***INTRODUCTION***

**A. Background**

In the selection or drug regimen should be based on the disease, age, sex, weight, and physiology of the patient. However, sometimes doctors prescribe drugs outside the indications listed on the label, or better known as off-label drugs. Off-label drugs are drugs that are prescribed but not used according to the indicated drug indications. These discrepancies include drug indications that are not in accordance with those stated by the marketing authorization as well as dose, patient age, and route of administration (Pratiwi, et al., 2013). One of the reasons for the use of off-label drugs is the lack of clinical response to previous treatment, contraindications to other alternative drugs such as the availability of approved drugs according to indications and patients with alternative treatments for clinical reasons. (Burkle, et al., 2012).

In the study of Eri Destin et al (2020) it was found that the use of off-label in prescribing acute respiratory infections for pediatric patients was 23% with the off-label category of age (15.67%), off-label dose ( 5.70%) , off-label route of administration (1.22%) and off-label indication (0.40%) and there were no off-label cases in the contraindication category. The most commonly prescribed off-label drug for pediatric ARI is chlorpheniramine maleate.

Safety and effectiveness assessment is one of the key aspects of using off-label prescriptions. The FDA recognizes that, under certain circumstances, the use of off-label drug products is approved if rational, and acceptable to medical practice. In this context, it is important that doctors should have access to accurate information about the drugs used that are not as indicative or off-label (Schultz, 2009).

Knowledge about off-label drugs is considered important to avoid the occurrence of medication errors or unwanted things. Drug selection in patients should be careful because not all drugs that are not given without indications can be used, in addition to having the advantage of off-label drug use also has disadvantages. Then medical personnel, especially pharmacists, are required to have more knowledge about drugs.

Before considering the off-label drugs used, safety support aspects and evidence of efficacy need to be evaluated to determine the risks and benefits that occur, especially drugs that have been approved by BPOM. Considering or reviewing the use of off-label drugs, health worker or medical personnel must be based on existing scientific evidence (evidence based) related to rational drug use.

The use of off-label drugs in Indonesia itself still has little evidence of prevalence data as well as known existence of its use. In a previous study, it was explained that the use of off-label drugs in prescribing acute respiratory infections was 23% in pediatric patients. One of the pharmacies in Tegal district that has a pediatrician practice is Saras Sehat pharmacy, where many pediatric patients carry out examinations at the site. Therefore, this study will identify how many off-label drug prescriptions in Indonesia, especially pediatric patients at the Saras Sehat Pharmacy in Tegal Regency.

1. **Formulators problem**

By paying attention to the background of the problem above, the research problem can be formulated as follows:

1. What is the description of off-label drug prescribing for pediatric patients at Saras Sehat Pharmacy, Tegal Regency?
2. What is the prevalence of prescribing off label drugs that are most widely prescribed at the Saras Sehat Pharmacy, Tegal Regency?
3. **Scope of problem**

The limitations of the problem in this study are as follows:

1. Retrospective data collection, by reviewing children's prescriptions in November 2021
2. The data sources studied are those that have met the inclusion and exclusion criteria
3. The children's recipes studied are recipes for children aged 0-12 years
4. The categories of off-label drugs that were examined were off-label indications, age, dosage, contraindications and route of administration.

**D. Research Objectives**

1. To find out the pattern of off-label drug prescribing for pediatric patients at the Saras Sehat Pharmacy, Tegal district
2. This study aims to determine the prevalence of off-label drug prescriptions at the Saras Sehat Pharmacy, Tegal Regency

**E. Research Benefits**

This research is expected to provide the following benefits:

1. As a consideration for pharmacists (especially at Saras Sehat Pharmacy) when they will serve off-label drug prescriptions and provide counseling, especially for pediatric patients.
2. Information material for other health workers regarding the use of off-label drugs.
3. **To Original Research**

Many studies regarding the identification of off-label drug prescribing in pediatric patients or children have been carried out, while studies related to off-label drug prescriptions in pediatric patients have not been found. Some of them can be seen in table 1, namely:

**Table 1. Research on Off-label Drug Prescribing**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No.** | **Research Title** | **Researcher Name** | **Metode** | **Result** |
| 1. | *Effects of the Off-Label Drug Prescription in the Pediatric* | Irene et al.,  2021. | Observational study of off-label prescribing in the under-18 population in primary health care in Spain | One of the most vulnerable population groups is neonates and infants up to 1 year of age, where the off-label prescription rate showed the highest increase during the post-follow-up period, which was statistically significant. |
| *Population in Spain from the Adoption of the Latest* |
| *European Regulation: A Pre-Post Study* |
| *Effects of the Off-Label Drug Prescription in the Pediatric* |
|  |
|  |
|  |
|  |
| 2. | *Evolution of pediatrics*  *off-label use after new significant medicines become available for adults: a study on triptans in Finnish children 1994–2007.* | [Lindkvistet](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lindkvist%20J%5Bauth%5D) | Memcompare | Pause off- |
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**CHAPTER II**

**LITERATURE REVIEW**

**2.1 Off-label drugs**

**2.1.1 Definition of Off-label Drug**

Off-label drugs are the use of drugs outside the indications approved by the authorized institution. The authorized institution is the Food and Drug Administration (FDA) in America, while in Indonesia it is the Food and Drug Supervisory Agency (BPOM). The use of off-label category drugs for therapeutic purposes must require a process of proving the efficacy and risk of side effects so that when the drug is used for certain therapeutic purposes it is safe (Rusli, 2018). Some people may be worried about the rise of doctors prescribing off-label drugs if they find out that off-label drugs are not approved by the competent authority (Dresser and Frader, 2009).

The purpose of granting marketing authorization is to ensure that the drug has been tested for safety, efficacy and quality. Drugs in circulation intended for adults have a license that explains the specific indication, dose and route of administration of the drug, or is called on-label. However, some drugs used for adult patients do not have a license for use in pediatric patients or use outside the terms of the license granted for the drug, or is called off-label (Victor, 2007).

Provisions apply that all drugs are. circulating must have a license to be circulated or a sales license, which is issued by the POM Agency. As explained above, the licensing system is designed to ensure that drugs have been tested for efficacy, safety and quality. Pharmaceutical companies apply for drug distribution permits and in the submissions are explained the indications, doses, administration methods and the age group of patients who will use the drug. In the consent request, information regarding use in adult patients may be limited or absent. Actually, drugs that are not licensed for use that are not listed on the label do not mean the drug is unsafe (the safety has not been proven), sometimes off-label use is only considered as non-compliance by drug manufacturers with the license granted (Victor, 2007).

