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Сравнение фармакопейных требований, предъявляемых к оценке качества субстанции рыбьего жира в США и Великобритании

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РЕЗЮМЕ

Введение. В настоящее время на мировом фармацевтическом рынке растет количество высокоэффективных лекарственных препаратов, а требования к методам оценки качества лекарственных субстанций становятся все более жесткими. В то же время наблюдается явное отставание отечественных разработок новых методов анализа по сравнению с зарубежными странами.

Цель исследования. Целью исследования является сравнение фармакопейных требований, предъявляемых к оценке качества субстанции рыбьего жира в США и Великобритании, а также определение потенциальных показателей качества субстанции рыбьего жира и методов их оценки, которые могут быть использованы отечественными производителями.

Методы. Сравнительный анализ фармакопейных источников и нормативных документов, находящихся в свободном доступе.

Результаты. Проведен анализ фармакопейных требований к оценке качества субстанции рыбьего жира в США и Великобритании. В результате сопоставления требований и методов стандартизации установлено, что нормативная документация, регулирующая оценку качества субстанции рыбьего жира в США, практически совпадает с требованиями Британской Фармакопеи. Это свидетельствует о тесном сотрудничестве западных стран в разработке новых методов оценки качества рыбьего жира и лекарственных форм на его основе.

Заключение. Зарубежный опыт применения современных методов анализа рыбьего жира может быть использован для совершенствования соответствующих статей отечественной фармакопеи, а также в различных нормативных документах.

Ключевые слова: рыбий жир, Фармакопея США, Британская Фармакопея, анализ качества, стандартизация лекарственных препаратов.

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COMPARISON OF PHARMACOPOEIAL REQUIREMENTS FOR THE QUALITY OF FISH OIL IN USA AND THE GREAT BRITAIN

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SUMMARY

Introduction. Currently, the number of highly effective drugs is growing on the global pharmaceutical market, and the requirements for methods for assessing the quality of medicinal substances are becoming more stringent. At the same time, there is a clear lag in domestic developments of new methods of analysis in comparison with foreign countries.

Aim of the study. The aim of the study is to compare the pharmacopoeial requirements for assessing the quality of a fish oil substance in the USA and Great Britain, as well as to determine potential indicators of the quality of a fish oil substance and methods for their assessment that can be used by domestic manufacturers.

Methods. Comparative analysis of pharmacopoeial sources and regulatory documents that are freely available.

Results. The analysis of pharmacopoeial requirements for assessing the quality of the substance of fish oil in the United States and the UK was provided. As a result of a comparison of requirements and standardization methods, it has been established that the regulatory documentation governing the assessment of the quality of the fish oil substance in the United States of America practically coincides with the requirements in the British Pharmacopoeia. This indicates close cooperation between Western countries in the development of new methods for assessing the quality of the fish oil substance and dosage forms based on it.

Conclusion. Foreign experience in the use of modern methods of analysis of fish oil can be used to improve the relevant articles of the domestic pharmacopoeia, as well as in various regulatory documents.

Key words: fish oil, Pharmacopoeia of the USA, British Pharmacopoeia, quality standards, standardization of medicines.

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The dynamically developing pharmaceutical industry determines the need for a new approach to the composition, properties, technologies, methods of assessing the quality of drugs that should not only help in the treatment of diseases, but also contribute to their prevention, preserve health and longevity. Analysis of the drug utilization and biological active supplements, containing fish oil, indicates on the dynamic growth of this segment of pharmacy sales, which leads to evaluation and improving already available methods [1–3].

Foreign experience in improving methods for assessing the quality of substances can be divided into two categories: the development of new methods of analysis and the modernization of existing methods [4]. The second category has the most interest, because, for example, combining quality assessment methods allows obtaining more accurate data, and also significantly reducing the financial costs of analytical instruments. Examples of such methods are the combination of GC-MS and NMR for the quantification of fatty acid content in fish oil or the analysis of fatty acids using supercritical liquid chromatography [5, 6].

