Legal procedures related to use, import, storage and treatment of VMPs/NSAIDs in North Macedonia

And Gap Analysis

Technical report under action A2 of the Egyptian Vulture New LIFE project (LIFE16 NAT/BG/000874)

Nenad Petrovski

Macedonian Ecological Society

February 2020

Recommended citation: Petrovski, N. 2020. Legal procedures related to use, import, storage and treatment of VMPs and NSAIDs in North Macedonia, and Gap Analysis on the publicly available information. Technical report under action A2 of the Egyptian Vulture New LIFE project (LIFE16 NAT/BG/000874). MES, Skopje.

Summary

This report presents the results of a desk-based study on legislation and publicly available information about veterinary medical products (VMPs) for the purpose of vulture conservation in North Macedonia. Targeted desk research was carried out between 2018 and 2020 in order to obtain publicly available information on the regulations of use, trade and transboundary control of VMPs. In North Macedonia, one law and a number of by-laws regulate all procedures related to production, storage, licensing and trade of veterinary medical products. The main legal acts regarding of VMPs, which are potentially dangerous to vultures are listed and described.

North Macedonia has fairly strict legislation on VMP use, production, trade and import. The legislation aims to ensure food safety and human and animal health. Environmental protection has been acknowledged as an objective in broader terms, again mostly related to human and livestock health. This is more directly related to prevention of pollution of water, soil, and air, as well prevention of disease spread. On a national level, there are 4 publicly available registers that are related to VMPs on the website of the Food and Veterinary Agency. All procedures require relevant stakeholders to keep detailed registers of their activities regarding production, trade and use of VMPs as livestock treatment. However, the law does not oblige them to give regular reports on these procedures and there is no official national register and data base concerning usage, storage and trade of VMPs. Applications for new VMPs authorization are based upon approval in EU member legislations.

The organization and control of use, trade, import and production of VMPs is centralized and most of the decision-making power is concentrated in just one person – Director of the Food and Veterinary Agency (FVA). Lack of sufficient transparency of in-situ implementation of the law is a weakness of this complex and strict legislation. The key role of implementation of the law,

especially as the supervisory authority, has been allocated to official veterinarians, which are persons responsible for regional veterinary activities. The legislation is focused on license and control mechanisms. There are several levels of control which are related to all the activities carried out by different bodies - use (treatment), trade (including import), and production of VMPs. At local level (farms, practicing veterinarians, pharmacies, producers of VMP) as well as at the state border, control is carried out by the official veterinarians.

As a conclusion, biodiversity has not been taken into consideration in legislation, especially in the context of endangered vulture species protection. Legal mechanisms necessary to protect biodiversity should be implemented and loopholes that would threaten the populations of protected species should be avoided. In addition to Diclofenac, it should be noted that six Nonsteroidal anti-inflammatory drugs (NSAIDs) dangerous to vultures were listed as permitted substances: flunixin, caprofen, ketoprofen, tolfenamic acid, phenylbutazone and metamizole. Authorization of a VMP in a EU member state should not be enough by itself for the drug to be authorized in North Macedonia. Different circumstances in countries mean that additional analyses of the outcomes should be conducted.

Table of contents

Contents

1 Subject and purpose of the report

This report was developed under the frames of action A2 of the LIFE+ project "Egyptian vulture New LIFE" (2020), further referred as "the LIFE project" funded by the European Commission and co-funded by the "A. G. Leventis Foundation" and implemented by the following partners of BirdLife International: Bulgarian Society for the Protection of Birds (BSPB), the Hellenic Ornithological Society (HOS), the World Wildlife Fund for nature - WWF Greece, the Royal Society for the Protection of Birds (RSPB), Doğa Derneği (DD), BirdLife Middle East, BirdLife Africa; as well as the organizations of A.P. Leventis Ornithological and Research Institute (APLORI), CMS1' Raptors Memorandum of Understanding and Green Balkans. Subcontracting partners for the implementation of action A1 are the Macedonian Ecological Society (MES / BirdLife affiliate in North Macedonia) and the Association of the Preservation and Protection of the Natural Environment in Albania (PPNEA).

The widespread use of antibiotics and other veterinary medicinal products (VMPs), and in particular non-steroidal anti-inflammatory drugs (NSAIDs) in livestock farming pose a serious threat to the health status of vultures (Cuthbert, Parry-Jones, Green & Pain, 2006). They can cause serious physical damage such as kidney failure in birds that feed on medicated livestock carrion.

The objectives of Action A2 were to:

- Explore the use of VMPs with a proven negative effect on vultures with emphasis on NSAIDs aceclofenac, ketoprofen, carprofen, flunixin, diclofenac, and nimesulide. In addition, all medications containing "fenac", as well as metamziole (also known as "analgin"), ibuprofen, mefenamic acid, tolfenamic acid, paracetamol (also known as acetaminophen), phenylbutazone, carprofen and piroxicam would be studied with higher priority, because their impact on vultures was expected to be similar as the VMPs mentioned above.

