B-LACTAM ANTIBIOTICS IN UKRAINE: MARKET AND CONSUMPTION ANALYSIS IN 2013–2018

© L. Iakovlieva, T. Bahlai

1. Introduction
After the discovery of penicillin in 1928 by a Scottish scientist and Nobel laureate, Alexander Fleming, antibiotics have come a long way to development [1].

More than 100 different types of antimicrobials (AMIs) have been invented to date. It has also been established that AMIs are active against different types of pathogens of infectious diseases, but there are "supermicroorganisms" with resistance to drugs, which creates new challenges for researchers.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues
Strategy against antibiotic resistance (ABR) is a global challenge for the scientific community for life and health of the population. Over the past decades around the world there has been a sharp increase in infections caused by pathogens with multiple ABR [2, 3].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers
The authors of the ABR study note the importance of a systematic view of current knowledge about the use of AMI and the prevention of infectious diseases [2–5]. Among publications, an important place is meta-analysis, which allows us to rely on a number of relevant sources about the relationship between AMI consumption and the development of ABR [4].

A study of the consumption of β-lactam antibiotics in Ukraine was conducted by prof. Iakovlieva L. V. and assistant Matyashova N. O., but their work was published in 2010-2013, which requires updating data in order to identify new trends in the use of these drug groups.
antibiotics (affordability through sale without prescription); the use of antibiotics with a wide spectrum of action in the case of the effectiveness of agents with a narrower spectrum; non-compliance by patients with certain conditions of admission and inappropriate prophylactic use; uncontrolled and unregulated use in veterinary and rural (agrarian) farming; the absence of new groups of antibacterial agents. An analysis of the relationship between AMI consumption levels and the development of ABR is one of the tools to curb the latter. Increasing AMI consumption can not only provide greater stability at the level of individual strains of pathogens to antibiotics, which creates problems for their further use [4, 5].

5. Formulation of goals (tasks) of article
The aim of this work is to analyze the market and consumption of AMI of the β-lactam group in Ukraine for 2013–2018, using the ATC / DDD methodology, identify trends in their use, and compare the obtained consumption volumes with similar results in the European Union.

6. Presentation of the main research material (methods and objects) with the justification of the results
Data on the consumption of the investigational drugs are determined using the ATC / DDD methodology recommended by the WHO. The DDDs per 1000 inhabitants per day (DID) were used to calculate the consumption of antibacterial agents of the study group. The value of DDD (Defined Daily Dose), each international non-proprietary name (INN), is presented on the WHO website. PDD (Prescribed Daily Dose) was used for those INN for which there is no calculated DDD on the WHO website [6].
The calculations were carried out according to the analytical system of the pharmaceutical market research “Pharmstandard” of “Morion” company.

Results and their discussion
Today, the group of β-lactam AMI includes a number of drugs, most of which are well-studied and have long existed on world markets.

β-lactam antibiotics are bactericidal agents that interrupt the formation of a bacterial cell wall as a result of covalent binding to etheric penicillin-binding proteins (PBPs), enzymes involved in the final stages of cross-linking peptidoglycan, a bacterial wall component in gram-negative and gram-positive bacteria. Each bacterial species has its own distinct set of PBPs, which can range from three to eight enzymes to one species. The death of a bacterial species has its own distinct set of PBPs (PBPs), enzymes involved in the final stages of cross-linking peptidoglycan, a bacterial wall component in gram-negative and gram-positive bacteria. Each bacterial species has its own distinct set of PBPs, which can range from three to eight enzymes to one species. The death of a bacterial species has its own distinct set of PBPs (PBPs), enzymes involved in the final stages of cross-linking peptidoglycan, a bacterial wall component in gram-negative and gram-positive bacteria. Each bacterial species has its own distinct set of PBPs, which can range from three to eight enzymes to one species. The death of a bacterial species has its own distinct set of PBPs [7].

Penicillin G (Benzylpenicillin) was the first β-lactam to be used in the clinic, most often for the treatment of streptococcal infections, to which it exhibited high activity. Another natural penicillin-Phenoxymethylpenicillin is used therapeutically and prophylactically for the mild and moderate severity of infections caused by susceptible Streptococcus spp., including use in children [8]. Among the penicillinase-resistant penicillins, clinical significance has Methicillin, Oxacillin, Cloxacillin and Nafcillin, and the latter is proposed as β-lactate for skin infections caused by methicillin-susceptible Staphylococcus aureus.

