the suspected products with the associated date of beginning and suspension, lot, route of administration and therapeutic indication; and other products that the patient is taking.

The community pharmacy and the professionals are also involved and possess an important role in an essential area which is the education to health. The education to health is an active process which pretends to create in the population knowledge, skills, and attitudes that allow preventing and dealing with the disease, providing the opportunity to participate in the decision making about their health. [1] The gold of this process is to change the individual risks behaviors and consequently improve the persons` health. Therefore, the pharmacy and the professionals are responsible for promotion of health and disease prevention, through different actions: dialogue with the patients about health topics; and development of specific programs. These actions must lead the patient to understand the need of being more and better informed about health issues and make decisions about behavior modifications, when necessary. In order to establish a good level of communication the professionals must identify personal and environmental factors improving the relation with the patients. The education process should be performed in a physical space with a proper environment to the acquisition of knowledge and abilities, also allowing the performance of individual or group educational techniques. [1] The professionals should also resort to educational material (graphic, written or audio-visual) adapting it to the necessities of the patient. The pharmacists must be encouraged to promote and participate in programs related with health along with other professionals and agencies related to health. These programs may be performed locally, nationally or internationally, in association with public or private entities.

2.9 Accounting and Management

As previously stated, all the products movements and the general stock management are properly registered in order to allow the processing and accounting associated with the pharmacy management. In most cases, the dispensed medication cost associated with medical prescriptions possesses a part supported by the state and other by the patient. The part supported by the state belongs to the pharmacy which has to monthly perform the prescriptions processing in order to get the reimbursement. In the back of the recipes is impressed the pharmacy identification, the technical director responsible, dispensation date, the operator code responsible for the dispensation, the number, lot and series of the prescription, the name, quantity, code and price of the product dispensed, the medication total cost and the values supported by the state and the patient with proper identification of the code associated with the supporting plan. All the dispensing processes are double checked and verified by the pharmacists to see if the financial charges are in order. Actions taken throughout the product route help to perform the accounting such as: when is performed the reception of the product is always made the verification and alteration of the selling price and profit margin according to the current legislation and indications of the providers; and during the dispensation is always indicated the organism in which the patient is included accompanied by the necessary documentation, in order to identify the paying entity. Daily, the technical director confers all the cash movements and verifies if all the processes are made correctly. In the end of the month, it is performed the lots closure. Each lot is composed by 30 recipes with the last lot able to possess a variable number of recipes inferior to 30. After the lots closure are emitted the notes which contain information about the number of recipes, the lot and serial number, the code of the supporting plan, the total value of the selling price to the public, and the costs supported by the patient and the responsible supporting entity. Finally, the documents are sent to the responsible entities in order to approve the documents and proceed to the financial balance with the pharmacy. The documentation can be sent to two different destinies: the recipes supported by the Health National Service are sent to the Conference Center of Invoices; the recipes supported by other entities are sent to the National Pharmacies Association who makes the negotiation with the responsible entities.

2.10 Bibliography

1. Manual of Good Practices for Community Pharmacy, Pharmaceutical Order, 2009.

2. Law nº 11/2012 from march 8th.

3. Ordinance nº 137-A/2012 from may 11th.

Chapter 3 – Antiviral Therapy for Influenza

This review was based upon search and selection of relevant articles, which was carried out in February 2015. Information was retrieved from B-on, PubMed and information websites of various health organizations in order to obtain and organize information related to the topic of this review.

The following terms were used to find relevant information: “Influenza”; “Antiviral therapy/drugs”; “Adamantanes”; “Neuraminidase inhibitors”. These terms were used alone or in combination in advanced search: “Influenza” with “effects of antiviral therapy/drugs”; “Antiviral therapy/drugs” or “Adamantanes” or “Neuraminidase inhibitors” with “adverse reactions” or “side effects”.

The only inclusion criteria were the date and language of publication – only the articles published in the last five years (from 1st January 2010 until 31st January 2015) in English, Spanish and Portuguese were selected for further analysis. After an extensive search, 41 articles were selected and from the references used by the authors, 7 articles with relevant information were also analyzed.

I. THE DISEASE: INFLUENZA

3.1 General Concepts and Epidemiological Aspects regarding Influenza

Flu is the term that most people commonly use to refer to Influenza, which is regarded as one of the most common acute infectious diseases that affects millions of individuals each year all over the world. This acute viral infection, which has the ability to spread easily from one person to another, represents a major public health problem with a high burden on communities in several aspects. [1][2][3][4] Influenza has been circulating for many years worldwide causing seasonal epidemic outbreaks, usually associated with high morbidity rates and considerable mortality rates, and occasionally pandemic outbreaks as the ones seen in: 1918 in Spain, also known as Spanish influenza pandemic, 1957 in Asia, also known as Asian influenza pandemic or 1968 in Hong Kong, also known as Hong Kong influenza pandemic, and more recently in 2009 the pandemic caused by the H1N1pdm09 virus – which are associated with high morbidity and mortality rates. Typically, seasonal epidemic outbreaks occur between the months of November (late Autumn) and March (early Spring). According to the WHO Update on the disease, consulted at the time of data search, Influenza remains widely spread with differing patterns in different continents and countries as shown in the table. [5]

Region	Predominant virus type(s)	Influenza activity
North America*	Influenza A(H3N2) Influenza B	High
Europe*	Influenza A(H3N2) Influenza A(H1N1)pdm09 Influenza B	High
Northern Africa*	Influenza A(H3N2) Influenza A(H1N1)pdm09 Influenza B	High
Central and Western Asia*	-	Low
Eastern Asia*	Influenza A(H3N2)	High
Tropical countries of the Americas/Central America and the Caribbean	Influenza A(H3N2)	Low
Central African tropical region	Influenza A(H3N29 Influenza B	Medium
Tropical Asia	Influenza A(H3N2) Influenza A(H1N1)pdm09 Influenza B	High
Countries in the temperate zone of the southern hemisphere	-	Low

Table 2.1 – Influenza Update (WHO – February 2015)

The main target of this infection is the respiratory tract – where the virus lodges and performs the replication process – but the clinical spectrum varies widely. Evidence suggests that a large amount of influenza infections are asymptomatic with the symptomatic cases ranging from mild illness to more severe and fatal situations. The majority of more severe cases are related to pneumonia, a secondary bacterial infection, which occurs more often in conjunction with other co morbidities. [3][6][7][8][9]

Influenza, as stated before, is a recognized global disease which affects different areas of the world associated with different factors such as climate and population density. However, a geographical area has been suggested as the possible home of this viral related infection: Asia, China, in particular. [9] This suggestion is well funded in a specific article (Webster, R.G. et al. Evolution and Ecology of Influenza A Viruses 1992) Taking into account several aspects that led to this hypothesis, the main reason, as evidence suggests, arises from the crowded conditions in which humans and other species (such as pigs, ducks and poultry) live, providing the ideal environment for transmission even among different species.

