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METHODOLOGICAL ASPECTS OF DRUG DEVELOPMENT IN THE FORM OF CHEWABLE TROCHES

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INFORMATION

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drug technology;
chewable troches.

ABSTRACT

The aim of the work. Study of the main methodological aspects of drug development in the form of chewable troches.
Materials and Methods. The objects of study were the works of domestic and foreign authors, electronic databases of the Ministry of Health of Ukraine and the own research. During the work methods of bibliosemantic analysis, systematization of theoretical and practical material and generalization of data were used.
Results and Discussion. The basic approaches to the pharmaceutical development of the original domestic medicines, in particular, in the dosage form of chewable troches in accordance with the requirements of the Guidance 42–3.1:2004. Quality guidelines Medicines: Pharmaceutical development, are described. The general scheme of pharmaceutical development of chewable troches is presented. The decision trees for the choice of gel-forming agent and flavorings to correct the taste characteristics are proposed.
Conclusions. The feasibility of developing a domestic original drug in the form of chewable troches is substantiated. The main steps of the pharmaceutical development of this dosage form are characterized.

Introduction. Oromucosal drugs (oral medicines) are solid, semi-solid or liquid medicines containing one or more active ingredients: intended for use in the oral cavity and/or throat for local or systemic action [1, 2].

Oromucosal drugs include throat rinsers, mouthwashes, gum solutions (gingival solutions), oromucosal solutions and oromucosal suspensions, semi-solid oromucosal medicines (including, for example, gels for gums, gum pastes, oromucosal gels, oromucosal pastes), oromucosal drops, oromucosal sprays, sublingual sprays (including oropharyngeal sprays), troches and lozenges, pressed lollipops, sublingual and lozenges tablets, oromucosal capsules, mucoadhesive drugs [1].

Recently, chewable troches are gaining popularity in the domestic pharmaceutical market, but their range is represented mainly with drugs of foreign production [3]: DuphaBears® (Amapharm GmbH, Germany), Flavo-Zinc (Solgar, USA), Supradyn® Gummies (Bayer Consumer Care, Germany), Vitatone (Newtone Pharma Limited, Great Britain), Immunovit (Swiss Energy, Switzerland). Unfortunately, most of these drugs are dietary supplements. Such drugs as Mycelex® (clotrimazole), Coenzyme Q10 100 mg and Lipoic Acid 100 mg Chewable Troches, Ketamine Hydrochloride 10-mg Troches and others are still not represented in Ukrainian pharmaceutical market. Therefore, the urgent goal of modern pharmacy is to develop the own domestic medicines in this dosage form.

The main task of pharmaceutical development is to create a drug of appropriate quality with the specified quality characteristics [4, 5]. To date, requirements for

planning a pharmaceutical experiment according to the Guidelines 42-3.1:2004 “Guidelines for Quality. Medicines. Pharmaceutical development” lie in the design.

The aim of the work. In order to adapt the requirements of the aforementioned guidelines, taking into account the requirements of the State Pharmacopoeia of Ukraine (SPhU) and the current legislation, the aim of this work is to study the main methodological aspects of drug development in the form of chewable troches.

Materials and Methods. The objects of study were the works of domestic and foreign authors, electronic databases of the Ministry of Health of Ukraine and the own research. During the work methods of bibliosemantic analysis, systematization of theoretical and practical material and generalization of data were used.

Results and Discussion. The general scheme of pharmaceutical development of chewable troches (Fig. 1) includes the selection of ingredients of the medicinal product (active pharmaceutical ingredients (API) and excipients), reasoning of rational technology of production, determination of risks and development of validated methods of quality control of the finished product [6, 7, 8].

API determines the pharmacological properties of the drug under development. In accordance with the requirements of Guidance 42–3.1:2004. “Quality guidelines Medicines: Pharmaceutical development” the choice of API and its concentration should be substantiated experimentally or by reference to relevant scientific sources of literature.

The second, not least important, step is the choice of the type of gel-forming agent, which is the carrier of the dosage form, providing its proper structural and mechanical properties and biopharmaceutical parameters. The decision tree for choosing a gel-forming agent is shown in Fig. 2.

