doi:10.25143/prom-rsu_2022-02_dts

Rīga Stradiņš University

Olga Kiseļova

Availability of Extemporaneous Preparations in Pharmacies in Latvia: a Quantitative and Qualitative Assessment of the Situation and Future Perspectives

Summary of the Doctoral Thesis for obtaining a doctoral degree "Doctor of Science (*Ph.D.*)"

Sector – Basic Sciences of Medicine, including Pharmacy
Sub-Sector – Dosage Form Technology

Riga, 2022

Olga Kiseļova

ORCID 0000-0002-5002-7629

Availability of Extemporaneous Preparations in Pharmacies in Latvia: a Quantitative and Qualitative Assessment of the Situation and Future Perspectives

Summary of the Doctoral Thesis for obtaining a doctoral degree "Doctor of Science (*Ph.D.*)"

Sector – Basic Sciences of Medicine, including Pharmacy

Sub-Sector – Dosage Form Technology

Riga, 2022

The Doctoral Thesis was developed at Rīga Stradiņš University, Latvia

Supervisor of the Doctoral Thesis:

Dr. pharm., Associate Professor **Baiba Mauriņa**,
Rīga Stradiņš University, Department of Applied Pharmacy, Latvia

Official Reviewers:

Dr. pharm., Assistant Professor **Inga Urtāne**,
Rīga Stradiņš University, Latvia
Dr. habil. biol., Professor **Ruta Muceniece**,
University of Latvia, Latvia
Ph.D., Professor **Jurga Bernatoniene** (Jurga Bernatonienė),
Lithuanian University of Health Sciences, Lithuania

Defence of the Doctoral Thesis will take place at the public session of the Doctoral Committee of the Basic Sciences of Medicine, including Pharmacy on 8 April 2022 at 12:00 on online platform *Zoom*.

The Doctoral Thesis is available in RSU Library and on RSU website: https://www.rsu.lv/en/dissertations

NATIONAL DEVELOPMENT PLAN 2020
EUROPEAN UNION
European Social Fund
INVESTING IN YOUR FUTURE

Project No. 8.2.2.0/20/I/004 “Support for involving doctoral students in scientific research and studies”

Secretary of the Promotion Council:

Dr. boil., Assistant Professor **Renāte Ranka**

Table of Contents

Abbreviations

APA	American Psychological Association
APF	Australian Pharmaceutical Formulary
CM Regulations	Cabinet of Ministers Regulations
DAC/NRF	German Drug Codex / New Prescription Formulary (abbreviation from German, *Deutscher Arzneimittel-Codex* / *Neues Rezeptur-Formularium*)
EU	European Union
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation (abbreviation from French, *Fédération Internationale Pharmaceutique*)
GMP	good manufacturing practice
GPP Guide	Guide to good practice for the preparation of medicinal products in health care establishments
ICMJE	International Committee of Medical Journal Editors
IM	individual merchant
JSC	joint stock company
LLC	limited liability company
OAIs	orphan active ingredients
PIC/S	Pharmaceutical inspection convention and Pharmaceutical inspection co-operation scheme
PSA	Pharmaceutical Society of Australia
SAM	State Agency of Medicines
the USA	United States of America
USP	United States Pharmacopeia
USSR	Union of Soviet Socialist Republics
VAT	value added tax
v/v	volume by volume
WHO	World Health Organization

Introduction

According to the scientific articles published in the last five years, extemporaneous preparations are still being prescribed and compounded all around the world – in Europe, North America, South America, Australia, Asia, and Africa.[1,2,3,4,5,6,7] This means that, despite the numerous industrially manufactured medicinal products available on the market, extemporaneous preparations are still occupying their niche among the services offered by the pharmacies. Physicians prescribe extemporaneous preparations in cases when the patient requires an individual approach, because industrially manufactured medicinal products are not available in a suitable dose, dosage form, or the desired combination of active ingredients or if the patient is allergic to an excipient used in industrially manufactured medicinal products.[5,8,9,10,11] Extemporaneous preparations often share similar availability issues with orphan drugs and medicinal products available for compassionate use.[12,13] Extemporaneous preparations are mostly used in otolaryngology, dermatology, paediatrics, ophthalmology, and dentistry branches.[12]

However, extemporaneous preparations are high-risk products due to various factors that influence their safety and efficacy.[5,14,15] In contrast to industrially manufactured medicinal products, extemporaneous preparations do not undergo clinical evaluation of their safety and efficacy.[5,15] Pharmacies often have limited quality control methods for testing the quality of the prepared medicinal products. Often the only available quality test just consists of pharmacist's notes that list the ingredients used in the preparation and their amounts.[16] Several articles and reports were published on errors in preparation of extemporaneous medicinal products in different countries that had serious consequences.[17,18,19,20] Most frequent and also some of the most dangerous errors are incorrect calculations or unit conversions leading to exceeded concentration of an active ingredient or another ingredient, as well as increased microbiological

contamination.[17,21] Fatal cases and serious health issues resulting from such errors have been recorded both in Europe and in the USA.[17,19] Even in cases when medicinal products prepared in pharmacies comply to microbiological requirements, all calculations have been done correctly, and appropriate compounding technology has been used, there is a risk that the prescribed composition will not be safe and / or effective.[22]

Aware of the risks associated with the prescribing, preparation, dispensing of extemporaneous preparations and at the same time aware of the need for these drugs, several European countries, the USA, and Australia have developed formularies containing standardized monographs on extemporaneous preparations as well as guidelines and recommendations for safe prescribing and preparation of extemporaneous drugs.[11,16,23,24,25] Databases of local and international scale have also been developed, such as CompoundingToday and Rezepturenfinder.[26,27] Each standardized monograph included in the main German information resource on extemporaneous preparations, hereinafter referred to as DAC/NRF, provides at least the following information: all active ingredients and excipients needed for the preparation; compounding technology; packaging appropriate to the composition and dosage form; required labelling; stability requirements; beyond-use date; quality control requirements; indications for use; dose; frequency of use.[23] On the other hand, USP Compounding Compendium created in the USA is part of the US Pharmacopeia. The monographs included in the resource also contain all the necessary information on the ingredients, compounding technology, packaging appropriate to the composition and dosage form, labelling, beyond-use date, and methods of analysis.[24] Since 1902, a national formulary has been available to Australian health care professionals containing not only clinical monographs on active ingredients used in Australia but also monographs on extemporaneous preparations. The formulary is published by the Pharmaceutical Society

of Australia (PSA) and its content is regularly reviewed and updated. Australian monographs on extemporaneous preparations provide information on all ingredients, their quantities, compounding technology, packaging, and beyond-use date as well as indications for use.[25] The monographs allow physicians to choose and pharmacists to prepare medicinal products with the active ingredients and combinations thereof with evidence-based use in the relevant fields. They also provide certainty that the prepared composition will be stable within the stated shelf life. Despite the importance of such resources, their cross-border use is limited because of the different levels of development of extemporaneous preparations worldwide and because no uniform standards for their preparation and control exist even in EU countries.[28] In addition, the share of community pharmacies preparing medicinal products varies across European countries. For example, all community pharmacies in Portugal and Germany offer the service "preparation of medicinal products in the pharmacy", while in Denmark, the production of extemporaneous preparations is centralized in just three community pharmacies.[29,30,31] Moreover, the laws and regulations governing the preparation of medicinal products in pharmacies are not harmonized between the European countries.[32] The Council of Europe emphasizes that all European patients have the right to receive medicinal products of equivalent quality. In order to prevent disparity of quality and safety, in 2011 the Committee of Ministers of the Council of Europe adopted for the first time the Resolution CM/ResAP(2011)1 on Quality and Safety Assurance Requirements for Medicinal Products Prepared in Pharmacies for the Special Needs of Patients. Member States were recommended to adapt their legislation to the principles set out in the Resolution.[33]

Documents related to extemporaneous preparations are being created not only at national or European Union level, but also at global level. Given that manufactured medicinal products for paediatric use are not always available, the

World Health Organisation (WHO) in collaboration with the International Pharmaceutical Federation (FIP) developed in 2016 guidelines for health care professionals outlining the main issues related to extemporaneous preparation and offering possible solutions.[34]

After the Resolution was first adopted, a study was carried in the European Union to determine whether and how the Resolution affected the national legislation of 12 European countries (Belgium, the Czech Republic, Denmark, Finland, Ireland, Italy, the Netherlands, Poland, Portugal, Serbia, the Swiss Confederation, and the United Kingdom). The researchers concluded that: "the overall results of the survey indicate that among the countries involved there is, in general, a clear commitment to implement the recommendations of the Resolution".[35] This survey did not include any data on Latvia. The Resolution was updated again in 2016.[33] Since most of Latvian regulatory enactments regulating this sector were adopted before the adoption of the Resolution, a question arises as to which paragraphs of the regulation are fulfilled in full or partially and which are not fulfilled.

Until 1991, Latvia was part of the USSR and the preparation of medicinal products in Latvia was regulated by the procedures adopted by the USSR in accordance with the USSR Pharmacopoeia and standardized formulations. It has been 30 years since Latvia regained its independence, but Latvia still does not have its own standardized formulations and official information resources in the state language. It is not known not only what extemporaneous preparation compositions are being prescribed, but also what specialties of physicians prescribe extemporaneous preparations and what their sales volumes are in different regions of Latvia. In a situation where the country has neither standardized formulations, nor guidelines or recommendations for prescribing and preparing extemporaneous medicinal products, the physician's knowledge of extemporaneous preparations and experience in prescribing them becomes

especially important. Therefore, it is crucial to know what specialties of physicians prescribe the most of extemporaneous preparations. In turn, the sales volume of extemporaneous preparations in different regions of Latvia would allow to assess the topicality of the service "preparation of medicinal products in the pharmacy" across Latvia. Currently, the list of pharmacies that have a permit for the special activity condition "preparation of medicinal products in the pharmacy" is published on the website of the State Agency of Medicines (SAM).[36] However, the list does not provide information on the sales volume of extemporaneous preparations in Latvian pharmacies, because the fact that a pharmacy has a permit to prepare medicinal products does not necessarily mean that the respective pharmacy exercises these rights. In Latvia, there have only been attempts to study individual pharmacy prescriptions within the framework of course papers, Bachelor's or Master's theses.[37,38,39] No studies that would collect data on extemporaneous prescriptions, describe the current situation in different regions of Latvia, and compare the prescriptions of Latvian pharmacies with the standardized formulations of European countries, the USA, and Australia have been performed so far. As standardized formulations, guidelines, and recommendations create preconditions for prescribing and compounding safe and effective medicinal products, it is important for Latvia to establish the relevant documents. Before deciding whether to develop any new information resources or use the experience of other countries for Latvian health care professionals, it is important to identify the compositions and dosage forms prescribed in Latvia, as well as understand whether the relevant active ingredients, active ingredient combinations, and excipients are used in the standardized formulations of other countries.

It would be crucial for Latvia as a member of the European Union (EU) to strive for a uniform approach to extemporaneous preparations. Since the approach depends on the regulatory enactments adopted in the country, it is

important to perform the analysis of Latvian regulatory enactments in the respective field and their comparison with the Resolution of the Committee of Ministers of the Council of Europe.

A study on the availability of extemporaneous preparations in Latvian pharmacies could not only help to assess the current situation and provide insight into the most promising development directions for extemporaneous preparations, but also contribute to the harmonization of processes related to extemporaneous preparations within Europe.

Aim of the study

To evaluate the regulatory framework and distribution of preparation of medicinal products, to compile and analyse the assortment of extemporaneous formulations in Latvian pharmacies comparing it with the standardized formulations of Germany, the USA, and Australia, and to create practical recommendations for improving the quality of medicinal products prepared in Latvian pharmacies and further development of this area.

Objectives of the study

1. To compare the Latvian regulatory enactments regulating the preparation of medicinal products in pharmacies with the Resolution of the Committee of Ministers of the Council of Europe.
2. To determine the sales volume of extemporaneous preparations in Latvian pharmacies that had the special operation condition "preparation of medicinal products in the pharmacy" specified in the annex to their licence in 2017.

3. To analyse the prescribed extemporaneous preparations prepared in Latvian pharmacies and identify the health care professionals who prescribed extemporaneous preparations, dosage forms, active ingredients, their number in the dosage forms, excipients.
4. To compare the data obtained on the dosage forms prescribed, the active ingredients and excipients used with data, stability studies, and guidelines from Germany, the USA, and Australia.
5. To identify and describe the problems associated with the prescribing, preparing, and dispensing of extemporaneous preparations in Latvia; to compare them with the experience of other EU countries, the USA, and Australia.
6. To provide practical recommendations to promoting safe and effective prescribing, preparing, and dispensing of extemporaneous preparations.

Hypotheses of the study

1. The extemporaneous formulations in Latvian pharmacies are different from the formulations used in Germany, the USA, and Australia in terms of active ingredients and excipients.
2. In extemporaneous formulations in Latvia, two or more active ingredients in one dosage form are widely used (> 50 %), which lacks studies on stability and compatibility of ingredients.

Novelty of the study

The preparation of extemporaneous medicinal products is the oldest function of a pharmacy that has survived to the present day. In the EU as well as the USA and Australia, the compositions and compounding technologies of these medicinal products continue to evolve, and new standardized formulations are

being developed. However, in each country, the preparation of the medicinal products has followed its own way of development, and a national health care system has been established, in which the preparation of the medicinal products has a different role and regulatory framework. To date, a number of studies have been carried out that provide an insight into the state of affairs regarding extemporaneous preparations in different EU countries. However, such studies concerning the Baltic States (Latvia, Lithuania, and Estonia) are lacking. For example, the study published in 2017 on the impact of the Resolution on the legislation of European countries does not include the Baltic States.[35] The peculiarity of the Baltic States in comparison with other EU member states lies in the fact that these countries were part of the USSR until 1991, and the preparation of medicinal products was regulated by the procedures adopted by the USSR in accordance with the USSR Pharmacopoeia and standardized formulations. A study of the current situation in the Baltic States is essential to develop a unified view of extemporaneous preparation-related processes across the EU. This study describes, for the first time, the current situation in the field of extemporaneous preparations in different regions of Latvia. The formulations of Latvian pharmacies are compared with the standardized formulations of European countries, the USA, and Australia to assess the safety of the existing extemporaneous preparations for Latvian patients.

Structure and volume of the Doctoral Thesis

The Doctoral Thesis is written in Latvian. It consists of 5 chapters: "Literature review", "Materials and methods", "Results", "Discussion" and "Conclusions". The volume of the Doctoral Thesis is 115 pages, the work contains 15 tables, 2 graphs and 3 supplements. The references of the Doctoral Thesis consist of 183 sources.

1 Materials and methods

1.1 Comparison of Latvian regulatory enactments regulating compounding of extemporaneous preparations with the Resolution of Council of Europe

In order to compare the regulatory framework of Latvia with the Resolution, the Latvian Pharmaceutical Law and the Cabinet of Ministers Regulations regulating prescription, compounding and control of extemporaneous preparations in community pharmacies were analysed.

1.2 Sales volume of extemporaneous preparations in Latvian pharmacies, which had a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence in 2017

50.07 % of community Latvian pharmacies had a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence in 2017.[40] The fact that pharmacies are allowed to compound medicinal products does not mean that the relevant pharmacy exercises these rights. Information about the scope of sale of extemporaneous preparations in these pharmacies is not publicly available. For this reason, in order to characterize the sales volume of extemporaneous preparations in Latvian pharmacies in 2017, I gained access to unpublished data of the State Agency of Medicines (SAM) on the turnover of extemporaneous preparations in 2017 in all statistical regions of Latvia.[41] In accordance with order No. 271 of the Cabinet of Ministers "On the Statistical Regions of the Republic of Latvia and Administrative Units Therein" Latvia is broken down into six statistical regions: Riga statistical region, Pieriga statistical region, Vidzeme statistical region, Kurzeme statistical region, Zemgale statistical region, Latgale statistical region. Furthermore, the regions consist of republican cities and municipalities.[42]

A separate Microsoft Excel spreadsheet was prepared for each statistical region in order to summarize the unpublished information of SAM on the turnover of medicinal products compounded extemporaneously in 2017 in all Latvian statistical regions. Each Microsoft Excel spreadsheet summarizes these data on each community pharmacy that compounded medicinal products in the respective region:

- Name of the pharmacy;
- Name of the company owning the pharmacy;
- Municipality or republican city, where the pharmacy is located;
- Amount of money (in euro, without VAT), which the pharmacy obtained from the sale of extemporaneous medicinal products to natural and legal persons;
- Share in percentage of the total amount of money (in euro, without VAT), which the pharmacy obtained from the sale of extemporaneous preparations to natural and legal persons. As the total sales volume of all Latvian community pharmacies for extemporaneous preparations (in euro, without VAT) is known, each pharmacy's share is expressed as a percentage from total sales volume.

The data were anonymized so that an individual provider of the service "preparation of medicinal products in the pharmacy" could not be identified.

Hospital pharmacies were not included in the study because no data were available on the turnover of extemporaneous preparations prepared in these pharmacies.

1.3 Selection of Latvian community pharmacies to be included in the study

In 2017, 384 community pharmacies in Latvia had a permit for the special operation condition "preparation of medicinal products in the pharmacy".[40] As already described in section 1.2, the existence of the permit does not necessarily mean that the pharmacy in question prepared extemporaneous preparations. In order to identify in which community pharmacies and in which statistical regions extemporaneous preparations were prepared in 2017, I used the SAM data on the turnover of extemporaneous preparations. As, analyzing the SAM data, I found out that extemporaneous preparations were sold in all statistical regions of Latvia, community pharmacies were selected according to the geographical distribution. Having initially evaluated and being aware of the time required to enter the prescription data within the framework of the preparation of the doctoral thesis, 165 pharmacies were approached, of which 17 pharmacies agreed to participate in the study. The pharmacies included in the research represented all six statistical regions, four republican cities, and seven municipalities:

- Riga statistical region – the research included seven pharmacies;
- Pieriga statistical region – the research included five pharmacies representing Adazi Municipality, Salacgriva Municipality, Carnikava Municipality, Salaspils Municipality, Incukalns Municipality;
- Vidzeme statistical region – the research included one pharmacy representing Aluksne Municipality;
- Kurzeme statistical region – the research included two pharmacies representing republican city Ventspils and Kuldiga Municipality;
- Zemgale statistical region – the research included one pharmacy representing republican city Jelgava;
- Latgale statistical region – the research included one pharmacy representing republican city Daugavpils.

Pharmacies included in the study represented three different limited liability companies (LLC).

Pharmacies compounding homeopathic medicines were not included in the study.

1.4 Analysis of extemporaneous prescriptions prepared in the selected community pharmacies in 2017

The primary data used in the dissertation were extemporaneous prescriptions. A database was created entering data on all the prescriptions prepared in the selected pharmacies in 2017 to summarize information on extemporaneous prescriptions. The data were obtained by visiting the pharmacies or offices of pharmacy chains and entered into the database on site. The data were collected from 25 December 2017 to 12 January 2019.

The following data were summarized about each prescription:

- The pharmacy, in which the medicine was prepared;
- The statistical region and the republican city or municipality, where the pharmacy is located;
- The month, in which the prescription was prepared;
- The speciality of the health care professional, who prescribed the prescription, in accordance with the classifier of professions of health care professionals;[43]
- The dosage form;
- All active ingredients;
- The number of active ingredients in the dosage form;
- All excipients.

Bulk drug substances and industrially manufactured finished dosage forms containing active ingredients—tablets, solutions, ointments, and creams – used instead of bulk drug substances are classified as active ingredients in this thesis.

1.5 Comparisons of Latvian Extemporaneous Formulations with German, USA, and Australian Formulations

In order to compare the extemporaneous formulations prescribed by Latvian health care professionals with German, USA, and Australian formulations, the sources containing compounded medication monographs as a standard of practice and quality in these countries were analysed.

- Deutscher Arzneimittel-Codex / Neues Rezeptur-Formularium (DAC/NRF);[23]
- United States Pharmacopeia Compounding Compendium (USP Compounding Compendium);[24]
- Australian Pharmaceutical Formulary (APF).[25]

The German DAC/NRF was selected because it contains the biggest collection of standardized extemporaneous prescriptions in Europe.[8] The content of the formulary is regularly reviewed and updated, obsolete compositions are excluded from the formulary.[12]

If the DAC/NRF did not contain any of the active ingredients prescribed in Latvia, they were searched in German professional literature on extemporaneous compounding, as well as in the database maintained by the

DAC/NRF, which contains more than 2.5 thousand formulations. These formulations are classified into three groups:

- Standardized and / or verified formulations;
- Formulations that can be prescribed and prepared provided that the database user evaluates the comments provided by the DAC/NRF team;
- Incompatible and / or doubtful formulations.