3.2 Mechanisms of Viral Transmission

This highly contagious disease is associated with a pattern of airborne spreading through respiratory droplets containing the virus, which escape from the respiratory tract of the infected individuals or animals. In this context, smaller droplets may remain suspended in the air for longer periods of time and may be inhaled by a new victim. However, there is lack of evidence for this and little is known about the mechanism of transmission of Influenza. [4][10]

This virus has the capability to infect humans, in any age group, and also a variety of animal species including domestic animals and wild birds. In fact, it is thought that the origin of influenza is associated with an ancestor present in an animal species, more specifically wild birds – due to several features including a high degree of adaptation to this type of host – which spread to other hosts through evolutionary patterns (Webster, R.G. et al. Evolution and Ecology of Influenza A Viruses 1992). Bird flu and Swine flu are known terms related to Influenza and represent outbreaks of this disease in these particular animals. Usually when these outbreaks appear in animals, a great proportion of human are also infected which correlates the presence of an Influenza virus that has the ability to evolve from animals and spread to humans.

3.3 Influenza viruses types and characteristics

The agents responsible for influenza are the influenza viruses – characterized by segmented, negative-strand RNA genomes. They belong to the *Orthomyxoviridae* family and there are

three known types, or genera: Influenza type A virus; Influenza type B virus; and Influenza type C virus.

Influenza A viruses are further categorized into subtypes based on the characteristics of two major surface proteins – haemagglutinin (HA) and neuraminidase (NA). References to these viruses are usually made in the standard nomenclature that includes: virus type; species from which it was isolated (if nonhuman); location at which it was isolated; isolate number; isolate year; and, for influenza A viruses only, HA and NA subtype – which provides more detailed information. [3][4][6][7][8][9][10]

The Influenza virus consists of two main structures: a) the envelope layer containing the HA and NA glycoproteins along with M2 protein ion channels which represent the main targets of the current antiviral therapy; and b) the internal core containing the components that allow the replication process with special emphasis on the RNA genome – specifically related to evolutionary patterns that allow these viruses to mutate in a way to sustain the replication process and survival, in order to gain ability to spread more widely.

The surface proteins, HA and NA, are responsible for the entry of the virus into cells (input), while M2 proteins supply the environmental conditions for such a process, and for the release of progeny virions from the host cells, respectively.

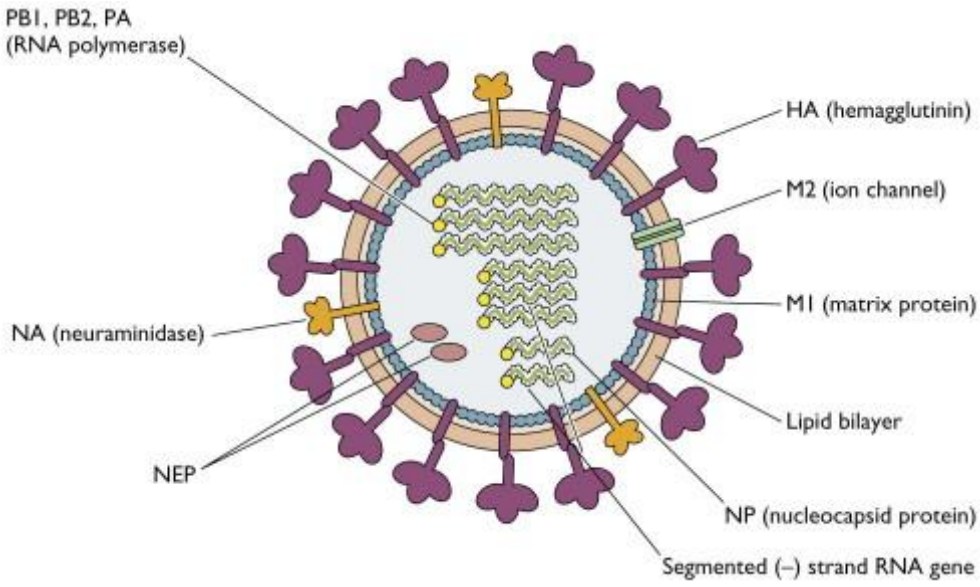

Fig 2.1 – Structure of Influenza virus.
(The image was withdrawn from the web: http://www.virology.ws/2009/04/30/structure-of-influenza-virus/)

Of the three types, influenza A and B viruses are much more similar in their structural organization than C viruses. In fact, C viruses possess distinct features including being able to form unique structures on the cell surface and having slight composition differences: only one

major surface protein and one minor envelope protein. Among the influenza A and B viruses, the main difference lies on the envelope: type A has an M2 ion channel protein and type B, instead of an M2 protein, has two different ones. The absence of these M2 proteins makes type B viruses capable of not being affected by a specific class of antivirals, Adamantanes, whose specific target is the M2 protein. Therefore this class is not capable of preventing the entry of protons to create the acidic environment needed to the release of the internal components of the virus in the host cell. [3][4][6][7][8][9][10]