The use of off-label drugs is a common use that is commonly used in clinical practice and is widespread throughout the world. However, the use of drugs outside of indications can cause some problems. Evidence about the inappropriate use of these drugs is strongly disapproved, and doctors have little information about how to use them. In addition, the use of off-label medications can cause side effects and risks that may outweigh the potential benefits. Ethical and legal issues relating to the commercial promotion of the use of these off-label drugs have also increased (Danés, et al., 2014).

Since 2009, Spanish law regulates and classifies the availability of drug use in special situations, namely the use of drugs under conditions that are not approved, the use of drugs that must be researched and the use of drugs that are not marketed in the country. Currently, only physician reports are used to justify the use of off-label drugs and patient consent is required. However, the widespread use of off-label drugs may often increase drug use, especially in hospitals. In order to avoid unwarranted risks and limited cost efficacy of the drug, Catalan Health Service has put internal procedures in place. This regulation states that the drug and therapy committee of each hospital needs to evaluate all cases of off-label drug use in special situations,

Few studies have evaluated the use of off-label drugs, but they have often focused on specific groups of drugs or drugs, such as the anticancer drug rituximab, or on specific populations, such as children. However, very few studies have evaluated the clinical outcomes of off-label drugs in terms of effectiveness and safety and associated costs (Danés, et al., 2014).

If there is no clinical evidence to support off-label use, such use is not recommended. According to several authors, the principles of Evidence Based Medicine (EBM) are applied in making clinical decisions about off-label, so there should be ethics and law, even in this case there is often a dilemma regarding the use of off-label drugs. However, it has been found that the prevalence of the use of off-label and unlicensed drugs has been found to be high. It is important for marketing authorization holders and relevant national and international regulatory authorities to monitor any safety concerns and to take appropriate action, as well as to identify research and clinical studies priorities to resolve important questions about off-label use and unlicensed drugs.

**2.1.2 Classification of Off-label Drugs**

Off-label drugs that do not comply with the product license requirements in terms of indication, age range, dose or route of administration (WHO, 2018). Drugs in use are categorized according to their labels, namely off-label and on-label. On-label category drugs are drugs that have a distribution permit issued by BPOM or the ministry of health. On-label category drugs by the authorities can guarantee that the drugs have been tested for safety, efficacy and quality so that the risks that occur can be overcome or minimized. The use of off-label category drugs can cause side effects and risks that may outweigh the potential benefits. The use of off-label drugs is classified (Rusli, 2018):

**1) Off-label Age**

Drugs are categorized as age off-label drugs if they are used outside the age range that has been approved by the POM. A small example in this regard is paracetamol given to premature infants for the purpose of antipyretic analgesics. Paracetamol is one example of the use of off-label age/weight category drugs (premature babies or babies with low body weight) (Rusli, 2018).

**2) Off-label Dosage**

Drug dosage is a very important value in drug use. Because each person's pharmacokinetic and pharmacodynamic profiles are different. It can be distinguished based on age, weight, comorbidities and other factors. When a drug is given at another dose, or outside the guidelines listed in the marketing authorization or sales license, the drug is categorized as an off-dose drug label. Drug use is classified as off-label if the dose, dose frequency, or age/weight of the patient does not match the specific information in the drug labeling. Regarding the off-label category, the dose of nebulizer ipratropium bromide is licensed for use up to three times a day but in hospitals it is used more than three times (Rusli, 2018).

**3) Off-label Indication**

Other than the 2 categories of off-label drugs above, Indication is an example of the most frequent use of off-label drug categories. Drugs are categorized as off-label indications if they are used outside of the indications listed in the drug brochure. An example of a drug is Misoprostol, which is a prostaglandin analogue class of drugs as cytoprotective in peptic ulcers, while for the off-label category the drug can be used for the purpose of inducing parturition (labor) therapy (Rusli, 2018).

**4) Off-label Route of Administration**

Drugs are said to be off-label route of administration, i.e., administration that is not permitted. For example: Vitamin K injectable drugs are often given orally to newborns to avoid diseases with bleeding manifestations because there are no suitable preparations available that are licensed (Rusli, 2018).

**5) Off-label contraindications**

Not only limited to the use of off-label categories based on dose, age, indication and route of administration. However, the use of off-label based on contraindications is also common. Drugs are said to be classified as off-label contraindications if they cause contraindications when given to patients whose age is not in accordance with the drug's designation. An example of a drug is Aspirin is contraindicated in children because it is associated with Reyes syndrome (a serious condition that can cause swelling of the liver and brain). However, Aspirin is used in heart patients for the purpose of being an antiplatelet (antithromboxane) (Rusli, 2018).

**2.1.3 Examples of Off-label Drug Use**

Here are some examples of off-label drugs (AHFS, 2005):

1) Actiq (oral transmucosal fentanyl citrate), is used off-label to treat chronic pain not caused by cancer, although the FDA-approved indication is for cancer pain.

2) Carbamazepine, an antiepileptic drug, is widely used as a mood stabilizer.

3) Gabapentin, approved as an anti-seizure and postherpetic neuralgia (nerve pain), is widely used off-label for bipolar disorder, tremors, migraine prevention, neuropathic pain, etc.

4) Sertraline, which is approved as an anti-depressant, is also widely prescribed off-label as a treatment for premature ejaculation in men.

**2.1.4 Reasons for Using Off-label Drugs**

The reasons for using off-label drugs are lack of clinical response to previous treatment, intolerance or contraindication to alternatives or other reasons such as availability of approved drugs according to indications or patients with alternative treatments for clinical or logistical reasons (Danés, et al., 2014).

Off-label treatment is not always bad and detrimental, this treatment is very useful especially when the patient has run out of options in therapy, for example in the case of cancer. The American Cancer Society states that cancer treatment often involves the use of off-label chemotherapy drugs, this is because one type of cancer drug is only approved for one type of cancer. The use of off-label cancer drugs in combination is often used for standard cancer therapy (Dresser and Frader, 2009)

*Beta blockers* is an example of a profitable off-label drug. The FDA approved this drug to be used as a treatment for hypertension, but it is widely recognized by cardiologists as the standard of care/therapy in heart failure patients. In fact, currently, several beta blockers have been officially approved by the FDA as a standard of care/therapy for heart failure patients (Dresser and Frader, 2009).