All these drugs were used primarily for the treatment of patients with Staphylococcus aureus before the onset of methicillin resistant S. aureus (MRSA) strains in 1979–1980 [9].

Penicillins with improved activity relative to gram-negative pathogens included bioavailable Ampicillin and Amoxicillin, both of which were marketed in the 1970s. These AMIs were initially used to treat infections caused by Enterobacteriaceae and did not effectively suppress the growth of Pseudomonas aeruginosa. Carbenicillin was the first anti-psudomonal penicillin, but did not have resistance to hydrolysis by β-lactamase and was less potent than Piperacillin or Ticarcillin. The latter preparations were considered as potent penicillins of a wide range of effects, which counteract penicillin-sensitive staphylococci, intestinal bacteria, anaerobes and P. aeruginosa. Since the late 1980s, they have been widely used to treat intra-infectious diseases, especially in combination with a β-lactamase inhibitor [11].
The increase in β-lactamase levels limited the therapeutic use of penicillins as monotherapy. Ampicillin, Amoxicillin, Piperacillin, and Ticarcillin are continued in combination with a β-lactamase inhibitor [10]. However, Ampicillin, Amoxicillin, Benzylpenicillin, and Phenoxymethylpenicillin are still active as monotherapy for Group A streptococci and Treponema pallidum, which do not produce β-lactamase [12].

In the 1950's, the discovery of natural penicillin-resistant Cephalosporin C indicated the pathway for the development of new cephalosporins for the treatment of infections, mainly caused by pathogens producing penicillinase (S. aureus). At that time dozens of cephalosporins were introduced into clinical practice either as parental or as oral agents [13]. The molecules showed antibacterial activity not only against staphylococci, but also against Streptococcus pneumoniae and non-β-lactamase-producing bacteria.

Cefazolin is often used for the prevention of surgery and the treatment of abdominal infections [14] and is effective as empirical therapy in 80% of Japanese children at the first infection of the upper urinary tract [15].
The total amount of AMI of the group β-lactams presented in the market of Ukraine in 2018 is 343 trade names (TNs), of which 92 are domestic and 251 foreign manufacturers, which indicates the high saturation of the Ukrainian pharmaceutical market with imported drugs (Table 1).

For comparison, in 2011 in the domestic market, 13 INN of penicillin group with 118 TNs were presented (26 domestic and 92 imported) [16]. From 2011 to 2018, 4 INNs were taken from the market - Ampicillin + Oxacycline, Amoxicillin + Sulbactam, Ticarcillin + Clavulanic acid, Amoxicillin + Cloxacillin sodium.

Cefalosporins in 2010 in the Ukrainian market were represented by 13 INNs, which are based on 128 TNs (domestic - 84 TNs and 44 TNs of foreign manufacturers) [17]. From the market went 2 INN - Cefadroxil and Cefpirome. Between 2010 and 2018, there were 7 INNs on the market, but only 3 INNs – Cefditoren (1 TN) and the combination of Cefoperazone + Sulbactam and Ceftriaxone + Sulbactam remained at the end of the period.
Table 1
Structure of the Ukrainian market of AMI of β-lactam group in 2018.

