












# AN INVESTIGATION ON AVAILABILITY AND EFFICACY OF ANTI-ANEMIC DRUGS FOR PIGS IN THE UKRAINIAN PHARMACEUTICALS

Iryna DERKACH , Serhii DERKACH , Volodymyr DUKHNYTSKYI , Oleksandr VALCHUK , Yurii ZHUK , Nataliia SLOBODYANYUK , Vadym KONDRATIUK , Sergii GRYSHCENKO , Maxim GUDZENKO , Tatyana ROZBYTSKA , Mykola GRUNTOVSKYI 

National University of Life and Environmental Sciences of Ukraine, Heroyiv Oborony st., 15, Kyiv, 03041, Ukraine

Email: [derkach\\_im@nubip.edu.ua](mailto:derkach_im@nubip.edu.ua)

Supporting Information

**ABSTRACT:** Antianemic drugs are used to prevent anemia, majorly iron deficiency anemia. Drugs with such pharmacological action are especially relevant for piglets, as animals of this species at this age are particularly sensitive to iron deficiency. The present investigation aimed at studying the pharmaceutical market of antianemic drugs registered in Ukraine during 2017-2022. It should be noted that if the drug is registered, it has been checked for safety according to the food industry standards of Ukraine. In 2017, the national market of veterinary iron-containing drugs was represented by 13 drugs from the group QB03A "Antianemic drugs. Drugs of iron", according to the ATC-vet classification. The range of these drugs by 38 % was provided by pharmaceutical products of Ukrainian manufacturers: "O.L.KAR-AgroZooVet-Service", "Pharmaton", "Brovapharma", "Experimental production of the Institute of Epizootology", "Biopharm", and "Vetsintez". Imported products (62 %) were represented by Pharmacosmos, Merial, Koofavet, "Vugen B&G", "Biovet Pulawy", "Interchem Verken De Adelaar", and "Bioveta". In general, the modern pharmaceutical market of veterinary drugs in Ukraine during 2017-2022 was sufficiently provided with antianemic drugs for pigs and mostly imported drugs. The percentage of antianemic drugs of Ukrainian production prevailed in 2020, however the imported drugs of this pharmacological group's was higher in 2022. It can be concluded that the drugs of non-Ukrainian production predominated among antianemic drugs in Ukraine during 2017-2022. Based on the obtained results, we can state that in Ukraine there is a need for the development and/or production of domestic anti-anemic drugs. They must be effective and ensure a reduction in the dependence of the national pharmaceutical market of drugs of this group on foreign manufacturers.

**Keywords:** Anemia, Availability, Iron, Pigs, Veterinary drugs.

## INTRODUCTION

Iron deficiency anemia is the most common anemic syndrome and accounts for approximately 80% of all anemias (Lopez et al., 2016). On the other hand, anemia is one of the most common diseases in newborn piglets (Szudzik et al., 2018). anemia is one of the most common diseases of newborn piglets, causing significant economic damage. Some reports describe that anemia rate in newborn piglets is 100%, and 20-30% of the mortality of young pigs in the first weeks of life is caused by iron deficiency. This is explained by the fact that the reserves of vital microelements deposited in the tissues are depleted within the first 5-7 days of piglets' life and this deficiency provokes the development of alimentary or iron deficiency anemia. This is one of the most important and unresolved issues in modern pig farming (Svoboda and Drabek, 2005; Levchenko et al., 2015; Perri et al., 2016).

In medicine and veterinary medicine of the twentieth century, internally used drugs were widely based on iron(II) sulfate, and parenteral used ones on iron(III) dextran (Svoboda et al., 2017; Szudzik et al., 2018). However, the use of iron dextran drugs in large doses is not always safe, because iron has prooxidant properties (Pamučar, 2018). Iron dextran drugs are still widely used in practical veterinary medicine. Consequently, the basis of treatment and prevention of anemia of pigs is the use of appropriate antianemic drugs. Moreover, their safe use in animals is important for the food industry's safety.

