LEGISLATIVE AND NON-LEGISLATIVE REGULATIONS CONCERNING Rx DRUG ADVERTISEMENT IN THE EUROPEAN UNION AND THE UNITED STATES – COMPARATIVE ANALYSIS

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Abstract: Drug advertising is one of the most popular forms of communication between pharmaceutical companies and prospect drug purchasers. In the face of strong competition on the pharmaceutical market on the one hand, and patient’s high susceptibility to various forms of advertising on the other, drug producers try to reach as wide a group of recipients as possible. However, proper medicine use requires not only doctor’s wide knowledge and experience, but also patient’s awareness of necessity of rational drug usage. Advertising activities related to this group of medicines are covered by rigorous law regulations, with taking into account above-mentioned issues, and other specific features of drugs available with prescription.

The aim of this article is to present legislative and non-legislative regulations concerning Rx drugs, taking into consideration law regulations that are in force in the European Union and the United States. Ethic codes implemented by drug producers associations were also used.

Keywords: medicinal product, Rx drug, drug advertisement

Advertising is a primary tool used by pharmaceutical companies to communicate with the purchasers of medicinal products. Due to the binding legal restrictions advertising of Rx medicines in the European Union member countries can be addressed solely to doctors and individuals who trade in drugs.

The contents of advertisements addressed to specialists are subject to milder legal restrictions than the contents of advertisements addressed to the general public. This situation results from the fact that doctors and pharmacists have much greater knowledge than an ordinary patient. Improper understanding of an advertisement results in this case in a much smaller risk of the incorrect use of a medicinal product.

The aim of this article is to present legislative and non-legislative regulations standardizing advertising activity for prescription-only medicinal products. Additionally, effective regulations in the EU and in the US are compared.

Legislative regulations
Legislation for Rx medications in the European Union


Article 86 of the pharmaceutical directive defines drug advertising as any form of door-to-door information, canvassing activity or motivation aiming at the prescription, supply, sale or use of medicinal products.

The legislator defines in detail which activities are deemed to represent the advertising of medicinal products and which activities are not covered by this term. The document in question indicates that the advertising of a medicinal product includes among other activities:

- advertising of medicinal products addressed to the general public;
- advertising of medicinal products to persons authorized to prescribe or supply such products;
- visits paid by sales representatives selling medicinal products to persons authorized to write prescriptions;
- supply of samples;
- providing incentives to prescribe or supply medicinal products in the form of gifts, offers or
promises of any benefit or bonus in money or in kind, except for the situation when their actual value is minimal;

- sponsorship of promotional meetings with the participation of persons authorized to prescribe or to supply medicinal products,

- sponsorship of scientific congresses with the participation of persons authorized to prescribe or to supply medicinal products and, in particular, covering travelling and accommodation expenses connected with such congresses.

The definition of advertising does not cover the following:

- labelling packages and the accompanying leaflets;

- correspondence accompanied by material of a non-promotional character essential to provide answer for a specific enquiry concerning a particular medicinal product;

- factual and abounding in information announcements and reference material relating to e.g., package changes, warnings against adverse reaction as part of general drug precautions, trade catalogues and price lists, as long as they include no reference to the properties of a particular product;

- information related to human health or diseases, unless there is reference, even indirect, to medicinal products (1).

The definition of the advertising of medications presented in the pharmaceutical directive refers to all medicines. In the said directive there is also a number of other provisions applicable both to prescription-only and non-prescription medicinal products.

In the case of each group of medications advertising must not be misleading. It should present a pharmaceutical objectively and provide information on its rational use. The European Union legislation also stipulates that advertising should not exaggerate the properties of the presented product (Article 87 Paragraph 3 of Directive 2001/83/EC). Advertising of a medicinal product must not be addressed to children. It is also prohibited to offer and promise any benefit in exchange for the purchase of a medicinal product or for the provision of a proof confirming that such a product has been purchased (2).

Directive 2001/83/EC introduces a ban on advertising to the general public of medicinal products which are prescription-only-medicines (3) and of products the cost of which may be reimbursed (4).

Any advertisement of a prescription-only medicinal product should include essential information consistent with the summary of the product characteristics and supply classification of the given medicinal product. Member States may also require the advertising of a medicinal product to include product’s selling price and information about the conditions for the reimbursement. In the case when an advertisement is only to perform the function of a reminder, it may include only the name of the medicinal product.