| ATC-code | International non-proprietary name | Number of items taking into account all dosage forms (pcs.) |
|----------|------------------------------------|----------------------------------------------------------|
|          |                                    | domestic | foreign | total |
| **β-lactamase sensitive penicillins** |                                    |          |         |       |
| J01CE01  | Benzylpenicillin                    | 3        | 1        | 4     |
| J01CE08  | Benzathine benzylpenicillin         | -        | 1        | 1     |
| J01CE30  | Benzathine benzylpenicillin + Benzylpenicillin | 2    | 2        |       |
| **Extended-spectrum penicillins** |                                    |          |         |       |
| J01CA01  | Ampicillin                          | 3        | –        | 3     |
| J01CA04  | Amoxicillin                         | 3        | 17       | 20    |
| J01CA51  | Ampicillin + Oxacycline             | Absent from 2015 |         |       |
| **Combinations of penicillins with β-lactamase inhibitors** | | | | |
| J01CR01  | Ampicillin + Sulbactam              | 1        | 1        | 2     |
| J01CR02  | Amoxicillin + Clavulanic acid       | 3        | 35       | 38    |
| J01CR02  | Amoxicillin + Sulbactam             | Absent from 2016 |         |       |
| J01CR03  | Ticarcillin + Clavulanic acid       | Absent from 2018 |         |       |
| J01CR05  | Piperacillin + Tazobactam           | –        | 6        | 6     |
| J01CR50  | Amoxicillin + Cloxacillin sodium    | Absent from 2015 |         |       |
| **Total penicillins** |                                    | 15       | 61       | 76    |
| **Other β-lactam antibiotics, cephalosporins of the first generation** | | | | |
| J01DB01  | Cefalexin                           | 2        | 5        | 7     |
| J01DB04  | Cefazolin                           | 8        | –        | 8     |
| J01DB05  | Cefadroxil                          | Absent from 2017 |         |       |
| **Other β-lactam antibiotics, cephalosporins of the second generation** | | | | |
| J01DC02  | Cefuroxime                          | 10       | –        | 10    |
| **Other β-lactam antibiotics, cephalosporins of the third generation** | | | | |
| J01DD01  | Cefotaxime                          | 10       | 4        | 14    |
| J01DD02  | Ceftriaxime                         | 4        | 16       | 20    |
| J01DD04  | Ceftriaxone                         | 23       | 36       | 59    |
| J01DD07  | Cefizoxime                          | Absent from 2017 |         |       |
| J01DD08  | Cefixime                            | –        | 13       | 13    |
| J01DD12  | Cefoperazone                        | 2        | 3        | 5     |
| J01DD13  | Cefpodoxime                         | –        | 17       | 17    |
| J01DD14  | Cefdituben                          | –        | 2        | 2     |
| J01DD16  | Cefditoren                          | –        | 1        | 1     |
| J01DD51  | Cefotaxime + Sulbactam              | Absent from 2015 |         |       |
| J01DD52  | Cefazidime + Sulbactam              | Absent from 2018 |         |       |
| J01DD62  | Cefoperazone + Sulbactam            | 7        | 9        | 16    |
| J01DD63  | Ceftriaxone + Sulbactam             | 1        | 3        | 4     |
| J01DD63  | Ceftriaxone + Tazobactam            | Absent from 2016 |         |       |
| **Other β-lactam antibiotics, cephalosporins of the fourth generation** | | | | |
| J01DE01  | Cefepime                            | 6        | 23       | 29    |
| J01DE02  | Cefpirome                           | Absent from 2015 |         |       |
| J01DE51**| Cefepime + Amikacin                 | Absent from 2015 |         |       |
| J01DE51**| Cefepime + Sulbactam                | Absent from 2018 |         |       |
| **Total cephalosporins** |                                    | 73       | 161      | 234   |
| **Other β-lactam antibiotics, carbapenems** | | | | |
| J01DH02  | Meropenem                           | 4        | 18       | 22    |
| J01DH03  | Ertapenem                           | –        | 1        | 1     |
| J01DH04  | Doripenem                           | –        | 1        | 1     |
| J01DH51  | Imipenem + Cilastatin               | –        | 9        | 9     |
| **Total carbapenems** |                                    | 4        | 29       | 33    |
| **Total AMI of β-lactams group** |                                    | 92       | 251      | 343   |
Data on the consumption of AMI β-lactams by the European Union (EU) in 2017 were taken from the reports of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [18].

In Ukraine, in 2017 penicillins consumed at 4.48 and 3.7 times less than the EU average and Italy (the country with the highest consumption), and cephalosporins and carbapenems are almost the same. Comparison with the Netherlands (the country with the lowest levels of consumption) suggests practically the same level of consumption of AMI of the β-lactam group and 51.3 times higher consumption of the subgroup of cephalosporins and carbapenems (Fig. 1).

The consumption of AMI of β-lactam group in the period from 2013 to 2018 in Ukraine has increased (Tabl. 2); although in 2015 there was a decrease in consumption.

