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GELS AS A PHARMACEUTICAL FORM IN THE STATE PHARMACOPOEIA XIV EDITION, REGULATORY LEGAL ACTS OF THE MINISTRY OF HEALTH OF RUSSIA AND THE STATE REGISTER OF MEDICINES

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The content analysis method was used to study the regulatory documentation and data of the State register of medicines for the nomenclature and classification of gels. The analysis of the range of medicines represented by the gel dosage form is carried out. The results of the analysis of the domestic pharmaceutical market of gels by trade names, pharmacotherapy groups, manufacturing countries, referentiality and interchangeability are presented. The current direction is the development of domestic gels from the point of view of import substitution of foreign medicines.

Keywords: dosage forms, gels, regulatory documents, State Register of Medicines

Currently, a large number of gel medicines are registered in Russia, and their further development, registration, production and use are very promising areas in medicine and pharmacy.

For external and local use, gels have an impressive set of advantages in comparison with ointments. For example, when spread on the skin, they form finest smooth films, providing, in some cases, rapid and complete absorption

of active substances, on the other hand, they form a resilient protective film with prolonged action; provide comfort (support normal heat-, moisture – and gas exchange in the skin, have a pH close to pH of human skin, do not have irritating effects, etc.); both hydrophilic and hydrophobic substances can be entered into gels; the high viscosity of the dispersion medium of gels prevents the interaction of chemically incompatible substances. Gels have good thixotropic properties, which specifies their optimal spreading ability, good squeezability out of the tube. When spread on the mucous membranes, the gels are well retained and provide long-term contact with the treated surface

The physical and chemical properties of gels allow us to consider them as a promising form for oral use. Oral gels combine the advantages of solid and liquid oral dosage forms. One of their advantages is the large bioavailability compared to solid dosage forms. The convenience of administration and the possibility of taste correction allow using medicines in the form of gels for oral administration in children's and geriatric practice, as well as for patients suffering

from chronic diseases, including those associated with swallowing disorders [3,4].

The purpose of the study: study of the current state of the nomenclature of medicines in the form of gels.

MATERIALS AND METHODS

The study was conducted using content analysis of data from the State Pharmacopoeia of the Russian Federation, edition XIV (SP XIV), normative legal acts of the Ministry of Health of the Russian Federation and the State Register of medicines.

RESULTS AND DISCUSSION

At the first stage of the study, the General Monographs (GM) included in the SP XIV, and normative legal acts of the Ministry of Health of the Russian Federation were reviewed. General Monographs and Pharmacopoeial monographs included in SP XIV were approved by the Order of Ministry of Health of the Russian Federation on October 31, 2018 №749 "On approval of General Monographs and Pharmacopoeial monographs and invalidation of certain orders of the Ministry of Health and Medical Industry of Russia, Ministry of Public Health and Social Development and Ministry of Health of Russia".

SP XIV, released in 4 volumes, came into force on December 1, 2018. Volume 2 begins with the section "Dosage forms of medicines and methods of their analysis", which includes the subsections "Dosage forms of medicines" and "Pharmaceutical and technological tests for dosage forms".

The list of General Monographs (GM) for various dosage forms has been significantly expanded – from 21 to 42. For example, along with traditional General Monographs (GM), such as "Aerosols and sprays", "Eye dosage forms", "Granules",

"Capsules", "Inhalation dosage forms", "Parenteral dosage forms", "Ointments", "Medical patches", "Powders", "Solutions", "Syrups", "Suppositories", "Suspensions", "Tablets", "Transdermal patches", "Emulsions", "Infusions and decoctions", "Tinctures", "Teas", "Extracts", "Cut and pressed pellets", the following General Monographs (GM) were introduced for the first time: "Medical gases", "Medicinal sponges", "Implants", "Drops", "Medicinal pencils", "Concentrates", "Lozenges", "Lyophilisates", "Pastilles", "Foams", "Films", "Bars", "Medical chewing gums", "Therapeutic Systems", "Juices", "Medical swabs", "Medical Shampoos", "Elixirs".