Considering that anemia causes great losses in pig farming worldwide (Godyń et al., 2016; Perri et al., 2016), many researchers are working on the pharmacological aspects of new anti-anemic drugs and methods of their administration. For instance, Maes et al. (2011) compared the effect of oral versus parenteral iron supplementation on the health and productivity of piglets; Meier et al. (2011) studied the physicochemical and toxicological characterization of a new generic iron sucrose preparation; Starzyński et al. (2013) analyzed correction of iron deficiency anemia without affecting plasma hepcidin levels; Streyl et al. (2015) described the field evaluation of the effectiveness of an oral toltrazuril and iron combination (Baycox® Iron) in maintaining weaning weight by preventing coccidiosis and anaemia in neonatal piglets;

Antileo et al. (2016) characterized a novel encapsulated oral iron supplement to prevent iron deficiency anemia in neonatal piglets; Gan et al. (2017) described the effect of iron dextran on the transcriptome of pig hippocampus; Szudzik et al. (2018) studied iron supplementation in suckling piglets as an ostensibly easy therapy of neonatal iron deficiency anemia; Churio et al. (2018) described the use of encapsulation technology to improve the efficiency of an iron oral supplement to prevent anemia in suckling pigs; Knight et al. (2018) analyzed the longitudinal effects of iron deficiency anemia and subsequent repletion on blood parameters and the rate and composition of growth in pigs; and Szudzik et al. (2020) showed the long-term effect of split iron dextran/hemoglobin supplementation on erythrocyte and iron status, growth performance, carcass parameters, and meat quality of pigs.

Some studies reported the application of iron-containing drugs in pregnant sows in the last weeks of (Ulyzko and Todorov, 2014; Bhattarai et al., 2019). Dukhnytsky et al. (2021) and Derkach et al. (2021) found that the content of iron in the colostrum of sows, supplemented with solutions of iron (IV) clatrocchelate and cyanocobalamin during gestation was about 52% higher than sows of the control group on the first day after farrowing. After 4 days, it was about 111 higher and after 7 days, about 175 % higher.

The present investigation aimed at analyzing the pharmaceutical market trends of the pharmaceutical market of antianemic drugs for pigs registered in Ukraine during 2017–2022. Official state websites with information on the registration of veterinary drugs were used in particular.

## MATERIALS AND METHODS

### Structure

The comparative analysis trends of the pharmaceutical market of antianemic drugs for pigs registered in Ukraine during 2017–2022 was conducted by analyzing literary information sources and official government sources in this regard. Description of the Experiment: we analyzed official state data on veterinary drugs registered in Ukraine, which were initially available via a link <http://vet.gov.ua/node/888> (no longer available), and in recent years, due to the reorganization of state structures, using another official source (<https://dpss.gov.ua/bezpechnist-harchovih-produktiv-ta-veterinarna-medicina/reystri>). Number of repeated analyses: 6 (every year from 2017 to 2022).

Design of the experiment: our experiment aimed at establishing the main trends of development in the pharmaceutical market of anti-anemic drugs. Official public state data showing the registration of veterinary drugs were used for this purpose. The number of anti-anemic drugs and their manufacturers during the last 6 years was analyzed. Also, the composition of drugs presented by various Ukrainian and foreign pharmaceutical companies was compared. Thus, it was concluded that the national pharmaceutical market of veterinary drugs is provided with anti-anemic drugs for pigs since the anemia problem in pig farming does not lose its relevance. It should be noted that if the drug is registered in Ukraine, it has been tested by all necessary procedures, the results of which prove its safety for the food industry of Ukraine.

The analysis of research results with the use of descriptive statistics is carried out. Statistical analysis data were prepared using Microsoft Excel.

## RESULTS AND DISCUSSION

The Ukrainian scientists are working on developing and studying the pharmacological action of new antianemic drugs to provide the national pharmaceutical market with high-quality drugs that can compete with imported ones and meet the demand for such drugs in Ukraine (Prokopenko and Martynov, 2012; Pristupa et al., 2013; Derkach et al., 2021; Dukhnytsky et al., 2021). Based on the fact that if dextran drugs contain only iron, the absorption of the drug after injection is 60–70%, besides the possible polyetiology of anemia, the researchers tried to combine iron dextrans with other trace elements (zinc, copper, and cobalt) and vitamins (B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, biotin, and ascorbic acid), or with protein drugs to stimulate hematopoiesis. Furthermore, because the complex drugs (microanemin, suiferovit) have the best results, their developers are trying to minimize the dose of iron for piglets. Todoruk (2011, 2012) proved the effectiveness of the microelement-containing composition of the drug minbevit in increasing the level of hemoglobin in the blood of animals. Levchenko et al. (2015) investigated the effect of the national drug ferrolife on hemocytopoiesis in young animals. Tokarchuk et al. (2016, 2017) studied the effect of vitamin E, citrates of Zinc, Iron and Germanium on body weight and morphological parameters of piglets' blood.