Gelatin is most often used as a gel-forming agent for the production of chewable troches, although the literature describes the use of agar and apple pectin [9–11]. The classic composition of the base of chewable troches is close to the gelatin-glycerin suppository base. But the final ratio of the components depends on the quantitative content and the aggregate state of the composition of the APIs. It is important to use gelatin of a certain density (not less 250 g/cm2, per Bloom) [12].

Also, acidity regulators (eg, citric acid), taste correctors (eg, glucose syrup, fructose, sorbitol, sugar), fruit flavorings and food colorants (permitted for use in pharmaceutical practice) are added to the proper quality of the finished product and its taste characteristics.

Gelatin and agar chewable troches are used prepared as follows: the calculated amount of gelatin is poured with the calculated amount of purified water and left for swelling. Separately the concentrate of the excipients is prepared through the dissolution of acidity regulator together with the flavorings, taste correctors and food colorants in the minimum amount of purified water. After swelling, the gelatin or agar is melted in a water bath and mixed with the concentrate. After that the API is introduced into the ready troche mass. The resulting mass is poured into silicone form and placed in a refrigerator for freezing.

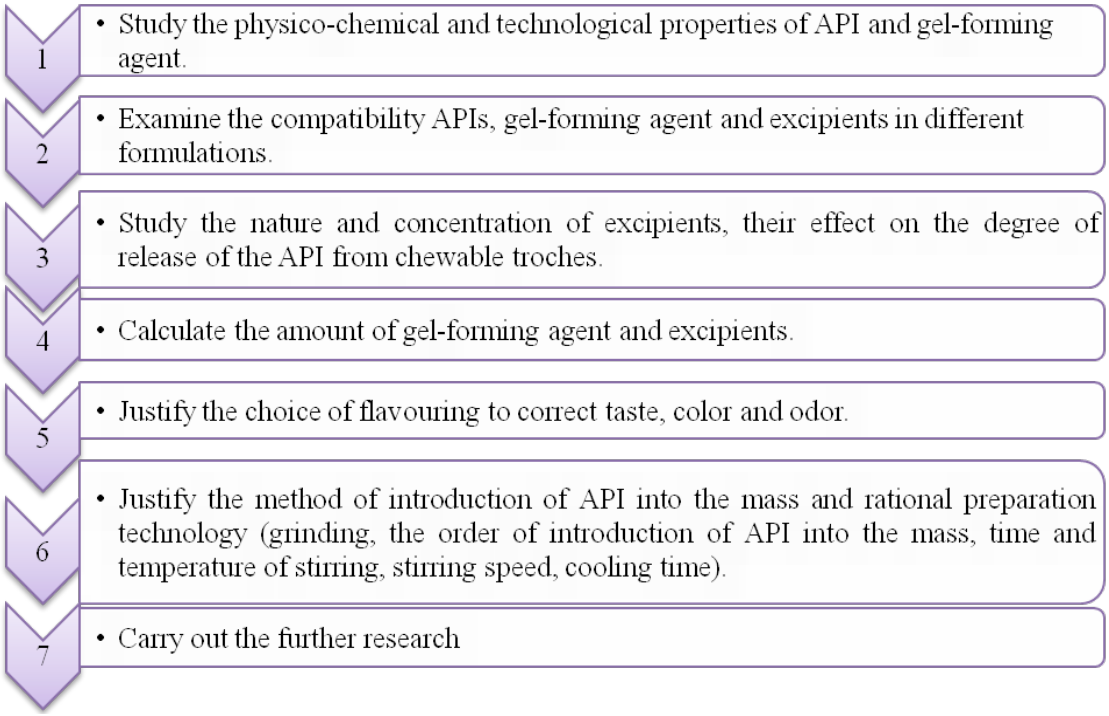

Fig. 1. General algorithm for the development of chewable troches.