- Investigate and identify potential alternatives to the dangerous drugs and advocate for their implementation.

This report was compiled thanks to the information gathered from conducting of a desk-based study on national legislation and publicly available information. Targeted desk research was carried out in order to obtain publicly available information about regulations of use, trade and transboundary control of VMPs, as well as the implementation of the legislation. After preliminary analysis of the publicly available information, a letter for access to public information was send to the FVA, in order to obtain further official information about the substances targeted under action A2. In addition, two meetings were held with the FVA.

2 List of the legal acts

The main law that gives guidelines on the procedures for trade, production, import, ownership, usage and control on the VMPs is the **Law on Veterinary Medicine Products** (Official Gazette 42/2010136/2011; 149/2015; 53/2016; 241/2018). Besides the law, regulations that are more specific and relevant to this subject are described in the next bylaws:

- List of veterinary medicine products for which there is approval for trade (Official Gazette no. 42/10, 136/11, 149/15, 53/16, 241/18, 268/19) https://drive.google.com/file/d/1fy12qe7p_aqh9xTHDyqyVJYopgHECT19/view
- Guidelines on keeping record trade of VMPs (Official Gazette no. 21/98) – here are explained the guidelines for record keeping that every seller of VMPs has to take.
- Rulebook on the information that have to be incorporated in the report for assessment of the veterinary medical products (Official Gazette no. 42/10 and 136/11) – for a product to approved for import or trade, first it has to be assessed. This document gives guidelines for which types of information have to be provided in that report.
- Rulebook for how a VMP can be approved for import (Official Gazette no. 42/10 and 136/11) – this document gives guidelines for how a VMP can be authorized for import in the country.
- Rulebook for keeping record on trade, storage, use and negative side effects of VMPs (Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18) – this document gives ground rules for keeping record on trade, storage, usage and negative side effects that has to be updated by the veterinary associations, livestock keepers. It also describes the procedures for record keeping for every type of VMP and depending on the type of animals that are being kept.
- List of pharmacological substances that are approved for usage in veterinary medicine (Official Gazette no. 42/10, 136/11, 149/15, 53/16, 241/18, 258/19) https://drive.google.com/file/d/108TtUyfeQatTlfP5cy8NEJADnX5nZxMj/view
- Rulebook for the format of the template of the request for approval of a VMP (Official

Gazette no. 42/10 and 136/11) – This document gives guidelines for the format of the request for approval of trade of the veterinary medical product, and the conditions that the product has to meet in order to approved.

- Rulebook for the means of conducting a formal assessment of the approval of VMP (Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18)
- Rulebook for classification of the types of VMPs and guidelines for prescribing VMPs (Official Gazette no. 42/10 and 136/11) – this document sets guidelines for classification of the types of VMPs and determines which can be freely sold and which are under more strict control
- Decision for issue of ban on production, import, possession, trade and/or usage of types of VMPs (Official Gazette no. 42/10) – this document lists all the VMPs, chemicals and substances that are banned for veterinary medical use in the country. https://doc-0g-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/6djbu68a8n2bq7jt6kmes3dakpp3t566/1582202700000/16614190090344306114/18282805278600029402/1iJrJqAAGxD3J4QSDE6u02Dd1DXygKcGj?e&authuser=0&nonce=i6d670hjbq95o&user=18282805278600029402&hash=fugofreepcsskf5s7aeqcm496583336d

2.1 Terminology

This section describes the most relevant terms in the law in regard to the usage, trade, permissions and possession of VMPs.

Veterinary medical product – every substance or a combination of substances that are proven to have medical characteristics or disease prevention for animals, or every substance or a combination of substances that can be used on animals in order to correct or modify the physiological functions for the purpose of imposing a certain pharmacological, immunological or metabolic activity, or for getting a medical diagnosis.

Adverse effect is a reaction induced by the veterinary medical product that is harmful and unexpected and is appearing after administration of normal doses of the product.

Unauthorized use – usage of the VMP in manners that are not prescribed in the manual or serious misuse of the product.

Wholesale of veterinary medical products is every activity that includes buying, selling, import, export or every other commercial transaction of veterinary medical product, no matter if the purpose is for profit or not with the exception:
- supplying on the behalf of the producer of the veterinary medical product is done by the producer itself,
- retail of the procured veterinary medical product is done by entities that are authorized under the guidelines of this law and the regulations for veterinary health.

Veterinary prescription is a prescription for a veterinary medical product that issued by a doctor for veterinary medicine in accordance with the regulations for veterinary health.

Potency is the property of the active substance quantitatively expressed in a single dose in relations to the volume or weight of the dosage.

Contact package is the container in which the veterinary medical product is in direct contact with.

External packaging is the package in which the contact package is contained.

