ПАТОЛОГИЯ ЖИВОТНЫХ, МОРФОЛОГИЯ, ФИЗИОЛОГИЯ, ФАРМАКОЛОГИЯ И ТОКСИКОЛОГИЯ / ANIMAL PATHOLOGY, MORPHOLOGY, PHYSIOLOGY, PHARMACOLOGY AND TOXICOLOGY

DOI: https://doi.org/10.23649/JAE.2023.40.9

KEY COMPONENTS OF BIOEQUIVALENCE ASSESSMENT OF MEDICINAL PRODUCTS FOR VETERINARY USE

Research article

Ponamarev V.S.[1, *]
[1] ORCID : 0000-0002-6852-3110;
[1] St. Petersburg State University of Veterinary Medicine, Saint-Petersburg, Russian Federation

* Corresponding author (psevdopyos[at]mail.ru)

Abstract

One of the key concepts associated with the simplified registration procedure is bioequivalence. Thus, the legislation allows providing bioequivalence studies in the registration dossier instead of a clinical trial report (confirming the clinical and therapeutic effectiveness of the medicine under investigation). However, the concept of bioequivalence itself is a complex concept.

All the components of bioequivalence are interconnected and interdependent. Pharmaceutical bioequivalence is the basis for assessing pharmacological equivalence. And therapeutic equivalence includes both pharmaceutical and pharmacological equivalence. A coincidence of only one type of equivalence does not allow us to draw a conclusion about the overall bioequivalence of the medicine under study.

Keywords: bioequivalence, pharmacokinetic equivalence, veterinary medicinal product.

КЛЮЧЕВЫЕ КОМПОНЕНТЫ ОЦЕНКИ БИОЭКВИВАЛЕНТНОСТИ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ ДЛЯ ПРИМЕНЕНИЯ В ВЕТЕРИНАРИИ

Научная статья

Понамарёв В.С.[1, *]
[1] ORCID : 0000-0002-6852-3110;
[1] Санкт-Петербургский государственный университет ветеринарной медицины, Санкт-Петербург, Российская Федерация

* Корреспондирующий автор (psevdopyos[at]mail.ru)

Аннотация

Одним из ключевых понятий, связанных с упрощенной процедурой регистрации, является биоэквивалентность. Так, законодательство разрешает предоставлять в регистрационном документе исследования биоэквивалентности вместо отчета о клиническом исследовании (подтверждающего клиническую и терапевтическую эффективность исследуемого препарата). Однако сама концепция биоэквивалентности является сложным понятием.

Все компоненты биоэквивалентности взаимосвязаны и взаимозависимы. Фармацевтическая биоэквивалентность является основой для оценки фармакологической эквивалентности. Терапевтическая эквивалентность включает в себя как фармацевтическую, так и фармакологическую эквивалентность. Совпадение только одного вида эквивалентности не позволяет сделать вывод об общей биоэквивалентности исследуемого препарата.

Ключевые слова: биоэквивалентность, фармакокинетическая эквивалентность, ветеринарное лекарственное средство.

Introduction

Veterinary medications play an important role in ensuring the health and welfare of animals. However, in order to introduce a new pharmaceutical to the market, the registration process can be quite extensive and complex. In recent years, simplification of the registration procedure for veterinary medicines has become a hot topic for discussion, especially since major changes in veterinary legislation also contribute to some simplification of such procedures [1], [2].

A simplified procedure for registration of veterinary drugs, based on the principle of bioequivalence, allows reducing the time and costs associated with research and testing. This is especially important for small and medium-sized manufacturers, who may not have sufficient financial resources to conduct extensive clinical trials [3], [4].

One of the key concepts related to the simplified registration procedure is bioequivalence. Thus, the legislation allows providing bioequivalence studies in the registration dossier instead of a clinical trial report (confirming the clinical and therapeutic effectiveness of the medicine under investigation). However, the concept of bioequivalence itself is a complex, composite concept [5], [6].

Recently, in international and national databases of scientific publications, there has been a growing number of publications describing the similarities in the pharmacokinetics of several pharmaceuticals, after which a conclusion is made about their bioequivalence, which is a rather controversial issue requiring discussion [7], [8].

The main goal of the study is to analyze national and supranational legislation in the field of drug bioequivalence studies and identify key points based on which the drugs under study can be considered truly equivalent.

Research methods and principles

The scientific novelty of the publication lies in the comprehensiveness of the review about the existing regulatory framework in the field of bioequivalence studies of medications. The search and processing of scientific publications was performed in accordance with the recommendations of H. Snyder for writing review articles. The information retrieval methodology was based on such general scientific methods of cognition as: a review of specialized search engines and scientific and research databases (Scopus, WoS, PubMed, scientific electronic library eLIBRARY.RU) over the past 10 years, from which the most informative ones were selected, analysis of identified results, comparing them by relevance. Articles published before 2013 were used only if they contained information critical to the topic that was missing in later publications.