Despite the differences among the three virus types, the greatest concern is related mainly with type A and, to a lesser extent, also type B. As evidence suggests, the gene pool of influenza A viruses present in aquatic wild birds enables continuous evolution and the consequent development of new strains with the potential to cause disease outbreaks. On the other hand, type B along with type C viruses only infect humans, which makes it difficult to create a gene pool in order to develop perpetuation and evolutionary mechanisms.
Several subtypes of HA and NA have been found in influenza A viruses - 17 for HA and 9 for NA – but few have caused outbreaks in humans – 3 types of HA (HA1, HA2 and HA3) and 2 types of NA (NA1 and NA2).
Among the three types of virus, evidence suggests that influenza A virus is the most virulent and causes more severe symptoms, being responsible for the majority of seasonal epidemics and sporadic pandemics. This may be related to the characteristics of the virus described above. [3][4][6][7][8][9][10]
The most characteristic feature of influenza virus is the ability to be constantly evolving due to antigenic variation, thereby leading to difficulties in controlling it. There are two main mechanisms of antigenic variation: antigenic drift associated with point mutations and antigenic shift associated with gene reassortment. Antigenic drift is related to point mutations, especially in the HA and Na antigens on the surface of the virus, that can improve some of the virulent properties related with the different components. On other hand, antigenic shift is related to gene reassortment between different viruses (for example, between avian and human strains) which enables exchange of RNA strands between different strains that could lead to a new pathogen with a genome capable of encoding for virus components with a good adaptation to human hosts. Both mechanisms potentiate the appearance of strains with higher pathogenic capabilities, with special emphasis on antigenic drift, which could lead to the emergence of new strains with the potential to cause epidemic or even pandemic outbreaks. [3][4][6][7][8][9][10]
This pattern, as stated before, is mainly verified in influenza A due to the presence of a gene pool.

3.4 Risk groups and risk factors

On the basis of the evidence provided by several studies, people at higher risk of influenza complications include:

- Children aged less than five years (especially those aged less than 2 years);
- Adults aged 65 years or more;
- Individuals with chronic pulmonary disorders (including asthma, COPD);
- Individuals with chronic cardiovascular disorders (hypertension as an independent risk factor is not included);
- Individuals with chronic renal disorders;
- Individuals with chronic hepatic disorders;
- Individuals with chronic hematologic disorders (including sickle cell disease);
- Individuals with chronic metabolic disorders (including diabetes mellitus);
- Individuals with neurological and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- Individuals with immunosuppression (including that caused by malignancy), malnutrition, medications or by HIV infection);
- Women who are pregnant or postpartum (within 2 weeks after delivery);
- Individuals who are 18 years old or less and who are receiving long-term aspirin therapy (risk of Reye`s syndrome);
- Individuals who are morbidly obese (BMI of 40 or above);
- Residents of nursing homes and other chronic-care facilities.

According to evidence, rates of illness are highest among children, and rates of serious illness and death are highest among persons aged 65 years or more, children aged 2 years or less, individuals of any age with underlying medical conditions that are at increased risk for complications and, more recently, individuals who are morbidly obese. [3][4][7][10][11]

3.5 Clinical aspects

The incubation period appears to be around one to three days, but some studies report cases to be as short as one day or extend to seven days.

The most affected major organs are the respiratory and gastrointestinal tract although other organs such as brain and muscles also experience some effects of the disease. The most common symptoms are fever and cough which are present in a high proportion in symptomatic infected individuals, alone or along with headache, rhinorrhoea and myalgia. Nausea,

vomiting and diarrhea are also likely to be experienced, especially in patients infected with strains of influenza B. [2][3][4][7][8][10]
Based on the symptoms present in an influenza infection it becomes clear that a firm diagnosis of the disease is difficult since the clinical manifestations are usually non specific and similar to those of other acute respiratory infections.

3.6 Complications/Burden of the disease

The burden of influenza virus infection is considered to be high and is reported to be unevenly distributed – children less than 5 years of age are reported to have more severe outcomes than older children and adults.
The most common complications of influenza infection are pulmonary, mainly bronchitis and pneumonia – primary influenza pneumonia occurs most commonly in adults and secondary bacterial infection is more common in children – and exacerbations of chronic underlying pulmonary diseases.
In infants and young children, mostly 5 years or less, one of the most common complications is otitis media. Respiratory tract infections as stated before are also frequent, with pneumonia being the most prevalent. Evidence also suggests that younger children have a higher tendency to be hospitalized. [1][2][3][4][10] Regardless of the different scenarios associated with influenza virus infection (type of influenza virus or subtype, absence or presence of co-morbidities, etc) a common pattern has been seen – young children remain particularly vulnerable to influenza.
Besides the clinical burden, influenza virus infection is also related to a high burden among the general community. Other aspects must be taken into account such as: number of work days lost for adults; number of school days lost for children who can also cause absence at work by the parents; and the several resources such as human and material that are needed for hospitalized patients and in other settings such as nursing facilities where a majority of older people live. This leads to a socioeconomic as well as clinical burden. [1][2][3][4][10]
The development of complications by the influenza virus is reported to be reduced with the administration of antiviral therapy.

3.7 Neurologic events

According to evidence, the neurologic system is universally recognized to be affected in the global scenario of the disease caused by the influenza virus. A great amount of patients with laboratory confirmed influenza virus infection is reported to experience events related to this system: from febrile convulsions, in less severe cases, to encephalitis and encephalopathy, in more severe cases, with possible fatal outcomes. Myositis and myocarditis represent less common complications associated with influenza but may also occur. Since these particular

events are both associated with the infection and the therapy used, sometimes it becomes difficult to identify the origin.

The events, which are currently discriminated in the summary of drug characteristics, at first, when the drugs became available, were not indicated as possible side effects related to the drug use. However, the publication of reports stating a possible relation between the antivirals and the occurrence of neurologic events took the drug agencies to attach information regarding these events to the general information documents of the drugs. The majority of the reports are related to publications with origin in Asia, which interestingly is pointed as possible epicenter of influenza and where are prescribed great amounts of antivirals as stated before. [12][13][14][15]

Regardless of the source, the influenza virus itself or the antivirals used for therapy, these particular events affect one of the most important and fragile organs of the human body. They acquire even more significance due the fact that is a pattern mostly seen and reported in a particular and vulnerable age group: children. This age group is also related to developmental processes, and some changes in development may be associated with the virus effect.