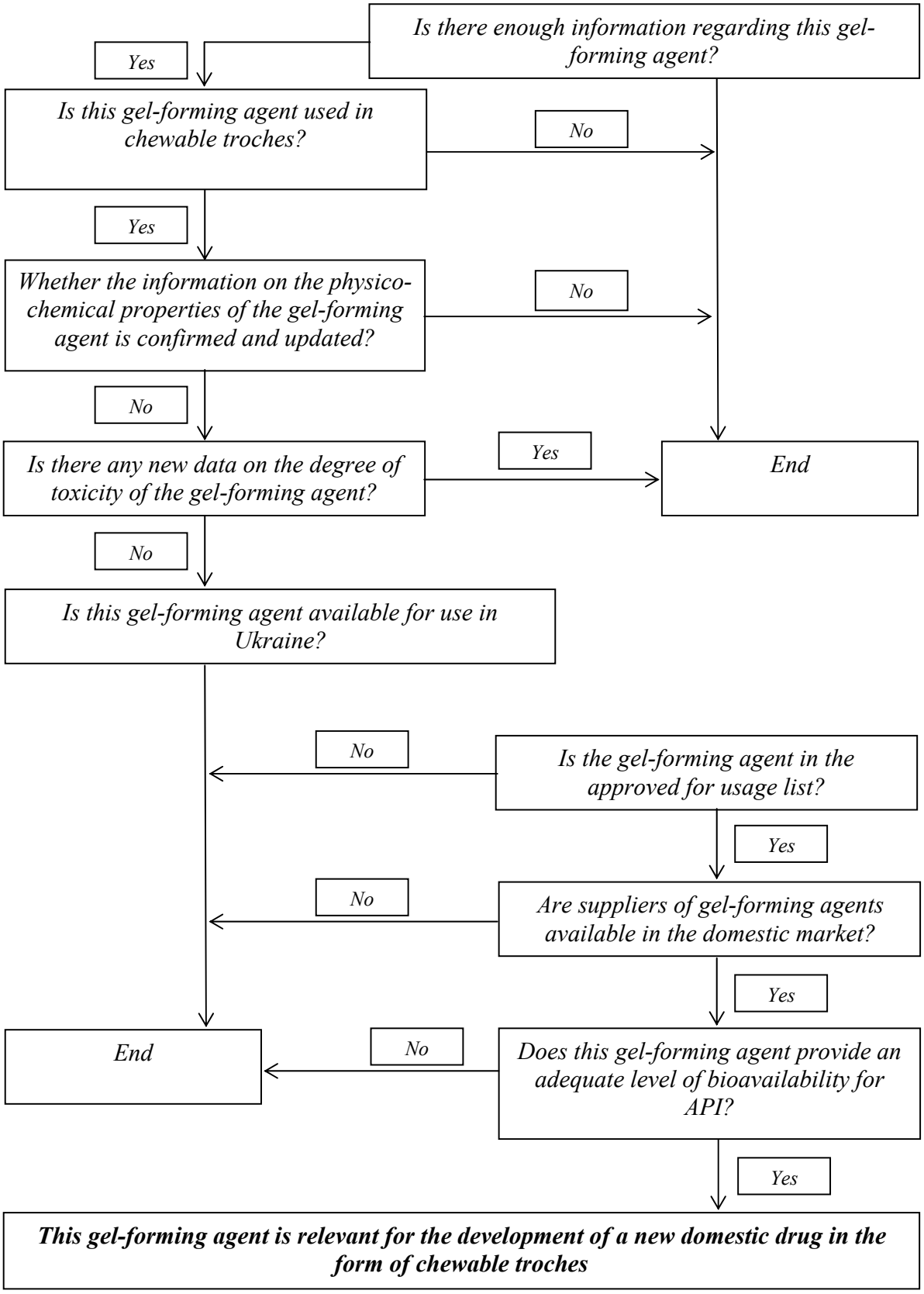

Fig. 2. Tree of decisions on the choice of gel-forming agent in the development of the composition of chewable troches.

Chewable troches with apple pectin are prepared by mixing with half of the sugar and heated to (50.0±2.0) °C with water purified with vigorous stirring. After swelling, previously prepared concentrate of excipients is added [13].

It is also important to calibrate the troche mold. The mold will need to be calibrated for each troche base: determine the average troche weight and calculate the density factor of substances that will be added to the troche base. Any additional substances added to the base will occupy a specific volume and an adjustment in the amount of base needed in the formulation will need to make [14].

The important step in the development of chewable troches is the choice of flavorings to correct the taste, color and odor. The decision tree for the choice of correctors of taste characteristics is shown in Fig. 3.