The USA USP Compounding Compendium was selected because it contains compounded preparation monographs, which are part of official text from the United States Pharmacopeia (USP) National Formulary (NF). The resource provides information not only on ingredients and compounding technology, but also on packaging, labelling, beyond-use date, and assay methods.[24,44]

The Australian Pharmaceutical Formulary (APF) was selected because it is published by the Pharmaceutical Society of Australia (PSA). The PSA is the only Australian Government-recognised national professional pharmacy organisation representing all of Australia's pharmacists.[45] National guidelines on compounding of medicines encourage pharmacists to use the APF to compound safe extemporaneous preparations.[11]

The active ingredients, combinations of active ingredients, and excipients prescribed by Latvian health care professionals were searched in these sources according to the dosage form.

1.6 Statistical methods of data processing

Data were analysed using descriptive statistical methods. The percentage distribution of extemporaneous preparation sales by regions and the percentage distribution of extemporaneous preparation dosage forms by specializations of health care professionals were determined. The percentage of active ingredients

and excipients in the prescriptions for extemporaneous preparations was determined, describing the most common dosage forms. The results were presented in accordance with the internationally recognized APA standard and ICMJE unified requirements.[46,47]

1.7 Ethical aspects

The study "Availability of extemporaneous preparations in pharmacies in Latvia: a quantitative and qualitative assessment of the situation and future perspectives" was allowed by the Ethics Committee of Rīga Stradiņš University (Identification code Nr. 14, date of approval 5 October 2017).

2 Results

2.1 Compliance of Latvian regulatory enactments regulating compounding of extemporaneous preparations in pharmacies with the requirements of the Resolution

The Resolution consists of 13 paragraphs, first of which explains the field of application of the Resolution, the second explains the definitions used in the Resolution, while Paragraphs 3–13 describe requirements for the quality and safety assurance of medicinal products prepared in pharmacies.[33]

In accordance with Paragraph 3 "Added value of pharmacy preparations and responsibilities of health care professionals" of the Resolution a pharmacist should check whether the prescribed pharmacy preparation has a suitable industrially manufactured equivalent available on the national market. This is partially described in CM Regulations No. 288, which provide: "If the medicinal product is not available in a ready-made form of medicinal product, the pharmacist shall ensure the preparation thereof."[48] Latvian laws do not stipulate replacement of extemporaneous preparations with industrial preparations, and neither the Pharmaceutical Law nor CM Regulations set a limit that a pharmacist is allowed to prepare only the medicinal products, which have no industrial equivalent. A patient may submit a prescription for an extemporaneous preparation to any community pharmacy in Latvia. All community pharmacies, whose licences do not include a special operation condition "preparation of medicinal products in the pharmacy" in their annex, should conclude an agreement on the preparation of the medicinal product with a pharmacy, which is offering this service. The prepared medicinal product is delivered to the pharmacy, to which the patient has submitted his or her prescription.[48] CM Regulations No. 304 provide: "The head of a pharmacy shall be liable for the quality of medicinal products prepared in the pharmacy."[49] This sentence

provides that the medicinal product preparing pharmacy is responsible for the quality of the particular product.

As to Paragraph 4 "Preparation process" of the Resolution, Latvian regulatory enactments do not currently contain requirements for the Good Manufacturing Practices Guide (GMP Guide) and the Guide to Good Practice for the Preparation of Medicinal Products in Health Care Establishments in Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S GPP Guide) for medicinal products prepared in community pharmacies, but the implementation of the PIC/S GPP Guide is planned in CM Regulations No. 288. The Latvian Language Agency translated the PIC/S GPP Guide into Latvian in 2017.[50] The quality of medicinal products compounded in a pharmacy is supervised by SAM, and its operational strategy for 2017–2019, section on the improvement of competences of SAM employees, emphasizes the need to increase competence in relation to the PIC/S standard.[51] In 2020, a continuing education course for pharmacists was organized within the framework of the European Social Fund project No. 9.2.6.0/17/I/001 "Further training of the health care and health care support personnel", one of the topics of which was "Requirements of the PIC/S Guide to Good Preparation Practice".[52] Although the implementation of the above-mentioned documents in Latvia is just a plan, currently valid regulatory enactments[48,49] contain paragraphs partially correlating with requirements of Paragraph 4 of the Resolution – when accepting a prescription and also when compounding extemporaneous preparations, the composition of the extemporaneous preparations should be evaluated to ensure safety and efficacy of the medicinal product. A pharmacist should observe compatibility and physical and chemical properties of substances, as well as principles of pharmaceutical technology. The requirements to the arrangement and location of premises for compounding of extemporaneous preparations are determined by CM Regulations No. 288. These premises depending on

the specifics of pharmacy prescriptions should have workplaces arranged and equipped for preparation and analysis of liquid, semi-solid and solid dosage forms. Aseptic conditions should be provided for the preparation of sterile dosage forms.[48] Education requirements to pharmacy staff involved in compounding and control of extemporaneous preparations are laid down by the Pharmaceutical Law, where the rights to perform these actions are granted only to specialists having pharmaceutical education – pharmacists and pharmacists' assistants.[53] CM Regulations No. 288 provide that the duty of the head of a pharmacy is to provide the pharmacy with appropriately qualified employees.[48]

At present, Latvian regulations do not contain the requirement regarding the creation of a product dossier for extemporaneous medicinal products as referred to in Paragraph 5. They also do not include the risk assessment of extemporaneous medicinal products recommended in Paragraph 5.2 "Risk assessment of a pharmacy preparation" consisting of two levels ("high-risk preparations" and "low-risk preparations"). In accordance with CM Reg. No. 304 and CM Reg. No. 377, a pharmacist, upon accepting a prescription for compounding, shall examine the prescribed composition, including the compatibility of components, the doses of strong effect substances, and ascertain that the maximum volumes of any ethyl alcohol, narcotic and equivalent psychotropic substances allowed on one prescription have not been exceeded.[49,54] In accordance with the Pharmaceutical Law, the State Agency of Medicines (SAM) shall evaluate and check compliance of manufacturers and importers of the active substance with GMP, and issue GMP certificates.[53] Furthermore, CM Regulations No. 344 provide that only those active substances can be used in the preparation of medicinal products, which were purchased from manufacturers and distributors registered with SAM.[55]

Paragraph 5.3 of the Resolution describes the availability of data for authorities for inspection or upon request. CM Regulations No. 304 provide that the Health Inspectorate shall conduct inspections in the pharmacies preparing medicinal products at least once a year. The Health Inspectorate is entitled to send samples of the extemporaneous preparations compounded, the purified water obtained, the concentrates and semi-finished products to be used for the compounding of extemporaneous preparations in a pharmacy to a laboratory for examination, including for microbiological testing, if there are doubts about their quality. Pharmacies shall document the process of preparation and analysis of medicinal products by making entries in the logs specified in the relevant regulations of the Cabinet of Ministers.[49]

The marketing authorisation referred to in Paragraph 6 of the Resolution has not been introduced in Latvia. Pursuant to the Pharmaceutical Law and CM Regulations No. 376, the medicinal products compounded for an individual patient do not require registration at SAM.[53,56]

Labelling of extemporaneous medicinal products generally meets the requirements of Paragraph 7 "Labelling" of the Resolution. CM Regulations No. 57 provide a detailed description of that. Unlike in the labelling of finished dosage forms, warnings are listed, which are added to labelling when needed, for example, "Shake before use". Latvian regulations do not include the requirements that labelling should contain information not only about the pharmacy, in which the medicinal product was prepared, but also should state the name, address and telephone number of the pharmacy, where the medicinal product was ordered and dispensed.[57]

Paragraph 8 of the Resolution is devoted to "Compliance with pharmacopoeial requirements". Latvia has no up-to-date version of national pharmacopoeia, neither any officially approved instructions and quality standards for preparation of medicinal products in a pharmacy. CM Regulations

No. 344 provide that only those active substances can be used in the compounding of extemporaneous preparations, which have been purchased from manufacturers and distributors registered with SAM. Active substances should be produced in accordance with principles of good manufacturing practice and guidelines.[55] CM Regulations No. 288 provide that it is the duty of the head of a pharmacy to draft instructions for compounding and control of extemporaneous preparations, while the pharmacist's task is to compound extemporaneous preparations in accordance with the instructions approved by the head.[48] After evaluating the quality of the compounded medicinal product, the pharmacist dispensing the medicinal product shall check the conformity of the packaging of the medicinal product with the physical and chemical properties of the components of the medicinal product.[49]

The Latvian regulatory enactments do not provide for reconstitution of medicinal products referred to in Paragraph 9 of the Resolution for use in health care establishments.

The Latvian regulations meet the requirements of the Resolution referred to in Paragraph 10 "Authorisation for pharmacies or licences for companies making preparations for pharmacies". In accordance with CM Reg. No. 800 a licence should be received to open a community pharmacy. A licence for opening (operation) of a pharmacy is issued by SAM, and it is also entitled to suspend and renew the licence.[58] In Latvia, preparation of extemporaneous medicinal products is within the competence of pharmacies only. The Pharmaceutical Law defines preparation of medicinal products as a component of pharmaceutical care.[53] In order to compound extemporaneous preparations, a pharmacy should receive permission from SAM, which specifies the special operation condition "preparation of medicinal products in the pharmacy" in the annex to the licence.[58] Community pharmacies may prepare medicinal products for an individual patient based on individual prescriptions or upon a written

request of a medical institution.[53] Since the compounding of extemporaneous preparations is an additional service of a pharmacy and not all Latvian pharmacies offer this service, the Latvian laws support the pharmacies preparing medicinal products. To protect these pharmacies, CM Regulations No. 610 provide that when a pharmacy is moved, it cannot be located within a radius of 500 metres of another community pharmacy, which prepares medicinal products.[59] This restriction for movement of pharmacies was first set in 2002.[60] Since then the number of pharmacies having a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence has increased more than three times — 120 pharmacies in 2003, 422 pharmacies in 2019.[61,62] The pharmacies, which do not compound extemporaneous preparations, should conclude an agreement on the compounding of medicinal products with a pharmacy, which has this special operation condition in the annex to its licence.[48]

Paragraph 11 of the Resolution is devoted to "Transparency and safety". As it was mentioned before, in accordance with CM Reg. No. 304, the process of preparation and analysis of medicinal products shall be documented by pharmacies. The Health Inspectorate shall inspect the pharmacies preparing medicinal products at least once a year.[49] State Agency of Medicines (SAM) has information about all the pharmacies preparing medicinal products, lists of these pharmacies are published on a regular basis.[36] At present, SAM does not have accurate data about the full composition of the available pharmacy preparations and preparing pharmacies' portfolio of different preparations. However, SAM has taken measures to obtain this information asking pharmacies to send compositions of prescriptions, which are compounded most often. Compositions of medicinal products prescribed by physicians and compounded by pharmacies are not subject to clinical expertise. In accordance with the Pharmaceutical Law, the Health Inspectorate is entitled to prohibit the distribution of any medicinal

products, active substances and excipients, if they have been found to be of inferior quality or falsified, but in the event of doubt as to their quality – to suspend the distribution of the medicinal products, active substances or excipients concerned until their quality has been definitively established.[53]

The requirements of Paragraph 12 "Communication and information to patients" of the Resolution are included in CM Regulations No. 304 and No. 57. The persons dispensing medicinal products must check the labelling of compounded extemporaneous preparations.[49] When dispensing the extemporaneous preparations, the pharmacist shall explain how to use and store the compounded extemporaneous preparation, and emphasize that this medicinal product can be used only during the period indicated by the physician and until their beyond-use date. Medicinal product administration conditions (dosage, route and frequency of administration), and special storage conditions, as well as the beyond-use date are always specified on the labelling of compounded medicinal products,[57] consequently, the patient receives information both orally and in writing.

Paragraph 13 "Distribution of pharmacy preparations" of the Resolution is partially mentioned in the Pharmaceutical Law and CM Regulations No. 416. SAM's duties include the evaluation of compliance of distributors of medicinal products and active substances with good distribution practices and issuing of good distribution practice certificates.[53] On the other hand, CM Regulations No. 416 provide: "In order to monitor the implementation of and compliance with the good distribution principle, the head of the pharmacy shall ensure self-control and record the self-control measures".[63] The Latvian law does not describe requirements for export and import of extemporaneous preparations.

2.2 Overview on the sales volumes of extemporaneous preparations in Latvian pharmacies, which had a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence in 2017

An accurate number of extemporaneous medicinal products prepared in Latvian pharmacies based on prescriptions issued by health care professionals in 2017 is unknown, however, the data on the market share of extemporaneous preparations are available. In accordance with SAM data, extemporaneous preparations accounted for a small market share compared to finished medicinal products (only 0.65 %), but the breakdown by Latvian pharmacies was uneven. In 2017, 384 pharmacies or 50.07 % of all the community pharmacies had a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence. Although many pharmacies were entitled to prepare medicinal products, the data below show that this service was not provided by all the pharmacies. Every year the pharmacies compounding medicinal products should submit to the SAM a report stating the amount of money (in euro, without VAT), which the pharmacy obtained from the sale of extemporaneous medicinal products to natural and legal persons.

Only 280 of 384 pharmacies submitted a report of sales of extemporaneous preparations for 2017 to the SAM. These pharmacies represented all Latvian statistical regions: Riga statistical region (108 pharmacies), Pieriga statistical region (39 pharmacies), Vidzeme statistical region (32 pharmacies), Kurzeme statistical region (35 pharmacies), Zemgale statistical region (27 pharmacies), Latgale statistical region (39 pharmacies). Extemporaneous medicinal products were mostly sold in Riga, and not only allopathic extemporaneous medicinal products, but also homeopathic medicinal products were compounded in Riga (Figure 2.1).

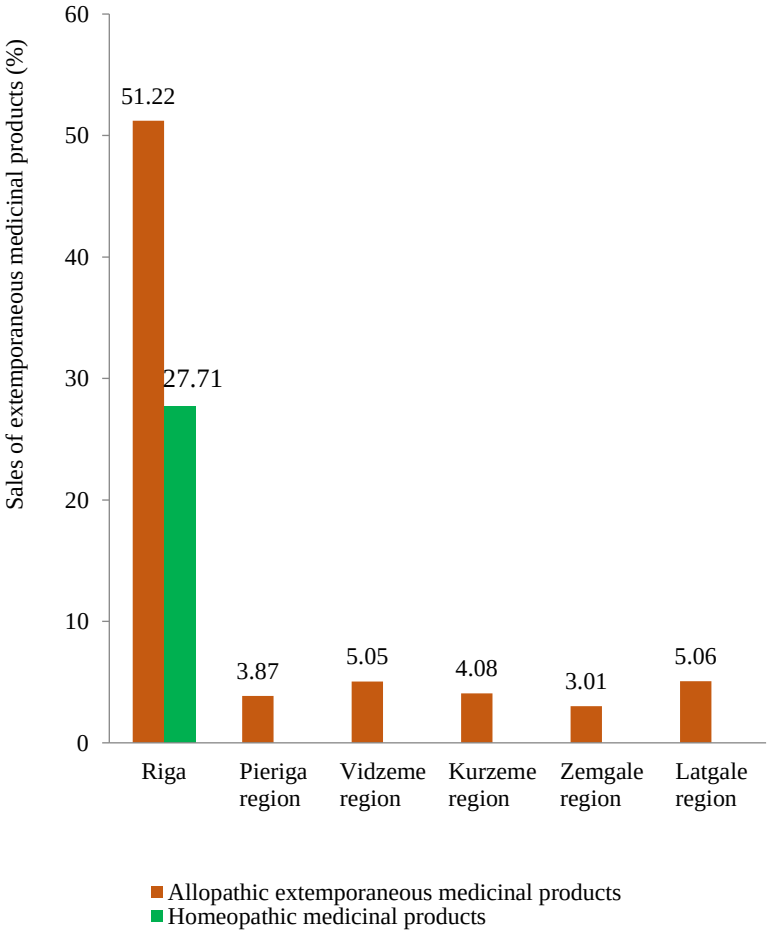

Figure 2.1. **Sales of extemporaneous medicinal products in Latvian statistical regions in 2017 (%)**

Pharmacies in Riga represented 12 different limited liability companies (LLC) and one joint stock company (JSC). The breakdown of extemporaneous preparations in these pharmacies was uneven. In 27 pharmacies, the share in the percentage of sales of extemporaneous medicinal products in total sales was

lower than 0.01 %. In 73 pharmacies it was within 0.01 % to 0.44 %. Only eight pharmacies crossed the 1 % barrier and their sales were within 1.22 % to 23.11 %.

In the Pieriga statistical region the pharmacies were located in one republican city (Jurmala) and in 16 municipalities. The pharmacies in Pieriga represented eight different LLCs and one JSC. None of pharmacies crossed the 1 % barrier. In seven pharmacies, the share in percentage of sales of extemporaneous medicinal products in total sales was lower than 0.01 %, in other 32 pharmacies it was within 0.01 % to 0.72 %.

In the Vidzeme statistical region the pharmacies were also located in one republican city (Valmiera) and in 16 municipalities. The pharmacies represented 14 different LLCs and one JSC. In four pharmacies, the share in percentage of extemporaneous medicinal products in total sales was lower than 0.01 %. One pharmacy crossed the 1 % barrier, its sales were 1.78 %. In other pharmacies it was within 0.01 % to 0.78 %.

In the Kurzeme statistical region the pharmacies were located in two republican cities (Liepaja and Ventspils) and in six municipalities. The pharmacies represented seven different LLCs and one JSC. In nine pharmacies, the share in percentage of extemporaneous medicinal products in total sales was lower than 0.01 %. Similarly, to the Vidzeme statistical region, only one pharmacy crossed the 1 % barrier, its sales were 1.57 %. In other pharmacies it was within 0.01 % to 0.82 %.

In the Zemgale statistical region the pharmacies were located in two republican cities (Jelgava and Jekabpils) and in nine municipalities. The pharmacies represented 11 different LLCs and one JSC. None of the pharmacies crossed the 0.5 % barrier. In four pharmacies, the share in percentage of extemporaneous medicinal products in total sales was lower than 0.01 %. In other pharmacies it was within 0.01 % to 0.48 %.

In the Latgale statistical region the pharmacies were located in two republican cities (Daugavpils and Rezekne) and in nine municipalities. The pharmacies represented 10 different LLCs, one JSC and one individual merchant (IM). In nine pharmacies, the share in percentage of extemporaneous medicinal products in total sales was lower than 0.01 %. Two pharmacies in Daugavpils crossed the 1 % barrier, their sales were 1.09 % and 1.08 %. In other pharmacies it was within 0.01 % to 0.65 %.

The data show that apart from Riga the main sales of extemporaneous medicinal products were observed in two republican cities and one municipality, however in much smaller amounts than in Riga.

2.3 Extemporaneous formulations prepared in Latvian pharmacies in 2017

Data from 17 Latvian pharmacies were collected. In total, 6227 extemporaneous formulations were prepared in these pharmacies based on prescriptions issued by health care professionals in 2017.

2.3.1 Health care professionals who prescribed extemporaneous prescriptions

Extemporaneous prescriptions were prescribed by physicians of 31 speciality, as well as dentists and physician assistants. The majority of the extemporaneous prescriptions that pharmacies received were from physicians of three specialities: dermatovenerologists, general practitioners, and otolaryngologists. These data can be considered as typical for Latvia, because, after the analysis of six pharmacy prescriptions, the results match the current data.[64] During the analysis period, a total of 5162 extemporaneous preparations were prepared following prescriptions issued by dermatovenerologists, general practitioners, and otolaryngologists.

2.3.2 Dosage forms prescribed by health care professionals and number of active ingredients in these dosage forms

Since dermatovenerologists, general practitioners, and otolaryngologists accounted for 82.89 % of all health care professionals, the prescriptions of these specialists were analysed in depth by looking at the prescribed dosage forms and the number of active ingredients in each dosage form.

Dosage forms prescribed by dermatovenerologists and number of active ingredients in these dosage forms

Dermatovenerologists mostly prescribed semi-solid dosage forms, suspensions, and topical solutions. These dosage forms comprised 92.58 % of the extemporaneous prescriptions prescribed by dermatovenerologists. Powders, oral solutions, and nasal drops were prescribed much less often – only 7.42 % of all dosage forms.