**2.1.5 Legal Provisions**

Some of these off-label drugs have been widely prescribed and used by doctors/clinics and have started to show results. However, the drug manufacturers that produce it, especially the innovator factories, have not submitted additional information on new indications for their medicinal products. If you have submitted a request to the competent regulatory agency, of course, the agency will evaluate the results of the clinical trial submitted with experts according to their field of expertise. If approved, new indication information can be added in the brochure or leaflet of the patent product (Danés, et al., 2014).

In Indonesia, all circulating drugs must have a distribution permit or a sales permit issued by the POM. This licensing system is designed to ensure that drugs have been tested for efficacy, safety and quality. In the process, the pharmaceutical company submits a request for a distribution permit for the drug to be marketed and in the submission it explains the patient's age, indication, dose and route of administration for using the drug. Drug information owned by the pharmaceutical company is provided to the public through drug brochures which contain information about drug use (BPOM, 2009).

**2.2 Pediatric Patients (Pediatrics)**

The development of infants and young children is very dynamic and can greatly affect drug metabolism. As children continue to grow until they reach maturity (adults), there are drastic changes in body shape and proportions that affect drug kinetics in the body (Jacqz-Aigrain and Choonara, 2006). In neonates, drug pharmacokinetics are affected by dynamic and dynamic physical and physiological changes (e.g., weight gain or increased GFR), making it difficult to use multiple drugs during the neonatal period (Stolk, et. al., 2002).

Some diseases require special treatment in pediatric patients to determine drug doses. The development of clinical disease management for pediatric patients is very significant. There are many pharmacotherapy principles that must be considered in the management of pediatric patients. Some definitions related to pediatrics are (DITJEN BINFAR, 2008):

1) pediatrics: children younger than 12 years old

2) Premature: babies born before 37 weeks

3) Neonates: 1 day to 1 month old

4) Baby: 1 month to 1 year old

5) Children: 1 year to 11 years old

6) Teenagers: 12 to 18 years old

It has been recognized that most of the prescriptions for allergy treatment in pediatrics in daily clinical practice are off-label drugs (Silva, et al., 2014). In a recent study of off-label drug use in an outpatient clinic, there were 422 (34.5%) incidences of off-label drug use for age (62.6%), dose (31.7%), and clinical indications (5.7%). Off-label use is more common in children aged <2 years (Morais-Almeida and Cabral, 2014).

**2.3 Definition of ATC Classification System**

Classification System ATC (Anatomical Therapeutic Chemical) is a system used to classify drugs. This system divides drugs into different groups according to the organ or system in which they exert their activity or therapeutic and chemical characteristics of the drug. Each ATC code contains an abbreviation for the pharmaceutical substance used, or a combination of substances, in a single indication or use. This means that one drug can have more than one code. For example, acetylsalicylic acid (aspirin), for example, has A01AD05 as a drug for local oral treatment, B01AC06 as a platelet inhibitor, and N02BA01 as an analgesic and antipyretic. ATC codes are listed in several international drug catalogs such as Martindale, European Drug Index, Nominum Index) and in several national drug catalogs (WHOCC, 2011).

In the ATC classification system, drugs are classified in groups at five different levels. Drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels of chemical/pharmacological/therapeutic sub-groups and the 5th level are chemical substances. The 2nd, 3rd and 4th levels which are often used to identify the pharmacological subgroup are considered more appropriate than the therapeutic or chemical subgroups. AZ index in the ATC classification system:

**Table. 2. Classification of ATC System**

|  |  |
| --- | --- |
| **Category** | **Anatomical System** |
| A | Digestive Tract and Metabolism |
| B | Blood and Blood Forming Organs |
| C | Cardiovascular System |
| D | Dermatologist |
| G | Urinary System and Sex Hormones |
| H | Hormone System Preparations Except Sex Hormones |
| J | Anti-infective for Systemic Use |
| L | Antineoplastic and Immunomodulating Agents |
| M | Musculoskeletal System |
| N | Nervous system |
| P | Antiparasitic Products, Insecticides, and Repellents |
| R | The respiratory system |
| S | Organ Sensor |
| V | Variation |

**CHAPTER III**

**RESEARCH METHODS**

1. **Research design**

This research is an observational study with retrospective data collection in the form of prescriptions from pediatricians. This study reviews or examines off-label drug prescribing and patterns of use. Identification of prescribed drugs including off-label categories or not based on the Drug Information Handbook (2009), Pediatric Dosage Handbook (2009), British National Formulary Children’s (2015), and the Indonesian National Drug Informatory (2015).

1. **Place and time**

This research was carried out at the Saras Sehat Pharmacy, Tegal Regency, with a period of three months to collect research data, from October to December 2021.

1. **Data Types and Sources**

The type of data in this study is in the form of secondary data taken retrospectively. The data source is a pediatrician's prescription for the period of November 2021 that meets the inclusion criteria.

1. **Population and Sample (Research Subject)**
2. Population

The population in this study is all prescriptions for pediatric patients for the period of November 2021 that were prescribed by Pediatricians at the Saras Sehat Pharmacy, Tegal Regency that met the inclusion and exclusion criteria. The population of children's prescriptions for the November 2021 period amounted to 1,495 prescription sheets, and those who met the inclusion criteria were 368 prescription sheets.

1. Sample

The sample in this study was all population prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency for the period November 2021, which met the inclusion criteria. The sampling technique was carried out using the Total Sampling method, where all members of the population who had met the requirements were used as samples (Sugiyono, 2014).

Inclusion and exclusion criteria in the population and sample of this study are as follows:

1. Inclusion Criteria
2. Prescription for pediatric patients for November 2021
3. Prescription for children aged 0-12 years
4. A complete prescription includes name, age, drug name, dose, dosage strength, instructions for use, duration of drug use and completeness of diagnostic data
5. Exclusion criteria

Research subjects who did not meet our inclusion criteria were excluded if the prescription was incomplete and damaged or illegible.