The American and British pharmaceutical industries operate according to international GMP standards, as a result of which requirements for the quality of medicines and methods for their standardization are tightened from year to year. The domestic pharmaceutical market is gradually moving to the international GMP standard, introducing the relevant indicators and quality assessment requirements. However, due to the peculiarities of the Russian legislation, this process is lengthy, therefore, in domestic documents, analysis methods are often presented that do not meet modern requirements.

The aim of the work is to compare the pharmacopoeial requirements for assessing the quality of the fish oil substance in the USA and the UK, as well as to determine the potential indicators of the quality of the fish oil substance and methods for their assessment that can be used by domestic producers.

Due to lack of essential changes between pharmacopoeias of USA in several years, Pharmacopoeia of USA 2009 was chosen as available representative. The British Pharmacopoeia was chosen for comparison as a foreign standard, as it essentially represents the base of the European Pharmacopoeia and includes similar methods for the analysis of substances and drugs.

In the Pharmacopoeia of USA, the source of cod liver oil could be the cod liver of the Atlantic – *Gadus morrhua* L., cod of the Baltic – *Gadus callarias* L., cod of the Pacific cod – *Gadus microcephalus* Tilesius, haddock – *Gadus aeglefinus* L., *Gadiae gadiae* families. The cod is previously desteharinized, and, if necessary, add flavoring or antioxidant. In the British Pharmacopoeia, only one species of cod, *Gadus morrhua* L., is described, but it is mentioned that other species of the *Gadiae* family can be used.

The methods for evaluating the «Authenticity» indicator in the Pharmacopoeia of USA and the British Pharmacopoeia are also different. Authenticity in the Pharmacopoeia of USA is proved by chemical reaction with antimony chloride in the presence of chloroform (the latter is colored in blue due to the presence of vitamin A in fish oil). In addition, method of gas chromatography for the determination of a mixture of fatty acids (palmitic, stearic, oleic and others) is presented. The British Pharmacopoeia offers spectrophotometry in qualitative analysis for trans-retinol, as well as liquid chromatography. For the qualitative determination of vitamin D_3 (cholecalciferol) the liquid chromatography method is used. Just like in the Pharmacopoeia of USA, a color reaction with antimony chloride is carried out.

Determination of the density (the same 0.917–0.930 g/cm^3), iodine value (140–175 and 150–180), unsaponifiable matter (no more than 1.3 and 1.5%), anisidine value (the same maximum 30.0), respectively, indicated in both the national and in the British Pharmacopoeia.

The quantitative determination of vitamin A in the British and American Pharmacopoeias is carried out by modern methods, such as UV-spectrophotometry and liquid chromatography; the method of liquid chromatography is used for vitamin D_3 determination.

Requirements for storage the substance of fish oil, presented in both Pharmacopoeia: in a well-closed container, protected from sunlight. However, the Pharmacopoeia of USA noted that the unused fish oil should be placed in an atmosphere with an inert gas or vacuum; and in the British Pharmacopoeia – the need to use fish oil as soon as possible or to place unused fish oil in the atmosphere only with an inert gas (this is also necessary in the absence of an antioxidant in the composition).

Regarding the differences between the two regulatory documents, it should be noted that the article in the British Pharmacopoeia begins with a description of the pharmacological action and application of fish oil that is not available in the Pharmacopoeia of USA. According to authenticity, gas chromatography determination of a mixture of fatty acids: palmitic, stearic, oleic and others takes place in the American Pharmacopoeia. British Pharmacopoeia uses spectrophotometry and liquid chromatography for the detection of trans-retinol

Comparison of Pharmacopoeial Requirements for Cod Liver Fish Oil by Pharmacopoeia of USA and British Pharmacopoeia