More than half of semi-solid dosage forms (77.71 %), suspensions (98.54 %), topical solutions (51.24 %), and topical powders (97.92 %) contained two or more active ingredients. Semi-solid dosage forms most commonly contained two active ingredients (32.56 %), suspensions – four active ingredients (46.34 %), topical solutions – one active ingredient (45.85 %), topical powders – two active ingredients (94.80 %). Oral solutions most often contained one active ingredient (62.92 %). An oral powder and nasal drops were prescribed once and, therefore, were not analysed in this study.

From the above, it can be seen that the most frequently prescribed number of active ingredients varied depending on the pharmaceutical dosage form. In several analysed prescriptions, physicians prescribed only the base without active ingredients, for example, ointment prepared from vegetable oil, purified water, and wool fat.

Dosage forms prescribed by general practitioners and number of active ingredients in these dosage forms

General practitioners most commonly prescribed nasal drops, topical solutions, and semi-solid solid dosage forms. The three mentioned dosage forms comprised 77.31 % of all the extemporaneous prescriptions prescribed by general practitioners. Suspensions, powders, oral solutions, and suppositories were prescribed less often.

More than half of nasal drops (64.02 %), semi-solid dosage forms (76.99 %), suspensions (97.30 %), oral solutions (68.18 %), and suppositories (94.44 %) contained two or more active ingredients. Nasal drops most commonly contained three active ingredients (36.75 %), semi-solid dosage forms – two active ingredients (21.37 %), suspensions – four active ingredients (41.89 %), oral solutions – two active ingredients (31.82 %), suppositories – seven active ingredients (83.33 %). In contrast, most topical solutions (91.87 %), topical powders (72.92 %), and oral powders (83.33 %) contained one active ingredient or base without active ingredients. Topical solutions most commonly did not contain active ingredients (71.95 %). Topical powders (70.84 %) and oral powders (83.33 %) most commonly contained one active ingredient.

As in the prescriptions issued by dermatovenerologists, the most frequently prescribed number of active ingredients in the prescriptions issued by general practitioners varied depending on the pharmaceutical dosage form. More than 500 prescriptions did not contain active ingredients, for example, often only ethanol solutions of various concentrations were prescribed.

Dosage forms prescribed by otolaryngologists and number of active ingredients in these dosage forms

Otolaryngologists prescribed mostly nasal drops and semi-solid dosage forms. These dosage forms comprised 90.14 % of all the extemporaneous prescriptions prescribed by otolaryngologists. Topical solutions, oral solutions, suspensions, and topical powders were seldom prescribed.

More than half of nasal drops (81.73 %), semi-solid dosage forms (99.55 %), suspensions (100.00 %), and topical powders (80.00 %) contained two or more active ingredients. Nasal drops most commonly contained three active ingredients (39.54 %), semi-solid dosage forms – six active ingredients (79.09 %), suspensions – three active ingredients (88.24 %), topical powders – four active ingredients (80.00 %). Topical solutions most often contained one active ingredient (67.65 %). An oral solution was prescribed once and, therefore, was not analysed in this study.

In the prescriptions issued by otolaryngologists, the most frequently prescribed number of active ingredients also varied depending on the pharmaceutical dosage form. Otolaryngologists, unlike dermatovenerologists and general practitioners, did not write prescriptions without active ingredients.

2.4 Active ingredients, combinations of active ingredients, and excipients prescribed by Latvian dermatovenerologists and comparison with German, USA, and Australian formulations

Active ingredients, combinations of active ingredients, and excipients were identified for each of the dosage forms prescribed by Latvian dermatovenerologists. Identified active ingredients, combinations of active ingredients, and excipients were searched in German, USA, and Australian literature according to the dosage form.

2.4.1 Semi-solid dosage forms

In total, 1032 semi-solid dosage forms were prepared based on prescriptions issued by dermatovenerologists.

Active ingredients used in preparation of semi-solid dosage forms, their most common combinations and comparison with German, USA, and Australian formulations

In total, 25 bulk drug substances and 37 industrially manufactured preparations were used in the preparation of semi-solid dosage forms. The following industrially manufactured dosage forms were mainly used: tablets, creams, and ointments.

The dissertation summary considers the 10 most commonly prescribed active ingredients.

The most popular active ingredient was salicylic acid. Salicylic acid is mentioned in the DAC/NRF in the composition of several ointments, creams, and pastes. In these formulations, salicylic acid is used as the only active ingredient or in combination with dithranol or solution of coal tar in ethanol 96 % (v/v) and polysorbate 80.[23] The USP Compounding Compendium describes the preparation of salicylic acid–zinc oxide paste.[24] Salicylic acid is mentioned in the APF in the composition of cream, as well as in the composition of several ointments and pastes. Several combinations of active ingredients are similar to those included in the DAC/NRF and USP Compounding Compendium. The APF, similarly to the DAC/NRF, contains ointment with salicylic acid as the only active ingredient, as well as formulations, where salicylic acid is combined with dithranol or solution of coal tar in ethanol 90 % (v/v) and polysorbate 80. The APF, similarly to the USP Compounding Compendium, describes the preparation of a paste, where salicylic acid is combined with zinc oxide. In the

APF formulations, salicylic acid were also used with the following ingredients: sulfur, benzoic acid, and trichloroacetic acid.[25]

In Latvia, salicylic acid was prescribed as the only active ingredient in 72 prescriptions. Salicylic acid – zinc oxide paste was found in 56 of the analysed prescriptions, but combination of salicylic acid and sulfur was found in 424 prescriptions. In the prescriptions issued by Latvian dermatovenerologists, salicylic acid was most frequently combined with sulfur (424 prescriptions), isoconazole nitrate and diflucortolone valerate cream (72 prescriptions), prednisolone tablets (66 prescriptions), and birch tar (60 prescriptions). Such combinations can neither be found in the DAC/NRF nor in the USP Compounding Compendium.[23,24] The APF contains a combination of salicylic acid and sulfur,[25] which is also the most common combination of salicylic acid in Latvia.

The second most frequently prescribed active ingredient was sulfur. The DAC/NRF does not contain formulations with sulfur. In 1996, an ointment containing it was excluded from the DAC/NRF due to a negative sulfur use benefit-and-risk assessment.[23] Prescription of sulfur in dermatological prescriptions is permitted with the evaluation of risks and benefits, and prescriptions with sulfur can be found in German dermatological literature,[65,66] as well as in the database maintained by the DAC/NRF.[27] The USP Compounding Compendium includes sulfur ointment, where sulfur is the only active ingredient.[24] The APF describes the preparation of a cream containing salicylic acid and sulfur.[25] In Latvia, sulfur was prescribed as the only active ingredient in three prescriptions. In other analysed prescriptions of Latvian dermatovenerologists, sulfur was most frequently combined with the same active ingredients, with which salicylic acid was combined. Sulfur together with salicylic acid were prescribed in 424 prescriptions, with isoconazole nitrate and diflucortolone valerate cream in 73 prescriptions, with prednisolone tablets in 50

prescriptions, with birch tar in 47 prescriptions, and with zinc oxide in 43 prescriptions.

The third most frequently prescribed active ingredient in semi-solid dosage forms was prednisolone. The DAC/NRF contains creams with prednisolone prodrug prednicarbate and prednisolone acetate. In these formulations, prednisolone acetate is used as the only active ingredient, but prednicarbate is used alone and in combination with octenidine hydrochloride.[23] Furthermore, prednisolone cream formulation can be found in German dermatological literature as a cheaper alternative for industrially manufactured prednisolone creams.[67] The USP Compounding Compendium and APF do not contain semi-solid dosage forms with prednisolone.[24,25] Unlike in Germany, analysed Latvian prescriptions used prednisolone tablets rather than bulk drug substance for the preparation of semi-solid dosage forms. In Latvia, prednisolone was prescribed as the only active ingredient in eight prescriptions. In the analysed prescriptions of Latvian pharmacies, prednisolone was most often combined with the following active ingredients: salicylic acid (66 prescriptions); ampicillin trihydrate from capsules (55 prescriptions); sulfur (50 prescriptions); zinc oxide (41 prescriptions); boric acid (39 prescriptions). Such combinations were not included in the DAC/NRF.[23]

The fourth most frequently prescribed active ingredient was zinc oxide. Zinc oxide is mentioned in the DAC/NRF in the composition of several pastes, in addition to as a cream. In these formulations, zinc oxide is used as the only active ingredient or in combination with the following active ingredients: dithranol; ichthammol; and bismuth subgallate.[23] The USP Compounding Compendium includes ointments and pastes containing zinc oxide, where zinc oxide is the only active ingredient or in the following combinations: zinc oxide–salicylic acid; zinc oxide–coal tar; zinc oxide–resorcinol–bismuth subnitrate–juniper tar.[24] Zinc oxide is mentioned in the APF in the composition

of several creams, ointments, and pastes. In these formulations, zinc oxide is used as the only active ingredient or in combinations. Several combinations of active ingredients are similar to those included in the DAC/NRF and USP Compounding Compendium. The APF, similarly to the DAC/NRF, contains formulations, where zinc oxide is combined with dithranol or ichthammol. The APF, similarly to the USP Compounding Compendium, describes the preparation of semi-solid dosage forms, where zinc oxide is combined with salicylic acid or coal tar. The APF also includes formulations, where zinc oxide is combined with the following ingredients: aluminium acetate solution and calamine.[25]

In Latvia, zinc oxide was prescribed as the only active ingredient in two prescriptions. In the analysed prescriptions of Latvian pharmacies, zinc oxide was most often combined with the following active ingredients: salicylic acid (56 prescriptions); ichthammol (47 prescriptions); sulfur (43 prescriptions); prednisolone tablets (41 prescriptions); birch tar (32 prescriptions); resorcinol (32 prescriptions); bismuth subgallate (30 prescriptions). Out of these combinations in the DAC/NRF, USP Compounding Compendium, and APF, none can be found of zinc oxide with sulfur, prednisolone, and birch tar.[23,24,25]

Metronidazole was often prescribed by Latvian dermatovenerologists. The DAC/NRF contains creams and a gel containing metronidazole as the only active ingredient and in combination with erythromycin.[23] Such a combination can also be found in the analysed Latvian prescriptions. Metronidazole was prescribed as the only active ingredient in 65 analysed Latvian prescriptions. The USP Compounding Compendium and APF do not include semi-solid dosage forms with metronidazole.[24,25] Metronidazole tablets rather than bulk drug substance were mainly used for the preparation of semi-solid dosage forms in the analysed Latvian prescriptions. Latvian dermatovenerologists most frequently combined metronidazole with the following active ingredients: sulfur

(31 prescriptions); salicylic acid (27 prescriptions); clotrimazole cream (20 prescriptions); isoconazole nitrate and diflucortolone valerate cream (13 prescriptions); erythromycin tablets (13 prescriptions). As already mentioned, out of these combinations, only a metronidazole combination with erythromycin can be found in the DAC/NRF.[23]

The next most frequently prescribed active ingredient was dexamethasone. The DAC/NRF describes only the preparation of dexamethasone 1 % and 10 % trituration, but the formulations containing dexamethasone are not included in this formulary.[23] Ointments, creams, and hydrogels containing dexamethasone can be found in German dermatological literature,[65,66] as well as in the database maintained by the DAC/NRF.[27] The USP Compounding Compendium and APF do not include semi-solid dosage forms with dexamethasone.[24,25] Dexamethasone tablets rather than bulk drug substance were used for the preparation of semi-solid dosage forms in the analysed prescriptions of Latvian pharmacies. Dexamethasone was prescribed as the only active ingredient in six prescriptions. In the analysed prescriptions of Latvian pharmacies, dexamethasone had been most frequently combined with the following active ingredients: salicylic acid (43 prescriptions); fluocinolone acetonide ointment (22 prescriptions); benzocaine (21 prescriptions); birch tar (21 prescriptions); sulfur (17 prescriptions).

The seventh most frequently prescribed active ingredient was birch tar. Birch tar is not included in any of the foreign sources.[23,24,25,65,66,67] The DAC/NRF includes coal tar, which is used in the preparation of ointments and creams. In the DAC/NRF, coal tar is not combined with other active ingredients, but is used as the only active ingredient.[23] The USP Compounding Compendium also uses coal tar, but in combination with zinc oxide in the respective ointment.[24] The APF, similarly to the DAC/NRF and USP Compounding Compendium, contains coal tar, which is used in the preparation of ointments, cream, and paste. In these

formulations, coal tar is combined with zinc oxide or salicylic acid.[25] In the analysed prescriptions of Latvian pharmacies, birch tar was most frequently combined with the following active ingredients: salicylic acid (60 prescriptions); sulfur (47 prescriptions); zinc oxide (32 prescriptions); turpentine oil (30 prescriptions); dexamethasone tablets (21 prescriptions). Birch tar was prescribed as the only active ingredient in three prescriptions.

The next most frequently prescribed active ingredient was boric acid. In Germany, the use of boric acid and its salts for the preparation of semi-solid dosage forms is prohibited due to low efficacy and risk of resorptive poisoning. Boric acid can be used only in the preparation of homeopathic preparations, as well as in the preparation of eye drops, where it is used as a buffer for the pH required.[23] The USP Compounding Compendium and APF also do not include semi-solid dosage forms with boric acid.[24,25] In the analysed prescriptions, the most common combinations were with prednisolone tablets (39 prescriptions), ampicillin trihydrate from capsules (36 prescriptions), and zinc oxide (13 prescriptions).

The ninth most frequently prescribed active ingredient was the mercuric oxide. In 1999, mercuric oxide was removed from the DAC/NRF.[23] It is also not included in the USP Compounding Compendium and APF.[24,25] In Latvia, mercuric oxide is still prescribed as the only active ingredient (38 prescriptions), but is also found in combinations. The most common combinations were with the following active ingredients: salicylic acid (16 prescriptions); prednisolone tablets (nine prescriptions).

The tenth most frequently prescribed active ingredient was ampicillin. Formulations with ampicillin are not included in the DAC/NRF, database maintained by the DAC/NRF, USP Compounding Compendium, and APF.[23,24,25,27] German literature on dermatological formulations states that the risk of sensibilization should be taken into account when prescribing

antibacterial agents topically. The rate of sensibilization when applied to the skin is many times higher than when administered orally. For this reason, topical use of penicillin and penicillin derivatives is contraindicated.[67] Latvian prescriptions include ampicillin trihydrate oral capsules rather than bulk drug substance; the most common combinations were with prednisolone tablets (55 prescriptions), boric acid (36 prescriptions), ichthammol (17 prescriptions), and zinc oxide (16 prescriptions). Ampicillin was not used as the only active ingredient in semi-solid dosage forms.

Excipients used in preparation of semi-solid dosage forms and comparison with German, USA, and Australian formulations

In total, 14 excipients (i.e., soft paraffin, wool fat, purified water, sunflower oil, potato starch, Wolff Basis Creme or Basiscreme DAC, olive oil, liquid paraffin, castor oil, glycerol, peach oil, Essex Hydrogel, ethanol, talc) were used in the analysed prescriptions prescribed by Latvian dermatovenerologists. The prescriptions also included excipients from finished industrially manufactured dosage forms.

The formulations of dermatological semi-solid dosage forms in the DAC/NRF contain excipients used in Latvia such as soft paraffin, wool fat, purified water, starch, Basiscreme DAC, liquid paraffin, glycerol, ethanol, and talc. Wolff Basis Creme is not included in the DAC/NRF, but there are standardized formulations with this cream that were created by the manufacturer.[23,27] The formulations included in the DAC/NRF, along with the traditional bases used in Latvia, also use other bases; for example, macrogols are used as water-soluble bases.[23]

Semi-solid dosage formulations in the USP Compounding Compendium, as in the DAC/NRF, contain soft paraffin, wool fat, purified water, starch, liquid paraffin, glycerol. Similarly to Germany, the USP Compounding Compendium

also uses other bases; for example, hydrophilic ointment USP is used as a water-removable base, and polyethylene glycol ointment NF is used as a water-soluble base.[24]

The APF, similarly to the DAC/NRF and USP Compounding Compendium, contains soft paraffin, wool fat, purified water, starch, liquid paraffin, and glycerol. Sunflower oil, olive oil, and peach oil are not included in the compositions of semi-solid dosage forms available in the APF, but formulations containing other vegetable oils (peanut oil and castor oil) are described in this formulary. Castor oil is also found in the analysed prescriptions of Latvian pharmacies. Wolff Basis Creme, Basiscreme DAC, ethanol, and talc are not included in the compositions of semi-solid dosage forms available in the APF. However, this formulary offers other bases that form the consistency of a cream. For example, aqueous cream, which consists of soft paraffin, liquid paraffin, cetostearyl alcohol, sodium lauryl sulfate, glycerol, phenoxyethanol, and purified water.[25]

2.4.2 Suspensions

In total, 820 suspensions were made after dermatovenerologists' prescriptions.

Active ingredients used in preparation of suspensions, their most common combinations and comparison with German, USA, and Australian formulations

In total, 25 bulk drug substances and 10 industrially manufactured preparations were used in the preparation of suspensions.

The dissertation summary considers the 10 most commonly prescribed active ingredients.

The most popular active ingredient was boric acid. As already mentioned above, it is prohibited to prescribe boric acid and its salts in the composition of dosage forms used in dermatology.[23] The USP Compounding Compendium also does not mention boric acid in suspensions; it is mentioned only as a potential stabilizer in the composition of aluminium subacetate topical solution and aluminium acetate topical solution.[24] The APF describes the preparation of a buffer solution containing boric acid.[25] In the analysed prescriptions of Latvian pharmacies, boric acid was most often combined with the following active ingredients: salicylic acid (561 prescriptions); sulfur (459 prescriptions); camphor (385 prescriptions); sulfathiazole (119 prescriptions); chloramphenicol (74 prescriptions), resorcinol (64 prescriptions).

The second most frequently prescribed active ingredient was salicylic acid. The DAC/NRF, USP Compounding Compendium, and APF do not contain suspensions with this active ingredient.[23,24,25] In Latvia, salicylic acid as the only active ingredient was prescribed in two of the analysed prescriptions, where its solubility limit in olive oil was exceeded and suspensions rather than solutions were prepared. In the prescriptions of suspensions prescribed by Latvian dermatovenerologists, most common combinations of salicylic acid were identical to the previously described combinations of boric acid: boric acid (561 prescriptions); sulfur (450 prescriptions); camphor (356 prescriptions); sulfathiazole (111 prescriptions); resorcinol (62 prescriptions); chloramphenicol (48 prescriptions).

The third most frequently prescribed active ingredient in suspensions was sulfur. As already mentioned above, the DAC/NRF does not contain formulations containing sulfur.[23] However, German dermatological literature includes suspensions with sulfur. For example, a suspension for use on skin is mentioned, where sulfur is combined with zinc oxide.[27] In Latvia, such a combination was found in 21 of the analysed prescriptions. Out of these

prescriptions, two contained only the said two active ingredients, but another 19 prescriptions had 1–4 active ingredients added to the combination of sulfur and zinc oxide. The USP Compounding Compendium and APF, similarly to the DAC/NRF, do not contain suspensions with sulfur,[24,25] but the USA extemporaneous literature describes a suspension containing sulfur for use on skin.[68] In the analysed prescriptions of Latvian pharmacies, sulfur was most often combined with the following active ingredients: boric acid (459 prescriptions); salicylic acid (450 prescriptions); camphor (355 prescriptions); sulfanilamide (52 prescriptions); chloramphenicol (48 prescriptions).

The next most frequently prescribed active ingredient was camphor. The DAC/NRF does not include liquid dosage forms containing camphor.[23] However, a standardized formulation of camphor alcohol is available in the German Pharmacopoeia.[27] The USP Compounding Compendium and APF do not include suspensions with camphor, but solutions containing camphor can be found in this sources.[24,25] The USP Compounding Compendium describes the preparation of camphor alcohol.[24] The APF contains a formulation of a compound alcohol solution, which consists of camphor, benzoic acid, anise oil, and ethanol.[25] In the analysed suspension prescriptions of Latvian pharmacies, camphor was used as an alcohol solution. Camphor alcohol was most often combined with the following active ingredients: boric acid (385 prescriptions); salicylic acid (356 prescriptions); sulfur (355 prescriptions); chloramphenicol (34 prescriptions); sulfanilamide (30 prescriptions).