1. **Identification of Research Variables and Operational Definitions**

1. Research Variables

The research variable in this study is Prescribing Off-Label Drugs in pediatric patients at the Saras Sehat Pharmacy, Tegal Regency.

2. Operational definition

1. A prescription is a written request from a doctor, dentist or veterinarian who is granted a permit based on the prevailing laws and regulations to a pharmacist managing a pharmacy to provide and deliver medicines for sufferers.
2. Off-label drugs are drugs prescribed by doctors outside the indications in the brochure or label that have been approved by the authorized agency or agency (BPOM or FDA) or are given in different dosage forms from those approved.
3. *Off – label* Age if used outside the approved age range
4. *Off - label* dose if used at a dose different from the approved dose
5. *Off - label* Indications if used beyond the indications stated on the label or approved brochure
6. *off-label* contraindicated if its use causes contraindications for patients whose age is not in accordance with the designation of the drug.
7. *0ff – label* route of administration Drugs are said to be off-label route of administration, i.e., if the drug is given through a method or route of administration that is not permitted or improperly as stated on the label.
8. Drug classification system ATC (Anatomical Therapeutical Chemical) is a system used to classify drugs in five different levels. Drugs are divided into fourteen main groups.
9. **Research Instruments**

To determine the prevalence of off-label drug prescribing in pediatric patients at the Saras Sehat Pharmacy, Tegal Regency, the research instrument used was pediatrician prescriptions for the period November 2021.

Drugs are classified according to the ATC system. and references to determine off-label drug prescribing in children, including the Drug Information Handbook (2009), Pediatric Dosage Handbook (2009), British National Formulary Children’s (2015), and the Indonesian National Drug Informatory (2015).

1. **Procedure**
2. Preparation

This preparatory stage includes making a research proposal according to the proposed title, then a preliminary study to determine the prevalence of off-label drug use, then proceeding with a proposal hearing and obtaining a research permit.

1. Permission

Permission to conduct research at Saras Sehat Pharmacy. The permit is issued by the Research and Development Center of the Harapan Bersama Tegal Polytechnic, then submitted to the Pharmacist in Charge of the Pharmacy.

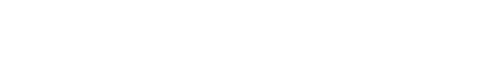
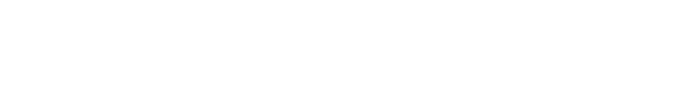
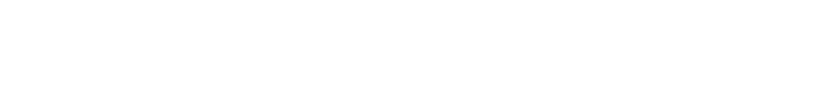
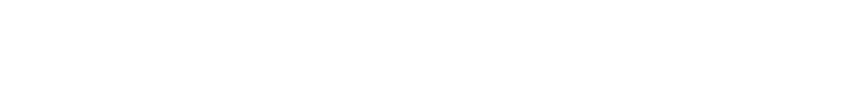
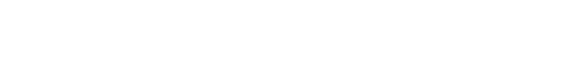
1. Data retrieval

Collecting data is done by screening prescriptions and medical record data, namely identifying the patient's name, age, gender and disease diagnosis. The drugs in the prescriptions were reviewed to determine the number of uses and identification of drugs classified as off-label. Questions and answers were also conducted with pharmacists at the Saras Sehat Pharmacy to ask questions related to prescriptions that could not be read by researchers.

1. Data management

Prescription screening data and medical records were then characterized according to gender, age and diagnosis. Use Prescription drugs are classified by the ATC system and as a percentage, what class of drugs is most prescribed. Off-label drug prescriptions were identified based on off-label categories (Age, indication, dose, contraindication, and route of administration) with references to DIH, PDH, BNFC, IONI and other supporting references.

**H. Work Step Schematic**



submit a proposal

Permission from Pharmacy Study Program

Permission to the pharmacy

Child patient prescription

Collecting data: name, child's age, diagnosis, drug name, and doctor's name

Ident Off-Label Drug Identification Category Indication

Analysis and discussion

Conclusion

**Figure 2.** go to work steps

|  |  |  |
| --- | --- | --- |
| **I.** | **Data analysis** |  |

Analysis of the data in the form of patient demographic data, drug use profiles, drug categories based on ATC and off-label drug prescriptions for indication categories, age, dose, contraindications and route of administration are presented in the form of tables and diagrams. Off-label drug identification refers to the reference DIH, PDH, BNFC, IONI.

Conclusions were drawn to determine the prevalence of off-label drug prescribing by percentage of what off-label categories were used the most.

**CHAPTER IV**

**RESULTS AND DISCUSSION**

* 1. **Characteristics of Research Subjects and Disease Diagnosis**

In this study, the population of children's prescriptions for the November 2021 period was 1,495 prescription sheets. According to the inclusion criteria, 368 prescription sheets were obtained and 1,127 prescription sheets were excluded from the study because the patient's age data were incomplete. Recipes that met the inclusion criteria were used as samples.

**Table. 3. Characteristics of Research Subjects**

|  |  |  |
| --- | --- | --- |
| NO | Patient Characteristics | Amount (%) |
| 1. | **Gender**  Man  Woman | 195 (52.99%)  173 (47.01%) |
| 2. | **Age**  0 – 5 years  5.1 years – 12 years | 271 (73.64%)  97 (26, 36%) |

The results of the study found that the number of male patients was more dominant (52.99%) than girls (47.01%). The dominance of patients aged under five (aged 0-5 years) was greater, namely 271 patients (73.64). Basically, the age of toddlers as a stage of development is quite vulnerable to various diseases. Several factors that trigger disease in toddlers include the structure and anatomy of the body's organs, the immune system is excessive so that it is easy to have allergies or deficiencies so that it is easy to become infected, infectious diseases that are not treated properly, genetic factors and geographical conditions (Kemenkes RI, 2015).

* 1. **Disease Diagnosis**

The results of the observation found that the distribution of disease diagnoses was ARI (25.54%), bronchitis (11.41%), diarrhea (11.41%), asthma (11.14%). The population of children is susceptible to respiratory tract diseases due to infection with pathogens (bacteria and viruses) and allergens.