As stated the central nervous system can be affected by the influenza virus and by medication, both causing several different events. The virus enter the body by way of the respiratory tract setting up the replication initial sites in these tissues. After this process, these agents can reach the CNS mainly by bloodstream or by other ways as by direct entry through infected air sinuses, with viruses having a time course to develop CNS signs (depends on the agent) around hours to 1 day. However, regardless of the several infections that we develop during our lifetimes, the responsible agents rarely reach the CNS. [48]

When it occurs **CNS infection** is characterized by inflammation of the meninges (meningitis) or brain (encephalitis) with the signs and symptoms depending on the site of the infection. Some of the common clinical features of meningitis are fever, headache, stiff neck and seizures. **Encephalitis** is described as a febrile illness with abrupt onset of **headache** and mental obtundation, with other features as **seizures**, **ataxia**, limb tremors and focal neurological signs. This illness is associated with neuronal necrosis and lysis of glial cells resulting in secondary cerebral edema with infiltration of inflammatory cells which can lead to neurologic sequelae. Encephalitis and meningitis differ mainly because patients with encephalitis develop mental changes and have minimal or absent stiff neck. [48]

The neurologic events presented here extol the importance that must be regarded to influenza and the antivirals available.

II. THE TREATMENT

3.8 Prevention

Vaccination is considered the main strategy for prevention of disease – and all individuals aged 6 months or older are recommended for annual influenza vaccination. [11][16]
Regardless of the sustained effectiveness of vaccination in prevention, two aspects are invariably related to this practice:

a) as vaccines are designed to match major HA epitopes (ex: H1 and H3) within the predicted circulating strains, when a new viral strain arises it brings the potential of a new pandemic, and the development and production of an effective vaccine may be too slow in order to be effective against the spread of infection;

b) in addition, an individual that has been vaccinated can still be infected.

For these reasons, antiviral therapy remains extremely important in the treatment of influenza virus infections. In addition, recent evidence has demonstrated that this type of therapy may also have a role in prevention of viral infections.

3.9 General aspects of pharmacological treatment

Antiviral medications, according to literature, are effective for the prevention and treatment of influenza. When used for prevention, a reduction in the risk of developing symptomatic influenza has been reported. As for treatment, the duration and severity of illness are reported to be reduced. The time between the onset of symptoms and beginning of treatment is considered to be crucial and early treatment can reduce the risk of severe illness or death – better outcomes are associated when the treatment is started within 48 hour after symptom onset. [11][16]-[25]

3.9.1 Classes of anti-viral drugs used for treatment

Currently, two classes of antiviral medications are approved for treatment: a) adamantanes (or M2 inhibitors) and b) neuraminidase inhibitors (NAIs). [11][17]-[25]

Adamantanes

Amantadine and Rimantadine represent the adamantanes class. These drugs have a mechanism of action which targets the M2 protein – a transmembrane ion channel- thereby blocking the movement of protons necessary for the acidic environment that allows the internal elements of the virus to exit the endosomal compartment and be released in the cytoplasm of the infected cell. In other words, these drugs prevent the uncoating of the virus.

Adamantanes are only effective against influenza A viruses because the target of this class – the M2 protein – is not present in influenza B viruses – instead it has two membrane proteins NB and BM2. In addition, widespread adamantane resistance among influenza A virus strains made this class less useful clinically. Therefore, this class is not recommended for antiviral treatment or prophylaxis. However, information about these drugs is provided for use in the context of a possible scenario of reemergence of adamantane-susceptible strains or in a potential beneficial combined treatment, which might change the current recommendations.

1) Amantadine can be used for the prevention and treatment in individuals older than 1 year of age with weight-based dose regimens for individuals aged between 1 and 9 years and 100mg twice daily for individuals who are 9 years of age and older; in individuals older than 12 years the 200mg daily dose can be taken in a single administration. [17][21][26]

2) Rimantadine can be used for the prevention among individuals older than 1 year of age and for treatment in individuals aged 17 years or older. The recommended dose for treatment is 100mg twice daily for 7 days after the onset of first symptoms. [17][21]

Pharmacokinetic properties

1) Amantadine

Absorption readily takes place in the gastrointestinal tract in a complete way, with elevated bioavailability associated. This drug is highly distributed in the tissues and is reported to cross the blood brain barrier and the placenta and to be excreted in milk. Approximately 2/3 binds to plasmatic proteins. In humans, it is not metabolized and in normal conditions the elimination half life is about 10 to 30 hours with an average of 15 hours, although in some cases, such as in renal impairment, it can be higher. It is almost exclusively eliminated in urine by glomerular filtration and a low amount in feces. Acidification of urine is reported to raise renal elimination. [17][21][26]

2) Rimantadine

Absorption occurs after oral administration. It is reported to be extensively metabolized in the liver with less than ¼ of the dose eliminated in urine as unchanged drug. The elimination half life is about 25 hours – hepatic impairment and old age are associated with changes in elimination half life, peak concentrations and average AUC values. [17][21]

Neuraminidase inhibitors

Neuraminidase Inhibitors, more specifically Oseltamivir and Zanamivir, constitute the primary antiviral agents recommended for the prevention and treatment of influenza. It should be noted that appropriate use of NAI´s for prevention should take into account the circumstances of each case. In exceptional situations, such as mismatch between the circulating and vaccine virus strains and/or a pandemic scenario, seasonal prevention could be considered in individuals who are one year of age or older. [17]-[25][27][28]