The next most frequently prescribed active ingredient was sulfathiazole. Since 1991, sulfathiazole monograph was removed from the DAC/NRF.[23] The reason for that is the low antimicrobial activity of sulfonamide group preparations and high risk of sensibilization.[69] The USP Compounding Compendium and APF also do not contain formulations with this ingredient.[24,25] In the analysed prescriptions of Latvian pharmacies, sulfathiazole was most often

combined with the following active ingredients: boric acid (119 prescriptions); salicylic acid (111 prescriptions); sulfur (15 prescriptions); camphor (nine prescriptions); calendula tincture (eight prescriptions).

The sixth most frequently prescribed active ingredient was zinc oxide. Zinc oxide is included in the composition of several suspensions in the DAC/NRF. Zinc oxide is used in them as the only active ingredient or in combination with ichthammol, solution of coal tar in quillaia bark tincture and ethanol 70 % (v/v), Lauromacrogol 400, and nystatin.[23] The USP Compounding Compendium describes preparation of a suspension containing zinc oxide, where zinc oxide is combined with calamine.[24] The APF, similarly to the USP Compounding Compendium, includes a lotion containing zinc oxide and calamine.[25] In Latvia, zinc oxide as the only active ingredient was prescribed in nine prescriptions, but zinc oxide in combination with ichthammol was found in one of the analysed prescriptions. In the prescriptions prescribed by Latvian dermatovenerologists, zinc oxide was most often combined with menthol (47 prescriptions), diphenhydramine hydrochloride (45 prescriptions), boric acid (39 prescriptions), sulfur (21 prescriptions), and benzocaine (16 prescriptions).

Chloramphenicol was often prescribed by Latvian dermatovenerologists. Due to the high risk of sensibilization, the DAC/NRF does not include chloramphenicol suspensions for use in dermatology.[23] The database maintained by the DAC/NRF describes a suspension for use on skin, where chloramphenicol is combined with zinc oxide, but its use is permissible only in exceptional cases.[27] The USP Compounding Compendium and APF do not contain formulations with this active ingredient for use in dermatology.[24,25] In Latvia, a combination of chloramphenicol and zinc oxide is only found in two of the analysed suspension prescriptions. In the analysed prescriptions of Latvian pharmacies, chloramphenicol was most often combined with boric acid (74 prescriptions),

salicylic acid (48 prescriptions), sulfur (48 prescriptions), and camphor (34 prescriptions).

Latvian dermatovenerologists also prescribed resorcinol. In 1996, all the formulations containing resorcinol were removed from the DAC/NRF.[23] Alternatives with a better risk–benefit ratio are offered.[70] Despite that, in the database maintained by the DAC/NRF, a suspension formulation for use in dermatology, where resorcinol is combined with salicylic acid and sulfur, is mentioned.[27] The USP Compounding Compendium and APF do not contain suspensions with resorcinol for use in dermatology.[24,25] In Latvia, suspensions, where resorcinol is in combination with salicylic acid and sulfur were found in 26 of the analysed prescriptions. In the prescriptions prescribed by Latvian dermatovenerologists, resorcinol was most often combined with boric acid (64 prescriptions), salicylic acid (62 prescriptions), sulfur (31 prescriptions), and camphor (25 prescriptions).

The next most frequently prescribed active ingredient was menthol. Although the DAC/NRF does not contain suspensions with menthol,[23] German dermatological literature considers the possibility of adding menthol to the DAC/NRF suspensions containing zinc oxide.[70] It is similar in the USA; the USP Compounding Compendium also does not contain suspensions with menthol,[24] but the USA dermatological literature mentions suspension formulations containing menthol.[68] The APF does not include menthol suspensions for use in dermatology.[25] In the analysed prescriptions of Latvian pharmacies, menthol was most often combined with zinc oxide (47 prescriptions), boric acid (26 prescriptions), diphenhydramine hydrochloride (17 prescriptions), and benzocaine (15 prescriptions).

The tenth most frequently prescribed active ingredient was sulfanilamide. In the DAC/NRF, sulfanilamide is mentioned only as a reagent for the preparation of the control solution.[23] The USP Compounding Compendium and

APF also do not contain formulations with sulfanilamide.[24,25] In Latvia, sulfanilamide is still being prescribed. In the analysed prescriptions of Latvian pharmacies, sulfanilamide was not prescribed as the only active ingredient; in all prescriptions, it was used in combinations with boric acid. An additional 1–5 other active ingredients were added to this combination, most frequently sulfur (52 prescriptions) and salicylic acid (44 prescriptions).

Excipients used in preparation of suspensions and comparison with German, USA, and Australian formulations

In total, 12 excipients (i.e., purified water, ethanol, glycerol, talc, ether, potato starch, sunflower oil, castor oil, olive oil, peppermint water, citral, and lavender oil) were used in the analysed prescriptions prescribed by Latvian dermatovenerologists. The prescriptions also included excipients from finished industrially manufactured dosage forms.

The formulations of dermatological suspensions in the DAC/NRF contain excipients used in Latvia such as purified water, ethanol, glycerol, talc, and olive oil. Unlike in Latvia, iron oxides used as color pigments were added to several suspensions containing zinc oxide.[23]

Excipients used in the preparation of suspensions in Latvia were not as widely represented in the USA sources as in the DAC/NRF. The possible reason for this is that the USP Compounding Compendium contains very few suspensions for topical use. The USP Compounding Compendium contains a calamine topical suspension formulation with excipients, which are also used in Latvia with water and glycerol. Ethanol is included in the composition of compound benzoin tincture.[24]

The APF contains calamine lotion, the composition of which is very similar to the USP Compounding Compendium calamine suspension. The excipients in this lotion include purified water and glycerol.[25]

2.4.3 Topical solutions

In total, 482 topical solutions were prepared based on prescriptions issued by dermatovenerologists.

Active ingredients used in preparation of topical solutions, their most common combinations and comparison with German, USA, and Australian formulations

In total, 23 bulk drug substances, as well as two industrially manufactured preparations (i.e., calendula tincture and iodine tincture 5 %), were used in the preparation of topical solutions.

The dissertation summary considers the 10 most commonly prescribed active ingredients.

The most popular active ingredient in topical solutions was acetic acid. The DAC/NRF does not contain formulations with acetic acid for use in dermatology; there is only one formulation of ear drops, which contains acetic acid as the only active ingredient.[23] However, acetic acid solutions of different concentrations can be found in German dermatological literature.[70] The USP Compounding Compendium includes a preparation monograph for diluted acetic acid (5.7 %–6.3 %).[24] The USA extemporaneous literature also includes a solution containing acetic acid. Acetic acid in this formulation is combined with lactic acid and salicylic acid, but a flexible collodion is used as a vehicle.[68] The APF also contains formulations with acetic acid. Acetic acid is mentioned as one of the components of Burow's solution. Similarly to the DAC/NRF, the APF also contains a formulation of ear drops with acetic acid.[25] In Latvia, acetic acid was prescribed both as the only active ingredient (86 prescriptions) and in combinations (116 prescriptions). In the analysed prescriptions, acetic acid was most often prescribed in the following three main combinations:

acetic acid–salicylic acid (43 prescriptions), acetic acid–iodine (39 prescriptions), and acetic acid–salicylic acid–iodine (25 prescriptions).

The second most frequently prescribed active ingredient was boric acid. The use of boric acid and its salts in liquid dosage forms in Germany, Australia, and the USA was already described in the section of suspensions. Contrary to Germany, Australia, and the USA, where boric acid is not used as an active ingredient,[23,24,25] Latvian dermatovenerologists still prescribe topical solutions containing boric acid. Boric acid was prescribed as the only active ingredient in 59 prescriptions for topical solutions, while the main combinations were as follows: boric acid–liquefied phenol–resorcinol (14 prescriptions) and boric acid–liquefied phenol–resorcinol–fuchsin (15 prescriptions); other components, which were added to these combinations, were acetone, ethanol, and purified water. In Latvia, these compositions are named "Castellani solution" and "Castellani solution, colorless". "Castellani solution" and "Castellani solution, colorless" were also prepared in Germany. As a result of research in Germany, the compositions of these solutions were improved and partially changed, but their names remained unchanged. For example, before 1983, Germany prepared the compositions currently used in Latvia; however, in 1983–1996, these compositions were prepared without boric acid, and phenol was replaced with chlorocresol. Today, Germany offers chlorhexidine alcoholic solution as a therapeutic alternative to "Castellani solution".[70,71]

Salicylic acid in the DAC/NRF is included in the composition of several topical solutions. In these formulations, it is the only active ingredient, or in combination with the lactic acid or triamcinolone acetonide.[23] In the USP Compounding Compendium, salicylic acid is used in combination with flexible collodion.[24] The APF contains several solutions with salicylic acid. In this solutions, salicylic acid is used as the only active ingredient or in combination with lactic acid or formaldehyde solution.[25] In Latvia, salicylic acid was

prescribed as the only active ingredient in 11 prescriptions for topical solutions. In the analysed prescriptions of Latvian pharmacies, salicylic acid was most frequently combined with acetic acid (69 prescriptions) and iodine (31 prescriptions).

The next most frequently prescribed active ingredient was iodine. The DAC/NRF describes the preparation of iodine water and glycerol solutions in different concentrations; however, they are not intended for dermatological indications.[23] The USP Compounding Compendium provides several formulations of solutions with iodine with different environments, for example, a solution, which consists of iodine, potassium iodide, and purified water.[24] This formulation is intended for a variety of indications (external and oral use).[72] The APF, similarly to the USP Compounding Compendium, contains formulation of solution, which consists of iodine, potassium iodide, and purified water, but dermatological use is not specified.[25] In Latvia, iodine as the only active ingredient was prescribed in 16 prescriptions; in other prescriptions it was combined with one or two other active ingredients as follows: iodine–acetic acid (39 prescriptions); iodine–salicylic acid (six prescriptions); iodine–acetic acid–salicylic acid (25 prescriptions); iodine–resorcinol–benzoic acid (30 prescriptions). Industrially manufactured iodine tincture 5 % in combination with acetic acid was prescribed in four prescriptions.

The fifth most frequently prescribed active ingredient was resorcinol. As already mentioned above, the formulations containing resorcinol were removed from the DAC/NRF. Before that, the formulary contained a formulation of topical solution, where resorcinol was in combination with salicylic acid, as well as formulations of Castellani solutions.[70] The APF does not contain formulations with resorcinol.[25] The USP Compounding Compendium describes the preparation of carbol–fuchsin topical solution, where resorcinol is combined with basic fuchsin and phenol.[24] The analysed prescriptions of Latvian

pharmacies also contained solutions with such a combination (15 prescriptions); however, unlike the USP Compounding Compendium, boric acid was added to the combination. Resorcinol was prescribed as the only active ingredient in Latvia in 14 prescriptions.

The next most frequently prescribed active ingredient was benzoic acid. The DAC/NRF and USP Compounding Compendium do not contain solutions for use in dermatology with benzoic acid as an active ingredient.[23,24] However, German literature mentions a formulation, where benzoic acid was combined with salicylic acid.[70] The APF describes the preparation of benzoic acid solution, which is intended to be used as a preservative in a concentration of 0.2 % in other liquid dosage forms.[25] In Latvia, a combination of benzoic acid and salicylic acid was found in 21 of the analysed prescriptions for topical solutions; in these prescriptions, 1–2 other active ingredients were added to the combination, most frequently boric acid (19 prescriptions). The most common combination was benzoic acid–resorcinol–iodine (30 prescriptions).

The next most frequently prescribed active ingredient was phenol. The DAC/NRF does not contain dosage forms with phenol for use in dermatology. In Germany, phenol as an active ingredient is not used on skin and mucous membranes, with the exception of individual cases, when it is used only once or in small amounts.[23] The USP Compounding Compendium includes the already mentioned carbol–fuchsin topical solution, as well as phenolated calamine topical suspension, where liquefied phenol is combined with calamine and zinc oxide.[24] The APF contains a lotion with liquefied phenol. In this lotion, phenol, similarly to USP Compounding Compendium formulation, is combined with calamine and zinc oxide.[25] In the analysed prescriptions of Latvian pharmacies, phenol was prescribed only in the composition of Castellani solution.

The DAC/NRF contains only one eye-drop formulation with chloramphenicol.[23] The database maintained by the DAC/NRF describes topical solutions containing chloramphenicol, but with an indication that the use of chloramphenicol on the skin is considered outdated and should be used only in exceptional cases.[27] The USP Compounding Compendium and APF also do not contain solutions with this active ingredient.[24,25] In Latvia, chloramphenicol was not used as the only active ingredient in preparation of topical solutions; instead, it was prescribed in the following combinations: chloramphenicol–boric acid (11 prescriptions) and chloramphenicol–benzocaine (five prescriptions).

The ninth most frequently prescribed active ingredient was fuchsin. At present, the DAC/NRF and APF do not contain formulations with fuchsin.[23,25] As already mentioned above, the USP Compounding Compendium includes a topical solution with basic fuchsin.[24] In the analysed prescriptions of Latvian pharmacies, fuchsin was prescribed only in the composition of Castellani solution (15 prescriptions).

The tenth most frequently prescribed active ingredient was borax. As the prescribing of boric acid salts in dermatological dosage forms is prohibited in Germany, the DAC/NRF do not contain topical solutions with borax.[23] The USP Compounding Compendium and APF also do not include solutions for dermatological indications with active ingredient borax.[24,25] In Latvia, borax was combined with sodium hydrogen carbonate in one prescription; in other prescriptions it was prescribed as the only active ingredient.

Excipients used in preparation of topical solutions and comparison with German, USA, and Australian formulations

In the analysed prescriptions of Latvian dermatovenerologists, 11 excipients (i.e., purified water, ethanol, glycerol, potassium iodide, castor oil, acetone, hydrochloric acid, sunflower oil, citral, peppermint water, ether) were used for the preparation of topical solutions.

The DAC/NRF formulations of topical solutions for use in dermatology contain the following excipients prescribed in the analysed prescriptions of Latvian pharmacies: purified water, ethanol, castor oil, and ether in the composition of collodion.[23]

The USP Compounding Compendium formulations of topical solutions contain the following excipients prescribed in the analysed prescriptions of Latvian pharmacies: purified water, ethanol, potassium iodide, castor oil, acetone, and ether in the composition of collodion.[24]

The APF formulations of topical solutions contain the following excipients prescribed in the analysed prescriptions of Latvian pharmacies: purified water, ethanol, castor oil, acetone, and ether in the composition pf collodion[25]

Latvia does not use several of the solvents often used in formulations in the DAC/NRF and APF, for example, isopropyl alcohol, octyldodecanol, and propylene glycol.[23,25]

2.4.4 Topical powders

In total, 96 topical powders were prepared based on prescriptions issued by dermatovenerologists.

Active ingredients used in preparation of topical powders and comparison with German, USA, and Australian formulations

In the analysed prescriptions of topical powders, nine active ingredients were prescribed. The most commonly prescribed combination contained two active ingredients from the group of sulphonamides–sulfanilamide and sulfathiazole in equal proportions (85 prescriptions for topical powders or 88.54 %). The DAC/NRF, USP Compounding Compendium, and APF do not contain formulations with these active ingredients.[23,24,25]

2.4.5 Oral solutions

In total, 89 oral solutions were prepared based on prescriptions issued by dermatovenerologists.

Active ingredients used in preparation of oral solutions and comparison with German, USA, and Australian formulations

In the analysed prescriptions of oral solutions, five active ingredients were prescribed. Sodium thiosulfate solution (43 prescriptions), calcium chloride (11 prescriptions), and their combinations (27 prescriptions) were prescribed most often. Out of these combinations, most of the prescriptions contained only the said two active ingredients (21 prescriptions); however, a third active ingredient (sodium bromide) was present in six prescriptions. Purified water was used in all the prescriptions as a solvent. Purified water was the only excipient; antimicrobial preservatives were not added to prescribed oral solutions.

The DAC/NRF does not contain oral solutions with sodium thiosulfate as an active ingredient; it contains only one potassium iodide oral drop formulation, where sodium thiosulfate is added as an excipient.[23] The USP

Compounding Compendium also does not contain a sodium thiosulfate oral solution.[24] However, this substance is mentioned as an excipient in the USA extemporaneous literature.[68] In the APF, sodium thiosulfate is mentioned only in the section of isotonic solutions.[25]

Oral calcium chloride solution, similarly to sodium thiosulfate solution, is not included in the DAC/NRF, USP Compounding Compendium, and APF.[23,24,25]

2.5 Active ingredients, combinations of active ingredients, and excipients prescribed by Latvian general practitioners and otolaryngologists and comparison with German, USA, and Australian formulations

Active ingredients, combinations of active ingredients, and excipients were identified for each of the dosage form prescribed by Latvian general practitioners and otolaryngologists. An analysis of prescriptions issued by general practitioners revealed that the compositions of semi-solid dosage forms for dermatological indications, suspensions and solutions for topical use were similar to those prescribed by dermatovenerologists. For both types of health care professionals, the most popular active ingredients and excipients in these dosage forms were identical; the only differences were identified in the frequency of prescribing. Unlike dermatovenerologists, general practitioners were more likely to prescribe solutions for topical use without active ingredients, for example, 512 prescriptions were issued for ethanol solutions of various concentrations. General practitioners prescribed extemporaneous preparations for intranasal use – nasal drops and semi-solid dosage forms – more often than dermatovenerologists. The most popular dosage forms among otolaryngologists were nasal drops and semi-solid dosage forms for the nasal cavity, accounting for 90.14 % of all prescriptions issued by otolaryngologists. Initially, prescriptions for intranasal use from general practitioners and otolaryngologists

were analysed separately. As the prescribed compositions were similar, the results were pooled. According to the prescriptions issued by general practitioners and otolaryngologists, 1094 extemporaneous preparations were prepared for use in the nasal cavity: 818 nasal drops and 276 semi-solid dosage forms.

2.5.1 Nasal drops

In total, 818 nasal drops were prepared based on prescriptions issued by general practitioners and otolaryngologists.

Active ingredients used in preparation of nasal drops and their most common combinations

In total, 15 bulk drug substances and 10 industrially manufactured preparations were used in the preparation of nasal drops.

The dissertation summary considers the 10 most commonly prescribed active ingredients.

The most popular active ingredient was ephedrine hydrochloride. In Latvia, ephedrine hydrochloride was prescribed as the only active ingredient in 10 prescriptions. In the analysed prescriptions, ephedrine hydrochloride was most frequently combined with the following active ingredients: prednisolone tablets (180 prescriptions); hydrocortisone acetate, lidocaine hydrochloride suspension for injection (129 prescriptions); dexamethasone sodium phosphate solution for injection (125 prescriptions); adrenaline solution for injection (93 prescriptions); nitrofural (75 prescriptions).

The second most frequently prescribed active ingredient was silver proteinate. Almost all prescriptions used silver proteinate as the only active ingredient for the preparation of nasal drops. In three analysed prescriptions,

silver proteinate was prescribed in combination with adrenaline solution for injection.

The next most frequently prescribed active ingredient was prednisolone. Prednisolone tablets were used for the preparation of medicines in Latvia. In the analysed prescriptions, prednisolone was most frequently prescribed in three main combinations: prednisolone tablets–ephedrine hydrochloride (110 prescriptions), prednisolone tablets–ephedrine hydrochloride–adrenaline solution for injection (68 prescriptions), and prednisolone tablets–adrenaline solution for injection–chloramphenicol (18 prescriptions).

Adrenaline was often prescribed by general practitioners and otolaryngologists. Adrenaline solution for injection was used for the preparation of medicines in Latvia. In the analysed prescriptions, adrenaline was most often combined with the same active ingredients as prednisolone. Adrenaline together with ephedrine hydrochloride were prescribed in 93 prescriptions, with prednisolone tablets in 86 prescriptions, with chloramphenicol in 28 prescriptions, with resorcinol in 20 prescriptions, and with hydrocortisone acetate, lidocaine hydrochloride suspension for injection in 18 prescriptions.

General practitioners and otolaryngologists also prescribed a manufactured product of hydrocortisone acetate, lidocaine hydrochloride suspension for injection. In the analysed prescriptions, this suspension was most frequently combined with ephedrine hydrochloride (129 prescriptions). Out of these prescriptions, 113 contained only the said three active ingredients, but another 16 prescriptions had one to three active ingredients added to the combination of hydrocortisone acetate, lidocaine hydrochloride suspension for injection and ephedrine hydrochloride.

The sixth most frequently prescribed active ingredient was dexamethasone. Dexamethasone sodium phosphate solution for injection and dexamethasone tablets were used in the analysed prescriptions. Both

dexamethasone sodium phosphate solution for injection and dexamethasone tablets were most commonly prescribed in combination with ephedrine hydrochloride (125 prescriptions and 26 prescriptions, respectively). Out of this prescriptions, 74 prescriptions contained only these two active ingredients, but 77 prescriptions had another one to two active ingredients added to this combination, most frequently nitrofural (44 prescriptions).