**Table 4. Disease Diagnosis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| NO | DIAGNOSIS | TOTAL(%) |  | NO | DIAGNOSIS | TOTAL(%) |
| 1 | ARI | 94 (25.54%) | 16 | Fever | 4 (1.09%) |
| 2 | Bronchitis | 42 (11.41%) | 17 | Ulcer | 3 (0.82%) |
| 3 | Diarrhea | 42 (11.41%) | 18 | Conjunctivitis | 3 (0.82%) |
| 4 | Asthma | 41 (11.14%) | 19 | Immunodeficiency | 2 (0.54%) |
| 5 | Typhoid Fever | 26 (7.06%) | 20 | Gastritis | 2 (0.54%) |
| 6 | Common Cold | 21 (5.71%) | 21 | scabies | 2 (0.54%) |
| 7 | Epilepsy | 18 (4.89%) | 22 | Pulmonary TB | 1 (0.27%) |
| 8 | Acute gastroenteritis | 15 (4.08%) | 23 | Anemia | 1 (0.27%) |
| 9 | GERD | 13 (3.53%) | 24 | Asthenia | 1 (0.27%) |
| 10 | Dermatitis | 11 ((2.99%) | 25 | CHF | 1 (0.27%) |
| 11 | UTI | 5 (1.36%) | 26 | Haemoraghia | 1 (0.27%) |
| 12 | Pharyngitis | 4 (1.09%) | 27 | fungal infection | 1 (0.27%) |
| 13 | Febrile convulsion | 4 (1.09%) | 28 | Allergy | 1 (0.27%) |
| 14 | Anorexia | 4 (1.09%) | 29 | Varicella | 1 (0.27%) |
| 15 | Constipation | 4 (1.09%) |  |  |  |

The percentage of children aged 1–5 years is more likely to go to the clinic than children aged 6–12 years and more boys than girls (Table 3). This is because children aged 1-5 years are more susceptible to infection than children aged 6-12 years. In general, children aged 1-5 years have a low immune system compared to older children (Jadhav S et al, 2018). In infants to toddlers, ARI is generally the first occurrence of infection and the immune process has not been formed optimally so that immunity not perfect. In addition, children under five often put something in their mouth that can be an intermediary for the entry of germs into the body (Maakh YF et al, 2017).

Based on the diagnostic data, the tendency for male patients is more often to develop respiratory tract diseases. Sex differences in the incidence of respiratory disease vary, depending on age and differences in biological characteristics. The role of genetics is very important in influencing the immune system, especially at an early age. The number of X chromosomes in women is more than in men, thus affecting the amount of micro-RNA that plays an important role in immunity. Another factor is that boys tend to be more active than girls so that they are more likely to be exposed to the causative agents of ARI. The incidence of respiratory disease in boys aged 2-5 years is 2 times more often than girls (Gina, 2021).

The results of our study are in line with the research of Maakh et al, as well as the results of Sujata Jadhav's study where non-pneumonia ARI patients were more common in boys aged 1-5 years than girls.

* 1. **Distribution of Patient Drug Use**

During the study, from 368 prescription sheets, 67 items were found with a total use of 2,743 times.

**Table. 5. Distribution of Drug Use**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| DRUG | N(%) |  | DRUG | N(%) |  | DRUG | N(%) |
| Cefixime | 300 (10.93) | Vitamin A | 28 (1.02) | Neomycin eye drop | 3 (0.11) |
| Cyproheptadine | 222 (8.09) |  | Multivitamins & calcium | 25 (0.91) |  | Zinc sulfate | 3 (0.11) |
| Triamcinolone | 212 (7.73) |  | Claritomicin | 25 (0.91) |  | Chlordiazepoxide | 2 (0.07) |
| Codeine HCl | 205 (7.47) |  | Erythromycin | 23 (0.84) |  | Dextromethorphan | 2 (0.07) |
| Triprolidine&Pseudoephedrine | 204 (7.44) |  | Cobamamide | 17 (0.62) |  | Nephrolite | 2 (0.07) |
| Ibuprofen | 168 (6,12) |  | Clobazam | 17 (0.62) |  | Furosemide | 2 (0.07) |
| Azythromicin | 163 (5.95) |  | Mometasone furoate | 15 (0.55) |  | Dexchlorpheniramine | 1 (0.036) |
| Erdostein | 130 (4.74) |  | valproic acid | 14 (0.51) |  | Lansoprazole | 1 (0.036) |
| Procaterol HCl | 114 (4,16) |  | Ketorolac | 13 (0.47) |  | Cotrimoxazole | 1 (0.036) |
| Cetirizine HCl | 109 (3.97) |  | Donperidone | 13 (0.47) |  | Loratadine | 1 (0.036) |
| Ambroxol | 92 (3.35) |  | Phenytoin | 13 (0.47) |  | Permethrin | 1 (0.036) |
| Paracetamol | 56 (2.04) |  | Mupirocin | 13 (0.47) |  | Iron vitamins | 1 (0.036) |
| Dexamethasone | 52 (1.90) |  | Omeprazole | 12 (0.44) |  | Rifampicin | 1 (0.036) |
| Thyamphenicol | 51 (1.88) |  | Diazepam | 10 (0.36) |  | Vitamin B6 | 1 (0.036) |
| Loperamide | 50 (1.82) |  | Sucralfate | 9 (0.33) |  | Co-amoxiclav | 1 (0.036) |
| theophylline | 46 (1.68) |  | Piracetam | 8 (0.29) |  | Prednisone | 1 (0.036) |
| Ondansetron | 42 ((1.53) |  | Methylprednisolone | 6 (0.22) |  | Captopril | 1 (0.036) |
| Lactobacillus | 41 (1.49) |  | Pipemidic acid | 5 (0.18) |  | Tranexamic acid | 1 (0.036) |
| Nifuroxazide | 39 (1.42) |  | Hyosine butyl bromide | 5 (0.18) |  | Ofloxacin ear drops | 1 (0.036) |
| luminal | 37 (1.35) |  | Carbamazepine | 5 (0.18) |  | Topical ketoconazole | 1 (0.036) |
| Metampiron | 34 (1.24) |  | Echinaceae | 4 (0.15) |  | Acyclovir | 1 (0.036) |
| Salbutamol | 30 (1.09) |  | Lactulose | 4 (0.15) |  |  |  |
| Metronidazole | 30 (1.09) |  | Triamcinolone oral base | 3 (0.11) |  |  |  |

The drug with the most use was Cefixime (10.93%) which was indicated as an antibacterial. Cefixime is a third-generation cephalosporin broad spectrum antibiotic used to treat a number of bacterial infections such as otitis media, urinary tract infections, strep throat, pneumonia, gonorrhea, and Lyme disease (BPOM, 2017).