The most commonly used drugs were INNs from the penicillin group – Amoxicillin and Amoxicillin with inhibitors of β-lactamase. This choice of physicians is due to the wide range of amoxicillin used as a monotherapy for infectious diseases caused by streptococci and the activity of combinations of amoxicillin with β-lactamase inhibitors to all cocccidion pathogens producing β-lactamase. In Ukraine, these combinations (see tab. 2) are used as first-line drugs that stimulate the development of ABR and should only be used as second-line drugs [19].

The leaders in terms of consumption among cephalosporins are INN Ceftriaxone (III generation) and Cefuroxime (II generation). The choice of these drugs is due to their pharmacological properties. Cefuroxime has a wider range of antimicrobial effects than I generation drugs and is widely used for monotherapy not only in Ukraine but also in Europe as a cheap generic drug. Ceftriaxone is widely used in connection with its pharmacokinetic properties, because it is sufficient to administer once a day, which characterizes its high compliance [19].

The consumption of AMI β-lactams group in 2017 in DID

![Fig. 1. Consumption of AMI β-lactams group in 2017 in DID](image)

| ATC-code | INN | DID, 2013 | DID, 2014 | DID, 2015 | DID, 2016 | DID, 2017 | DID, 2018 |
|----------|-----|-----------|-----------|-----------|-----------|-----------|-----------|
| J01CE01  | Benzylpenicillin | 0.02526807 | 0.020134595 | 0.01678717 | 0.0150048 | 0.015336723 | 0.01500076 |
| J01CE08  | Benzathine benzylpenicillin | 0.001649271 | 0.001505727 | 0.000952328 | 0.000057648 | 0.001717412 | 0.00016052 |
| J01CE30  | Benzathine benzylpenicillin + Benzylpenicillin | 0.277156233 | 0.225740965 | 0.201470371 | 0.126706359 | 0.161092185 | 0.186163267 |
| J01CA01  | Ampicillin | 0.157458578 | 0.148354107 | 0.129336352 | 0.114465254 | 0.100101304 | 0.10019797 |
| J01CA04  | Amoxicillin | 1.49576407 | 1.449766877 | 1.23464417 | 1.36392695 | 1.29446641 | 1.41922942 |
| J01CA51  | Ampicillin + Oxacycline | 0.00862075 | 0.000353343 | 0 | 0 | 0 | 0 |
| J01CR01  | Ampicillin + Sulbactam | 0.000319876 | 0.002284162 | 0.001999695 | 0.002462311 | 0.0019926 | 0.002261964 |
| J01CR02  | Amoxicillin + Clavulanic acid | 0.900023924 | 0.850775222 | 0.770569519 | 0.917767377 | 0.991406093 | 1.213728191 |
| J01CR03  | Amoxicillin + Sulbactam | 0.008942711 | 0.000215455 | 0.000020532 | 0.000008919 | 0.00000071 | 0 |
| J01CR05  | Piperacillin + Tazobactam | 0.000030162 | 0.000054478 | 0.00008014 | 0.000221418 | 0.000297439 | 0.000396671 |
| J01CR50  | Amoxicillin + Clavulanic acid sodium | 0.000631398 | 0.000053343 | 0 | 0 | 0 | 0 |

**Table 2**

Consumption of AMI β-lactam group from 2013 to 2018 in Ukraine
### Other β-lactams (cephalosporins, penems)