The seventh most frequently prescribed active ingredient was nitrofural. In the analysed prescriptions, nitrofural was most frequently combined with the following active ingredients: ephedrine hydrochloride (75 prescriptions); dexamethasone sodium phosphate solution for injection or dexamethasone tablets (44 prescriptions); hydrocortisone acetate, lidocaine hydrochloride suspension for injection (15 prescriptions); adrenaline solution for injection (12 prescriptions); and sulfanilamide (nine prescriptions).

The next most frequently prescribed active ingredient was chloramphenicol. In the analysed prescriptions of nasal drops, chloramphenicol was most frequently combined with the following active ingredients: adrenaline solution for injection (28 prescriptions); prednisolone tablets (18 prescriptions); ephedrine hydrochloride (11 prescriptions); dexamethasone sodium phosphate solution for injection (nine prescriptions); and resorcinol (nine prescriptions).

Latvian general practitioners and otolaryngologists also prescribed resorcinol. In all the analysed prescriptions of nasal drops containing resorcinol, it was combined with adrenaline solution for injection (20 prescriptions). Seven prescriptions contained only these two active ingredients, but the third active ingredient was prescribed in 13 prescriptions, most frequently chloramphenicol (nine prescriptions).

The tenth most frequently prescribed active ingredient was triamcinolone. Triamcinolone tablets were used for the preparation of medicines in Latvia. In all the analysed prescriptions of nasal drops, triamcinolone was combined with

ephedrine hydrochloride (15 prescriptions). Of the 15, 14 prescriptions were supplemented by adrenaline solution for injection.

Comparison of active ingredients and combinations most frequently used in preparation of nasal drops with German, USA, and Australian formulations

During the research, I found out that the USP Compounding Compendium does not include nasal drop formulations,[24] therefore the active ingredients prescribed in Latvia and their combinations could be compared only with the German and Australian formulations.

The DAC/NRF includes the following standardized nasal drop formulations for use in rhinology: sodium chloride isotonic (0.9 %) and hypertonic (1.5 %) solutions; silver proteinate (2 % and 5 %) solutions.[23]

As already mentioned above, nasal drops with silver proteinate are widely prescribed in Latvia. Unlike Germany, no 5 % solution was prescribed in prescriptions of Latvian pharmacies. Latvian otolaryngologists and general practitioners prescribed silver proteinate solutions with lower concentrations – 1 % and 2 %.

The analysed prescriptions did not contain compositions of solutions with sodium chloride as the only active ingredient, but the manufactured products isotonic and hypertonic seawater solutions are available in the Latvian market. In the prescriptions prescribed by Latvian otolaryngologists and general practitioners, sodium chloride was mainly prescribed with nitrofural (86 prescriptions). Sodium chloride is necessary to improve solubility of nitrofural in water. In the remaining 11 prescriptions, sodium chloride was most probably used for tonicity adjustment. For both of these reasons, sodium chloride was included in the next section of the dissertation on excipients used in the preparation of nasal drops.

The database maintained by the DAC/NRF contains several standardized and verified nasal drop formulations. These formulations also include the active ingredients prescribed in Latvia, but their combinations are different.[27]

The database maintained by the DAC/NRF also includes nasal drop and nasal spray formulations, which are not standardized, but the use of which is permissible evaluating the comments provided in the database. Several compositions use active ingredients prescribed in Latvia (e.g., dexamethasone, adrenaline, ephedrine hydrochloride).[27] The database contains a combination of dexamethasone and adrenaline, which can be found in seven analysed prescriptions of Latvian pharmacies, as well as a combination of dexamethasone and ephedrine hydrochloride, which can be found in 151 analysed prescriptions of Latvian pharmacies.

In Australia, similarly to Germany, there are not many formulations for use in rhinology. The APF includes only two formulations of nasal drops and one formulation of alkaline nasal douche. In nasal drops, ephedrine hydrochloride or phenylephrine hydrochloride is used as the active ingredient. Solution for nasal douche contains sodium hydrogen carbonate and sodium chloride.[25]

As already mentioned above, ephedrine hydrochloride was the most popular active ingredient in nasal drops prescribed by Latvian otolaryngologists and general practitioners. Unlike in Australia, ephedrine hydrochloride was mostly prescribed in combination with other active ingredients and not as the only active ingredient. Phenylephrine hydrochloride was not found in the analysed prescriptions of Latvian pharmacies. Industrially manufactured nasal drops are available in Latvia, where phenylephrine is combined with dimetindene maleate.[73] The combination of sodium hydrogen carbonate and sodium chloride was not found in the analysed prescriptions of Latvian pharmacies. However, there were two prescriptions of nasal drops, where sodium hydrogen carbonate was used as the only active ingredient.

Excipients used in preparation of nasal drops and comparison with German, USA, and Australian formulations

In total, nine excipients (i.e., purified water, ethanol, sodium chloride, peppermint water, boric acid, olive oil, glycerol, liquid paraffin, sunflower oil) were used in the analysed prescriptions prescribed by Latvian otolaryngologists and general practitioners. The prescriptions also included excipients from finished industrially manufactured dosage forms.

The USP Compounding Compendium does not include nasal drop formulations,[24] therefore the excipients prescribed in Latvia were compared only with the German and Australian formulations.

The formulations of nasal drops and nasal sprays included in the DAC/NRF and the database maintained by the DAC/NRF contain several excipients used in Latvia (i.e., purified water, isotonic sodium chloride solution, glycerol, liquid paraffin).[23,27] When viewing the excipients used in Latvia compared to those used in Germany, another detail should be mentioned. Apart for the finished industrially manufactured forms, most of the analysed prescriptions of Latvian pharmacies contained only one excipient – purified water. Unlike in Germany, the excipients necessary for isotonization of nasal drops were rarely added. In Germany, sodium chloride, glycerol, propylene glycol, sorbitol, and glucose are used for isotonization of nasal drops.[74] The APF formulations of nasal drops contain only one active ingredient (ephedrine hydrochloride or phenylephrine hydrochloride). Similarly to Germany, the APF also adds several excipients to avoid adverse effects on the nasal mucosa. For this purpose, the following excipients are used: purified water; sodium chloride; propylene glycol; and preservative chlorobutanol.[25] In Latvia, preservatives were not added, when preparing ephedrine hydrochloride water solutions.

In Latvia, ethanol was prescribed, which does not appear in German formulations. In the analysed prescriptions, ethanol was prescribed to make it easier to crush the tablets. Ethanol was most frequently added to crush prednisolone tablets (101 prescriptions).

Other excipients are also used in Germany, for example, medium-chain triglycerides are used as synthetic oils, hydroxyethylcellulose is used as an organic gelling agent, benzalkonium chloride is used as an antimicrobial preservative, but polysorbate 80 is used as an emulsifier.[27,75]

2.5.2 Semi-solid nasal preparations

In total, 276 semi-solid nasal preparations were prepared based on prescriptions issued by general practitioners and otolaryngologists.

Active ingredients used in preparation of semi-solid nasal preparations and their most common combinations

In total, 14 bulk drug substances and 15 industrially manufactured preparations were used in the preparation of semi-solid nasal preparations.

Of semi-solid nasal preparation prescriptions, 63.41 % (175 prescriptions) contained the same combination of active ingredients, as listed below:

- Sulfanilamide;
- Camphor;
- Adrenaline solution for injection;
- Dexamethasone sodium phosphate solution for injection;
- Ampicillin trihydrate from capsules, and;
- Peppermint oil.

The nasal ointments containing a combination of these active ingredients were prepared in seven analysed pharmacies, which represented four statistical regions. Therefore, the possibility for the prescriptions to be prescribed by one specialist may be excluded.

The dissertation summary considers the 10 most commonly prescribed active ingredients.

The most popular active ingredient in semi-solid nasal preparations was sulfanilamide. In the analysed prescriptions, sulfanilamide was most frequently combined with the following active ingredients: camphor (206 prescriptions); adrenaline solution for injection (193 prescriptions); ampicillin trihydrate from capsules (184 prescriptions); dexamethasone sodium phosphate solution for injection (181 prescriptions); peppermint oil (176 prescriptions); ephedrine hydrochloride (38 prescriptions); sulfathiazole (22 prescriptions); eucalyptus oil (22 prescriptions).

The second most frequently prescribed active ingredient was camphor. In the prescriptions analysed, camphor was most frequently combined with the same active ingredients with which sulfanilamide was combined. Camphor together with sulfanilamide were prescribed in 206 prescriptions, with adrenaline solution for injection in 193 prescriptions, with ampicillin trihydrate from capsules in 181 prescriptions, with dexamethasone sodium phosphate solution for injection in 177 prescriptions, with peppermint oil in 175 prescriptions, with ephedrine hydrochloride in 35 prescriptions, with sulfathiazole in 23 prescriptions, and with eucalyptus oil in 22 prescriptions.

The third most frequently prescribed active ingredient was adrenaline. Adrenaline solution for injection was used for the preparation of medicines in Latvia. Adrenaline was most frequently prescribed in the above-mentioned most common combination, as well as with ephedrine hydrochloride

(21 prescriptions), menthol (15 prescriptions), and prednisolone tablets (13 prescriptions).

Also, dexamethasone sodium phosphate solution for injection, like adrenaline, was most commonly prescribed in the above-mentioned combination. Apart from these active ingredients, dexamethasone sodium phosphate solution was prescribed with 11 other active ingredients, but very rarely, with each of them in four or less prescriptions.

The next most frequently prescribed active ingredient was ampicillin. Ampicillin trihydrate from capsules was used for the preparation of medicines in Latvia. It was most frequently prescribed in the above-mentioned most popular combination, as well as with prednisolone tablets (9 prescriptions). Only a few prescriptions were prescribed with other active ingredients.

The sixth most frequently prescribed active ingredient was peppermint oil. Peppermint oil was prescribed in combination with amoxicillin trihydrate from capsules only in one prescription; in other prescriptions it appeared in the above-mentioned most commonly prescribed combination.

The next most frequently prescribed active ingredient was ephedrine hydrochloride. In the analysed prescriptions, ephedrine hydrochloride was most frequently combined with the following active ingredients: sulfanilamide (38 prescriptions); camphor (35 prescriptions); menthol (29 prescriptions); triamcinolone acetonide ointment or triamcinolone tablets (24 prescriptions); sulfathiazole (23 prescriptions); eucalyptus oil (22 prescriptions); adrenaline solution for injection (21 prescriptions).

The eighth most frequently prescribed active ingredient was menthol. In the analysed prescriptions, menthol was most frequently combined with the following active ingredients: ephedrine hydrochloride (29 prescriptions); adrenaline solution for injection (15 prescriptions); camphor (12 prescriptions);

triamcinolone acetonide ointment or triamcinolone tablets (11 prescriptions); prednisolone ointment or tablets (11 prescriptions).

The next ingredient was triamcinolone. Triamcinolone tablets and triamcinolone acetonide ointment were used in the analysed prescriptions. In all the analysed prescriptions, triamcinolone tablets and triamcinolone acetonide ointment were prescribed in combination with ephedrine hydrochloride (24 prescriptions). Eight prescriptions included only these two active ingredients, but 16 prescriptions had another one to four active ingredients added to this combination, most commonly adrenaline solution for injection (11 prescriptions), menthol (11 prescriptions), and sulfanilamide (10 prescriptions).

Sulfathiazole was prescribed in 23 prescriptions. Out of this prescriptions, 22 prescriptions contained the following combination of active ingredients: camphor–ephedrine hydrochloride–sulfanilamide–sulfathiazole–eucalyptus oil.

Comparison of active ingredients and combinations most frequently used in preparation of semi-solid nasal preparations with German, USA, and Australian formulations

The USP Compounding Compendium does not include semi-solid nasal preparation formulations,[24] therefore the active ingredients prescribed in Latvia and their combinations were compared with the German and Australian formulations.

The DAC/NRF includes an ointment with menthol, which is used in case of rhinitis.[23] In Latvia, nasal ointments containing menthol were also prescribed, but unlike in Germany, in the analysed prescriptions of Latvian pharmacies, menthol was not used as the only active ingredient; in all the prescriptions menthol was prescribed in combination with at least one other active ingredient.

The database maintained by the DAC/NRF includes formulations of semi-solid nasal preparations, which are not standardized, but the use of which is permissible evaluating the comments provided in the database. The formulations contain several active ingredients used in Latvia (e.g., adrenaline, dexamethasone, hydrocortisone, as well as menthol). Like in Latvia, the industrially produced adrenaline solution for injection is used for the preparation. Several formulations of nasal creams, which are included in the database, contain a combination of three active ingredients (i.e., menthol, adrenaline solution for injection, aluminium acetate-tartrate solution).[27] As mentioned previously, the combination of menthol and adrenaline solution for injection can also be found in the analysed prescriptions of Latvian pharmacies.

The APF includes one formulation of nasal paste. The paste contains two active ingredients (i.e., cocaine and adrenaline). This paste is used as a local anaesthetic.[25] In the analysed prescriptions of Latvian pharmacies, only adrenaline was found. Unlike in Latvia, APF uses bulk drug substance rather than industrially manufactured ampoules.[25]

Excipients used in preparation of semi-solid nasal preparations and comparison with German, USA, and Australian formulations

In total, 11 excipients (i.e., soft paraffin, wool fat, citral, olive oil, ethanol, liquid paraffin, sunflower oil, purified water, glycerol, boric acid, hard paraffin) were used in the preparation of semi-solid nasal preparations. The prescriptions also included excipients from finished industrially manufactured dosage forms.

The USP Compounding Compendium does not include semi-solid nasal preparation formulations,[24] therefore the excipients prescribed in Latvia were compared with the German and Australian formulations.

The formulations of semi-solid nasal preparations included in the DAC/NRF and the database maintained by the DAC/NRF contain several excipients used in Latvia (i.e., soft paraffin, wool fat, olive oil, liquid paraffin, purified water).[23,27] One formulation included in the database uses lemon oil; citral is one of its components.[27] Sunflower oil is not found in German formulations, while the database includes a formulation with another vegetable oil (peanut oil).[27]

Other excipients are used in Germany in the preparation of semi-solid dosage forms in addition to the above-mentioned bases, for example, propylene glycol is used as an antimicrobial preservative,[70] medium-chain triglycerides are used as synthetic oils.[75]

As already mentioned above, the APF includes one nasal paste. The following excipients are used in the preparation of the paste: chlorobutanol, liquid paraffin, and soft paraffin.[25]

2.6 Active ingredients used in Latvia, the use of which in the preparation of medicines in Germany is classified as unsafe

Having analysed the compositions prescribed in dermatology and rhinology, several substances were identified, the use of which in Germany was controversial or even unacceptable in certain dosage forms. The DAC/NRF contains information on the substances, the use of which in pharmacy preparations is classified by the Drug Commission of the German Pharmacists as unsafe. Information is available in the DAC/NRF table "Tab. I.5.–2: Substances and formulations, issuing of which is forbidden" (*Tab. I.5.–2: Bedenkliche Stoffe / Rezepturen, deren Abgabe verboten ist*).[23] German pharmacists and physicians are encouraged to consider the information available on the listed substances by conducting a risk/benefit assessment for the individual patient.

The presence of such substances in Latvian prescriptions constitutes a risk to patient safety. Since previously only part of the collected prescriptions was analysed, the relevant substances were searched in all the collected prescriptions (6227 prescriptions). Seven substances were identified, the use of which in Germany is classified as unsafe and is permitted only in individual exceptional cases (Table 2.1).

Table 2.1

Substances, which can be found in the prescriptions issued by Latvian health care professionals, but the use of which in the preparation of medicines in Germany is restricted

No.	Substance	Number of extemporaneous prescriptions, n (%)
1.	Boric acid	1190 (19.11)
2.	Mercuric oxide	116 (1.86)
3.	Sodium bromide	114 (1.83)
4.	Borax	58 (0.93)
5.	Liquified phenol	36 (0.58)
6.	Potassium bromide	11 (0.18)
7.	Formaldehyde solution (35 %)	7 (0.11)

2.7 Problems associated with the prescribing, preparing, and dispensing of extemporaneous preparations in Latvia and recommendations for their prevention

2.7.1 Choice in favour of extemporaneous preparations or industrially manufactured drugs

At present, the Latvian regulatory framework does not stipulate that a pharmacist is allowed to prepare extemporaneous preparations only if they do not have an industrially manufactured analogue. Nevertheless, when analyzing prescriptions prepared in Latvian pharmacies, it has been established that Latvian physicians prescribed only those formulations for which, according to the information provided in the Medicinal Product Register of Latvia, at the time of prescription, no analogue industrially manufactured products were available.

Before prescribing and preparing extemporaneous preparations, the physician and pharmacist should ascertain that a suitable pharmaceutical equivalent with a marketing authorisation is not available on the market.[11,16,33,34,76,77,78] Industrially manufactured drugs are the first choice, as the quality, safety, and efficacy of each industrially manufactured drug are assessed by a competent authority before it is placed on the market.[16,76] If a pharmacist finds that a suitable licensed medicinal product is available on the market, he / she should contact the physician and inform him / her about this possibility before replacing the prescribed extemporaneous composition.[76] A consultation with a physician is important because the physician may have issued an extemporaneous prescription because the patient is allergic to any of the excipients in the industrially manufactured drug.[11]

2.7.2 Beyond-use date of extemporaneous preparations and factors affecting it

As there are no standardized formulations in the official language in Latvia, the pharmacy in which the respective extemporaneous drug was prepared is obliged to assess the composition of the drug and assign an appropriate beyond-use date.[48,57] Generally, drugs prepared in Latvian pharmacies have a shelf life of one – two months.[79]

For formulations, the use of which is evidence-based, the beyond-use dates and storage conditions can usually be found in the relevant information resources. Examples include the following information resources: DAC/NRF; USP Compounding Compendium; APF; Handbook of Extemporaneous Preparation.[19,23,24,25] The existence of such resources allows the physician to prescribe and the pharmacist to prepare the preparation in the amount that the patient will be able to use before the beyond-use date. However, health care professionals should be aware that in-use storage conditions may differ

significantly from those recommended in the literature. In this case, shortening the shelf life should be considered.[34]

It should also be remembered that the packaging can significantly affect the shelf life after first opening.[23] When compiling and entering the data of Latvian prescriptions in the database, the information on packaging was not entered. Analyzing the compositions used in rhinology, it was found out that nasal sprays were not prescribed in Latvian pharmacy prescriptions, only nasal drops, which indicates that the choice of appropriate packaging is also relevant for Latvia. It was also found that excipients for adjusting the tonicity of nasal drops were rarely added.

The DAC/NRF includes sodium chloride solutions of various concentrations for nasal use. It has been stated that, for hygienic reasons, the shelf life of nasal drops is very limited. With nasal sprays, the risk of microbiological contamination is much lower, which allows a longer period of use. The same is true with semi-solid dosage forms. They can be packaged in a tube, jar with screw cap or jar systems with means of a piston system pushed from the bottom can be used. The period of use of semi-solid dosage forms of identical composition may vary considerably depending on the packaging chosen.[23] When choosing a packaging, it should be taken into account that a number of active ingredients are light-sensitive,[66] so it is safer to use light-protective containers.[34]

If a composition is prescribed that is not found in the evidence-based literature, the pharmacist should consider measures to reduce the risks associated with storing such a preparation. For example, granting restricted shelf life and storing it in a cold or cool place.[76] The DAC/NRF states that if the stability of a preparation is in doubt, the period of use should be limited to one month. If necessary, an even shorter period of use may be set for the preparation.[23]

When determining the shelf life, it should be noted that the stability of the preparation depends on many factors, including the risk of microbiological contamination.[34] If such a risk exists, preservatives are usually added.[76] The choice of preservative should take into account the pH range required for its operation. [34] If the physician does not want preservatives to be added to the preparation, this should be indicated in the prescription. In Germany, a pharmacist may not change or add active ingredients in an extemporaneous preparation without the consent of the prescribing physician, but this restriction does not apply to excipients. If a non-standardized preparation is prescribed, pharmacists are advised to evaluate the prescribed composition and, if necessary, improve it, for example by adding buffers or choosing a more suitable base.[76]

2.7.3 Number of active ingredients in extemporaneous preparations

Analysing the prescriptions prescribed by Latvian physicians, it was found out that more than half of the compositions prescribed in dermatology and rhinology contained two or more active ingredients.