1. Oseltamivir is indicated for the treatment of influenza in patients who are one year of age or older who present typical symptoms of flu, when influenza virus is circulating in the community. In infants less than one year of age, treatment is indicated during a pandemic influenza outbreak. As for prevention, oseltamivir is indicated for post-exposure prophylaxis in individuals who are one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. In infants who are less than one year of age, oseltamivir is indicated during a pandemic outbreak. The recommended oral dose for treatment of adults and adolescents who are older than 12 (body weight higher than 40kg) is 75mg twice daily for 5 days. For children between 1 and 12 years of age body weight-adjusted dosing regimens are recommended. For infants who are less than 1 year of age the recommended dose is aged-based and ranges between 2mg/Kg and 3mg/kg twice daily for 5 days during a pandemic influenza outbreak. The recommended dose for post-exposure prevention for adults and adolescents who are older than 12 years (body weight higher than 40kg) following close contact with an infected individual is 75mg once daily for 10 days. As for children between 1 and 12 years of age and infants who are less than 1 year of age the recommended doses are also weight-adjusted and age-adjusted, respectively lasting 10 days. The recommended dose of Oseltamivir when used for prevention of influenza during a community outbreak is 75mg once daily for up to 6 weeks for adults and adolescents older than 12 (body weight higher than 40kg). In children less than 12 years of age, evidence is scarcer. It is available in two bioequivalent formulations, as hard capsules and suspension for those who are unable to swallow capsules and for infants below 1 year of age. In infants below 1 year of age, in the absence of a suitable formulation a pharmacy compounded preparation is recommended to be preferentially used due to possible dosing inaccuracies related to the syringes provided along with the powder for oral suspension – recommendations for extemporaneous formulation are also available and pharmacy preparation should be preferred to home preparation especially for this particular group.

2. Zanamivir is indicated for the treatment and prevention of infection by influenza A and B viruses in adults and children who are 5 years of age or older. Treatment

indications include patients who present typical symptoms of flu when influenza virus is circulating in the community. In terms of prevention, zanamivir is indicated for the post-exposure prophylaxis in those who had contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. The recommended dose for treatment is two inhalations (2 x 5mg) twice daily for 5 days which corresponds to a total inhaled dose of 20mg daily. As for prevention, the recommended dose is two inhalations (2 x 5mg) once daily for 10 days. Zanamivir recommended dose when used for prevention of influenza during a community outbreak is two inhalations (2 x 5mg) once daily for 28 days. Zanamivir is also available for intravenous delivery by compassionate use mechanisms and as part of clinical studies.

Treatment with NAI´s must be initiated as early as possible: within 48 hours after the onset of symptoms for adults and children for oseltamivir; within 48 hours and 36 hours after the onset of symptoms for adults and children, respectively, for zanamivir. For post-exposure prophylaxis, oseltamivir and zanamivir must be initiated within 48 hours and 36 hours of exposure to an infected individual.
Generally, NAI´s have a higher level of efficacy in the treatment of influenza A compared with influenza B – this pattern may be due to greater conformational changes in binding of NAI´s to influenza B neuraminidase than to influenza A neuraminidase. [17]-[25][27][28]

This class also includes other members such as Peramivir and Laninamivir, which have a more restrict pattern of utilization because of their recent development and, consequently, lack of scientific evidence related to the inherent aspects associated to its use as efficacy, safety, etc. [29]-[32]
The drugs that belong to this class of antivirals have a mechanism of action – as the class designation suggests – that specifically targets the neuraminidase surface proteins, thereby inhibiting the sialidase activity which is essential to the cleavage of terminal sialic acid residues and consequent release of the newly-formed viral particles (virions). In other words, it prevents the release of progeny virions from the infected host cell in which they emerged.

Pharmacokinetic properties

1) Oseltamivir

Oseltamivir phosphate (pro-drug), is readily absorbed from the gastrointestinal tract after oral administration, and is extensively converted to oseltamivir carboxylate (active metabolite) – evidence indicates that ¾ of an oral dose reaches the systemic circulation as the active metabolite. Plasma concentrations of both compounds are unaffected by co-administration with food. The mean volume of distribution of the active compound is equivalent to extracellular body fluid which distributes it to all sites of influenza virus spread given that neuraminidase activity is extracellular – binding to human plasma protein is

insignificant. The conversion of oseltamivir phosphate to oseltamivir carboxylate is carried out predominantly by hepatic esterases and is the principal elimination process in which the active metabolite is then entirely eliminated by renal excretion. The half life of the active metabolite is indicated to range from 6 to 10 hours and both oseltamivir phosphate and carboxylate are not substrate or inhibitors of the major cytochrome P450 isoforms – this feature along with low protein binding suggest that clinically significant drug interactions are unlikely. [17]-[25][27]

2) Zanamivir

According to evidence, the absolute oral bioavailability in humans is low with an average of 2%. When inhaled, 10 to 20% of the dose is systemically absorbed. These low systemic concentrations due to weak absorption do not induce a significant systemic exposure to Zanamivir. Peak concentrations in serum are achieved in 1 to 2 hours. Serum half life varies between 2 and 5 hours. After inhalation, the drug extensively lodges along the respiratory tract being released at the site of infection – the main deposition site is oropharynx and some premature deposition in the lungs is reported. High drug concentrations at the infection site must allow a quick start of action. Zanamivir is not metabolized and is reported to be totally eliminated unchanged in urine – studies report an absence of effect on isoenzymes of human hepatic microsomes and therefore, metabolic interactions with other drugs are unlikely.

Other NAIs are being studied for potential use. Peramivir, offered only as an intravenous formulation, and Laninamivir, another inhaled NAI that is currently licensed in Japan, already mentioned. Favipiravir is an investigational agent that differs from NAIs and adamantanes by selectively targeting other component of the virus structure, the RNA-dependent viral RNA polymerase. Development of novel antivirals with different mechanisms of action is important due to the rise of drug-resistant influenza viruses. [17]-[25][28]

3.9.2 Combination therapy

Given that there is increasing concern for viral resistance, combination therapy has been considered. It consists of NAIs plus adamantanes and ribavirin (an RNA polymerase inhibitor more commonly used for the treatment or respiratory syncytial virus and hepatitis C virus infections), and other combinations.