| AMI Code | Name | 2015-2018 Population DDDs | 2009-2013 Population DDDs | 2003-2005 Population DDDs | 2000-2001 Population DDDs | 1999-2000 Population DDDs | 1998-1999 Population DDDs | 1997-1998 Population DDDs | 1996-1997 Population DDDs | 1995-1996 Population DDDs | Total other β-lactams |
|----------|------|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------|
| J01DB01 | Cefalexin | 0.046096712 | 0.03842212 | 0.040549185 | 0.039318209 | 0.03294064 | 0.033812803 | 0.02913727 | 0.028004736 | 0.027389671 | 1.10284327 | 4.2783404 |
| J01DB02 | Cefazolin | 0.028900426 | 0.024824942 | 0.018263735 | 0.016463447 | 0.014087073 | 0.012142283 | 0.010203923 | 0.009479124 | 0.009479124 | 0.692756273 | 0.724812373 |
| J01DB03 | Cefadroxil | 0.001426198 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.0002136987 | 0.648478971 | 0.710039182 |
| J01DB04 | Cefuroxime | 0.237972182 | 0.23271682 | 0.25325516 | 0.26154427 | 0.27320269 | 0.28142246 | 0.28571428 | 0.28571428 | 0.28571428 | 0.664878971 | 0.710039182 |
| J01DB05 | Cefotaxime | 0.042510725 | 0.036586907 | 0.021800941 | 0.029547082 | 0.025665575 | 0.022150384 | 0.020304078 | 0.013771381 | 0.013771381 | 0.684487971 | 0.710039182 |
| J01DB06 | Cefazidime | 0.015811968 | 0.014346836 | 0.012999263 | 0.016545000 | 0.017959010 | 0.022132702 | 0.014783068 | 0.017650589 | 0.017650589 | 0.664878971 | 0.710039182 |
| J01DB07 | Ceftriaxone | 0.672952673 | 0.72413833 | 0.684487971 | 0.710039182 | 0.692891371 | 0.718067922 | 0.14873068 | 0.017650589 | 0.017650589 | 0.718067922 | 0.718067922 |
| J01DB08 | Cefotaxime | 0.020304078 | 0.019213042 | 0.015426556 | 0.017124064 | 0.015426556 | 0.017124064 | 0.014873068 | 0.011765059 | 0.011765059 | 0.718067922 | 0.718067922 |
| J01DB09 | Ceftriaxone | 0.000939223 | 0.000424895 | 0.000019802 | 0.000010002 | 0.000019802 | 0.000010002 | 0.000019802 | 0.000010002 | 0.000010002 | 0.718067922 | 0.718067922 |
| J01DB10 | Cefazolin | 0.001931611 | 0.002488001 | 0.001223237 | 0.000468221 | 0.00001576 | 0.000000000 | 0.000000000 | 0.000000000 | 0.000000000 | 0.718067922 | 0.718067922 |

7. Conclusions from the conducted research and prospects for further development of this field

1. Antimicrobial preparations of the β-lactam group are well-studied and widely used in medical practice.
2. Preparations of the β-lactam group are widely represented in the Ukrainian market (343 TNs), but only less than a third of them (92 TNs) of domestic production, indicating a high saturation of the Ukrainian pharmaceutical market with imported drugs.
3. The volume of consumption of AMI of the β-lactam group (penicillins) in Ukraine is almost 4.5 times lower than in the EU, which may indicate unbalanced use of different groups of AMI in terms of DDDs per 1000 inhabitants per day (DID).
4. Consumption in general of all β-lactam groups from 2013 to 2018 has increased, although years of decline in consumption (2015) have been noted.
5. The most consumed during the study period are drugs Amoxicillin - a group of broad-spectrum penicillins and among cephalosporins preparations Ceftriaxone and Cefuroxime.

### References

1. Bennett J. W., Chung K.-T. Alexander Fleming and the discovery of penicillin // Advances in Applied Microbiology. 2001. P. 163–184. doi: https://doi.org/10.1016/s0065-2164(01)49013-7
2. Chellat M. F., Raguz L., Riedl R. Targeting Antibiotic Resistance // Angewandte Chemie International Edition. 2016. Vol. 55, Issue 23. P. 6600–6626. doi: https://doi.org/10.1002/anie.201506818
3. Van Loon K., Voor in ’t holt A. F., Vos M. C. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae // Antimicrobial Agents and Chemotherapy. 2017. Vol. 62, Issue 1. doi: https://doi.org/10.1128/aac.01730-17
4. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance / Bell B. G., Schellevis F., Stobberingh E., Goossens H., Pringle M. // BMC Infectious Diseases. 2014. Vol. 14, Issue 1. doi: https://doi.org/10.1186/1471-2334-14-13
5. Intensive care antibiotic consumption and resistance patterns: a cross-correlation analysis / Baditioiu L., Axente C., Lungeanu D., Muntean D., Horhat F., Moldovan R. et. al. // Annals of Clinical Microbiology and Antimicrobials. 2017. Vol. 16, Issue 1. doi: https://doi.org/10.1186/s12941-017-0251-8
6. Use of ATC/DDD // WHO. URL: https://www.whocc.no/use_of_atc_ddd/
7. Georgopapadakou N. H., Liu F. Y. Penicillin-binding proteins in bacteria // Antimicrobial Agents and Chemotherapy. 1980. Vol. 18, Issue 1. P. 148–157. doi: https://doi.org/10.1128/aac.18.1.148
8. Use of Antibiotics in Children / Pottégard A., Broe A., Aabenhus R., Bjerrum L., Hanss J., Damkier P. // The Pediatric Infectious Disease Journal. 2015. Vol. 34, Issue 2. P. e16–e22. doi: https://doi.org/10.1097/inf.0000000000000519
9. Saroglou G., Cromer M., Biso A. L. Methicillin-Resistant Staphylococcus Aureus: Intermediate Spread of Nosocomial Infections with Emergence of Gentamicin-Methicillin Resistant Strains // Infection Control. 1980. Vol. 1, Issue 02. P. 81–89. doi: https://doi.org/10.1017/s0195941700052590
10. Bush K. Proliferation and significance of clinically relevant β-lactamases // Annals of the New York Academy of Sciences. 2013. Vol. 1277, Issue 1. P. 84–90. doi: https://doi.org/10.1111/nyas.12023