The information included in an advertisement addressed to the persons authorized to write prescriptions and to persons who trade in medicinal products should be reliable, complete, verifiable and up-to-date. It is important that it includes the date of drawing up or updating the given information. The advertising of Rx medications may include tables, quotations and illustrations borrowed from literature or scientific works. They should be reproduced faithfully and annotated with the source they come from.

The advertising of a medicinal product which has not been granted marketing authorization in accordance with the EU law is unlawful.

Pharmaceutical directive obliges Member States to monitor the advertising of medicinal products. If any discrepancies are established, courts and administrative authorities are vested the right to: order the cessation of misleading advertising or institute appropriate court proceedings to order the cessation of the said advertising, or prohibit the said advertising or to institute appropriate proceedings to order a prohibition thereof if the misleading advertising has not yet been published but its publication is near, even if there is no proof of loss or damage or intention or negligence on the part of the advertiser. In order to eliminate long-lasting consequences of misleading advertising, the cessation of which has been ordered, appropriate authorities have the right to require the publication of the said decision in full or in part in a form which they regard as adequate and additionally to require the publication of a corrective statement.

Legislation for Rx medications in the United States


A basic characteristic, which distinguishes regulations in the United States from regulations in
most other countries, is the possibility to address the advertising of prescription-only medications to patients. Although in the European Union countries such activities are perceived as contrary to the principles of ethics, studies concerning the influence of the advertising of Rx medications on patients in the United States unambiguously indicate positive influence of such an activity.

By way of example, FDA studies performed in 2004 in the group of 500 doctors indicate that 73% of those surveyed is of the opinion that the advertising of Rx medications to the general public constitutes a factor facilitating conversations with patients about their health and possible treatment. Moreover, 91% of those surveyed stated that patients did not insist on prescribing a particular, advertised medicinal product (5). Interestingly enough, similar studies conducted simultaneously by Prof. J.S. Weissman Physicis Report on Patient Encounters Involving Direct-to-Consumer Advertising, published by the journal Health Affairs (6) and studies conducted two years later by Albert Morris For the Good of the Patient, Survey of the Physicians of the National Medical Association Regarding Perceptions of DTC Advertising (published in March 2007 in Journal of the National Medicine Association) (7) confirmed with incredible accuracy the conclusions drawn by FDA.

With reference to particular groups of the recipients of medicine advertising, it is worth noticing that in accordance with Federal Food, Drug and Cosmetic Act healthcare professionals are not only doctors and pharmacists but also nurses. Interestingly enough, the abovementioned act allows for particular information concerning safety, effectiveness and benefits of medicinal products, access to which in most countries have only doctors and pharmacists, to be provided to insurers and government agencies (8).

According to the law of the United States, all the data concerning medicinal products should be reliable and consistent with the contents of the label of the given product. Additionally, it is required that advertising information be reviewed by experts having experience in assessing safety and effectiveness of medicinal products. In the case when the information provided to healthcare professionals is incomplete or misleading, appropriate body of government administration may order that the information be deleted or completed (9).

Part 202.1 of The Code of Federal Regulation includes more specific information concerning the regulation of the advertising of Rx medications in the United States. In accordance with the said document, all the information included in the advertising of a medicinal product (among other information: order of listed substances and the amount thereof) should be consistent with the data included on the product’s label. Similarly as in the EU provisions, statements involved in the advertisements of Rx medications must not be misleading, especially when they refer to safety or composition of a medicinal product. Moreover, the advertisement must not include such a name of a medicinal product which can make it possible to confuse the given medication with another medication due to the similarity in spelling or pronunciation.

The Code of Federal Regulation presents a number of cases in which the advertising of a medicinal product does not fulfill the criteria of reliability and honesty. It is prohibited to:

- omit in an advertisement the information concerning contraindications and side effects which may result from the use of the medicinal product;
- present in an advertisement improper balance between the effectiveness of a medicinal product and side effects and contraindications as to the use of the said medicinal product;
- use in advertisements statements which may suggest that the given medicinal product is better, more effective and safer than other product when it has not been proven by scientific research;
- refer to out-of-date scientific proof, quotations or other sources which include favorable information about the given medicinal product;
- to present data from a clinical study in the manner suggesting that the study represents a bigger or more general experiment than it really is;
- use statements, quotations or reference to the literature suggesting that the given medicinal product can be used for the treatment of ailments for which it has not been approved;
- to include data or conclusions from a preclinical study (in vitro or studies in animals) in the manner suggesting that they are of clinical relevance whereas in fact such relevance has not been proven;
- to present conclusions from studies, the results of which may be the consequence of combined treatment or to present conclusions from studies in healthy persons;
- use data favorable for the given medicinal product obtained from patients treated with doses different than those indicated on the product’s package;
- use charts, figures or other graphic material in the manner which may mislead the recipients of the advertisement;
- misuse the results of statistical analyses, e.g., use statistical validity to prove a particular conclusion
without disclosing the clinical relevance of a study (10).