When prescribing an extemporaneous prescription, one must be aware that several active ingredients in a single preparation increase the risks of their interaction.[22,78,80] The more active ingredients the preparation contains, the more difficult it is to evaluate and ensure the quality of the dosage form. For this reason, it is recommended that two or more active ingredients are included in one preparation only in duly justified exceptional cases.[80]

2.7.4 Prescription design of extemporaneous preparations

All the analysed prescriptions of Latvian pharmacies indicated the dosage form, names of ingredients, their quantities or concentrations. Abbreviations were rarely used, but sometimes the name of a substance was written as a formula rather than in words. For example, 16 prescriptions used the formula "NaCl" instead of "sodium chloride", four prescriptions used the formula "H2O2" instead of "hydrogen peroxide".

Abbreviations in a prescription can cause errors both in the drug preparation process and in the use of the drugs.[68] The literature contains information on potentially dangerous and error-prone medical abbreviations and symbols. It is not recommended to write substance formulas, instead it is safer to write names with full words.[68,81]

CM Regulations No. 175 on manufacture, storage and writing of prescription forms stipulate that instructions to the patient shall indicate the doses, when, how often and how the medicinal products shall be used.[82] Analyzing the prescriptions written by Latvian physicians, it was found that the directions for use of most prescriptions intended for dermatological indications were general. The most common text in the section on use was "Externally" or "For external use".

When writing a prescription, it is important to give precise directions for use to improve patient adherence.[68,78] The literature has suggested a template that could be useful for physicians in writing directions for use: Verb – Quantity – Dosage Form – Route – Frequency.[68] When prescribing cutaneous preparations, it is recommended to indicate not only the part of the body on which the patient should apply the respective preparation, but also to indicate how thick a layer should be applied.[76] Vague instructions for use such as "Take as directed" are not recommended.[68] This information is necessary for the pharmacist for several reasons. Firstly, when receiving a prescription,

the pharmacist must carry out a safety assessment of the prescription – assess the prescribed composition of the drug, as well as check that the doses are not exceeded.[68,48] Secondly, communication between pharmacists and patients receiving extemporaneous drugs is extremely important.[11,33] Accurate medical instructions must be available to the pharmacist to provide appropriate consultation for patients or their caregivers on the use of the prepared drugs.[68]

Until 2018, printed prescriptions were mostly used in Latvia. Today, thanks to the e-health system, the number of printed prescriptions has decreased significantly and most physicians prescribe electronic prescriptions. The printed prescription form does not have a separate section for refills.[82] In the analysed prescriptions of Latvian pharmacies, if the extemporaneous preparation was to be prepared repeatedly, physicians indicated it right below the instructions for use or in the upper right corner of the prescription next to the prescription number. If the prescription is prescribed electronically, the physician has the opportunity to indicate the number of preparations and when dispensing the preparation, the pharmacist may indicate that the prescription has been dispensed partly.

2.7.5 Bulk drug substances and industrially manufactured dosage forms in extemporaneous preparations

Analyzing the prescriptions written out by Latvian health care professionals, it has been found that Latvian physicians widely prescribe industrially manufactured dosage forms in the composition of extemporaneous preparations, including tablets and capsules. For example, omeprazole capsules have been prescribed for the preparation of oral powders. The granules of the capsules in question have an enteric coating, which means that it is not allowed to crush them.[83] There have also been cases where a physician has prescribed a bulk drug substance, but the pharmacy replaced it with an industrially

manufactured dosage form. Triamcinolone tablets were found in the analysed prescriptions. These tablets were used in the preparation of semi-solid dosage forms for dermatological application, but this chemical form of triamcinolone has no effect on the skin.[76]

When prescribing and preparing a drug, it should be borne in mind that the stability and effectiveness of the drug may depend on the use of a bulk drug substance or manufactured dosage forms. When using tablets and capsules in the preparation of drugs, one should be aware of the potential risks. Firstly, one should remember that excipients in tablets and capsules may increase or decrease the stability of preparations. Secondly, one must make sure if it is allowed to crush or open the tablets and capsules. For example, crushing or opening modified-release tablets and capsules affects the bioavailability and stability of the active ingredients.[34] Whereas, crushing of enteric-coated tablets leads to damage to the protective coating, which may reduce the effectiveness of the active ingredient.[84,85] Third, if the tablet needs to be split, one should be aware that it can lead to large dose deviations or weight losses. To reduce dose deviations, it is recommended to use a splitting device instead of performing splitting manually or with a kitchen knife.[86]

It is also important to pay attention to the chemical form of the active ingredient. The effectiveness of the prepared drug may depend on the chemical form of the active ingredient. For example, it is known that triamcinolone has no effect on the skin, whereas its ester does.[76]

2.7.6 Extemporaneous preparations for children

When compiling data on Latvian prescriptions, patient data, including age, were not entered into the database, therefore I do not have information on patient age. However, paediatricians prescribed 163 prescriptions or 2.62 % of

all the analysed prescriptions. Also, there are children among the patients of general practitioners, dermatovenerologists, and otolaryngologists.

The active ingredients and excipients must be chosen with great care when prescribing and preparing drugs for children. For example, it is not recommended to administer preparations containing salicylic acid on the skin of children younger than two years.[76] Also, it is not recommended to administer menthol and camphor to the nostrils of infants.[23,70,87] Salicylic acid, menthol, and camphor have been identified in the prescriptions of semi-solid dosage forms prescribed by Latvian paediatricians. Ointments containing salicylic acid were prescribed by paediatricians in eight prescriptions, while menthol was prescribed in two prescriptions and camphor in 15 prescriptions.

It should be understood that the use of an excipient in adults does not mean that the excipient is safe for children.[34] Improperly selected excipients may contribute to the development of adverse reactions that were not observed in adults or were observed to a much lesser extent.[77]

For children, doses are calculated based on the body weight or surface area.[34] When prescribing drugs with active ingredients with a narrow therapeutic index, it is recommended to calculate and adjust doses according to the body surface area.[76]

In order to improve the adherence of the paediatric population, it is important to pay attention to the taste of the preparation.[88] Flavoured syrup vehicles for the preparation of oral solutions and suspensions are available on the market to mask unpleasant tastes.[89]

2.7.7 Proper dosing when using extemporaneous preparations

Analyzing the prescriptions prescribed by Latvian physicians, it was found that the directions for use of all oral solutions containing herbal tinctures and bromides, as well as calcium chloride and sodium thiosulphate were

indicated in spoons (teaspoons, dessert spoons and tablespoons) and not in millilitres. This suggests that it was intended to use some kind of kitchen spoon instead of an accurate measuring device.

When dispensing an oral solution, the pharmacist must make sure that the patient or their caregiver is able to operate the measuring device and that the correct dose will be taken each time.[34] One of the information resources designed to educate parents about their child's medicines emphasizes that a kitchen teaspoon should not be used as a measuring device for liquid medicines. Parents are advised to consult a pharmacist to get an oral syringe or medicine spoon.[90] It should be noted that it is not possible to ensure that the required volume is measured with all dosing devices. Particular attention should be paid to the measurement of small volumes, making sure that it can be done accurately.[34]

3 Discussion

This study investigated and described the current situation in the field of extemporaneous preparations in different regions of Latvia for the first time. After the analysis of previously unpublished data of the State Agency of Medicines (SAM), the first comprehensive report on the sales of extemporaneous preparations in all regions of Latvia was provided. Analyzing the Latvian regulatory enactments that regulate the preparation of medicinal products in pharmacies, their compliance with the requirements of the Resolution of the Committee of Ministers of the Council of Europe was assessed for the first time. Data on extemporaneous prescriptions were collected from 17 community pharmacies representing all six statistical regions of Latvia. The study identified which health care professionals issue extemporaneous prescriptions most often, which dosage forms are the most popular, and how many active ingredients are most often combined in different dosage forms. In order to assess the conformity of the extemporaneous preparations in Latvia with modern European and global practice, the active ingredients identified in the prescriptions, their combinations, and excipients were compared for the first time with the professional literature of Germany, the USA, and Australia – DAC/NRF, USP Compounding Compendium, APF. Practical recommendations were provided to Latvian health care professionals in order to promote safe and effective prescribing, preparation, and dispensing of extemporaneous preparations.

3.1 Differences in Latvian regulatory enactments regulating compounding of extemporaneous preparations in pharmacies and in the recommendations of the Resolution of the Committee of Ministers of the Council of Europe

The Latvian regulation does not include all paragraphs of the Resolution re-adopted in 2016. Most of the paragraphs of the Resolution are described in Latvian regulatory enactments only partially. This may be explained by the fact

that in the majority of cases CM Regulations regulating preparation of medicinal products in a pharmacy were adopted before the adoption of the Resolution. Time is required to introduce changes to currently applicable regulations. Similar data were also obtained in the survey regarding the impact of the Resolution adopted in 2011 on the legislation of 12 European countries. Although most of the countries did not fulfil all paragraphs of the Resolution, the researchers found that adapting national legislation to the Resolution was a long-term process and concluded that the overall results of the survey indicated a clear commitment by countries to implement the Resolution's recommendations. The paragraphs, which are fully described in Latvian regulatory enactments, are mainly described also in other European countries. For example, Belgium, the Czech Republic, Denmark, Finland, Ireland, Italy, the Netherlands, Poland, Portugal, Serbia, Switzerland, and the United Kingdom like Latvia comply with recommendations mentioned in paragraph "Labelling". The paragraph of the Resolution named "Marketing authorisation" is not included in the Latvian regulatory enactments. Other European countries face a similar situation. The above-mentioned survey revealed that only one of 12 countries included in the survey partially implemented recommendations about marketing authorisation.[35] In the Netherlands, formulations of extemporaneous preparations must be registered with the Dutch Medicines Agency.[91] According to the Dutch Medicines Act, all medicines available on the Dutch market must be evaluated for efficacy, safety, and quality. The assessment is carried out by the Dutch Medicines Board. However, there are exceptions, registration is not mandatory if the pharmacist prepares medicinal products on a small scale.[35]

3.2 Prevalence of extemporaneous compounding in Latvia and Europe

In Latvia, more than half (50.07 %) of community pharmacies have a special operation condition "preparation of medicinal products in the pharmacy" in the annex to their licence.[40] The share of community pharmacies compounding extemporaneous preparations varies across European countries. Unlike in Latvia, all community pharmacies in Germany compound extemporaneous preparations.[30] In Finland and Portugal, as in Germany, all community pharmacies are required to have a laboratory for pharmaceutical compounding.[29,92] In Spain, most community pharmacies also compound non-sterile extemporaneous preparations.[92] While the compounding of extemporaneous medicinal products in Denmark is centralized in three community pharmacies.[31]

Sales volume of extemporaneous preparations in Latvia in community pharmacies is low (0.65 %) compared to industrially manufactured medicinal products. Unfortunately, data on the volume of extemporaneous preparations in other countries are not widely available and not directly comparable. The volume of extemporaneous preparations is expressed both as a part of the prescriptions received in pharmacies and as a part of all sold industrially manufactured medicinal products. It is only possible to conclude that, similarly, in other European countries, extemporaneous preparations have a small market share, despite the number of pharmacies offering this service. For example, extemporaneous preparations dispensed in Finland account for 0.5 % of all medicines sold.[93] Also in Spain, non-sterile extemporaneous preparations account for only about 2 % of all the medicines dispensed based on prescriptions. The situation is similar in the Netherlands, where extemporaneous preparations accounted for around 3.4 % of the analysed prescriptions from 79 community pharmacies.[92]

The sale of extemporaneous preparations took place mainly in Riga, the capital of Latvia. This can be explained by general trends. EU countries have also seen an increase in urban population over the last 50 years. According to Eurostat, 72 % of the EU population lives in cities, of which 41 % live in large cities.[94] The situation in Latvia is no different from the EU – at the beginning of 2017 the largest number of Latvian residents lived in Riga (32.9 %).[95] Riga also employs the largest number of physicians – 62 % of the total number of physicians. This indicator is significantly lower in other regions (6–9 %).[96]

3.3 Health care professionals who prescribed extemporaneous preparations in Latvia, Europe, and USA

The total number of the pharmacies (17) and extemporaneous prescriptions (6227) shows the extemporaneous preparation prescribing trends in Latvia. The majority of the extemporaneous prescriptions were from dermatovenereologists, general practitioners, and otolaryngologists. Similar data were obtained in Slovakia, where the majority of the extemporaneous preparations were prescribed by the same health care professionals as in Latvia: general practitioners, dermatologists, and otolaryngologists.[97] Also, in Germany, according to an analysis of 1.9 million extemporaneous prescriptions, they were mainly prescribed by dermatologists and general practitioners. Dermatologists prescribed more than half of all the prescriptions (53.6 %). Contrary to Latvia, otolaryngologists were not among the physicians who prescribe extemporaneous preparations most often.[1] Dermatologists are also the health care professionals that prescribe extemporaneous preparations most often in the USA.[98] Naturally, the most common extemporaneous dosage forms in the USA and Germany are dosage forms for topical application, likewise in Bulgaria and Netherlands.[1,92,98,99] In Latvia, the main extemporaneous preparation prescribers were dermatovenerologists. Accordingly, also in Latvia, topical dosage forms

were prescribed more often; powders and solutions for oral use were prescribed less frequently.

3.4 Issues for discussion in the compositions of extemporaneous prescriptions prescribed by dermatovenerologists and their possible solutions

The results of the survey show that Latvian dermatovenerologists prescribe both the active ingredients currently used in Germany, Australia, and the USA, and the active ingredients, the use of which in dermatology is subject to discussions. For example, boric acid can be used in Germany only as an excipient for preparation of individual non-dermatological dosage forms.[23] After topical application of boric acid, excretion is slow and causes the risk of cumulative toxicity, and the effect of boric acid in nontoxic concentrations is controversial.[100] In Latvia, boric acid is widely prescribed in the composition of dermatological dosage forms. The situation is similar also in other European countries, where boric acid can be found in the composition of several topical products. In the composition of individual extemporaneous formulations used in Hungary for dermatological indications, boric acid and borax are prescribed as active ingredients.[101] In the Czech Republic, boric acid preparations are also widely used in dermatology, where solutions and ointments containing boric acid are available on the market.[100] To be noted, Italy has industrially manufactured antiseptic solutions with boric acid, but Poland produces powder, where boric acid is used as one of the active ingredients.[102] Nevertheless, there have been reports of adverse reactions following topical application of boric acid preparations.[100]

Sulfathiazole can be mentioned as another substance subject to discussion, which is one of the most common active ingredients used in suspensions in Latvia, while, in the USA, sulfathiazole is classified as an unsafe

or not effective drug product and is included in the Food and Drug Administration Negative List. Therefore, in the USA, sulfathiazole may not be used for human drug compounding.[21] The situation is similar in Germany, where the sulfathiazole monograph was removed from the DAC/NRF more than a quarter of a century ago.[23]

In Latvia, topical dosage forms containing two or more active ingredients were widely prescribed. Up to seven active ingredients have been prescribed in the analysed prescriptions. Similar data were obtained in Lithuania, where 48 % of all the prescriptions analysed in the particular study contained two or more active ingredients.[103] A large number of active ingredients causes the risk that the prescribed ingredients interact among themselves or with any of the excipients.[22] Therefore, standardized formulations mainly contain one to two active ingredients, as we can see from the analysis of the standardized compounded preparation monographs included in the DAC/NRF, USP Compounding Compendium, and APF.[23,24,25]

Despite the relatively large diversity of active ingredients in dosage forms prescribed by Latvian dermatovenerologists, the range of excipients is not wide. For example, in suspensions and topical solutions for antimicrobial purposes, only ethanol and glycerol were predominantly used. German, USA, and Australian professional literature offers a much broader range of antimicrobial preservatives for topical preparations; for instance, other monovalent alcohols such as isopropyl alcohol and benzyl alcohol are offered in addition to ethanol, as well as propylene glycol.[23,25,68] Oral solutions prepared in Latvian pharmacies contained only one vehicle — purified water. For antimicrobial reasons, it is essential to protect prepared oral solutions, whereby antimicrobial preservatives must be added to preparations.

The dissertation revealed that Latvian dermatovenerologists frequently prescribed industrially manufactured finished dosage forms (ointments, creams, solutions, oral capsules, and tablets) in the composition of extemporaneous preparations. The USA and other European countries, for example, the Czech Republic, also have such practices.[21,104] When using a manufactured drug product as a source of active ingredient, it should be taken into account that all commercially available medications also contain excipients, which may affect the efficacy, safety, and stability of the final compounded preparation.[21] Since industrially manufactured preparations create additional risks, several countries implemented measures to reduce the use of these preparations in extemporaneous compounding. For example, a project was implemented in the Czech Republic, the purpose of which was to provide pharmacies in the Czech Republic with bulk drug substances necessary for the preparation of extemporaneous medicines, which were absent on the national market. The project envisaged the possibility to purchase bulk drug substances in small packages, which is very important for the pharmacies preparing medicines in small amounts.[104]

Since compositions prescribed by Latvian dermatovenerologists are often not standardized, prescriptions should be carefully evaluated by pharmacists before preparation to eliminate incompatibility. Not only Latvian dermatovenerologists prescribe extemporaneous medicines, compositions of which are not standardized. Although Germany and the USA have standardized compounded preparation monographs, physicians still prescribe extemporaneous prescriptions for individual patients not included in the compendium or formulary.[9,105] Such formulations require special attention of pharmacists and physicians. German literature describes several examples, when incompatibility of ingredients was identified as a result of cooperation between a pharmacist and a dermatovenerologist, and the prescribed composition was corrected.[22,106]

Analysed prescriptions show deviations of prescription trends from the USA, German, and Australian norms. This can be partially explained by history of Latvia. In Latvia, as in the former Union of Soviet Socialist Republics (USSR), until the collapse of the USSR, the preparation of extemporaneous medicines was carried out in accordance with uniform procedures and regulatory enactments adopted by the USSR. 30 years passed since Latvia regained independence, but some active ingredients and combinations of active ingredients mentioned in books of that time are still prescribed in Latvia, such as suspensions where sulfathiazole is combined with boric acid and sulfur.[107] Historically used substances could be associated with health risks. Another reason is the limited import of some medicines. For instance, an industrially manufactured ointment with two active ingredients (salicylic acid and mometasone furoate) was not available on the Latvian market for some time, which is why specialists prescribed an extemporaneous composition, which consisted of industrially manufactured mometasone furoate ointment and salicylic acid. Another possible reason is the differences in offered information sources, because Latvia, unlike Germany, Australia, and the USA, does not have any officially approved standardized compounded preparation monographs.

In order to ensure safe and effective use of extemporaneous medicines for Latvian patients, it is necessary to prescribe those active ingredients and combinations of active ingredients, for which their use in dermatology is evidence-based. Adopting the German, USA, and Australian experiences would be the first step in the creation of standardized formulations. Since the dermatovenerologist and the pharmacist are jointly responsible for the quality of prescribed and prepared medicines, it is feasible to organize seminars and other further education activities, where pharmacists and dermatovenerologists would be educated on standardized, proven extemporaneous formulations.

3.5 Peculiarities of extemporaneously compounded nasal preparations prescribed by Latvian otolaryngologists and general practitioners in comparison with European, USA and Australian formulations

Latvian otolaryngologists and general practitioners, similarly to dermatovenerologists, prescribe such active ingredients and combinations of active ingredients, which cannot be found in the German, USA, and Australian literature. Sulfanilamide should be mentioned as an example. In Latvia, this active ingredient was prescribed most often in the composition of semi-solid nasal preparations.

However, silver proteinate, which is widely prescribed as part of nasal drops in Latvia, is also used in Germany for the preparation of nasal drops. The combination of silver proteinate with adrenaline solution for injection, which was prescribed in several analysed prescriptions of Latvian pharmacies, raises discussions. Sodium chloride is one of the excipients in adrenaline solutions for injection.[108] In this case, an interaction between silver proteinate and chloride ions is possible, as a result of which the dosage form does not meet the quality requirements. When examining silver proteinate nasal drops, it is also important to mention excipients. As discussed previously, Latvia uses only purified water for the preparation of these drops, while Germany adds glycerine for isotonization of drops. Nasal drops must be prepared to be isotonic with body fluids to reduce damage to nasal mucosa.[21,109] This problem is typical for Latvia because excipients for adjusting the tonicity were not added frequently when preparing other nasal solutions. For example, prescriptions containing only two components – ephedrine hydrochloride and purified water – were prescribed by Latvian otolaryngologists and general practitioners. The Australian APF contains a nasal drop formulation, in which sodium chloride, chlorobutanol, and propylene glycol are added in addition to the above ingredients.[25] British literature also includes a nasal drop formulation with ephedrine hydrochloride.