Our research has established that in 2017, 13 iron-containing drugs (38 %) were registered on the Ukrainian pharmaceutical market. These drugs were provided provided by the national manufacturers: Ferolife ("O.L.KAR AgroZooVet-Service"), Feropharm ("Pharmaton"), Brovaferan-100 ("Brovapharma"), Ferodev ("Experimental production of the Institute of Epizootology", "Biopharm"), Ferovet + B<sub>12</sub> ("Vetsintez"). One drug was offered by the foreign manufacturers: Pharmacosmos (Kingdom of Denmark), Merial (France), Wugen (South Korea), by Biovet Pulawy (Poland). Two drugs was offered by the foreign manufacturers: Interchem Verken "De Adelaar" (Estonia; drugs Intrafer-200 B<sub>12</sub>, Intrafer-100 B<sub>12</sub>), Bioveta (Czech Republic; drugs Ferribion 10%, Gafervit). These drugs are in great demand as anti-anemic drugs abroad, in particular in the countries that produce them.

These drugs include the dextran complex of iron (III) hydroxide, and 46% of such drugs contain its combinations with other substances. For example, 4 drugs, Intrafer-100 B<sub>12</sub>, Intrafer-200 B<sub>12</sub>, Ferovita 200, and Ferrovit+B<sub>12</sub> contain cyanocobalamin. There are 2 more antianemic drugs, which are multi-component drugs. Thus, Gafervit (Bioveta, Czech Republic) includes iron (III) dextran complex, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, calcium pantothenate, copper chloride, cobalt chloride, and inactivated normal pig serum. Suiferovit (Biovet Pulawy, Poland) contains active substances: immunoglobulin of normal pig serum, iron dextran, thiamine chloride, riboflavin, pyridoxine hydrochloride, nicotinamide, calcium pantothenate, copper chloride, cobalt chloride.

According to the international ATC-vet classification, these iron-containing drugs belong to the pharmacological group with the code QB03A antianemic. Such drugs have an antianemic effect due to the presence of low-toxic and water-soluble iron dextran complex. They stimulate the functional state of the hematopoietic system and the synthesis of hemoglobin, which leads to an increase in the number of erythrocytes. The activation of metabolic processes in tissues stimulates animal growth, increasing their resistance to the effects of negative environmental factors. Salts of copper and cobalt, and vitamins of group B act synergistically, enhancing the effect of iron, regulating metabolism, and compensating for the lack of these elements in the food. After intramuscular injection of iron, dextran is rapidly absorbed through capillaries and lymphatic vessels. It is removed from blood plasma by cells of the reticuloendothelial system, then divided into iron and dextran. Iron binds to proteins to form hemosiderin, ferritin, and transferrin complexes. Vitamin B<sub>12</sub> is required for DNA synthesis.

In 2018, the national market for iron-containing veterinary drugs was equally represented by national and foreign drugs. We also analyzed the market of food additives and premixes containing iron. Thus, ones for pigs were presented in dry dosage forms. In the list registered in 2018, the number of drugs in Ukraine was 55, 14 (26% of the total) of which were Ukrainian-made. There was a tendency for one manufacturer or several in cooperation to produce several drugs for animals of different ages and species, taking into account the body's physiological needs.

The analysis of the pharmaceutical market of iron-containing drugs registered in Ukraine in 2020 showed that the share of Ukrainian drugs in this group outweighed the share of imported ones and was 10 (64%) of the total. It is noteworthy that one of the trends in the development of this market of pharmaceutical products was that the drugs were produced in cooperation with several companies; for example, Ferroselenite was represented by manufacturers "Circle" and "Nova Plus".

In 2021, the pharmaceutical market of national antianemic drugs expanded. In particular, the drug Ferum+, was registered by Biotestlab.