If an advertisement of a medicinal product is published on several pages of a magazine, bulletin or newspaper, it is required on every page to include the information concerning contraindications or side effects or to make a reference to such information.

According to the American law, every presentation of the trade name of a medicinal product in an advertisement should be followed by the presentation of the international name of the product. In the case of a uniform advertising text both names of medications should be written in the same font; however, it is required that the international name in the advertising headings be half the size of the trade name of the product. If an advertisement presents a medicinal product in different forms, which have no commonly accepted names, it is required that the international names of particular active components be listed next to the trade name of the product.

Any advertisement of a medicinal product should include clear information on the form of a medication, its contents, effectiveness, dosage, side effects and contraindications. This requirement also refers to the advertisements broadcast by means of media.

Statements concerning the effectiveness of a medicinal product do not have to refer to every intended use of the product. It is acceptable to restrict this information to the intended use, which the product is recommended for in the advertisement. Such statements, however, must be precise. For instance, if a medicinal product is antibacterial, the advertising should include the name and type of bacteria for which this product is clinically effective according to the information which has been approved and is presented on the label of the medicinal product (11).

A similar situation may take place in the case of presenting in an advertisement adverse events or contraindications for medicinal products. Therefore, it is permitted to limit the information to what the given medicinal product is recommended for.

Provisions of The Code of Federal Regulation allow for the use of one term for a group of side effects or contraindications in the advertising. The use of a single term (e.g., blood dyscrasia) instead of particular side effects or contraindications (e.g., leukopenia, agranulocytosis, neutropenia) (12) is possible, however, only in the case when such terminology has been approved on the label of the medicinal product.

An advertisement of a prescription-only medication, which is a reminder of a full advertisement, is exempt from the abovementioned requirements (defined in part 201.100 and 200.1 CFR), if it fulfills the following criteria:

1. The only aim of the reminder is to provide information concerning the price charged for the prescription for a particular medicinal product.
2. The reminder advertisement of a medicinal product contains no description or suggestion concerning safety, effectiveness or indications for use.
3. Advertising includes trade name of a medicinal product, its international name and strength as well as price charged for the prescription for a specific quantity of the medicinal product.
4. The price presented in the reminder advertisement as that charged for a prescription includes all charges covered by the consumer, including, but not limited to, the cost of the medicinal product, charge for issuing the product and handling fees (13).

Reminder advertisement of a medicinal product informing about the price of a drug may also include written, printed or graphic material concerning e.g., the functioning of a pharmacy, services rendered by the pharmacists, provided that it is not misleading and does not include detailed information about a medicinal product.

However, it is prohibited to distribute reminder advertisements in the case of medications, which include warnings against serious dangers to health connected with the use of such medications and in the case of medications whose effectiveness has not been graded as more than “possible”.

The advertising of Rx medications to medicine distribution agents encouraging the sale of big amount of medications in accordance with the commonly binding principles of trade is also exempt from the requirements included in parts 201.100 and 201.1 of CFR. Legal regulations in the United States clearly separate advertising of medicinal products from mail-order information about medications provided to healthcare professionals. However, it is required that all mail including such information look in a characteristic, defined by the provisions of law manner so that they can be instantly recognized and read by doctors or other persons responsible for taking care of a patient.

Moreover, pharmaceutical companies are allowed to provide pharmacists with information concerning precautions, recommendations or dosage of prescription-only medicinal products. It is important that these materials are not available for patients. It is prohibited to use such information as a tool for the advertising of medications.
Non-legislative regulations for Rx medications in the European Union

In the countries of the European Union the advertising of prescription-only medicinal products is regulated, among other documents, by Ethical Criteria for Medicinal Drug Promotion, IFPMA Code of Pharmaceutical Marketing Practices, EFPIA Code of Practice on Relationships between the Pharmaceutical Industry and Patient Organisations and EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with Healthcare Professionals.