According to SP XIV, all dosage forms can be hierarchically classified: by aggregate state, type of a dispersed system, route of administration and type of release (Table 1).

For the first time in SP XIV, the concepts of a medicine "for external use" and "for topical use" are clearly specified. Medicines for external use are dosage forms applied on intact and/or damaged skin, including wound and/or burn surfaces, and/or hair, and/or nails: ointments, solutions, aerosols. Medicines for topical use are dosage forms applied on the mucous membranes, including eye, nasal, rectal, vaginal application, application on the gums, on the oral mucosa, etc., as well as introduction to the external auditory canal: ointments, solutions, aerosols.

The term "for topical use" is used if the dosage form is intended for three or more methods/routes of administration and application related to topical use; if methods/routes are less than three, specify a specific method/route of administration/application (for example, urethral gel).

If the dosage form for topical use in the oral cavity is intended for three or more methods of application (for example, for applying on the oral mucosa, teeth, gums, etc.), use the term "dental"; if there are one or two methods of application, then specify a specific method of application (for example, for applying on the oral mucosa).

Table 1

CLASSIFICATION OF DOSAGE FORMS

Level	Criterion of classification				
1	<i>Dosage forms by aggregate state</i>				
	solid	liquid	soft	gas	
2	<i>Dosage forms by type of a dispersed system</i>				
	homogeneous	heterogeneous		combined	
3	<i>Dosage forms by a route of administration</i>				
	for oral use	for external use	for topical use	for parenteral use	for inhalational use
4	<i>Dosage forms by a type of release</i>				
	immediate release		modified release		

Gels as medicines are designated in three General Monographs: OFS.1.4.1.0003.15 "Eye dosage forms", OFS.1.4.1.0007.15 "Dosage forms for parenteral use", OFS.1.4.1.0008.15 "Ointments".

In accordance with the OFS.1.4.1.0008.15 "Ointments", gels are classified as ointments. Ointments is a soft dosage form intended for application on the skin, wounds and mucous membranes. According to the consistency, ointments are divided into proper ointments, creams, gels, pastes and liniments.

Gels is a soft dosage form as a colloidal dispersion obtained by gelation with the use of special substances. The main applications of gels are indicated, for example, hydrophilic gels for application on the oral mucosa, periodontal gels, gels for application on gums, dental and stomatologic gels are referred to as dosage forms for use in the oral cavity. Gels (usually hydrophilic) can be for oral administration, and can also be used to prepare oral suspensions by dispersing in the appropriate solvent.

There are also gels for administration into the body cavity using appropriate applicators: endocervical gels are intended for administration into the cervical canal, and urethral gels are intended for administration into the urethra.

Intestinal gels are gels intended for administration into the intestine (duodenum, small intestine, ileum, colon). Transdermal gels are gels intended to be applied on the skin in order to provide a systemic effect due to the penetration of active substances into the bloodstream through the skin barrier.

Dosage forms for parenteral use include gels for injection and gels for subcutaneous administration, which are hydrophilic gels intended for injection into certain tissues and organs or for injection directly under the skin. Eye dosage forms, for example, include eye gels, which are a sterile dosage form, intended, as a rule, for application on the mucous membrane of the eye (conjunctiva).

Gels of high-molecular carbohydrates (cellulose esters, starch, agar) and proteins (gelatin, collagen, etc.), gels of inorganic substances (bentonite), gels of synthetic high-molecular compounds (polyethylene oxide, polyvinylpyrrolidone, polyacrylamide), etc. are used as bases for production of gels. There are oleogels i.e. gels prepared on bases consisting of a hydrophobic solvent (vaseline or vegetable oil, etc.) and a lipophilic gelling agent (polyethylene wax, colloidal silicon dioxide, aluminum or zinc

soap, etc.); hydrogels i.e. gels prepared on bases consisting of water, a hydrophilic mixed or non-aqueous solvent (glycerol, propylene glycol, ethanol, isopropanol) and a hydrophilic gelling agent (urea, cellulose derivatives, tragacanth, etc.) [5,7].