Main results

The main guidance documents regulating the conduct of bioequivalence studies of medicinal products for veterinary use are: Rules for regulating the circulation of veterinary medicinal products in the customs territory of the Eurasian Economic Union, Federal Law dated 04/12/2010 N 61-FZ (as amended on 08/04/2023) “On the circulation of medicines” (with amendments and additions, entered into force on September 1, 2023) [9], Decision of the Eurasian Economic Commission No. 85 of November 3, 2016 “On approval of the rules for conducting bioequivalence studies of medicines within the Eurasian Economic Union" [10], order No. 846 “On approval of the Administrative Regulations of the Federal Service for Veterinary and Phytosanitary Surveillance for the provision of state services for state registration of medicinal products for veterinary use” dated July 28, 2021 [11]; Order of the Ministry of Agriculture of the Russian Federation dated March 6, 2018 No. 101 “On approval of the rules for conducting a preclinical study of a medicinal product for veterinary use, a clinical trial of a medicinal product for veterinary use, a study of the bioequivalence of a medicinal product for veterinary use” [12].

Summarizing the above regulatory documents, we can conclude about the structure of a multi-stage study that allows drugs to be considered bioequivalent, namely: the components of bioequivalence include pharmaceutical bioequivalence, pharmacological equivalence and therapeutic equivalence. Each of these components has its own role and significance in the evaluation and comparison of various medicines.

Pharmaceutical bioequivalence is the first step in evaluating the equivalence of medications. It means that two pharmaceuticals containing the same active substance in the same dosage should be as similar in physical and chemical properties as possible. This includes parameters such as tablet size, shape, color, consistency, and other physical characteristics. Pharmaceutical bioequivalence ensures that both drugs have the same pharmaceutical form and properties, which is important to ensure their stability and safety. In this study, the most debatable issue is the influence of excipients on the overall conclusion of pharmaceutical bioequivalence. The key to this issue is to compare the solubility/degradability of the dosage form or a reference to other forms of equivalence.

Pharmacological equivalence is the next step in bioequivalence assessment. It suggests that two medicines that are pharmaceutically equivalent should have a similar pharmacokinetic profile. This means that after taking the medication, it must be adequately absorbed, distributed, metabolized and eliminated from the body. Pharmacological equivalence ensures that both drugs have the same bioavailability and effect, which is important for achieving the desired therapeutic effect.

Therapeutic equivalence is the final step in assessing bioequivalence. It assumes that two pharmaceuticals that are pharmacologically equivalent should have similar therapeutic effects. This means that they must have the same efficacy and safety when used in clinical practice. Therapeutic equivalence ensures that medicine can be used interchangeably and still achieve the expected outcome for the patient.

All the components of bioequivalence are interconnected and interdependent. Pharmaceutical bioequivalence is the basis for assessing pharmacological equivalence, and therapeutic equivalence includes both pharmaceutical and pharmacological equivalence. The coincidence of only one type of equivalence does not allow us to draw a conclusion about the general bioequivalence of the drugs under study.

Conclusion

In conclusion, the components of bioequivalence — pharmaceutical bioequivalence, pharmacological equivalence, and therapeutic equivalence — are key elements in the evaluation and comparison of different drugs. Their comprehensive consideration makes it possible to determine how similar the medications are to each other and how they can be interchangeable in clinical practice. This is important to ensure the safety and effectiveness of pharmaceutical treatment.

Interest in bioequivalence studies continues to grow, since the development of new pharmaceuticals and their analogues requires mandatory verification of identity and the acceptability of substitutions. Thanks to these studies, both animals and veterinary professionals can be confident in the quality and safety of the medications they use.

Конфликт интересов

Не указан.

Рецензия

Сообщество рецензентов Международного научно-исследовательского журнала
DOI: https://doi.org/10.23649/JAE.2023.40.9.1

Conflict of Interest

None declared.

Review

International Research Journal Reviewers Community
DOI: https://doi.org/10.23649/JAE.2023.40.9.1

Список литературы / References

1. Талибов О.Б. Нюансы клинической фазы исследований биоэквивалентности / О.Б. Талибов // Разработка и регистрация лекарственных средств. — 2014. — № 1(6). — С. 82-85.

2. Драницына М.А. Свойства процедуры двух односторонних тестов для признания биоэквивалентности лекарственных препаратов / М.А. Драницына, Т.В. Захарова, Р.Р. Ниязов // Ремедиум. — 2019. — № 3. — С. 40-47. — DOI: 10.21518/1561-5936-2019-3-40-47.

3. Яичков И.И. Основные ошибки в аналитической части исследований биоэквивалентности и фармакокинетики / И.И. Яичков, Ю.А. Джурко, Л.Н. Шитов // Медицинская этика. — 2018. — Т. 6. — № 1. — С. 33-38.