Ethical Criteria for Medicinal Drug Promotion regulate the ethical issues of the advertising of medications and have been published by World Health Organisation. The aim of this document is to support the improvement of healthcare through the rational use of medicinal products. Undoubtedly, the interpretation of what is ethical and unethical differs in particular countries and societies, therefore, the criteria issued by WHO constitute only general ethical principles which may be adjusted by governments depending on cultural conditions and the level of development of a particular country.

World Health Organisation defines advertising as information and activities used by producers and distributors of medicinal products to increase the delivery, purchase, prescription and use of medicinal products (14).

Ethical Criteria for Medicinal Drug Promotion allows the advertising of Rx medications addressed only to professionals. The information included in such advertisements must be precise, objective and based on reliable scientific research. The scope of advertising information should be consistent with the binding regulations in particular countries, however, it is suggested that such information should include: international names of active ingredients, pharmacological data, clinical information and pharmaceutical information (15).

According to the criteria of World Health Organisation, an advertisement of a prescription-only medicinal product which serves the purpose of a reminder advertisement may include exclusively the name of a drug (trade name or international name), names of active substances and name and address of the producer or distributor of the given product (16).

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) is an organisation of 26 drug producers and 44 drug industry associations from all over the world. IFPMA Code of Pharmaceutical Marketing Practices includes the regulations of Ethical Criteria for Medicinal Drug Promotion recommended by WHO and its aim is to provide doctors and patients with the access to reliable information about medicinal products.

IFPMA defines the advertising of medicinal products as an activity undertaken or sponsored by a pharmaceutical company, addressed to healthcare professionals in order to increase the prescription, recommendation and purchase of medications. Such an activity can take place by means of various media, including the Internet (17). In accordance with the provisions of the Code a healthcare professional, who the advertising may be addressed to, is not only a doctor, dentist, pharmacist but also a nurse.

The European Codes, both EFPIA Code of Practice on Relationships between the Pharmaceutical Industry and Patient Organisations and EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with Healthcare Professionals, published by European Federation of Pharmaceutical Industries and Associations (EFPIA) prohibit the advertising of prescription-only medications to the general public.

The first of the abovementioned codes regulates the relationships between pharmaceutical companies and patient organisations (primarily sponsoring), the latter includes the principles of the honest advertising of Rx medications and the rational selection of a pharmacological therapy for a patient.

The provisions of EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with Healthcare Professionals refer to every form of the advertising of prescription-only medications, including oral and written information, communications, articles, direct advertising, the activities of medical sales representatives, audiovisual advertising, sponsorship of conferences, provision of drug samples and gifts.

European Federation of Pharmaceutical Industries and Associations defines the promotion of medications as an activity undertaken, organized or sponsored by a member of EFPIA or a person authorized by a member with the aim to promote the prescription, supply, sale, recommendation and use of a medication produced by the member [18].

The EFPIA Code requires that an advertisement of a medicinal product be consistent with its characteristics and suggest the use of a medication for the approved indications only. European Federation of Pharmaceutical Industries and Associations insists on objective and fair advertising and prohibits the use of statements in an advertisement indicating that a medication causes no side
effects or addiction. With reference to promotional materials EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with Healthcare Professionals emphasizes that the use of fax, electronic mail, automated systems of text messages or other electronic data communications for the promotion of medicinal products is allowed only with the prior permission or upon the request of the recipient (19).

The regulations of this EFPIA Code sets forth that every pharmaceutical company, which has committed itself to obeying the rules of the Code, should employ a doctor or a pharmacist who would be responsible for approving all the advertising materials of medicinal products before the release thereof in accordance with the requirements of the Code, national law and Summary of Product Characteristics (20).

The codes presented above represent no obligatory principles for all the members of International Federation of Pharmaceutical Manufacturers and Associations or European Federation of Pharmaceutical Industries and Associations. However, it is recommended that these guidelines be adjusted to the conditions of particular countries and that they create additional ethical requirements helpful in relations between pharmaceutical companies and both healthcare professionals and individual patients.

Non-legislative regulations for Rx medications in the United States

A fundamental document regulating advertising activity in the United States is AMA Code of Medical Ethics drawn up by American Medical Association. AMA Code is valid in most states in the US as an important supplement to legislative regulations.

AMA Code of Medical Ethics includes regulations concerning the advertising of both prescription-only medications and OTC medicinal products. It covers advertising, sale promotion and sponsorship conducted by pharmaceutical companies. Most regulations are directly addressed to healthcare professionals, mainly doctors.