In accordance with the OFS.1.4.1.0003.15 "Eye dosage forms", soft eye dosage forms for topical use include eye gels. This is a dosage form containing one or more active substances, dissolved or dispersed in a suitable base, intended for application on the eye mucous membrane (conjunctiva), on the eyelids and cornea.

In OFS.1.4.1.0007.15 "Dosage forms for parenteral use" soft dosage forms for parenteral use include gels for injection and gels for subcutaneous administration. Their definition is also provided in the OFS.1.4.1.0008.15 "Ointments".

According to the classification presented in SP XIV (Table 1), gels are classified as soft dosage forms and can be homogeneous, heterogeneous and combined, intended for oral, external, topical and parenteral use with immediate and modified release [1].

The analysis of regulatory legal acts of the Ministry of Health of Russia has shown that the main regulatory document on the classification and nomenclature of dosage forms is the Order of the Ministry of Health of the Russian Federation of July 27, 2016 No. 538H "On approval of the List of dosage forms of medicines for medical use" (hereinafter – Order No. 538H).

Order No. 538H includes [6]:

- 32 basic dosage forms (aerosol, medical gas, gel, granules, dispersion, liquid, implant, drops, capsules, concentrate, cream, liniment, lyophilizate, ointment, oil, tincture, sticks, paste, foam, patches, films, powder, solution, syrup, system, spray, suppositories, suspension, tablets, medical swabs, extract, emulsion);
- 17 other dosage forms (medicinal sponge, pills, medicinal pencil, pharmaceutical nail polish, lozenges, pastilles, medicinal plates, bars,

medical chewing gum, medicinal absorbable wipes, medicinal shampoo, elixir, cut-pressed granules, infusions and decoctions, tablets, teas, juice);

- 6 special forms of homeopathic medicines (homeopathic opodeldok, homeopathic impregnated pills, homeopathic mixtures, homeopathic triturations, homeopathic solutions and liquid dilutions, homeopathic matrix tinctures);
- 2 types of solvents (solvent for preparation of dosage forms for injection, solvent for preparation of vaccines for injection).

Order No.538n not only describes the dosage forms, but also specifies their variants. For example, a gel is a soft dosage form represented by colloid dispersion obtained by gelation using special substances, which fully coincides with the definition presented in SP XIV. The order specifies 20 types of gels depending on the place of application with their description (Table 2).

At the second stage of the study, the nomenclature of gels included in the State register of medicines was reviewed. Content analysis of the product range of the pharmaceutical market of medicines represented by the gel dosage form showed that the product range is represented by 205 trade names (as of 30.11.2019) [2].

Analysis of data from the State register of medicines under the section "Form of presentation" showed that the range is represented by 16 varieties of gels, among which the largest share is taken by the dosage form of gels for external use – 77% (158 TN out of 205 TN) (Table 3).

Study of the range of gels on the basis of "Pharmacotherapeutic group" has shown that, according to the State register of medicines of the Russian Federation, gels are represented by 33 pharmacotherapeutic groups, among which the following groups have the largest relative share: "Non-steroidal anti-inflammatory medicines" (34%, 70/205 TN), "Anticoagulants of indirect action" (10%, 21/205 TN), "Venotonic