* 1. **Classification of Drugs Based on the ATC System**

The use of drugs is then grouped based on the ATC (Anatomical Therapeutic Chemical) system, which is the system used to classify drugs. This system divides drugs into different groups according to the organ or system in which they provide activity or the therapeutic and chemical characteristics of the drug (WHOCC, 2011).

**Table. 6. Classification of Drugs Based on the ATC System**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| No | ATC System Category | N Total (%) | Drug | Amount (%) |
| 1. | Respiratory system | 950  (34.63%) | Cyproheptadine HCl | 222 (23.37%) |
| Triprolidine & Pseudoephedrine | 204 (21.47%) |
| Erdostein HCl | 130 (13.68%) |
| Procaterol HCl | 114 (12%) |
| Cetirizine HCl | 109 (11.47%) |
| Ambroxol | 92 (9.68%) |
| Theophylline | 46 (4.84%) |
| Salbutamol | 30 (3.18%) |
| Dextromethorphan HBr | 2 (0.21%) |
| Dexchlorpheniramine HCl | 1 (0.10%) |
| 2. | Anti-infective for systemic use | 635  (23.15%) | Cefixime | 300 (47.24%) |
| Azythromicin | 163 (25.67%) |
| Thyamphenicol | 51 (8.03%) |
| Nifuroxacide | 39 (6.14%) |
| Metronidazole | 30 (4.72%) |
| Clarythromicin | 25 (3.94%) |
| Erythromycin | 23 (3.62%) |
| Cotrimoxazole | 1 (0.16%) |
| Rifampicin | 1 (0.16%) |
| Co-amoxiclav | 1 (0.16%) |
| Acyclovir | 1 (0.16%) |
| 3. | Central nerve system | 582  (21.22%) | Codeine HCl | 205 (35.22%) |
| Ibuprofen | 168 (28.87%) |
| Paracetamol | 56 (9.62%) |
| luminal | 37 (6.36%) |
| Metampiron | 34 (5.84%) |
| Clobazam | 17 (2.92%) |
| valproic acid | 14 (2.41%) |
| Ketoroac HCl | 13 (2.23%) |
| Phenytoin | 13 (2.23%) |
| Diazepam | 10 (1.72%) |
| Piracetam | 8 (1.37%) |
| Carbamazepine | 5 (0.86%) |
| Cordiazeposide | 2 (0.34%) |
| 4. | Preparation of the hormonal system except sex hormones and insulin | 271  (9.88%) | Triamcinolone Acetonide | 212 (78.23%) |
| Dexamethasone | 52 (19.19%) |
| Methylprednisolone | 6 (2.21%) |
| Prednisone | 1 (0.37%) |
| 5. | Digestive Tract and Metabolism | 192  (6.99%) | Loperamide HCl | 50 (26.04%) |
| Ondansetron | 42 (21.87%) |
| Lactobacillus | 41 (21.35%) |
| Cobamamide | 17 (8.85%) |
| Donperidon | 13 (6.77%) |
| Omeprazole | 12 (6.25%) |
| Sucralfate | 9 (4.69%) |
| Lactulose | 4 (2.08%) |
| Zinc sulfate | 3 (1.56%) |
| Lansoprazole | 1 (0.52%) |
| 6. | Vitamins and Immunomodulators | 59  (2.15%) | Vitamin A | 28 (47.46%) |
| Multivitamins and Calcium | 25 (42.37%) |
| Echinaceae | 4 (6.78%) |
| Vitamin B6 | 1 (1.69%) |
| Iron vitamins | 1 (1.69%) |
| 7. | Dermatology | 30  (1.09%) | Mometasone furoate | 15 (50%) |
| Mupirocin | 13 (43.33%) |
| Permethrin | 1 (3.33%) |
| Loratadine | 1 (3.33%) |
| 8. | Etc | 8  (0.29%) | Triamcinolone oral base | 3 (37.5%) |
| Neomycin eye drop | 3 (37.5%) |
| Ofloxacin ear drops | 1 (12.5%) |
| Topical ketoconazole | 1 (12.5%) |
| 9. | Urinary System | 7  (0.26%) | Pipemidic acid | 5 (71.43%) |
| Nephrolite | 2 (28.57%) |
| 10. | Antispasmodic | 5  (0.18%) | Hyosine Butyl Bromide | 5 (100%) |
| 11. | Cardiovascular System | 3 (0.11%) | Furosemide | 2 (66.67%) |
| Captopril | 1 (33.33%) |
| 12. | Blood and blood-forming organs | 1  (0.04%) | Tranexamic Acid | 1 (100%) |

From the results of the analysis based on the ATC system, the highest drug prescription was for the respiratory system drug category (34.63%). This result is in accordance with the data on the diagnosis of the disease that most patients suffer from, namely respiratory tract diseases (Table 4). At the age of toddlers are very susceptible to respiratory tract diseases such as ARI, bronchitis, asthma, common cold and pharyngitis. Basically, toddlers are quite vulnerable to the emergence of various kinds of infectious diseases. This is associated with the structure and anatomy of organs and the immune system that is not yet fully developed. Cyproheptadine, Triprolidine, Pseudoephedrine was more dominantly prescribed, followed by Erdostein HCl, Procaterol HCl, Cetirizin HCl and Ambroxol. The drug prescribing profile is in accordance with the dominance of the disease diagnosis, namely ARI.