AMA Code clearly allows the advertising of Rx medicinal products to the general public. This activity is defined as direct to consumer advertising. Due to the fact that drug promotion brings numerous dangers, AMA Code of Medical Ethics advises the doctors participate actively in the studies concerning the influence of advertising on patients’ health. In the case when patients make unfounded requests to have a particular drug prescribed, a doctor should suggest other forms of treatment, paying special attention to the necessity of the change of lifestyle (21). Under no circumstances is the doctor allowed to set his interest (especially financial interest) above patient’s good (22). According to AMA Code, the aim of doctor’s profession is to render medical services to improve patients’ health condition. Therefore, it is unethical to prescribe a medication for a patient or to send a patient to a test when there are no medical indications for it.

The issue of the advertising of prescription-only drugs has been broadly discussed in the guidelines PhRMA Guiding Principles Direct to Consumer Advertisements About Prescription Medicines, published by the American organisation The Pharmaceutical Research and Manufactures of America, which aims at providing patients with complete, reliable and objective information presented in direct to consumer advertisements. These communications are required to be consistent with the provisions of FDA, that is to be precise, unambiguous and consistent with the information included on a label. In an advertisement it is also important to present properly the proportion between risk and benefit resulting from the use of a particular medicinal product.

Appendix Questions and Answers to the document Guiding Principles Direct to Consumer Advertisements About Prescription Medicines presents the definitions of two types of the advertising of prescription-only medicinal products:

1. direct to consumer television advertisement – the amount of television air time purchased by a pharmaceutical company in order to present information about one or more of the companies medicinal products,
2. direct to consumer print advertisement – space in a newspaper or magazine bought by a pharmaceutical company in order to present one or more of the companies medicinal products (23).

Additionally, FDA allows the advertising of medicinal products by means of telecommunications – provided that patients have the possibility to obtain detailed information about the medicinal products.

It is important to promote medicinal products exclusively for the purposes approved by FDA. In the case of the advertisements of Rx medications on the radio and on the television and in the printed materials, it should be clearly marked that a pharmaceutical is a prescription-only medicinal product. It is also necessary to present in detail indications for the use of a medicinal product and the risk connected with the use of it (24).

According to FDA, the most common mistake in the advertisements of medicinal products is inap-
propriate risk presentation. The results of FDA studies indicate that 60% of patients are of the opinion that the advertisements of a medicinal product do not provide them with the information about the risk connected with the use of the medicine. Seventy two percent of doctors claim that the presentation of information in advertisements is little comprehensible for patients (this refers in particular to the information about the risk and contraindications for the use of a medicine) (25).

Advertisements addressed to the general public should present benefits and risk connected with the advertised medication in a balanced manner. Such information should be presented in a visible place in a neutral manner and in a non-medical language understandable for the patients (26).

Detailed principles of an appropriate presentation of information concerning the proportion between benefits and risk of a given medicinal product in an advertisement are presented in an FDA document Guidance for Industry Presenting Risk Information in Prescription Drug and Medical Device Promotion.

In accordance with the recommendations of the abovementioned American organisation, The Pharmaceutical Research and Manufactures of America, pharmaceutical companies should inform the patients about the appearance of actors playing the roles of healthcare professionals in commercials. Similarly, doctors appearing in a commercial of a particular medicine are obliged to inform the recipients of the commercial about this fact.

In the case when a direct to consumer advertisement includes an opinion of a publicly known person it is necessary to render this opinion precisely. Moreover, pharmaceutical companies should indicate whether that person has used the advertised medicinal product or not.

According to the opinion of PhRMA, every advertisement of Rx medication addressed to the general public should include the information about the ways of eliminating ailments, which the advertised medicine is recommended for, e.g., appropriate diet, change of a lifestyle. It is also necessary that directed to consumer advertisements include telephone number and website address, by means of which patients may report the observed adverse events connected with the use of the given pharmaceutical.

In addition, Guidance for Industry – Consumer-Directed Broadcast Advertisements obliges pharmaceutical companies to provide every person with complete information about medications. Because of the fact that a part of patients has an impeded access to the Internet, it is recommended that companies open a free of charge telephone line through which patients may obtain detailed information about particular medicinal products. Every patient should have a possibility to obtain complete information about a medication both from a call operator and by mail. It is important to provide patients in search of the information about medicinal products with personal data protection.