3.9.3 Other therapeutic agents

It is known that influenza infections are related to inflammatory reactions which can have serious consequences for the outcome of the infection and may be a cause of morbidity and mortality. Therefore, a range of other therapeutic agents such as NSAIDs, analgesics and corticosteroids, used in different clinical situations associated with inflammatory reactions

are also administered in cases of infection by influenza viruses. Novel applications of drugs that affect production or actions of inflammatory mediators are also being considered and include statins, macrolide antibiotics and even natural products such as flavonoids and flavones. Adverse reactions and other characteristics of these agents have been studied elsewhere – it should be noted that NSAIDs, which are widely used, are related to risk of adverse reactions associated with the gastrointestinal tract, kidneys and liver that can deteriorate the patient condition. This matter raises concerns related to the relevance of certain inflammatory reactions that could be important to the host and further analysis is required to assess the relationship between these agents and influenza infection. However, these drugs are almost exclusively associated with symptomatic relief, whereas the recommended antiviral medications have mechanisms of action that are able to stop the spread of the virus in the body.

3.10 Adverse reactions/Secondary effects

In most cases, when information is available, adverse reactions are usually placed into categories according to the estimated frequency of occurrence arising from the analysis of clinical studies. The categories are: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); and very rare (< 1/10,000) – and are further discriminated by body system which allows a better understanding of the structures affected. For some adverse reactions related to certain body systems, the frequency of occurrence, due to a lack of available data, is unknown. Nevertheless those reactions are also discussed in detail. [17]-[28]

3.10.1 Adamantanes

Amantadine

The adverse reactions of amantadine typically arise over the first two or four days after the beginning of treatment, and are usually transitory, disappearing in 24 to 48 hours after treatment is interrupted.

Disorders of blood and lymphatic system are very rare and consist of leucopenia and reversible increase of hepatic enzymes.

Cardiac disorders fall into three categories: leg edema and “livedo reticularis” (usually after high doses) are very common; orthostatic hypotension and palpitations are common; congestive heart failure and cardiac failure are considered very rare adverse reactions.

Disorders of the gastrointestinal tract include dry mouth, nausea, anorexia, vomiting and constipation which are considered common, and rarely diarrhea.

Skin and subcutaneous tissue disorders include diaphoresis which is considered common, cutaneous eruptions and photosensitivity are considered rare and very rare respectively.

Eye disorders fall into two categories: blurred vision, which is considered common; and corneal lesion which is regarded as a rare adverse reaction.
Myalgia falls into the category of common adverse reactions related to skeletal muscle and connective tissue disorders.
Urinary and renal disorders include urinary retention and urinary incontinence which are considered rare.
Nervous system disorders include several adverse reactions that fall into two categories: drowsiness or insomnia, depression, agitation states, vertigo, headaches, hallucinations, confusion, dizziness, lethargy, nightmares, ataxia and speaking difficulties which are considered common; seizures, disorientation, psychosis, tremors, dyskinesia and neuroleptic syndrome which are considered rare.
The general side effects are nervousness, anxiety, agitation, insomnia and difficulty in concentrating.

Other studies also report most common side effects as leg edema and "livedo reticularis" (normally associated with elevated doses). Other common effects are orthostatic hypertension, palpitations, insomnia or sleepiness, depression, vertigo, headaches, hallucinations, confusion, lethargy, ataxia, nausea, vomiting, blurred vision and myalgia. More rare effects reported are diarrhea, rashes, urinary retention, urinary incontinence and corneal lesion.
Amantadine may cause insomnia, therefore the last dose is recommended to be taken several hours before sleep.
Information regarding the use of this drug in specific situations as prevention or treatment of this disease is scarce. [17][21][26]

Rimantadine

Common side effects include nausea, stomach pain (upset stomach), nervousness, tiredness, lightheadedness, trouble sleeping and difficulty in concentrating.
Adverse effects related to this drug are limited and are reported to involve the CNS and the gastrointestinal system.
Other effects reported consist of tiredness, lightheadedness, trouble sleeping and difficulty in concentrating. [10][17][21]

3.10.2 Neuraminidase inhibitors

Oseltamivir

In prophylaxis, reports suggest that increases the risk of psychiatric adverse events (during the combined "on treatment" and "off-treatment" periods) that may occur in adults and a dose-response effect has been reported. The psychiatric events were nervousness, aggression,

suicide ideation, paranoia and depression. Oseltamivir is also associated with an increased risk of headaches, renal events and nausea while receiving treatment – a dose-response effect was reported for headaches.
Adults have an increased risk of nausea and vomiting. Treatment of children is associated with an increased risk of vomiting which usually develop on the first or second day of treatment and resolve spontaneously within 1 to 2 days.
Other adverse reactions include hepatobiliary disorders as such as hepatitis and an increase in liver enzymes.

In adults and adolescents:
Thrombocytopenia is considered a rare adverse reaction related to blood and lymphatic system disorders.
Immune system disorders include hypersensitivity reactions considered common and anaphylactic/anaphylactoid reactions which are considered rare.
Visual disturbance is considered rare and cardiac arrhythmia is considered uncommon, both related to eye disorders and cardiac disorders respectively.
Respiratory, thoracic and mediastinal disorders include cough, sore throat and rhinorrhea considered common adverse reactions.
Gastrointestinal disorders include the very common adverse reaction nausea, as vomiting, abdominal pain and dyspepsia considered common and gastrointestinal bleeding and hemorrhagic colitis considered rare.
Hepatobiliary disorders include elevated liver enzymes which are considered uncommon and fulminant hepatitis, hepatic failure and hepatitis considered rare.
Skin and subcutaneous tissue disorders include uncommon adverse reactions such as eczema, dermatitis, rash and urticarial, and reactions that are considered rare such as angioedema, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Nervous system disorders include the very common adverse reaction which is headache, with insomnia considered common and altered level of consciousness and convulsions considered uncommon.
Agitation, abnormal behavior, anxiety, confusion, delusions, delirium, hallucinations, nightmares and self-injury are considered rare adverse reactions related to psychiatric disorders.
In children:
Otitis media related to infections and infestations and conjunctivitis related to eye disorders are considered common adverse reactions.
Ear and labyrinth disorders include earache considered common and tympanic membrane disorder considered uncommon.
Cough and nasal congestion, and rhinorrhoea are considered very common and common adverse reactions, respectively related to respiratory, thoracic and mediastinal disorders.