According to the available information sources in the list of veterinary drugs for pigs registered in Ukraine as of 1.01.2022, 11 were identified, of which 5 (45%) are Ukrainian products (manufacturers "Biotestlab", "Brovapharma", "Vetsintez", and "Fortis-pharma"). 6 (55%) of such drugs are offered by foreign pharmaceutical companies, including companies from France, the Czech Republic, Estonia, and Denmark. manufacturers such as Bioveta a.s. and Interhemi Verken De Adelaar Esti AS offer two antianemic drugs on the Ukrainian pharmaceutical market of veterinary drugs. The results of the analysis show that the registration of drugs is valid during 2022–2026: for Ferofort – until 2022; for Ferro 2000 and Uniferon – until 2023; for Bioferon Forte, Ferrovit + B<sub>12</sub>®, Ferribion 10%, Intrafer-200 B<sub>12</sub> – until 2024; for Brovaferan-100, Gafervit, Intrafer-100 B<sub>12</sub> – until 2025; for Iron+ – until 2024 (Table 1).

**Table 1 - Iron-containing drugs registered in Ukraine as of 1.01.22**

Name of drug	Date of registration	Registration is valid until	Procedure of registration	Manufacturer	Country of manufacture
Iron +	04.03.2021	03.03.2026	re-registration	Biotestlab	
Brovaferan-100	24.12.2020	23.12.2025	re-registration	Brovapharma	
Ferrovit +B <sub>12</sub> ®	26.11.2019	25.11.2024	re-registration	Vet-synthesis	Ukraine
Ferofort	12.04.2017	11.04.2022	registration	Fortis-pharma	
Bioferon Forte	26.11.2019	25.11.2024	registration	Biopharm	
Ferro 2000	07.07.2020	16.12.2023	changes	Dopharma France	France
Gafervit	07.07.2020	06.07.2025	re-registration	Bioveta, a.s	Czech Republic
Ferribion 10 %	15.07.2019	14.07.2024	re-registration		
Intrafer-100 B <sub>12</sub>	07.07.2020	06.07.2025	re-registration	Interchem Verken	Estonia
Intrafer-200 B <sub>12</sub>	04.03.2019	03.03.2024	re-registration	"De Adelaar" Esti AS	
Uniferon	28.02.2018	27.02.2023	re-registration	Pharmacocosmos A/S	Denmark

As for the composition of antianemic drugs, their main active ingredient is a complex of iron (III) hydroxide with low molecular weight dextran. In addition to this combination, the following drugs contain Ferrovit B<sub>12</sub>, Intrafer-200 B<sub>12</sub>, Intrafer-100 B<sub>12</sub> – cyanocobalamin; Iron+ – cyanocobalamin, folic acid; Ferofort – vitamins B<sub>6</sub> and B<sub>12</sub>; Bioferon forte – copper chloride, cobalt chloride, cyanocobalamin. The most diverse composition is in the drug Gafervit, which contains

normal pig serum immunoglobulin, iron dextran, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, nicotinamide, calcium pantothenate, copper chloride, and cobalt anhydrous chloride.

Thus, according to the results of our research, the modern pharmaceutical market of veterinary drugs in Ukraine during 2017–2022 was sufficiently provided with antianemic drugs for pigs, and mostly imported drugs.

As seen from Table 1, the part of Ukrainian antianemic veterinary drugs for pigs registered was slightly higher in 2020. Still, in 2022 the ratio of imported drugs of this pharmacological group again prevailed.

## CONCLUSION

The modern pharmaceutical market of veterinary drugs in Ukraine from 2017 to 2022 was analyzed. Analysis of the national market of veterinary iron-containing drugs in 2017, showed that it was represented by 13 drugs of group QB03A «Antianemic drugs. Drugs of iron», according to the ATC-vet classification. 38% of this market was provided with pharmaceutical products from Ukrainian manufacturers. According to the results of our research, the modern pharmaceutical market of veterinary drugs in Ukraine during 2017–2022 was sufficiently provided with antianemic drugs for pigs, but mostly imported drugs. This motivates Ukrainian scientists and manufacturers to work on creating and producing national antianemic drugs to reduce Ukraine's dependence on foreign manufacturers.

## DECLARATIONS

### Corresponding author

E-mail: [derkach\\_im@nubip.edu.ua](mailto:derkach_im@nubip.edu.ua)

### Authors' contribution

The authors participated equally in data analysis and writing the manuscript.

### Conflict of Interests

The authors have not declared any conflict of interests.

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