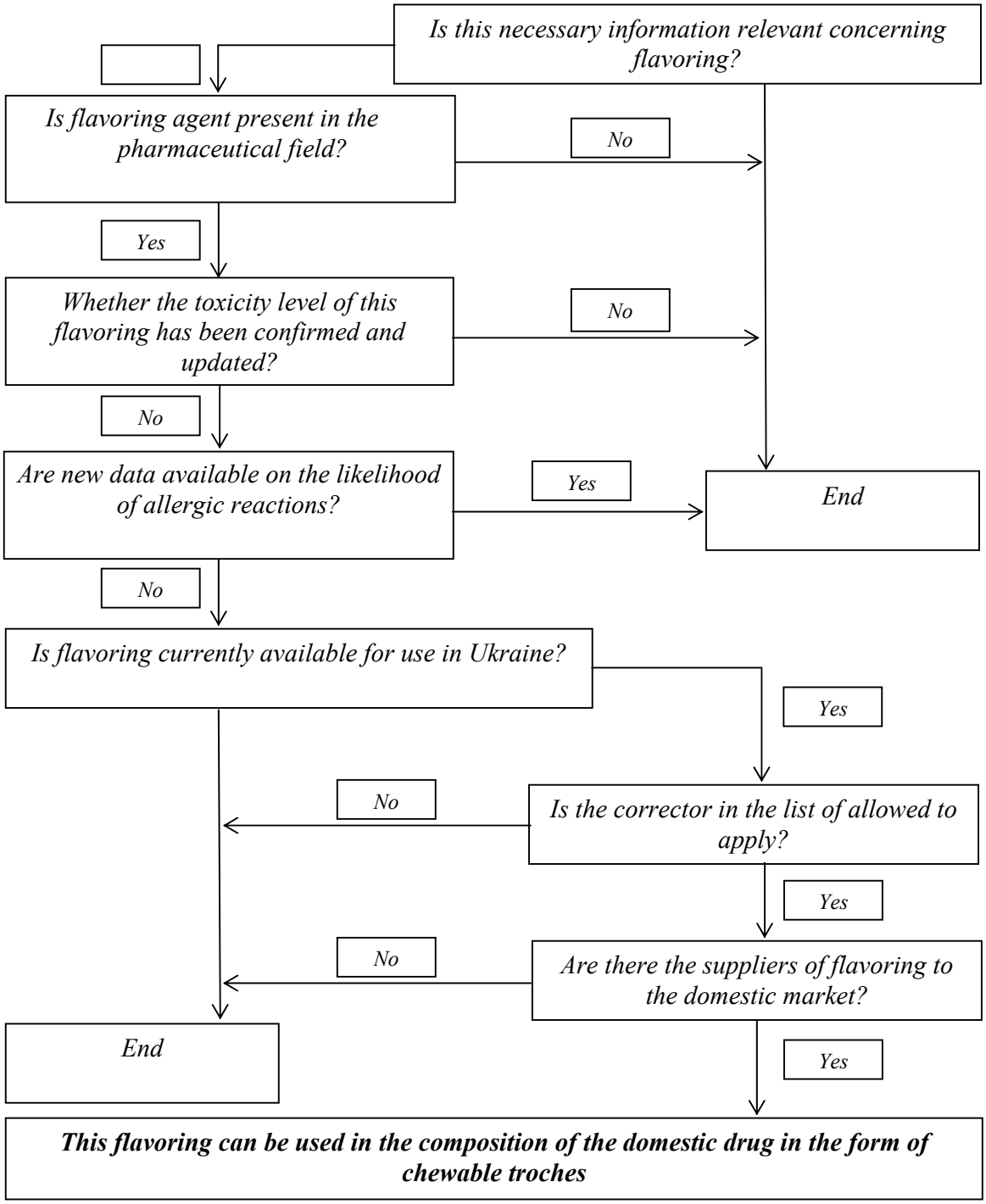

Fig. 3. Tree of decisions on the choice of flavorings to correct taste characteristics in the development of the composition of chewable troches

Thus, the first stage is the study of the physicochemical and pharmacotechnological properties of the selected API, as well as a theoretical justification for the choice of gel-forming agent (Fig. 2) and a number of excipients.

The following study of model samples of chewable troches of different formulations allows establishing the compatibility of the components and the most suitable ratio of excipients and gel-forming agent to ensure the proper quality of the medicinal product.