This formulation is similar to the Australian formulation, the following excipients are used: purified water, sodium chloride and chlorobutanol.[110]

Several active ingredients used in Latvia should be prescribed with considerable caution to small children. An example is camphor, which is included in the analysed extemporaneous formulations and also in several manufactured inhaled nasal decongestant preparations. German and British literature emphasizes that camphor preparations should not be used for the treatment of nasal mucosa of infants because they may cause the immediate collapse of nostrils.[70,87] Another example is menthol. Preparations containing menthol should not be administered to the nostrils of infants, as menthol may cause breathing disorders.[23,87] Upon analyzing prescriptions provided by Latvian pharmacies, it was found that no patient data had been entered in the database that was created by author. Therefore, I do not have information about the age of patients, but since camphor and menthol are widely prescribed, it would be useful to remind physicians and pharmacists during continuing education activities about age restrictions for the use of these active ingredients.

In the prescriptions issued by Latvian otolaryngologists and general practitioners, similarly to the prescriptions of Latvian dermatovenerologists, industrially manufactured dosage forms were widely prescribed. Use of systemic medicines on skin and mucous membranes is subject to discussions. On the one hand, when prescribing preparation locally, the risk of systemic side effects reduces. On the other hand, studies are necessary to understand whether the use of systemic medicines on skin and mucous membranes is efficient.[111]

The nasal preparations prescribed by otolaryngologists and general practitioners were analysed in this dissertation. Physicians in both specialities prescribed nasal preparations to treat rhinologic diseases. In other countries (e.g., the USA, Germany), nasal preparations are used not only for ear, nose, and throat disorders, but also for other indications. For example, the USA literature

describes the preparation of fentanyl citrate nasal spray for analgesia in oncology.[21,112] Presumably, the use of nasal preparations for a systemic effect will develop further. Several studies have been described studying the possibility of using different psychoactive drugs intranasally, such as prochlorperazine.[113]

It is important to select the appropriate packaging for nasal preparations. The period of use of the preparations after their first opening depends on its packaging. For example, the sodium chloride solutions included in the DAC/NRF have a significantly different shelf life depending on the type of packaging. If nasal drops are prepared, then the period of use is only two weeks. However, if a nasal spray is prepared, then the period of use is extended to six months.[23]

3.6 Future perspectives of medicinal product preparation

Although I have repeatedly mentioned the need for uniform standards and conditions in the field of medicinal product preparation in this dissertation, it also has its downsides. Aiming to achieve uniform standards in Europe and, in part, in the world, could lead to the disappearance of medicinal product preparation, as it has already happened in many pharmacies in the USA. In recent years, there has been a centralization of laws and standards in the USA in the field of extemporaneous drug preparation. Many pharmacies in the USA stopped compounding medicinal products because the USA agencies and regulators set requirements for the preparation of extemporaneous preparations that are almost identical to GMP requirements. Pharmacies do not have the ability to meet such requirements and ensure preparation of the medicinal products that the patients need. This directly affects millions of people in the USA, especially those living outside the large cities. For this reason, many states currently accept the requirements of the Pharmacopeia for extemporaneous preparations only partially and allow their modifictions.[114] This step helps keep the preparation of

medicinal products in the USA pharmacies, because the oldest pharmacy function still justifies its existence in the 21st century. Medicinal product preparation has proved its worth during the COVID-19 pandemic, when pharmacies around the world were compounding hand sanitizers, as well as the industrially manufactured medicinal products missing on the market. The formulations of hand sanitizers published by the World Health Organization (WHO) in 2009 became popular during the COVID-19 pandemic and were used in many countries in the spring of 2020 to fill the global shortage of these products.[115] The WHO had specified pharmacists as producers of these products and pharmacies as one of the possible production sites.[116] Such products were prepared in Latvian pharmacies, too.[117] On March 27, 2020, the Food and Drug Administration (FDA) published the compositions of hand sanitizers for the USA pharmacists based on WHO recommendations.[2] In addition to the need to prepare hand sanitizers during the pandemic, the preparation of oral suspensions from industrially manufactured tablets has also been reported in the USA. In connection with COVID-19, mostly oral hydroxychloroquine suspensions from tablets were prepared in the spring of 2020. Saccharin solutions, which are needed to test masks (FIT testing for N95 masks) in health care facilities, were also prepared in the USA pharmacies.[2]

In recent years, extemporaneous preparations have been used in Europe and America to provide treatment to patients in need of orphan drugs. In Belgium, for example, standardized formulations for orphan active ingredients (OAIs) are being developed. In 2019, a study was published in which Belgian researchers described standardized formulations with seven orphan active ingredients. Particular attention was paid to the choice of orphan active ingredients. The ingredients were selected based on the list approved by the Belgian National Formulary commission. Solutions and capsules for oral use containing the orphan active ingredients were prepared. Shelf life and optimal

storage conditions were determined for the prepared medicinal products.[118] Extemporaneous preparations may also play the role of orphan dosage form. For example, in 2020, Argentine researchers published a study evaluating different strategies for preparing sildenafil citrate liquid dosage form for oral use in children. This active ingredient is used to treat pulmonary hypertension in children, but there is a lack of industrially manufactured dosage forms for children. Particular attention was paid to the excipients in order to provide a taste that promotes patient adherence as well as to allow the preparations to be used by diabetic patients.[119]

Conclusions

1. Latvian regulatory enactments on compounding of extemporaneous preparations complies with the following paragraphs of the Resolution of the Committee of Ministers of the Council of Europe: “Labelling”; “Authorisation for pharmacies or licences for companies making preparations for pharmacies”; and “Communication and information to patients”. The following paragraphs are only partially described in Latvian regulatory enactments: “Added value of pharmacy preparations and responsibilities of health care professionals”; “Preparation process”; “Product dossier”; “Compliance with pharmacopoeial requirements”; “Transparency and safety”; “Distribution of pharmacy preparations”. The following paragraphs of the Resolution are not described: “Marketing authorisation”; “Reconstitution of medicinal products in health care establishments”. The full implementation of the Resolution is time consuming, but there are a number of activities that are relatively easy to implement and nonetheless effective, such as the implementation of the PIC/S GPP Guide in Latvian national legislation and the requirement to prepare extemporaneously only those medicinal products that have no industrially manufactured analogues on the national market.
2. The service “preparation of medicinal products in the pharmacy” is offered in all statistical regions of Latvia. The SAM received reports on sales of extemporaneous preparations from 36.51 % of all community pharmacies, which indicates the demand for this service. Most of the extemporaneous preparations are compounded in the Riga statistical region (78.93 %) and amounts in other regions are considerably smaller.
3. Most extemporaneous prescriptions were issued by dermatovenerologists, general practitioners, and otolaryngologists. Extemporaneous dosage forms for topical use were most commonly prescribed. More than half of topical

preparations prescribed by dermatovenerologists contained two or more active ingredients. More than 70 % of extemporaneous preparations for intranasal use (nasal drops and nasal ointments) prescribed by otolaryngologists and general practitioners contained two or more active ingredients.

4. The analysed prescriptions of Latvian dermatovenerologists, otolaryngologists, and general practitioners contained active ingredients currently used in Germany, the USA, and Australia, as well as active ingredients, the use of which in Germany, the USA and Australia is limited and is permissible only in exceptional cases. In the analysed prescriptions, along with bulk drug substances, industrially manufactured preparations were also used, such as ointments, creams, solutions, suspensions, tablets, and capsules.
5. The excipients most commonly used in the analysed prescriptions of Latvian pharmacies can also be found in Germany, the USA, and Australia. The German, USA, and Australian information sources used in the study (DAC/NRF, USP Compounding Compendium, APF) offer a wider range of excipients compared to Latvia. There were not many excipients in the extemporaneous dosage forms of Latvian pharmacies, but their numbers significantly increased in prescriptions, which used industrially manufactured preparations such as tablets, creams, and ointments.
6. The main problems in prescribing and preparing extemporaneous preparations in Latvia are related to the prescription design, the number of active ingredients in one preparation, the use of industrially manufactured medicinal products instead of the bulk drug substances, selecting appropriate packaging and measuring devices, and the determination of the shelf life.

7. In order to improve the safety of Latvian patients, the attention of health care professionals should be drawn to the relevant problems and possible solutions thereto using the experience of other countries.

Publications and reports on research topic

Publications

Publications in international peer-reviewed scientific journals:

1. **Kiselova, O.**, Maurina, B., Sidlovska, V. 2021. Safety aspects of extemporaneous prescriptions prescribed by Latvian healthcare specialists. *International Journal of Pharmaceutical Compounding*. 25(4), 288–295.
2. **Kiselova, O.**, Maurina, B., Sidlovska, V. 2020. Analysis of extemporaneously compounded nasal preparations prescribed by Latvian otorhinolaryngologists and general practitioners and comparison with German formulations. *International Journal of Pharmaceutical Compounding*. 24(6), 491–500.
3. **Kiselova, O.**, Maurina, B., Sidlovska, V. 2020. Analysis of extemporaneous prescriptions prescribed by dermatovenerologists in Latvia and comparison with standardized compounded preparation monographs of Germany and the USA. *Medicina*. 56(1), 29.
4. **Kiselova, O.**, Maurina, B., Sidlovska, V., Zvejnieks, J. 2019. The extent of extemporaneous preparation and regulatory framework of extemporaneous compounding in Latvia. *Medicina.* 55(9), 531.
5. **Kiselova, O.**, Maurina, B., Sidlovska, V., Rogovska, I. 2019. Trends of extemporaneous drug prescription in Latvia in 2017. *International Journal of Pharmaceutical Compounding*. 23(3), 245–249.

Reports (theses, posters, and oral reports)

International scientific conferences:

1. **Kiseļova, O.**, Mauriņa, B., Šidlovska, V. 2019. Research on combinations of substances, found in Latvia, and their possible compatibility in extemporaneous dosage forms for dermatology. *RSU International Research Conference "Knowledge For Use In Practice"*. Riga, Latvia, 01.–03.04.2019. Poster and thesis.
2. **Kiselova, O.**, Maurina, B., Sidlovska, V. 2018. Extemporaneous medicine prescribing trends in Latvia. *78th FIP World Congress of Pharmacy and Pharmaceutical Sciences*. Glasgow, the United Kingdom, 02.–06.09.2018. Poster and thesis.
3. **Kiseļova, O.**, Mauriņa, B., Šidlovska, V. 2018. Nasal drops in extemporal prescriptions – report for 6 Riga pharmacies. *BaltPharm Forum*. Tartu, Estonia, 14.04.2018. Poster and thesis.

4. **Kiseļova, O.**, Mauriņa, B., Čulkstena, S., Šidlovska, V. 2017. Qualitative analysis of extemporaneous preparations in "Dzirciems" pharmacy. *BaltPharm Forum*. Jurmala, Latvia, 28.–30.04.2017. Poster and thesis.

Local scientific conferences:

1. **Kiseļova, O.**, Mauriņa, B., Šidlovska, V. 2018. Palīgvielas ekstemporālajā receptūrā. *RSU zinātniskā konference*. Riga, Latvia, 22.–23.03.2018. Oral report and thesis.
2. **Kiseļova, O.**, Čulkstena, S., Mauriņa, B., Šidlovska, V. 2017. Ekstemporāli pagatavoto zāļu nepieciešamība Latvijas aptiekās. *RSU zinātniskā konference*. Riga, Latvia, 06.–07.04.2017. Poster and thesis.

Bibliography

1. Staubach, P., Salzmann, S., Peveling-Oberhag, A., Weyer, V., Zimmer, S., Gradl, G. and Lang B. M. 2018. Extemporaneous formulations in Germany - relevance for everyday clinical practice. *J Dtsch Dermatol Ges*. 16(5), 566–574. Available from: doi: 10.1111/ddg.13519 [viewed 24.04.2021.].

2. McElhiney, L. F. 2020. Pharmacies on the frontline: responding to the COVID-19 pandemic. *IJPC*. 24(4), 287–295.

3. Pramar, Y. V., Mandal, T. K., Bostanian, L. A., Le, G., Morris, T. C. and Graves, R. A. 2020. Physicochemical stability of compounded allopurinol suspensions in PCCA Base, SuspendIt. *IJPC*. 24(5), 413–419.

4. Lafuente, Y., García, M. C. and Jiminez-Kairuz, A. 2019. Extemporaneous indomethacin oral suspension prepared from injectable ampules for therapy in premature infants and pediatric patients. *IJPC*. 23(4), 324–331.

5. Falconer, J. R. and Steadman, K. J. 2017. Extemporaneously compounded medicines. *Aust Prescr*. 40(1), 5–8. Available from: doi: 10.18773/ austprescr.2017.001 [viewed 24.04.2021.].

6. Kristina, S. A., Wiedyaningsih, C., Widyakusuma, N. N. and Aditama, H. 2018. Profile and determinants of compounding services among pharmacists in Indonesia. *Asian Journal of Pharmaceutics*. 12(3), S966–S970.

7. Yusuff, K. B. 2019. Extent of extemporaneous compounding and pattern of prescribing and use of extemporaneous medicines in a developing setting. *Journal of Pharmaceutical Health Services Research*. 10(2), 255–260. Available from: doi: 10.1111/jphs.12297 [viewed 24.04.2021.].

8. Staubach, P., Melhorn, S., Hünerbein, A. und Peveling-Oberhag, A. 2016. Neue Entwicklungen der Magistralrezepturen [New developments in extemporaneous formulations]. *Hautarzt*. 67(10), 833–844. Available from: doi: 10.1007/s00105-016-3868-1 [viewed 24.04.2021.].

9. Sherr, Z. and Karara, A. H. 2014. Evaluation of the most frequently prescribed extemporaneously compounded medications in a rural setting: A case study from the Delmarva Peninsula. *IJPC*. 18(6), 462–468.

10. Mohiuddin, A. 2019. Extemporaneous compounding: cautions, controversies and convenience. *IJMHS*. 9(1), 252–264. Available from: doi: 10.15520/ ijmhs.v9i1.2420 [viewed 26.04.2021.].

11. Pharmacy Board of Australia. 01.08.2017. Guidelines on Compounding of Medicines. *Codes, Guidelines and Policies of the Pharmacy Board of Australia*. Available from: https://www.pharmacyboard.gov.au/codes-guidelines.aspx [viewed 04.05.2021.].

12. DAC/NRF. 2021. DAC/NRF: English version. *DAC/NRF*. Available from: https://dacnrf.pharmazeutische-zeitung.de/index.php?id=28 [viewed 04.05.2021.].

13. Zāļu valsts aģentūra. 2021. Zāles lietošanai līdzjūtības dēļ. *Zāļu valsts aģentūra – industrijai*. Available from: https://www.zva.gov.lv/lv/industrijai/zalu-registracijas-apliecibu-ipasnieki/pirms-registracijas/zales-lietosanai-lidzjutibas-del [viewed 30.04.2021.].

14. Logrippo, S., Ricci, G., Sestili, M., Cespi, M., Ferrara, L., Palmieri, G. F., Ganzetti, R., Bonacucina, G. and Blasi, P. 2017. Oral drug therapy in elderly with dysphagia: between a rock and a hard place! *Clin Interv Aging.* (12), 241–251. Available from: doi: 10.2147/CIA.S121905 [viewed 26.04.2021.].

15. Gudeman, J., Jozwiakowski, M., Chollet, J. and Randell, M. 2013. Potential risks of pharmacy compounding. *Drugs R D*. 13, 1–8. Available from: doi: 10.1007/s40268-013-0005-9 [viewed 26.04.2021.].

16. Pharmaceutical Society of Ireland. 01.06.2015. Guidance for Pharmacists on Extemporaneous Dispensing. *Pharmaceutical Society of Ireland*. Available from: https://www.thepsi.ie/gns/Pharmacy_Practice/practice-guidance.aspx [viewed 04.05.2021.].

17. The Pew Charitable Trusts. 02.03.2020. U.S. illnesses and deaths associated with compounded or repackaged medications. *The Pew Charitable Trusts*. Available from: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2020/us-illnesses-and-deaths-associated-with-compounded-or-repackaged-medications-2001-19 [viewed 04.05.2021.].

18. Valizadeh, S., Rasekhi, M., Hamishehkar, H., Asadollahi, M. and Hamishehkar, H. 2015. Medication errors in oral dosage form preparation for neonates: The importance of preparation technique. *J Res Pharm Pract*. 4(3), 147–152. Available from: doi: 10.4103/2279-042X.162362 [viewed 26.04.2021.].

19. Jackson, M. and Lowey, A., eds. 2010. *Handbook of Extemporaneous Preparation*. London: Pharmaceutical Press.

20. Perez, M. 15.10.2007. Intoxication mortelle avec un produit amaigrissant. *Le Figaro*. Available from: https://www.lefigaro.fr/sciences/2006/04/25/01008-20060425ARTFIG90080intoxication_mortelle_avec_un_produit_amaigrissant.php [viewed 30.04.2021.].

21. Allen, L. V., Jr. 2016. *The Art, Science, and Technology of Pharmaceutical Compounding*. 5th ed. Washington, D.C.: American Pharmacists Association.

22. Wolf, G. 2009. Viele Wirkstoffe – höheres Kompatibilitätsrisiko [Many active ingredients – higher compatibility risks]. *Hautarzt*. 60(7), 534–535. Available from: doi: 10.1007/s00105-009-1796-z [viewed 26.04.2021.].

23. Bundesvereinigung Deutscher Apothekerverbände (ABDA). 2021. *Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium (DAC/NRF), Online-Angebot*. Eschborn: Avoxa-Mediengruppe Deutscher Apotheker GmbH.

24. The United States Pharmacopeial Convention. 2020. *USP Compounding Compendium, Current with United States Pharmacopeia 43-National Formulary 38*. Rockville: US Pharmacopeial Convention.

25. Pharmaceutical Society of Australia. 2021. *Australian Pharmaceutical Formulary and Handbook (APF): a guide to best practice, digital version*. 25th ed. Canberra: PSA.

26. International Journal of Pharmaceutical Compounding (IJPC). 2021. Welcome to CompoundingToday.com! *CompoundingToday.com website*. Available from: https://compoundingtoday.com/ [viewed 02.03.2021.].

27. DAC/NRF-Team. 2021. *DAC/NRF-Rezepturenfinder, Online-Angebot*. Eschborn: Avoxa-Mediengruppe Deutscher Apotheker GmbH.

28. Carvalho, M., Tuleu, C. and Taylor, K. M. G. 2008. Current compounding practices in Europe. *IJPC*. 12(2), 94–97.

29. Reis, M., Carvalho, M. and Rodrigues, A. 2014. Compounding practices in a Portuguese community pharmacy. *IJPC*. 18(5), 392–395.

30. Federal Union of German Associations of Pharmacists (ABDA). 2018. German Pharmacies: Figures, Data, Facts. Berlin: ABDA.

31. Herborg, H., Sørensen, E. W. and Frøkjaer, B. 2007. Pharmaceutical care in community pharmacies: practice and research in Denmark. *Ann Pharmacother*. 41(4), 681–689. Available from: doi: 10.1345/aph.1H645 [viewed 26.04.2021.].

32. Minghetti, P., Pantano, D., Gennari, C. G. M. and Casiraghi, A. 2014. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. *Health Policy*. 117(3), 328–333. Available from: doi: 10.1016/j.healthpol.2014.07.010 [viewed 26.04.2021.].

33. Committee of Ministers. 2016. Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. *Council of Europe Portal*. Available from: https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168065c132 [viewed 04.05.2021.].

34. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 2016. FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products. In: *Fiftieth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva: WHO Press. 87–109.

35. Scheepers, H. 2017. *Pharmacy Preparations: European Quality Standards and Regulation*. Maastricht: Datawyse/Universitaire Pers Maastricht.

36. Zāļu valsts aģentūra. 2019. FDU reģistrs – aptiekas. *Zāļu valsts aģentūras aptieku karte.* Available from: https://www.zva.gov.lv/zvais/aptieku-karte/ [viewed 30.04.2021.].

37. Krišjāne, M. 2016. *Pediatrijas praksē izmantojamie ekstemporālie zāļu pagatavojumi "Saules Aptiekā" no 2014. gada līdz 2015. gadam: pētnieciskais darbs*. Rīga: Rīgas Stradiņa universitāte.