4. Ромодановский Д.П. Регуляторные требования Европейского агентства по лекарственным средствам к оценке биоэквивалентности препаратов с модифицированным высвобождением / Д.П. Ромодановский, Н.Н. Еременко, Д.В. Горячев // Ведомости Научного центра экспертизы средств медицинского применения. — 2019. — Т. 9. — № 1. — Р. 28-33. — DOI: 10.30895/1991-2919-2019-9-1-28-33.

5. Свидетельство о государственной регистрации программы для ЭВМ № 2020666714 Российская Федерация. Прогнозирование результатов биоэквивалентности лекарственных препаратов / Ромодановский Д.П., Горячев Д.В., Уварова Н.Е.; заявитель Научный центр экспертизы медицинских изделий. — № 2020666151: заявка. 08.12.2020: опубл. 12.14.2020

6. Умарова З.Х.А. Биологическая доступность и биоэквивалентность лекарственных средств / З.Х.А. Умарова, О.В. Малыхина, К.С. Юсупова [и др.] // Информационное обеспечение как двигатель научного прогресса. — Оренбург: ОМЕГА САЙНС, 2019. — Т. 2. — С. 9-11.

7. Хохлов А.Л. Организационные аспекты проведения исследований биоэквивалентности / А.Л. Хохлов, И.Н. Каграманян, Е.Г. Лилеева [и др.] // Саратовский научно-медицинский журнал. — 2014. — Т. 10. — № 1. — С. 203-210.

8. Борщевская М.И. Описание профилей растворения в рамках исследования биоэквивалентности "in vitro" / М.И. Борщевская, А.И. Гризодуб, О.С. Ремез [и др.] // Управління, економіка та забезпечення якості в фармації. — 2013. — № 4(30). — С. 23-29.

9. Российская Федерация. Законы. Об обращении лекарственных средств: федер. закон: [от 12.04.2010 N 61-ФЗ]. — Москва: Проспект; СПб.: Кодекс, 2010. — 124 с.

10. Об утверждении Правил проведения исследований биоэквивалентности лекарственных средств в рамках Евразийского экономического союза: Решение Совета Евразийской экономической комиссии от 3 ноября 2016 г. № 85 (ред. от 15 февраля 2023 г). — Астана, 2016. — 161 с.

11. Российская Федерация. Приказ. Об утверждении Административного регламента Федеральной службы по ветеринарному и фитосанитарному надзору по оказанию государственных услуг по государственной регистрации лекарственных препаратов для ветеринарного применения: Приказ № 846: [утвержден Федеральной службой по ветеринарному и фитосанитарному надзору 28 июля , 2021: Зарегистрировано в Минюсте России 24 ноября 2021 года]. — Москва, 2021. — 58 с.

12. Российская Федерация. Приказ. Об утверждении правил проведения доклинического исследования лекарственного препарата для ветеринарного применения, клинического исследования лекарственного препарата для ветеринарного применения, исследования биоэквивалентности лекарственного препарата для ветеринарного применения: приказ № 101: [утверждён Министерством Минсельхоза РФ 6 марта 2018 г.: Зарегистрировано в Минюсте России 5 июня 2018 г]. — Москва, 2018. — 25 с.

Список литературы на английском языке / References in English

1. Talibov O.B. Njuansy klinicheskoj fazy issledovanij biojekvivalentnosti [Nuances of the Clinical Phase of Bioequivalence Studies] / O.B. Talibov // Razrabotka i registracija lekarstvennyh sredstv [Development and Registration of Medicines]. — 2014. — № 1(6). — P. 82-85. [in Russian]

2. Dranicyna M.A. Svojstva procedury dvuh odnostoronnih testov dlja priznanija biojekvivalentnosti lekarstvennyh preparatov [Properties of the Procedure of Two One-sided Tests for Recognizing the Bioequivalence of Drugs] / M.A. Dranicyna, T.V. Zaharova, R.R. Nijazov // Remedium. — 2019. — № 3. — P. 40-47. — DOI: 10.21518/1561-5936-2019-3-40-47. [in Russian]

3. Jaichkov I.I. Osnovnye oshibki v analiticheskoj chasti issledovanij biojekvivalentnosti i farmakokinetiki [Main Errors in the Analytical Part of Bioequivalence and Pharmacokinetics Studies] / I.I. Jaichkov, Ju.A. Dzhurko, L.N. Shitov // Medicinskaja jetika [Medical Ethics]. — 2018. — Vol. 6. — № 1. — P. 33-38. [in Russian]