Gastrointestinal disorders include vomiting which is considered very common and abdominal pain, dyspepsia and nausea considered common.
Dermatitis is an uncommon adverse reaction related to skin and subcutaneous tissue disorders. [17]-[25][27][33]-[38]

Zanamivir

Data with information regarding the related effects associated with the use of Zanamivir as prophylaxis and treatment of influenza virus infections, is more sparse and less conclusive. Zanamivir harmful effects appear to be minor - a possible explanation is the low bioavailability as previously mentioned in the pharmacokinetic properties of this specific drug. Bronchospasm and deterioration of respiratory function have been reported after administration, mostly in patients with underlying respiratory diseases (asthma; COPD) which explains why the use of this drug is only licensed for people without underlying respiratory or cardiac disease. Allergic reactions, including oropharyngeal or facial edema also have been reported. Neurological and psychiatric adverse events such as seizures, decreased conscience, abnormal behavior, hallucinations and delirium also have been reported, mainly in children. Given that Zanamivir is administered as an inhaled powder, its use may cause the constriction of airways leading to shortness of breath. Rare cases of acute bronchospasm or serious decline in respiratory function have been reported in patients with previous history of respiratory disease; in patients with no history of respiratory disease these events have been reported very rarely.

Immune system disorders include allergic reactions such as oropharyngeal edema but are considered uncommon, and anaphylactic reactions and facial edema are considered rare.
Skin and subcutaneous tissue disorders include cutaneous eruptions which are considered common, urticaria which is considered uncommon and serious cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis which are considered rare adverse reactions.
Nervous system disorders have been reported and include seizures, decreased level of consciousness, abnormal behavior, hallucinations and delirium which mainly affect children. Vasovagal type reactions have been reported and are considered uncommon. [17]-[25][28][39][40]

3.10.3 Structures affected by the influenza medication and Incidence

By the adverse reactions reported in available studies, the body structures affected very widely according to the drug used and several aspects related, as formulation and dose, and to the group population in which is administered. The incidence of these events also differ but with slight variations among the studies.

According to evidence, the main affected structures consist of the gastrointestinal tract, with high incidence of nausea and vomiting, and the nervous system which is related to a considerable number of reports of neuropsychiatric events. [17]-[38]

3.11 Risk groups and Interactions

Special concerns must be taken into account when these drugs are administered in certain group populations due to specific properties, both related to the drugs and to the population groups, which could increase the risk of adverse reactions.

3.11.1 Adamantanes

Amantadine

In patients with prostatic hypertrophy, agitation or confusion states and with syndromes of delirium or exogenous psychosis, special precautions must be taken when amantadine is used. Precautions should also be taken with patients with hepatic impairment, history of epilepsy, congestive heart failure, orthostatic hypotension, peripheral edema and with eczema and rash which can potentially exacerbate those situations. Patients at risk of electrolyte imbalance also must be properly followed up.

In patients with renal impairment, the dose must be adjusted according to the creatinine clearance due to the almost exclusively unchanged elimination by urine. Individuals older than 65 years of age may be more susceptible to the effects of amantadine, and therefore the dose must be adjusted in view of possible reductions in creatinine clearance.

Amantadine is contraindicated during pregnancy and breastfeeding periods due to adverse effects reported mainly in animal studies and some human reports – in these cases it should only be used if extremely necessary, and tight monitoring must be carried out. This drug is also contraindicated in individuals with some cardiac disorders, with seizures, with history of gastric ulcer, with severe renal impairment and with closed angle glaucoma related to the anticholinergic effects.

In terms of drug interactions, amantadine is contraindicated with some drugs that induce QT prolongation. The concomitant use of amantadine and anticholinergic drugs can intensify the adverse reactions of the latter, especially confusion and hallucinations, since CNS sympathomimetic drugs potentiate the central effects of amantadine. Memantine can potentiate the therapeutic effect and adverse reactions when used concomitantly. Amantadine decreases alcohol tolerance with the combination being able to produce effects in the CNS.

Some adverse reactions may induce a reduction in the capacity of concentration and reaction which compromises the ability to drive and operate machinery. [17][21][26]

Rimantadine

Individuals with renal impairment or liver disease and the elderly are recommended to take lower doses of rimantadine (100mg once daily). [10][17][21]

3.11.2 Neuraminidase Inhibitors

Oseltamivir

For individuals with renal impairment (moderate or severe) dose adjustment is recommended based on creatinine clearance – this adjustment of the dose is recommended for adults and adolescents (13 to 17 years of age) for prevention and treatment regimens, as for infants and children (12 years of age and younger) insufficient clinical data is available.
Almost no information regarding safety and efficacy is available in patients with severe concomitant conditions. Furthermore, for patients with chronic cardiac disease and/or respiratory disease efficacy of treatment has not been established.
Immunocompromised patients may need a longer duration of seasonal prophylaxis of up to 12 weeks. However, no solid conclusions regarding prevention and treatment with oseltamivir in this specific population were able to be withdrawn due to a lack of clinical data available regarding this specific group.
In pregnancy and breastfeeding cases oseltamivir may be prescribed with special caution and after considering the available information regarding the scenario in which this drug is going to be used – where there is a clear potential benefit.
Oseltamivir is contraindicated in individuals with hypersensitivity to the active substance or to any of the excipients.
Interactions with other medicinal products or other forms of interaction are unlikely – special caution must be taken when oseltamivir is prescribed in individuals taking co-excreted agents with a narrow therapeutic margin and when renal function is impaired.
Especially in children and adolescents, neuropsychiatric events have been reported with use of Oseltamivir – these patients should be closely monitored for behavioral changes. [17]-[25][27][33]-[38]

Zanamivir

The risk of adverse events during the use of Zanamivir, as mentioned before, is highly related to deterioration of respiratory function and bronchospasm, and this drug is contraindicated in individuals with underlying respiratory disease.
The licensed formulation contains lactose which may cause allergic reactions in patients who are allergic to cow´s milk proteins.