Table 2

CLASSIFICATION OF GELS DEPENDING ON THE PLACE OF APPLICATION

Nº	Name of a dosage form	Description of of a dosage form
1.	Vaginal gel	Gel intended for injection into the vagina to provide local action
2.	Ophthalmic gel	Sterile gel intended for application on the eye mucous membrane (conjunctiva)
3.	Injection gel	Sterile hydrophilic gel intended for injection into certain tissues and organs
4.	Topically-applied gel	Gel intended for topical use
5.	Gum paint-on gel	Gel intended for application on the gums in order to provide local action
6.	Gel for application on the oral mucosa (gel for the oral mucosa)	Hydrophilic gel intended for application on the oral mucosa in order to provide local action
7.	Gel for cutaneous use	Gel intended for cutaneous use
8.	Gel subcutaneous administration	Sterile hydrophilic gel intended to be injected directly under the skin
9.	Gel for preparation of suspension for oral use (gel for suspension for oral administration)	Gel intended for preparation of a suspension for oral administration by dispersion in an appropriate solvent
10.	Oral gel	Gel (usually hydrophilic) intended for oral administration
11.	Dental gel	Hydrophilic gel intended for application on the teeth and/or gums by rubbing in
12.	Intestinal gel	Gel intended for injection into the intestine (duodenum, small intestine, ileum, colon) using an appropriate device
13.	Nasal gel	Gel intended for injection into the nasal cavity or application on the nasal mucosa
14.	Periodontal gel	Gel intended for injection into the pocket between the tooth and gum
15.	Rectal gel	Gel intended for injection into the rectum to provide local action
16.	Stomatological gel	Gel intended for three or more routes of administration (for example, for periodontal application on the teeth, gums, and oral mucosa)
17.	Transdermal gel	Gel intended for application on the skin in order to provide a systemic effect due to the penetration of active substances into the bloodstream through the skin barrier
18.	Urethral gel	Gel intended for injection into the urethra using an appropriate applicator
19.	Ear gel	Gel intended for introduction into the external auditory canal, if necessary with a tampon impregnated with it
20.	Endocervical gel	Gel intended for injection into the cervical canal using an appropriate applicator

and angioprotective agents" (8%, 16/205 TN) (Fig. 1). Group 'Others' combined the gels of the following pharmacotherapeutic groups: "Decongestants", "Rosacea treatment agent", "Anti-Inflammatory agent", "Homeopathic agent", "Antiparkinsonian agent", "Antifoaming agent", "Antiviral agent", "Psoriasis treatment agent", "Local irritants", "Keratoprotective agent", "Hyper-cicatrizant", "Glucocorticoid for topical use" and others.

The analysis of gels on the basis of "Country-manufacturer" showed that the State register of medicines of the Russian Federation contains a range of gels from 25 manufacturing countries, among which the leaders in the number of trade names produced in this country, namely: Russia

(40%, 83/205 TN), Germany (11%, 23/205 TN), India (10%, 21/205 TN) (Fig. 2). The "Others" group includes the following countries-manufacturers: Finland, Hungary, Austria, Estonia, Latvia, Slovenia, Turkey, Spain, Norway, Ireland, Denmark, Bosnia and Herzegovina, and the United States.

Study of the range of gels on the basis of "Referentiality" has shown that the number of trade names of gels registered in the State register of medicines of the Russian Federation with the attribute "Reference" is 46% of the total number of trade names, "Interchangeable" – 53% (Fig. 3.). For 3 TN this attribute is not specified in the State register of medicines of the Russian Federation.

Table 3

DISTRIBUTION OF THE RANGE OF GELS IN ACCORDANCE WITH THE STATE REGISTER OF MEDICINES

Nº	Varieties of gels	Number of trade names	Example
1.	For external use	162	Androgel®
2.	Intestinal	1	Duodopa®
3.	For application on gums (paediatric)	1	Lidocain + Cetylpyridinium chloride
4.	Dental	8	Cholisal®
5.	Ophthalmic	4	Oftagel®
6.	Nasal	3	Rinorus®
7.	Vaginal	7	Krinon®
8.	Transdermal	1	Oestrogel®
9.	For oral use	3	Pepsan-R®
10.	Intracervical	2	Prostenongel®
11.	Topical	9	Kamistad®
12.	For external use homeopathic	1	Arnigel®
13.	For topical administration	5	Panavir®
14.	For external and topical use	1	Viferon®
15.	For rectal and external use	1	Fissario
16.	For preparation of suspension for oral use	1	Enterosgel®

CONCLUSION

As a result of the content analysis of data from the RF State Pharmacopoeia XIV edition (SP XIV), regulatory legal acts of the Ministry of Health of the Russian Federation and the State

register of medicines, it was found that gels are a popular dosage form in the development and production of modern medicines, the range of the domestic market of gels includes 205 trade names of medicines, which are represented by 16 varieties.