Index	Pharmacopoeia of USA	British Pharmacopoeia
Source	The cod liver of the Atlantic – *Gadus morrhua* L., cod of the Baltic – *Gadus callarias* L., cod of the Pacific cod – *Gadus microcephalus* Tilesius, haddock – *Gadus aeglefinus* L., *Gadiae gadiae* families. The cod is previously desteharinized, and, if necessary, add flavoring or antioxidant	Liver cod Atlantic – *Gadus morrhua* L., as well as other species of the cod family – *Gadiae* (not specified)
Authenticity	1. Color reaction with antimony chloride in chloroform (the chloroform layer turns blue due to the presence of vitamin A in fish oil). 2. Gas Chromatography (determination of a mixture of fatty acids: palmitic, stearic, oleic and others)	1. Color reaction with antimony chloride in chloroform (the chloroform layer turns blue due to the presence of vitamin A in fish oil). 2. Spectrophotometry and Liquid chromatography (the presence of trans-retinol). 3. Liquid Chromatography (vitamin D_3)
Relative density, 20°C, g/cm^3	0.917–0.930	0.917–0.930
Acid value	–	Maximum 2.0
Iodine value	145–180	150–180
Saponification value	180–192	–
Unsaponifiable matter, %	Maximum 1.3	Maximum 1.5
Anisidine value	Maximum 30.0	Maximum 30.0
Stearin	Remains clear after cooling in iced water for 3 hours (the quantity of sample is notspecified)	10 ml remains clear after cooling in iced water for 3 hours
Color value	To withstand comparison with the standard of color	–
Peroxide value	–	Maximum 10,0
Assay	Vitamin A: UV-spectrophotometry and HPLC. Vitamin D: HPLC. Composition of fatty acids: GC	Vitamin A: UV-spectrophotometry and HPLC. Vitamin D: HPLC. Composition of fatty acids: GC
Storage	In an airtight and well-filled container, protected from light. It is possible to use a vial or containers to store fish oil. Unused fish oil should be placed in an atmosphere with an inert gas or vacuum	In an airtight and well-filled container, protected from light. If no antioxidant is added, store under an inert gas. Once the container has been opened, its contents are used as soon as possible and any part of the contents not used at once is protected by an atmosphere of inert gas
Use	–	Source of vitamins A and D

and liquid chromatography for vitamin D_3. Also in the British Pharmacopoeia, the amount of the acid value (maximum 2.0) and the peroxide value (not more than 10.0) is present. These indicators are absent in the Pharmacopoeia of USA. However, in the American Pharmacopoeia there is such an indicator as «Saponification value» and «Color value», which is absent in the British Pharmacopoeia. The difference also applies to the quantitative determination: in the British Pharmacopoeia, the content of the composition of fatty acids is normalized by the method of gas chromatography.

The British and American pharmacopoeial articles on fish oil contain almost the same quantity indicators for assessing the quality of the substance. This can be explained by developed communications between scientific and governmental societies in both countries, which help them to evaluate available methods and develop news. The results of a comparison of the pharmacopoeial requirements for assessing the quality of the fish oil substance in the USA and the British are presented in the Table.

Conclusion

The analysis of the requirements imposed by the Pharmacopoeia of USA and the British Pharmacopoeia for the analysis of the quality of the fish oil substance revealed both the most frequently encountered research methods and methods that, due to their physicochemical characteristics, are not suitable for standardization in modern conditions. Among the first it should be noted chromatographic studies, which are suitable for both qualitative analysis and quantitative determination. The use of a qualitative reaction with antimony chloride remains a sensitive and simple method of detecting vitamin A in the substance of fish oil, therefore, it is also used in modern practice. In the American and British Pharmacopoeias, a more modern and informative chromatography method is used for quantitative analysis.

Improving methods for assessing the quality of substances is an integral part of the developing pharmaceutical industry. Foreign state standards are constantly updated, which is associated with the development of new modern methods that meet the requirements for assessing the quality of drugs derived from substances of natural origin [7, 8]. Updating the regulatory documentation of the pharmaceutical industry in the Russian Federation is quite rare. It should also be noted that when updating regulatory documents, positive foreign experience is not always taken into account. For example, the State Pharmacopoeia of the Russian Federation XIV edition in the pharmacopoeia article «Fish liver oil fat» normalizes the content of only eicosapentaenoic and docosahexaenoic acids, as well as the content of the sum of polyunsaturated acids, while the American Pharmacopoeia analyzes the fatty acid profile of the fish oil substance [9].

The use and interpretation of foreign experience, as well as the improvement of domestic regulatory documentation governing the quality of the substance of fish oil and preparations based on it, is one of the main tasks of Russian pharmacy.

Conflict of interest
The authors declare no conflict of interest

Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов

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