*Cyproheptadine*is an antihistamine drug that is of great use in the treatment of nasal allergies, allergic rhinitis, to relieve red eyes, watery eyes, irritation, itching, sneezing, and runny nose caused by allergies, airborne irritation, and fever. Triprolidine and Pseudoephedrine are decongestant drugs that can be used to treat nasal congestion symptoms in cases of flu or colds, as well as other respiratory diseases. Erdostein HCl belongs to the class of mucolytic drugs, namely drugs that are useful for thinning phlegm. Usually, this drug is used to treat acute cough symptoms in people with chronic bronchitis. Procaterol HCl is a drug to treat shortness of breath due to asthma and Chronic Obstructive Pulmonary Disease or COPD. Ambroxol is a medicine to relieve cough with phlegm caused by several conditions, such as bronchitis or emphysema. In conditions of cough with phlegm caused by a bacterial infection, the use of ambroxol can be combined with antibiotics. (BPOM, 2017).

* 1. **Off-Label Drug Prescribing Characteristics**

Based on research from a sample of 368 prescriptions, which were identified off-label were 177 prescription sheets (48.10%) and on-label were 191 prescription sheets (51.9%) (Fig. 1).

**Figure 1. Number of comparisons of Off-label and On-label prescriptions**

Category off-label indication (1.46%), off-label age (12.43%), off-label contraindication (0.80%), off-label dose (0.11%), category off-label route gift not found. Off-label drug prescribing profiles are presented in Table. 7.

**Table. 7. Profile of Off-Label Drug Prescribing by Category**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Category Off Label | Drug | Authorized Use According to BNFC (2015) | Recipe Case | Amount | N Total (%) |
| Indication | Ondanstron | Treatment of nausea and vomiting due to chemotherapy, radiotherapy and post-surgery | Nausea and vomiting are not caused by chemotherapy, radiotherapy and post-surgery, but because of cases of gastroenteritis | 26 | 40 (1.46%) |
| Cyproheptadine | Treatment of hay fever, urticaria and allergic rhinitis | Treatment of anorexia | 14 |
| Age | Triprolidine and Pseudoephedrine | Limitation of use in children less than 6 years old | Used in children aged 1 month -1 years, and 1.1 years - 5 years | 124 | 341 (12.43%) |
| Triamcinolone acetonide | Limitation of use in children less than 6 years old | Used in children aged 2 months -1 years, and 1.1 years - 5 years | 77 |
| Codeine HCl | Not intended for children under 2 years old | Used in children aged 1 month - 23 months | 62 |
| Cyproheptadine | Restrictions on use for children less than 2 years old | Used in children aged 1 month - 23 months | 62 |
| Salbutamol | Not recommended for toddlers less than 5 years old | Used in children aged 3 months, 11 months, 15 months, 17 months, 2.5 years, 3 years, 4.5 years | 14 |
| Dextromethorphan | Restrictions on use for children less than 6 years old | Used in children aged 4.5 years | 2 |
| Contraindications | Loperamide | Contraindicated in children less than 3 years | Used in children aged 7 months – 2.5 years | 22 | 22 (0.80%) |
| Dose | Cefixime | It is given as a single dose or in 2 divided doses every 12 hours | Given in doses 3 times a day | 3 | 3 (0.11%) |
| Way of giving | - | - | - | - | - |

1. **Category Off-Label Indication**

The most dominant use of off-label indicated drugs in children in this study was Ondansetron, which was 26 cases. Ondansetron is an anti-emetic drug class 5-HT3 blocker that works by blocking serotonin in the body to prevent nausea and vomiting. Some guidelines do not recommend antiemetics for the management of gastroenteritis in children. This is due to concerns about the side effects of anti-emetic drugs, namely sedation, extra pyramidal reactions, and diarrhea. *Food and Drug Administration* (FDA) also only recommends ondansetron to prevent and treat vomiting due to chemotherapy (Hanuscin, 2020).

Cyproheptadine is used to relieve allergies, such as in cases of allergic rhinitis, allergic conjunctivitis, and mild allergic manifestations of the skin such as urticaria and angioedema. Cyproheptadine is also used in cases of vascular migraine (MIMS, 2020). Cyproheptadine is often used off-label to stimulate appetite and weight gain in children and adults; but only a few indications for clinical use (IAI, 2016).

1. **Category Off-Label Age**

In this study, the off-label age category was the dominant one. Most pediatric patients get drugs with restrictions on use for a certain age. Types of decongestant and antihistamine drugs (Triprolidin, Pseudoephedrine, and Cyproheptadine) are drugs with restrictions on use for children under 6 years. Meanwhile, according to DIH (2010) Triprolidine, Pseudoephedrine and Codeine are not intended for children under 2 years of age. The use of Tripolidin in children can cause hallucinatory effects.

Triamcinolone is a corticosteroid drug class as anti-inflammatory in various medical conditions, such as allergies, asthma, various skin diseases, adrenal insufficiency, and symptom relief in arthritis. Corticosteroids are used for the management of reversible and irreversible airway disease. British National Formulary of Children (2015 limits the use of triamcinolone for children less than 6 years. Some unwanted side effects if long-term use is that it can cause growth retardation in children and affect pubertal development. Long-term use of corticosteroids can increase susceptibility to infection and exacerbate or worsen the infection (PIONAS, 2015)

Salbutamol is also a drug within a certain age limit. Salbutamol is a beta-2 agonist drug that plays a role in the management of asthma or chronic obstructive pulmonary disease (COPD). Therapy with oral bronchodilators is not recommended in children because of the slower onset of action and the higher incidence of side effects compared to the inhalation route (GINA, 2014). Although the risk of ingestion is small, the side effects of oral salbutamol that may occur in children are hypokalemia, hypoglycemia, restlessness, tremor, tachycardia, and peripheral vasodilation (Andrzejowski et. al, 2016). The British Medical Association and the Royal Pharmaceutical Society of Great Britain (2017) state that oral salbutamol is not recommended for children younger than 3 years and intravenously is not recommended for children younger than 12 years. IONI (2020) states that the efficacy of Salbutamol for children aged <18 months is still in doubt.

Codeine is an opioid that is widely used for both analgesic and antitussive. Codeine has a detrimental effect that is fatal for pediatric patients, this is due to polymorphisms in the gene that metabolizes codeine. The UM (Ultrarapid Metabolizer) gene causes high levels of morphine in the patient's blood, causing respiratory depression and death. Therefore, the use of codeine in children is not recommended and the drug should be replaced with other drugs that are safer for pediatrics, namely Levodoprofizine and Moguisteine ​​(Lubis, 2018).