38. Bormane, L. 2013. Ekstemporālās zāļu formas "Smiltenes aptiekā 2". *Latvijas Universitātes bakalaura un maģistra darbi*. Available from: https://dspace.lu.lv/dspace/handle/7/20414 [viewed 04.05.2021.].

39. Bormane, L. 2015. Efedrīna saturošās ekstemporālās zāļu formas aptiekās "Smiltenes aptieka 2" un "Jaunā Valmieras aptiekā". *Latvijas Universitātes bakalaura un maģistra darbi*. Available from: https://dspace.lu.lv/dspace/handle/7/30871 [viewed 04.05.2021.].

40. Zāļu valsts aģentūra. 23.01.2017. *Licencēto aptieku saraksts*. Rīga: Zāļu valsts aģentūra.

41. Zāļu valsts aģentūra. 2018. *Dati par aptieku skaitu, kas ekstemporāli izgatavo zāles. Ekstemporāli izgatavojamo zāļu apgrozījums 2017.gadā [Nepublicētie materiāli]*. Rīga: Zāļu valsts aģentūra.

42. Ministru Kabinets. 01.05.2004. Par Latvijas Republikas statistiskajiem reģioniem un tajos ietilpstošajām administratīvajām vienībām. Ministru kabineta rīkojums Nr. 271. *Latvijas Vēstnesis*. 69.

43. Ministru Kabinets. 27.05.2016. Ārstniecības personu un ārstniecības atbalsta personu reģistra izveides, papildināšanas un uzturēšanas kārtība. MK noteikumi Nr. 317. *Latvijas Vēstnesis*. 102.

44. Allen, L. V., Jr. 2019. Basics of compounding: summary of the official United States Pharmacopeia monographs for compounded preparations. *IJPC*. 23(2), 135–143.

45. Pharmaceutical Society of Australia. 2021. About PSA. *Pharmaceutical Society of Australia*. Available from: https://www.psa.org.au/about/about-psa/ [viewed 01.05.2021.].

46. American Psychiological Association. 2019. *Publication Manual of the American Psychological Association*. 7th ed. Washington, D.C.: American Psychiological Association.

47. International Committee of Medical Journal Editors. 2019. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. *International Committee of Medical Journal Editors*. Available from: http://www.icmje.org/recommendations/ [viewed 20.09.2021.].

48. Ministru Kabinets. 31.03.2010. Aptieku darbības noteikumi. MK noteikumi Nr. 288. *Latvijas Vēstnesis*. 51/52.

49. Ministru Kabinets. 08.05.2006. Noteikumi par zāļu ražošanas un kontroles kārtību, par zāļu ražošanu atbildīgās amatpersonas kvalifikācijas prasībām un profesionālo pieredzi un kārtību, kādā zāļu ražošanas uzņēmumam izsniedz labas ražošanas prakses sertifikātu. MK noteikumi Nr. 304. *Latvijas Vēstnesis*. 70.

50. Farmaceitiskās inspekcijas konvencija un Farmaceitiskās inspekcijas sadarbības shēma (PIC/S). 2017. PIC/S labas prakses norādījumi zāļu izgatavošanai veselības aprūpes iestādēs – Valsts valodas centra tulkojums. *Valsts valodas centrs*. Available from: https://vvc.gov.lv/index.php?route=product/category&path=60_109_110_116_131&page=2 [viewed 04.05.2021.].

51. Zāļu valsts aģentūra. 2017. *Zāļu valsts aģentūras darbības stratēģija 2017. - 2019. gadam*. Rīga: Zāļu valsts aģentūra.

52. Veselības ministrija. 2020. Labas ražošanas prakses piemērošana zāļu izgatavošanā aptiekās. *Ārstniecības un ārstniecības atbalsta personāla kvalifikācijas uzlabošana*. Available from: https://talakizglitiba.lv/labas-razosanas-prakses-piemerosana-zalu-izgatavosana-aptiekas [viewed 04.06.2021.].

53. Latvijas Republika. 24.04.1997. Farmācijas likums: Latvijas Republikas likums. *Latvijas Vēstnesis*. 103.

54. Ministru Kabinets. 03.06.2005. Spirta aprites kārtība farmaceitiskās darbības uzņēmumos, veterinārfarmaceitiskās darbības uzņēmumos, aptiekās, ārstniecības iestādēs un veterinārmedicīnā. MK noteikumi Nr. 377. *Latvijas Vēstnesis*. 88.

55. Ministru Kabinets. 28.06.2013. Aktīvo vielu importēšanas un izplatīšanas kārtība. MK noteikumi Nr. 344. *Latvijas Vēstnesis*. 123.

56. Ministru Kabinets. 22.06.2006. Zāļu reģistrēšanas kārtība. MK noteikumi Nr. 376. *Latvijas Vēstnesis*. 97.

57. Ministru Kabinets. 24.01.2006. Noteikumi par zāļu marķēšanas kārtību un zāļu lietošanas instrukcijai izvirzāmajām prasībām. MK noteikumi Nr. 57. *Latvijas Vēstnesis*. 14.

58. Ministru Kabinets. 27.10.2011. Farmaceitiskās darbības licencēšanas kārtība. MK noteikumi Nr. 800. *Latvijas Vēstnesis*. 170.

59. Ministru Kabinets. 11.08.2011. Aptieku un aptieku filiāļu izvietojuma kritēriji. MK noteikumi Nr. 610. *Latvijas Vēstnesis*. 125.

60. Ministru Kabinets. 26.03.2002. Aptieku un aptieku filiāļu izvietojuma kritēriji. MK noteikumi Nr. 102. *Latvijas Vēstnesis*. 47.

61. Veselības ministrija. 29.09.2016. Ministru kabineta noteikumu projekta „Aptieku darbības noteikumi" sākotnējās ietekmes novērtējuma ziņojums (anotācija). *Latvijas Republikas Ministru kabineta tiesību aktu projekti*. Available from: http://tap.mk.gov.lv/lv/mk/tap/?dateFrom=2017-05-04&dateTo=2021-05-04&text=aptieku+darb%C4%ABbas+noteikumi&org=0&area=0&type=0 [viewed 04.05.2021.].

62. Zāļu valsts aģentūra. 2019. FDU reģistrs – aptiekas. *Zāļu valsts aģentūras aptieku karte.* Available from: https://www.zva.gov.lv/zvais/aptieku-karte/ [viewed 15.06.2019.].

63. Ministru Kabinets. 29.06.2007. Zāļu izplatīšanas un kvalitātes kontroles kārtība. MK noteikumi Nr. 416. *Latvijas Vēstnesis*. 104.

64. Kiseļova, O., Mauriņa, B. and Šidlovska, V. 2018. Extemporaneous medicine prescribing trends in Latvia. *78th FIP World Congress of Pharmacy and Pharmaceutical Sciences – Abstracts*. Available from: https://www.fip.org/abstracts?page=abstracts&action=item&item=20297 [viewed 04.05.2021.].

65. Plaza, T. und Ziegler, A. S. 2014. *Dermatologische Rezepturen für Ärzte*. 1. Auflage. Stuttgart: Deutscher Apotheker Verlag.

66. Ziegler, A. S. 2015. *Wirkstoffe in der Rezeptur*. 2. Auflage. Stuttgart: Deutscher Apotheker Verlag.

67. Garbe, C. und Reimann, H. 2017. *Dermatologische Rezepturen: Richtig Verschreiben – Individuell Therapieren*. 3. Auflage. Stuttgart: Georg Thieme Verlag KG.

68. Elder, D. L. 2018. *A Practical Guide to Contemporary Pharmacy Practice and Compounding*. 4th ed. Philadelphia: Wolters Kluwer Health.

69. Fischer, H. und Reimann, H. 10.07.2000. Sulfonamide nicht auf die Haut. *Pharmazeutische Zeitung*. Available from: https://www.pharmazeutische-zeitung.de/inhalt-28-2000/pharm2-28-2000/ [viewed 01.05.2021.].

70. DAC/NRF-Team. 2021. *DAC/NRF-Rezepturhinweise Datenbank, Online-Angebot*. Eschborn: Avoxa-Mediengruppe Deutscher Apotheker GmbH.

71. Reimann, H. 19.11.2001. Castellani-Lösung. Rot, farblos oder grün? *Pharmazeutische Zeitung*. Available from: https://www.pharmazeutische-zeitung.de/inhalt-47-2001/pharm2-47-2001/ [viewed 01.05.2021.].

72. International Journal of Pharmaceutical Compounding (IJPC). 2021. Strong iodine solution USP [Lugol's solution], human, veterinary, avian, formula number: 3109. *CompoundingToday.com formulas*. Available from: https://compoundingtoday.com/Formulation/ [viewed 02.03.2021.].

73. GSK Dungarvan. 2020. *Zāļu apraksts "Vibrocil 2,5 mg/0,25 mg/ml deguna pilieni, šķīdums"*. Rīga: Zāļu valsts aģentūra.

74. Daniels, R. 13.04.2017. Nasalia: Applikationsroute mit Tücken. *Pharmazeutische Zeitung*. Available from: https://www.pharmazeutische-zeitung.de/ausgabe-162017/applikationsroute-mit-tuecken/ [viewed 01.05.2021.].

75. Schmidt, P. C. und Lang, S. 2013. *Pharmazeutische Hilfsstoffe: Eigenschaften, Anwendung und Handelsprodukte*. Eschborn: Govi-Verlag Pharmazeutischer Verlag Gmbh.

76. Bouwman-Boer, Y., Fenton-May, V. and Le Brun, P., eds. 2015. *Practical Pharmaceutics: An International Guideline for the Preparations, Care and Use of Medicinal Products*. 1st ed. Heidelberg: Springer International Publishing. Available from: doi: 10.1007/978-3-319-15814-3 [viewed 04.05.2021.].

77. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 2012. Development of paediatric medicines: points to consider in formulation. In: *Forty-sixth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva: WHO Press. 197–225.

78. Krochmal, L. 2009. Considerations before choosing (extemporaneously) compounded products. *Dermatol Ther*. 22(3), 225–228. Available from: doi: 10.1111/j.1529-8019.2009.01235.x [viewed 26.04.2021.].

79. Ritene, A. 31.01.2019. Medikamentus tieši jums pagatavo aptiekā. *Mana Aptieka*. Available from: https://manaaptieka.lv/medikamentus-tiesi-jums-pagatavo-aptieka/ [viewed 01.05.2021.].

80. Staubach-Renz, P., Hünerbein, A., Melhorn, S., Reimann, H. und Gehring, W. 2017. *Leitlinie der GD Gesellschaft für Dermopharmazie e. V. Dermatologische Rezepturen*. Köln: GD Gesellschaft für Dermopharmazie.

81. The Joint Commission. 2019. Official "Do Not Use" list. *The Joint Comission*. Available from: https://www.jointcommission.org/-/media/tjc/documents/resources/patient-safety-topics/do_not_use_list_6_28_19.pdf [viewed 01.05.2021.].

82. Ministru Kabinets. 23.03.2005. Recepšu veidlapu izgatavošanas un uzglabāšanas, kā arī recepšu izrakstīšanas un uzglabāšanas noteikumi. MK noteikumi Nr. 175. *Latvijas Vēstnesis*. 48.

83. Ratiopharm. 2020. *Zāļu apraksts "Omeprazole-ratiopharm 20 mg zarnās šķīstošās cietās kapsulas"*. Rīga: Zāļu valsts aģentūra.

84. Cornish, P. 2005. "Avoid the crush": hazards of medication administration in patients with dysphagia or a feeding tube. *CMAJ*. 172(7), 871–872. Available from: doi: 10.1503/cmaj.050176 [viewed 01.05.2021.].

85. Medicines for Children. 01.2018. Omeprazole for gastro-oesophageal reflux disease (GORD). *Medicines for Children*. Available from: https://www.medicinesforchildren.org.uk/omeprazole-gastro-oesophageal-reflux-disease-gord [viewed 01.05.2021.].

86. Verrue, C., Mehuys, E., Boussery, K., Remon, J. P. and Petrovic, M. 2011. Tablet-splitting: a common yet not so innocent practice. *J Adv Nurs*. 67(1), 26–32. Available from: doi: 10.1111/j.1365-2648.2010.05477.x [viewed 26.04.2021.].

87. Sweetman, S. C., ed. 2009. *Martindale: The Complete Drug Reference*. 36th ed. London: Pharmaceutical Press.

88. Mennella, J. A., Spector, A. C., Reed, D. R. and Coldwell, S. E. 2013. The bad taste of medicines: overview of basic research on bitter taste. *Clin Ther*. 35(8), P1225–1246. Available from: doi: 10.1016/j.clinthera.2013.06.007 [viewed 26.04.2021.].

89. Medical Flavouring Systems. 2021. Products. *Medical Flavouring Systems*. Available from: https://medicalfs.net.au/products/flavorx [viewed 01.05.2021.].

90. Medicines for Children. 09.12.2011. How to give medicines: liquid medicine. *Medicines for Children*. Available from: https://www.medicinesforchildren.org.uk/how-give-medicines-liquid-medicine-0 [viewed 01.05.2021.].

91. Jānis Zvejnieks. 2020. Zāļu gatavošana aptiekās Latvijā un Eiropā, esošā situācija un nākotnes perspektīva. *Materia Medica*. (1), 32–35.

92. Carvalho, M. 2013. *Compounding Practices in Europe: Extemporaneously Compounded Oral Medicines in European Hospital Pharmacies*. London: UCL School of Pharmacy.

93. Bell, J. S., Väänänen, M., Ovaskainen, H., Närhi, U. and Airaksinen, M. S. 2007. Providing patient care in community pharmacies: practice and research in Finland. *Ann Pharmacother*. 41(6),1039–1046. Available from: doi: 10.1345/aph.1H638 [viewed 26.04.2021.].

94. Nabielek, K., Hamers, D. and Evers, D. 2016. *Cities in Europe. Facts and Figures on Cities and Urban Areas*. Hague: PBL Netherlands Environmental Assessment Agency.

95. Centrālā statistikas pārvalde. 2019. Iedzīvotāju skaits Rīgā 2017. gadā. *Oficiālās statistikas portāls – Latvijas oficiālā statistika*. Available from: http://data1.csb.gov.lv/pxweb/en/iedz/iedz__iedzskaits__ikgad/ISG020.px/ [viewed 09.08.2019.].

96. Ministru Kabinets. 09.08.2017. Par konceptuālo ziņojumu "Par veselības aprūpes sistēmas reformu". Ministru kabineta rīkojums Nr. 394. *Latvijas Vēstnesis*. 157.

97. Špringer, V., Kišška, I. 2002. Lieková politika na Slovensku a jej odraz v preskripcii. 2. Preskripcia IPL podĺa odbornosti lekárov [Drug policy in Slovakia and its reflection in prescriptions. 2. Prescriptions of individually prepared drugs based on the medical specialty]. *Ceska Slov Farm*. 51(4),186–189.

98. Nagel, K., Ali, F., Al-Khudari, S., Khan, A., Patel, K., Patel, N. and Desai, A. 2010. Extemporaneous compounding of medicated ointment. *IJPC*. 14(6), 472–478.

99. Todorova, A., Gugleva, V. and Georgieva, L. 2016. Doctors' point of view on pharmacy compounding – advantages and disadvantages. *IAIM*. 3(2), 45–50.

100. Jiráková, A., Rajská, L., Rob, F., Gregorová, J. and Hercogová, J. 2015. Dermatitis toxica faciei after boric acid. *Dermatol Ther*. 28(1), 52–55. Available from: doi: 10.1111/dth.12180 [viewed 26.04.2021.].

101. Vecsernyés, M., Bácskay, I., Fenyvesi, F., Váradi, J. and Fehér, P. 2011. *Practicals in Pharmaceutical Technology - Prescription Pharmacy*. Debrecen: Department of Pharmaceutical Technology, Medical and Science Center, University of Debrecen.

102. Drugs.com. 2019. Boric Acid. *Drugs.com*. Available from: https://www.drugs.com/international/boric-acid.html [viewed 12.11.2019.].

103. Kavaliauskaitė, E. 2016. *Veiksniai, įtakojantys gamybinės vaistinės receptūrą. Klaidingai išrašytų 1 formos ekstemporalių receptų analizė visuomenės gamybinėje vaistinėje: magistro baigiamasis darbas*. Kaunas: Lietuvos Sveikatos Mokslų Universitetas.

104. Sklenář, Z., Horáčková, K. 2012. Moznosti inovace individuální prípravy lecivých prípravků v lékárnách v Ceské republice [The possibilities of innovation of extemporaneous preparation in pharmacies in the Czech Republic]. *Ceska Slov Farm*. 61, 11–16.

105. Reimann, H. 2010. Das Neue Rezeptur-Formularium (NRF) im DAC. Gestern - Heute - Morgen [The new drug formulary (NRF) of the German drug codex. Yesterday - Today - Tomorrow]. *Pharm Unserer Zeit*. 39(4), 274–279. Availabe from: doi: 10.1002/pauz.201000372 [viewed 01.05.2021.].

106. Melhorn, A. 22.08.2019. Betamethasonvalerat: Stabilität abschätzen. *PTA-Forum*. Available from: https://ptaforum.pharmazeutische-zeitung.de/stabilitaet-abschaetzen/ [viewed 01.05.2021.].

107. Melzobs, M., Paliņš A. un Baltkājs J. 1981. *Receptūra*. Rīga: Zvaigzne.

108. Sopharma. 2019. *Zāļu apraksts "Adrenaline Sopharma 1 mg/ml šķīdums injekcijām"*. Rīga: Zāļu valsts aģentūra.

109. Allen, L. V., Jr. 2000. Compounding ear, nose and throat preparations. *IJPC*. 4(3), 164–169.

110. Marriott, J. F., Wilson, K. A., Langley C. A. and Belcher, D. 2010. *Pharmaceutical Compounding and Dispensing*. 2nd ed. London: Pharmaceutical Press.

111. Chiu, H. Y. and Tsai, T. F. 2011. Topical use of systemic drugs in dermatology: a comprehensive review. *J Am Acad Dermatol*. 65(5), 1048.e1–1048.e22. Available from: doi: 10.1016/j.jaad.2010.08.034 [viewed 26.04.2021.].

112. Banala, S. R., Khattab, O. K., Page, V. D., Warneke, C. L., Todd, K. H. and Yeung, S. J. 2020. Intranasal fentanyl spray versus intravenous opioids for the treatment of severe pain in patients with cancer in the emergency department setting: a randomized controlled trial. *PLoS One*. 15(7), e0235461. Available from: doi: 10.1371/journal.pone.0235461 [viewed 20.10.2021.].

113. Yellepeddi, V. K. 2018. Stability of extemporaneously prepared preservative-free prochlorperazine nasal spray. *Am J Health Syst Pharm*. 75(1), e28–e35. Available from: doi: 10.2146/ajhp160531 [viewed 04.06.2021.].

114. Allen, L. V., Jr. 2021. Prescription: the past (→2020), the present, and the future (2021→). *IJPC*. 25(2), 92.

115. Suchomel, M., Steinmann, J. and Kampf, G. 2020. Efficacies of the original and modified World Health Organization-recommended hand-rub formulations. *J Hosp Infect*. 106(2), 264–270. Available from: doi: 10.1016/j.jhin.2020.08.006 [viewed 26.04.2021.].

116. WHO. 2010. Guide to Local Production: WHO-recommended Handrub Formulations. Geneva: WHO.

117. Kinca, A. 30.04.2020. Tukumā roku dezinfekcijas līdzekli gatavo aptiekā. *Latvijas Sabiedriskie Mediji*. Available from: https://www.lsm.lv/raksts/zinas/latvija/tukuma-roku-dezinfekcijas-lidzekli-gatavo-aptieka.a358116/ [viewed 01.05.2021.].

118. Vanhoorne, V., Peeters, E., Van Tongelen, I., Boussery, K., Wynendaele, E., De Spiegeleer, B., Remon, J. P. and Vervaet, C. 2019. Pharmaceutical compounding of orphan active ingredients in Belgium: how community and hospital pharmacists can address the needs of patients with rare diseases. *Orphanet J Rare Dis*. 14, 186. Available from: doi: 10.1186/s13023-019-1154-x [viewed 05.05.2021.].

119. Morri, M., Casabonne, C., Leonardi, D. and Vignaduzzo, S. 2020. Orphan Formulations for Pediatric Use: Development and Stability Control of Two Sildenafil Citrate Solutions for the Treatment of Pulmonary Hypertension. *AAPS PharmSciTech*. 21, 221. Availabe from: doi: 10.1208/s12249-020-01768-z [viewed 05.05.2021.].