11. Antibiotic therapy for Pseudomonas aeruginosa bacteremia: Outcome correlations in a prospective study of 200 patients / Hilf M., Yu V. L., Sharp J., Zuravleff J. J., Korvick J. A., Muder R. R. // The American Journal of Medicine. 1989. Vol. 87, Issue 5. P. 540–546. doi: https://doi.org/10.1016/s0002-9343(89)80611-4

12. Group A streptococci are protected from amoxicillin-mediated killing by vesicles containing -lactamase derived from Haemophilus influenzae / Schaar V., Uddback I., Nordstrom T., Riesbeck K. // Journal of Antimicrobial Chemotherapy. 2014. Vol. 69, Issue 1. P. 117–120. doi: https://doi.org/10.1093/jac/dct307

13. Abraham E. P. Cephalosporins 1945-1986 // Drugs. 1987. Vol. 34. P. 1–14. doi: https://doi.org/10.2165/00003495-198700342-00003

14. Perioperative Antibiotics Covering Bile Contamination Prevent Abdominal Infectious Complications After Pancreatectoduodenectomy in Patients With Preoperative Biliary Drainage / Sudo T., Murakami Y., Uemura K., Hashimoto Y., Kondo N., Nakagawa N. et al. // World Journal of Surgery. 2014. Vol. 38, Issue 11. P. 2952–2959. doi: https://doi.org/10.1007/s00268-014-2688-7

15. Validation of Cefazolin as Initial Antibiotic for First Upper Urinary Tract Infection in Children / Abe Y., Wakabayashi H., Ogawa Y., Machida A., Endo M., Tamai T. et al. // Global Pediatric Health. 2016. Vol. 3. P. 2333794X1562529. doi: https://doi.org/10.1177/2333794x15625297

16. Yakovlieva L., Matyashova N. A. The estimation out-patient consumption of penicillins in Ukraine // Farmatsevtychnyi zhurnal. 2013. Issue 1. P. 26–31. URL: http://nbuv.gov.ua/UJRN/pharmazh_2013_1_6

17. Yakovlieva L. V., Matvieieva O. V., Matiashova N. O. Doslidzhennia spozhyvannia antybiotykiv hrupy tsefalosporyniv, predstavlenykh na farmatsevtychnomu rynku Ukrainy // Klinichna farmatsiya. 2010. Issue 2. P. 22–26. URL: http://dspace.nuph.edu.ua/handle/123456789/179

18. European Centre for Disease Prevention and Control. Antimicrobial consumption // ECDC. Annual epidemiological report 2017. Stockholm: ECDC, 2018.

19. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases / J. E. Bennett, R. Dolin, M. J. Blaser (Eds.). Elsevier, 2015. 3904 p.

Дата надходження рукопису 12.03.2019

Yakovlieva Larysa, Doctor of Pharmaceutical Sciences, Professor, Merited worker of science and technology of Ukraine, Head of Department, Department of Pharmacoeconomics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Bahlai Tetiana, Postgraduate student, Department of Pharmacoeconomics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002