It is mandatory to carry out biopharmaceutical studies to determine the pharmacokinetic parameters of a medicinal product, including: the speed and completeness of API release. Since chewable troches must have pleasant taste characteristics, it is necessary to carry out biopharmaceutical studies to determine the taste index, which allows justifying the choice and concentration of flavorings (Fig. 3).

Thereby, the pharmaceutical development of drugs in the form of chewable troches involves the preliminary planning of the development stages, which are shown in Fig. 1.

Based on the findings, it is possible to determine the optimal composition of chewable troches for each individual APIs composition and to develop the appropriate preparation technology, taking into account the critical parameters of the production process.

Further studies relate to the adaptation of the proposed troches production technology to the actual conditions of the production process and the development of validated quality control techniques at each stage of production.

The quality control of the obtained chewable troches must correspond to the requirements of the SPhU and must include the uniformity of dosage units, uniformity of content, uniformity of mass.

Conclusions. 1. The main methodological aspects of the development of modern drugs in the form of chewable troches are described, taking into account the main stages of development of this dosage form.

2. The general algorithm of development of chewable troches is described and the basic stages of development of this dosage form are described.

3. The decision trees for the choice of gel-forming agent and flavorings to correct the taste characteristics for the development of chewable troches are given.

Conflicts of interest: authors have no conflict of interest to declare.

Конфлікт інтересів: відсутній.

МЕТОДОЛОГІЧНІ АСПЕКТИ РОЗРОБКИ ЛІКАРСЬКИХ ЗАСОБІВ У ФОРМІ ЖУВАЛЬНИХ ПАСТИЛОК

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Мета роботи. Вивчення основних методологічних аспектів розробки лікарських препаратів у вигляді жувальних пастилок.

Матеріали і методи. Об'єкти дослідження: праці вітчизняних і зарубіжних авторів, електронні бази даних Міністерства охорони здоров'я України та власні дослідження. Під час роботи були використані методи бібліосемантичного аналізу, систематизації теоретичного та практичного матеріалу та узагальнення даних.

Результати й обговорення. Описано основні підходи до фармацевтичної розробки оригінальних вітчизняних лікарських засобів, зокрема, у лікарській формі жувальних пастилок відповідно до вимог Настанови 42–3.1: 2004. Настанови з якості. Лікарські препарати: Фармацевтична розробка. Описано загальну схему фармацевтичної розробки жувальних пастилок. Запропоновано дерева рішень щодо вибору гелеутворювача та ароматизаторів для корекції смакових характеристик.

Висновки. Обґрунтовано доцільність розробки вітчизняного оригінального препарату у вигляді жувальних пастилок. Описано основні етапи фармацевтичної розробки цієї лікарської форми.

Ключові слова: методологія; фармацевтична розробка; технологія ліків; жувальні пастилки.

МЕТОДОЛОГИЧЕСКИЕ АСПЕКТЫ РАЗРАБОТКИ ЛЕКАРСТВЕННЫХ СРЕДСТВ В ФОРМЕ ЖЕВАТЕЛЬНЫХ ПАСТИЛОК

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Цель работы. Изучение основных методологических аспектов разработки лекарственных препаратов в виде жевательных пастилок.
Материалы и методы. Объекты исследования: труды отечественных и зарубежных авторов, электронные базы данных Министерства здравоохранения Украины и собственные исследования. Во время работы были использованы методы библиосемантического анализа, систематизации теоретического и практического материала и обобщения данных.
Результаты и обсуждение. Описаны основные подходы к фармацевтической разработке оригинальных отечественных лекарственных средств, в частности, в лекарственной форме жевательных пастилок в соответствии с требованиями Руководства 42-3.1: 2004. Руководства по качеству. Лекарственные препараты: Фармацевтическая разработка. Описана общая схема фармацевтической разработки жевательных пастилок. Предложены дерева решений по выбору гелеобразователя и ароматизаторов для коррекции вкусовых характеристик.
Выводы. Обоснована целесообразность разработки отечественного оригинального препарата в виде жевательных пастилок. Описаны основные этапы фармацевтической разработки данной лекарственной формы.

Ключевые слова: методология; фармацевтическая разработка; технология лекарств; жевательные пастилки.

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