Cyproheptadine is a first-generation antihistamine and serotonin antagonist with anticholinergic effects. This drug is mainly indicated as an antiallergic drug with mild complaints, such as allergic rhinitis and cold urticaria, and can be used for migraines.. Cyproheptadine is only recommended for use in children aged 2 years and over. A significant side effect of cyproheptadine is central nervous system depression. (Najib. K, 2014).

Dextromethorphan is a cough suppressant. This drug works by inhibiting the response or cough reflex in the brain. Please note that this drug is not effective for relieving cough with phlegm or cough caused by chronic bronchitis, asthma, emphysema. The main indication for dextromethorphan is as an adult antitussive in conditions associated with infection or allergies, such as upper respiratory tract infections (ARI). Use as an antitussive in children is not recommended, the use of dextromethorphan in children has not been proven effective and causes side effects of nausea, gastrointestinal disturbances, drowsiness, and dizziness. (MIMS, 2021)

1. **Category Off-label Contraindications**

In this study, 22 cases of off-label contraindications were found, namely Loperamide HCl or about 0.8% of the total drug use. Loperamide is indicated for symptomatic relief in acute or chronic diarrhea, such as gastroenteritis, inflammatory bowel disease, or traveler's diarrhea. Its use is prohibited and not recommended for children. (BNFC, 2015)

Loperamide works by reducing bowel movements so that it stops diarrhea, in adults this mechanism may be used because the immune system is already good, but in children it is dangerous, because basically the cessation of bowel movements causes the viruses/bacteria that cause cannot get out of the body and can cause some things like fever and viral/bacterial growth becomes excessive. In addition, children's gastrointestinal nervous system that is not yet perfect will also be at risk of prolonged 'limp' due to this drug and cause paralytic ileus, and in some cases can 'skid' causing a condition called intussusception/invagination which is very dangerous. (BPOM RI, 2017).

1. **Category Off-label Dosage**

Dosage information is important in treatment because the pharmacokinetic and pharmacodynamic profiles of each individual age range are different. Drugs that are given at doses other than those listed in the marketing authorization or sales license are categorized as off-label drugs. In this study, an off-label dose category was found, namely the dose of Cefixime drug use.

Cefixime is indicated for the treatment of uncomplicated urinary tract infections, pharyngitis, tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis and uncomplicated gonorrhea with different doses for adults, children, and special populations. The general recommended dose for oral use is as a single dose once daily, or in 2 divided doses every 12 hours (twice daily). The results of the study found 3 cases of off-label doses or about 0.11% of the use of Cefixime, namely its use 3 times a day, not according to the dosage/rules of use recommended in the brochure or approved label. (BPOM RI, 2017).

The use of off-label drugs is generally carried out by doctors with a note if there is no standard dosage or use to treat certain diseases or if the standard treatment that has been carried out is not successful. The use of off-label drugs must be based on strong scientific evidence, especially regarding the evaluation, efficacy and safety of drugs.

Until now, the use of off-label drugs in Indonesia is still being applied so that off-label drug prescribing cannot be categorized as a prescription that violates the law. Because the use of off-label drugs may benefit the patient more when there are no other options for therapy. However, prescribing off-label drugs still carries a high risk because data on adverse drug reactions (ESOs) are likely to emerge.

**CHAPTER V**

**CONCLUSIONS AND SUGGESTIONS**

1. **CONCLUSION**

Based on the research that has been done, the following conclusions are obtained:

* 1. Off-label prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency are still quite high, with 48.10% off-label prescriptions and 51.9% on-label prescriptions.
  2. The prevalence of off-label categories for age (12.43%), off-label indications (1.46%), off-label contraindications (0.80%) and off-label doses (0.11%). No category of Off-Label route of administration was found. The most widely prescribed Off-Label drugs are decongestant drugs, namely Triprolidine and Pseudoephedrine.

1. **SUGGESTION**
2. For further researchers, it is hoped that a study of the use of Off-Label drugs in children in several pharmacies in Tegal Regency can be carried out.
3. For pharmacists at Saras Sehat Pharmacy so always update knowledge regarding the validity of off-label drug indications so as not to cause differences in perception with the doctor concerned.
4. For pharmacists in general need to broaden scientific knowledge and always update knowledge about new drugs as well as new clinical evidence that is developing very quickly.

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**attachment**

**Details of Realized Research Costs**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Tools and materials | | | | | |
|  |  | Ingredient | Amount | Unit price | Amount |
| A | Materials and Ingredients |  |  |  |  |
|  | 1 | 80 gram A4 paper | 2 Rims | 50000 | 100000 |
|  | 2 | Stationary | 6 dozen | 30000 | 180000 |
|  | 3 | Souvenirs for pharmacists | 1 person | 150000 | 150000 |
|  | 4 | Questionnaire | 200 bundles | 1000 | 200000 |
| B | Administration and Honorarium |  |  |  |  |
|  | 1 | Licensing Fee |  | 500000 | 500000 |
|  | 2 | Honor data taker | 3 x Pickup | 50000 | 150000 |
|  | 3 | Data processing | 2 x Data Processing | 100000 | 200000 |
| C | Communication |  |  |  |  |
|  | 1 | Researcher and Student Quota | 3 people | 50000 | 150000 |
| D | Transportation |  |  |  |  |
|  | 1 | to the pharmacy | 3x pick up | 50000 | 150000 |
| E | Data Capture Consumption |  |  |  |  |
|  | 1 | Consumption for 3 people | 3x | 25000 | 225000 |
|  | 2 | Consumption of coordination meeting | 3x | 25000 | 225000 |
| F | Miscellaneous expense |  |  |  |  |
|  | 1 | Proposals and Reports |  | 300000 | 300000 |
|  | 2 | Publication |  | 500000 | 500000 |
|  | Total |  |  |  | 3030000 |

**RESEARCH ORGANIZATIONAL STRUCTURE**

* + - 1. **chairman**

Name : apt., Susiyati, M. Farm,

NIPY : 09,017.359

NIDN : 0627057502

Rank/Goal : III b

Functional : Expert Assistant

Structural Position :-

Knowledge field : Community Pharmacy

* + - 1. **Member 1**

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Functional : Expert Assistant

Structural Position :-

Knowledge field : Pharmaceutical Chemistry