An alternative solution for pharmaceutical companies may be to provide patients with the access to package inserts with complete information about medicinal products in the most often visited places such as doctor’s offices, hospitals, pharmacies, libraries, public schools or even groceries. Special attention should be paid to offer patients the possibility to obtain the information they are interested in without leaving the area of their activity. This solution is usually feasible only in the case of pharmaceuticals used by a particular group of patients (27).

It is recommended that the advertising activities of pharmaceutical companies reach only the target group. Therefore, an appropriate choice of promotional material and time and place of the publication thereof is very important. For instance, medicines used solely by adults should be advertised in magazines or between television programmes which are primarily addressed to adults (28).

If new information concerning serious adverse events connected with the use of a particular medicine appears, pharmaceutical companies should alter the information addressed to the general public or fully cease to advertise the given pharmaceutical.

When judging the contents of the advertisements of medicinal products, FDA takes into consideration an advertisement as a whole. However, every advertisement of a medicinal product should include the following:
- indications for the use of a given medicine,
- information about diseases for the treatment thereof the medicine is recommended,
- data concerning the effectiveness of a medicinal product,
- information encouraging patients to consult a doctor prior to the use of a given medicine,
- information which a patient should pass on the doctor prior to the use of the given medicine (29).

The information above can be supplemented by the FDA recommendations included in Guidance for Industry – Prescription Drug Marketing Act (PDMA) Requirements, Guidance for Industry – Accelerated Approval Products – Submission of Promotional Materials (this document includes requirements for the advertising of medicinal prod-
ucts entitled to accelerated registration proceedings) and Ethical Criteria for Medicinal Drug Promotion recommended by World Health Organisation.

CONCLUSION

Regulations concerning the advertising of prescription-only medicinal products in the European Union and the United States are not the same. European law regulations and the ethical codes of European associations of medicine producers are more rigorous in this respect.

It is worth remembering that the aim of such broad legal restrictions is primarily to protect the health and life of patients – the consumers of medications. Although the advertising of Rx medicinal products to the general public is banned in European Union, it is still important that the communications addressed to specialists be objective and reliable. Doctors and pharmacists are often involuntary intermediaries in the advertising of medications. The information addressed to specialists should be fully consistent with the clinical study for a medicinal product and include the data on the benefits resulting from the use of a given pharmaceutical as well as the information about the possible adverse events.

REFERENCES

20. EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with


Received: 29.09.2011
In the paper: “Preparation and \textit{in vitro} evaluation of chitosan microgranules with clotrimazole,” by Emilia Szymańska and Katarzyna Winnicka, Vol. 69, No. 3, page 511, in Table 1 some parts were misprinted. The correct version of this Table is given below.

Table 1. Composition of various chitosan microgranules formulations (F1–F9).

<table>
<thead>
<tr>
<th>COMPOUND/FORMULATION</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
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<tbody>
<tr>
<td>Chitosan (g)</td>
<td>4.0</td>
<td>4.0</td>
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<tr>
<td>Clotrimazole (g)</td>
<td>0.4</td>
<td>1.0</td>
<td>0.4</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
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<tr>
<td>2% CH₃COOH (mL)</td>
<td>16.0</td>
<td>15.0</td>
<td>16.0</td>
<td>17.0</td>
<td>16.0</td>
<td>18.0</td>
<td>16.0</td>
<td>16.0</td>
<td>17.0</td>
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<tr>
<td>10% TPP solution (w/v)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pH of 10% TPP solution</td>
<td>9.1</td>
<td>8.8</td>
<td>6.55</td>
<td>8.8</td>
<td>6.55</td>
<td>–</td>
<td>6.55</td>
<td>6.55</td>
<td>6.55</td>
</tr>
<tr>
<td>Volume of 10% TPP solution (mL)</td>
<td>8.0/–</td>
<td>4.5/3.5*/</td>
<td>4.0/2.0*/</td>
<td>8.0/–</td>
<td>5.0/4.0*</td>
<td>–</td>
<td>5.0/4.0*</td>
<td>8.0/–</td>
<td>8.0/–</td>
</tr>
</tbody>
</table>

*) in some formulations, cross-linking solution of 10% TPP was divided into two parts—after adding the first one granules were dried (at a temperature of 35°C ± 0.5°C for 30 min.), and next the remaining volume of TPP solution was dropped. **) solution of 10% TPP with 0.5% SDS