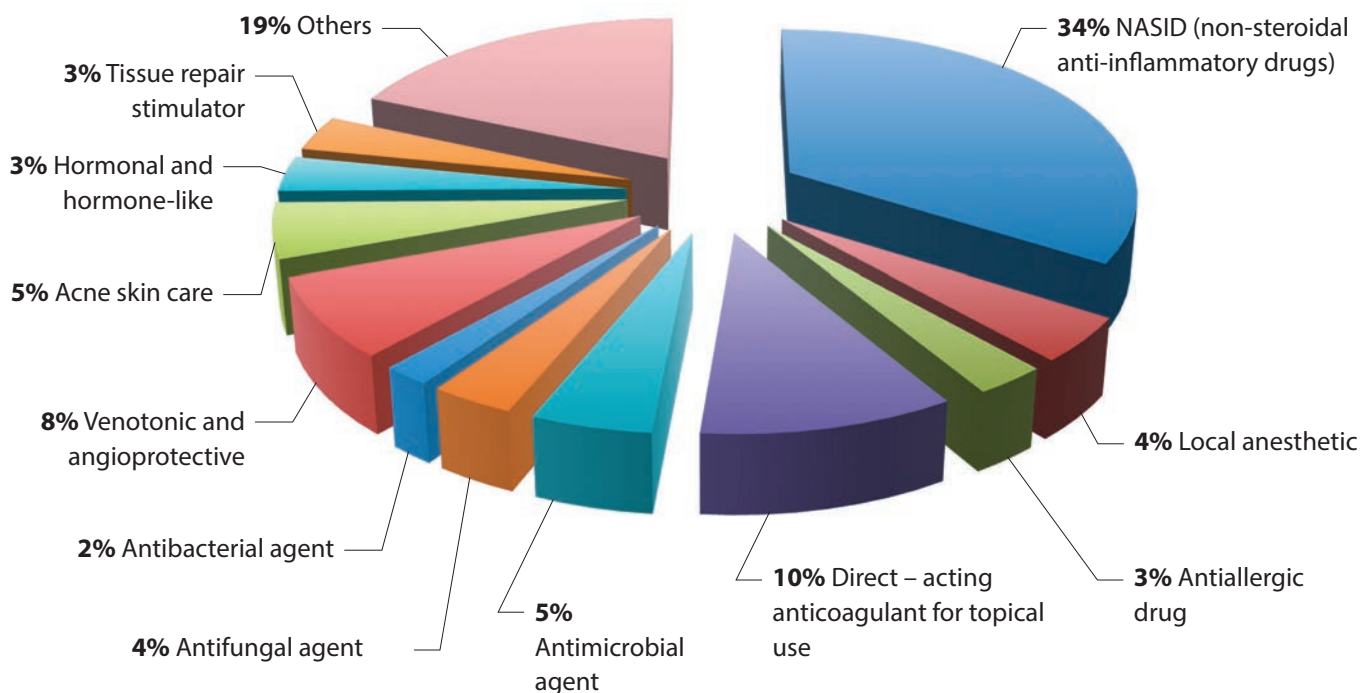


FIG. 1. Percentage of registered gels by “Pharmacotherapeutic group” in the total number of trade names