4. Romodanovskij D.P. Reguljatornye trebovanija Evropejskogo agentstva po lekarstvennym sredstvam k ocenke biojekvivalentnosti preparatov s modificirovannym vysvobozhdeniem [Regulatory Requirements of the European Medicines Agency for Assessing the Bioequivalence of Drugs with Modified Release] / D.P. Romodanovskij, N.N. Eremenko, D.V. Gorjachev // Vedomosti Nauchnogo centra jekspertizy sredstv medicinskogo primenenija [Bulletin of the Scientific Center for Expertise of Medicinal Products. Regulatory Research and Examination of Medicines]. — 2019. — Vol. 9. — № 1. — P. 28-33. — DOI: 10.30895/1991-2919-2019-9-1-28-33. [in Russian]

5. Certificate of state registration of a computer program No. 2020666714 Russian Federation. Prognozirovanie rezul'tatov biojekvivalentnosti lekarstvennyh preparatov [Forecasting the Results of Bioequivalence of Drugs] / Romodanovskij D.P., Gorjachev D.V., Uvarova N.E.; applicant Scientific Center for Expertise of Medical Products. — № 2020666151: application. 12/08/2020: publ. 12/14/2020 [in Russian]

6. Umarova Z.H.A. Biologicheskaja dostupnost' i biojekvivalentnost' lekarstvennyh sredstv [Biological Availability and Bioequivalence of Medicines] / Z.H.A. Umarova, O.V. Malyhina, K.S. Jusupova [et al.] // Informacionnoe obespechenie kak dvigatel' nauchnogo progressa [Information Support As An Engine Of Scientific Progress]. — Orenburg: OMEGA SAJNS, 2019. — Vol. 2. — P. 9-11. [in Russian]

7. Hohlov A.L. Organizacionnye aspekty provedenija issledovanij biojekvivalentnosti [Organizational Aspects of Conducting Bioequivalence Studies] / A.L. Hohlov, I.N. Kagramanjan, E.G. Lileeva [et al.] // Saratovskij nauchno-medicinskij zhurnal [Saratov Medical Scientific Journal]. — 2014. — Vol. 10. — № 1. — P. 203-210.[in Russian]

8. Borshhevskaja M.I. Opisanie profilej rastvorenija v ramkah issledovanija biojekvivalentnosti "in vitro" [Description of Dissolution Profiles within the Framework of an “in Vitro” Bioequivalence Study] / M.I. Borshhevskaja, A.I. Grizodub, O.S. Remez [et al.] // Upravlinnja, ekonomika ta zabezpechennja jakosti v farmaciï [Management, Economics and Quality Assurance in Pharmacy]. — 2013. — № 4(30). — P. 23-29. [in Russian]

9. Rossijskaja Federacija. Zakony. Ob obrashhenii lekarstvennyh sredstv [Russian Federation. Laws. On the circulation of medicines]: Federal Law: [dated April 12, 2010 N 61-FZ]. — Moscow: Prospekt; SPb.: Kodeks, 2010. — 124 p. [in Russian]

10. Ob utverzhdenii Pravil provedenija issledovanij biojekvivalentnosti lekarstvennyh sredstv v ramkah Evrazijskogo jekonomicheskogo sojuza [On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union]: Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 N 85 (as amended on February 15, 2023). — Astana, 2016. — 161 p. [in Russian]

11. Rossijskaja Federacija. Prikaz. Ob utverzhdenii Administrativnogo reglamenta Federal'noj sluzhby po veterinarnomu i fitosanitarnomu nadzoru po okazaniju gosudarstvennyh uslug po gosudarstvennoj registracii lekarstvennyh preparatov dlja veterinarnogo primenenija [Russian Federation. Order. On Approval of the Administrative Regulations of the Federal Service for Veterinary and Phytosanitary Supervision for the Provision of State Services for State Registration of Medicinal Products for Veterinary Use]: Order № 846: [adopted by the Federal Service for Veterinary and Phytosanitary Surveillance on July 28, 2021: Registered with the Ministry of Justice of Russia on November 24, 2021]. — Moscow, 2021. — 58 p. [in Russian]

12. Rossijskaja Federacija. Prikaz. Ob utverzhdenii pravil provedenija doklinicheskogo issledovanija lekarstvennogo preparata dlja veterinarnogo primenenija, klinicheskogo issledovanija lekarstvennogo preparata dlja veterinarnogo primenenija, issledovanija biojekvivalentnosti lekarstvennogo preparata dlja veterinarnogo primenenija [Russian Federation. Order. On Approval of the Rules for Conducting a Preclinical Study of a Medicinal Product for Veterinary Use, a Clinical Trial of a Medicinal Product for Veterinary Use, a Bioequivalence Study of a Medicinal Product for Veterinary Use]: Order № 101: [adopted by the Ministry of Agriculture of the Russian Federation on March 6, 2018: Registered with the Ministry of Justice of Russia on June 5 2018]. — Moscow, 2018. — 25 p. [in Russian]