Information about safety in pregnant women and women who are breastfeeding is sparse and is mostly related to studies in animal models – the use of Zanamivir is not recommended, unless the benefits expected for the mother outweigh the risks to the fetus.
The principal concern about the use of Zanamivir is related to children, especially young children. However, information collected from studies is also sparse, the results vary widely and occasionally report worrying adverse events – a pronounced and large variability in systemic exposure was associated with younger children. [17]-[25][28][39][40]

3.12 Resistance to antiviral drugs

The current approved classes for antiviral therapy have been associated with another emergent problem: resistance of influenza viruses to these drugs. As happens with antibiotics, treatment-induced resistance is also associated with the previous use of influenza and other antiviral drugs, although several isolated and studied influenza viruses have been reported to present resistance towards adamantanes and/or NAIs without any previous exposure to the drugs.

3.12.1 Resistance to adamantanes

Adamantanes, besides their ineffectiveness against influenza B viruses as mentioned earlier, are no longer recommended because of the established resistance patterns observed among influenza A strains. The resistance to this class of drugs is related to single nucleotide changes which lead to amino acid substitutions within the transmembrane region of the M2 protein that may change the ability of adamantanes to induce their antiviral effect. Several mutations have been investigated and reported – V27A and S31N are the two most common mutations. Resistance to adamantanes is reported to be a class effect which means that influenza strains resistant to one agent will be resistant to the other. Currently, influenza A (H1N1)pdm2009 and A (H3N2) are resistant to adamantanes as for seasonal influenza A (H1N1), which have these mutations, identified by analysis of the strains. [41]-[45]

3.12.2 Resistance to neuraminidase inhibitors

More recently, NAI-resistant strains have emerged, especially to Oseltamivir. Resistance to this class occurs via mutations in the coding sequence of the neuraminidase gene which lead to changes in amino acids in the NA active site. These changes result in conformational modifications which alter the contact/interaction with the drug. Different mutations can lead to different drug susceptibility or resistance, depending on the drug-NA interaction which is also related to the chemical structures of the inhibitors – ideally the NAI should be as similar to the natural substrate as possible. Additionally there are mutations which confer resistance in only one subtype: H274Y is associated with oseltamivir resistance only in N1, and E119V and R292K are associated with high-level oseltamivir resistance only in N2.

Due to similarities in the chemical structure between some NAIs, specific mutations are able to decrease sensitivity to more than one NAI. In this context, H274Y decreases sensitivity to both oseltamivir and peramivir.

Oseltamivir is associated with conformational changes in the receptor binding site, as Zanamivir, due to is similarity to the substract of the NA, does not need these conformational changes to bond. Therefore, resistance to oseltamivir is more likely to arise due to the several point mutations that can modify the conformation of the receptor binding site making impossible the connection between Oseltamivir and the NA structure.

When influenza strains resistant to Oseltamivir are identified, use of Zanamivir is recommended in patients infected with those strains.

Oseltamivir-resistant influenza A (H1N1)pdm2009 virus infections have been identified, as well as influenza A (H3N2) and influenza B isolates that are also reported to be resistant. Although the incidence of resistance remains low, it has been rising – among seasonal influenza A (H1N1) resistance is reported to reach nearly 100%.

Zanamivir is associated with very low levels of resistance among current influenza viruses, although some mutations capable of conferring this characteristic have been identified. This pattern is also related to the few conformational changes reported to be needed in the interaction of this drug with its target. [41]-[47]

3.13 Conclusions

There is a strong evidence of the efficacy of the most common antivirals used for prevention and treatment of influenza virus infections, Oseltamivir and Zanamivir. However, their global use is also associated with problems related to the adverse reactions of these drugs.

Resistance of the Influenza virus to the two classes of available antivirals represents another current problem which may also be related to the use of these drugs- weight-based regimens rise concerns related to potential delivery of suboptimal concentrations of oseltamivir, thereby facilitating selection of resistant viruses.

Side effects of adamantanes and NAIs are a special concern when antivirals, in a pandemic scenario, can be given to a large number of individuals including a high number of asymptomatic cases following implementation of pandemic plans - this is reflected in the WHO Rapid Containment Protocol.

Among the effects reported for oseltamivir, psychiatric and nervous system events stand out and make this drug subject of controversy mainly due to postmarketing reports in pediatric and adolescent patients, especially from Japan where an estimated ¾ of the world´s oseltamivir prescriptions are written. Taking into account that Asia is strongly affected by influenza and many reports emerge from that area, more specific data is needed regarding the possible contribution of Oseltamivir to the occurrence of those events which can affect a population group that is associated with higher risk for severe complications when infected by influenza and could benefit from Oseltamivir use. However, such neuropsychiatric events

have also been reported in patients infected with influenza who were not taking Oseltamivir which makes it hard to correlate them with drug use.

In the case of Zanamivir, the little evidence available does not suggest an association between the use of Zanamivir and an increased risk of reported side effects. However, some reports of specific side effects are known, which alerts to the need of more scientific studies addressing this issue.

There are very few clinical trials assessing the antiviral safety for adverse events and most of these studies have been performed by the pharmaceutical companies that are responsible for the production and marketing of the drugs. Few independent studies of adverse reactions of antiviral medications are available, which might clarify the real rate of occurrence of these events.

This absence of specific data is also seen in current antiviral therapy drug classes which lack sufficient available clinical data regarding different population groups in which they are used. This feature is particularly verified in special populations, when assessing for other characteristics beyond adverse events. For instance, Oseltamivir lacks information in dosing recommendations, in pediatric patients with hepatic disorder and infants and children aged less than 12 years of age with renal impairment. Zanamivir lacks information in effectiveness and safety determinations in patients with severe asthma or other respiratory chronic diseases and pregnant women.

More clinical studies and evaluation studies are needed for this group of medications in order to use them in a sensible and scientific way with patients, avoiding risk factors, adverse effects and increased resistance.

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