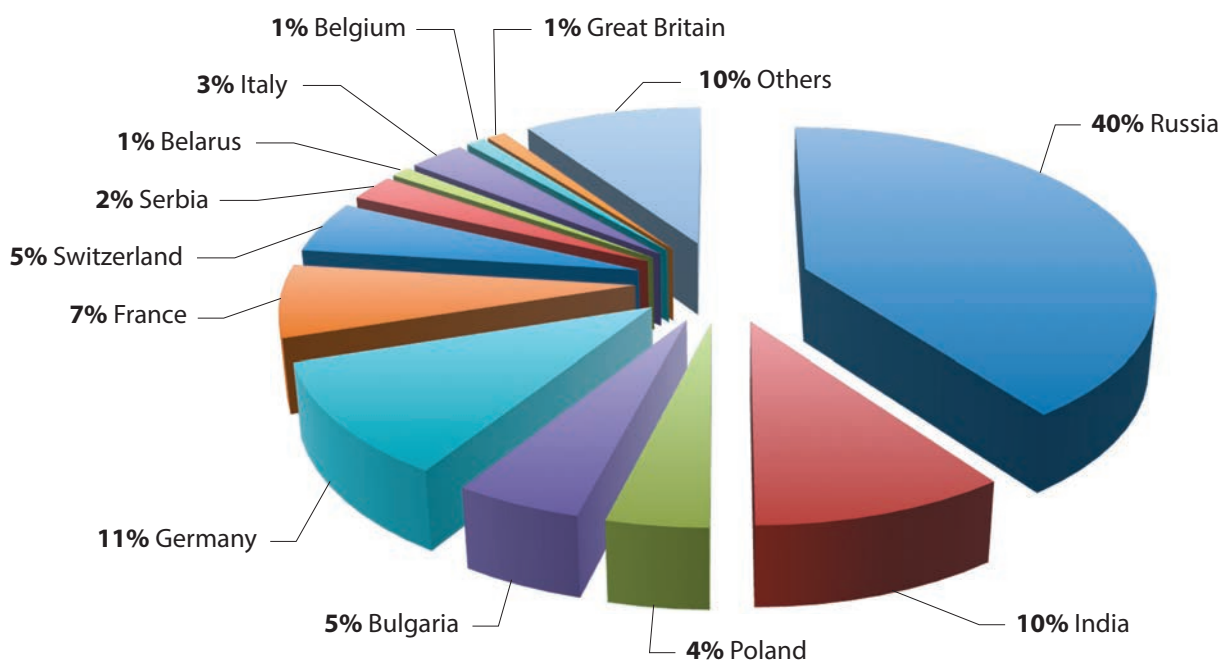


FIG. 2. Percentage of registered gels by “Country-manufacturer” in the total number of trade names

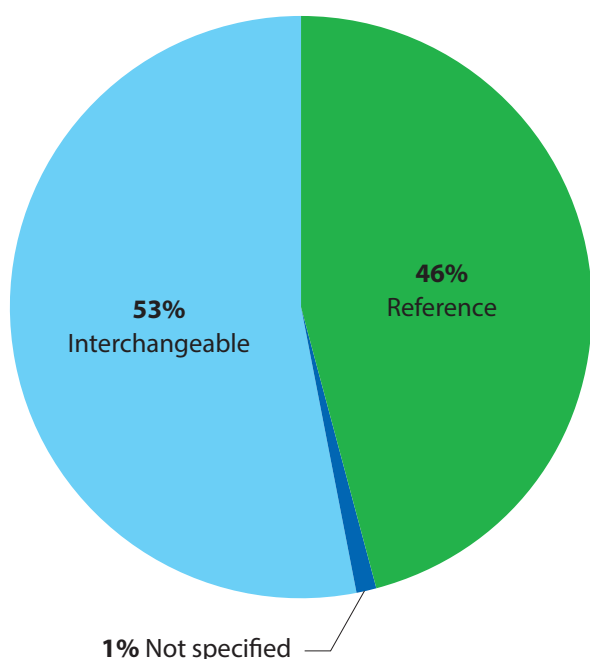


FIG. 3. Percentage of registered gels by "Referentiality" in the total number of trade names

It was found that the range of gels is diversified by pharmacological groups (33), among which the largest relative share is occupied by the following groups: "Non-steroidal anti-inflammatory medicines", "Anticoagulants", as well as "Venotonic and angioprotective agents".

A study of the range of gels according to countries of origin showed that the largest number of registered gels was produced in Russia, Germany and India. Most of the reference products in the form of gels are represented by imported products, and in Russia, to a greater extent, the interchangeable medicines are produced. Some gels are presented only by foreign manufacturers.

Based on the above, one of the most relevant areas of the pharmaceutical industry is the development of gels for domestic production for the purpose of import substitution, as well as

the development of unique and highly effective medicines in the form of gels that have no analogues abroad.

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