Declaration is the information provided on the contact or external package

User manual is the manual for that contains the information that the user has to obey.

Illegal treatment is the usage of unauthorized products or usage of authorized products in manners that differ from the guidelines proposed by the Law on Veterinary Medical Products.

Unauthorized substance or product is a VMP whose usage on animals is prohibited by the Law on Veterinary Medical Products.

Active ingredient is an active substance of a certain pharmacological dosage that is responsible for the pharmacological effect of the veterinary medical product.

Pharmaceutical form is the form of the veterinary medical product appropriate for its administration (pills, capsules, ointment, injection solution etc.)

Good Laboratory Practice (GLP) is a system for quality of the logistics and planning circumstances, implementation, record keeping, control and reporting on the preclinical laboratory studies.

Good distributive practice (GDP) is a system for quality that refers to organization, implementation and control of the distribution of the veterinary medical products. This system gives guidelines about the transport, custody and keeping circumstances beginning with the producer following to the final user.

Good Storing Practice (GSP) is a system for quality of the organization, control, and storage of the veterinary medical product according to the designated methods of storage.

Summary of Product Characteristics (SmPC) is a document produced by the manufacturer that contains the basic information about the traits of the product.

Authorization holder is a company who has acquired an authorization for trading of certain veterinary medical product.

2.2 Competent authorities

The only responsible body for implementation of the administrative, technical and expert activities designated by the Law on Veterinary Medical Products (Article 5) is the *Food and Veterinary Agency***.** It is an independent government body responsible for all of the activities related to food control and animal food control. It is also responsible for implementation, control and supervision for the veterinary activities in the area of animal health, animal welfare, veterinary public health and control of the laboratories that provide support for the needs of the Agency.

2.3 Commission for Veterinary Medical Products

For the purpose of approving of the VMP for trade, and the system for keeping track of the adverse effects, a Commission for Veterinary Medical Products is formed under the Law on Veterinary Medical Products. The director of the Agency, after opening a public call, is responsible for designation of its members. The commission consists of five members, two of which are from the Agency and three are prominent veterinary medicine and pharmacology experts. The mandate of the commission members is three years with the possibility of reappointment. It is possible that additional experts join the work of the commission based on their specific scientific competency and for the purpose of dealing with certain scientific and technical aspects.

The commission provides opinions regarding the applications for approval of VMP trade, temporary ban, and permanent ban. It also provides a report assessing the VMP based on the results of the pharmaceutical and safety tests, as well as preclinical and clinical trials. The

reports of the Commission should be publicly available on the website of the Agency according to the Law on Veterinary Medical Products (Article 6 (14)), however the link on the website did not work at the time during the creation of this report (http://fva.gov.mk/mk/registri-veterinarno-medicinski-preparati).

The procedures for the formal assessment of the VMPs for the purpose of giving of rejecting the permission are described in a separate bylaw called: Guidelines for the formal assessment of the veterinary medical product for the purpose of authorization of usage and sale. The document is publicly available on the website of the Agency.

2.4 National Referent Laboratory

The analytical testing for quality control of the VMPs for the purpose of the Agency are conducted by the National Referent Laboratory for veterinary medical products. The analytical testing of VMPs for the purposes of the producers and the sides involved in trade can be conducted in laboratories authorized by the Director of the Food and Veterinary Agency.

3 Procedures

3.1 Request for authorization for sale of VMPs

In order to acquire a permission for sale of a VMP, first a formal request has to be sent to the Food and Veterinary Agency. The commission will than make an assessment whether the product should be used and sold for veterinary use. The procedure for requesting for such permission and the format of the authorization are described in a separate bylaw called "Rulebook for the method of approval and sale of the veterinary medical product and the format of the approval for import". The document is publicly available on the website of the Agency (https://drive.google.com/file/d/0B5GXGNKqbR0Ta3hiOWxGWF9kMXJaNjU0MWRyZElRYTVuSVZj/view).

If the active substances in the product are not on the list of substances that are authorized for use in veterinary medicine, then it is impossible to acquire an authorization for usage and sale of the veterinary medical product before the substance is not authorized. In order for a substance to be authorized for use, first, the agency has to propose a maximum residual level of the substance (in case the animals are used for food). There is a period of six months before the request for assessing the maximum residual level and the request for authorization for sale and usage of a veterinary medical product.

Additionally, the request for authorization for sale of the VMP has to contain information and scientific documentation necessary for proof regarding the quality, safety and efficiency of the VMP (Law on Veterinary Medical Products Article 19(1)).

3.2 Procedure for authorization for sale

The Food and Veterinary Agency is responsible for authorization of the VMP within a period of 210 days (Law on Veterinary Medical Products Article 23) from the day of accepting the request with the necessary documentation. The Agency through the Commission for VMP is responsible for implementing the following activities:

- Checking the documentation of the request that has been sent by the manufacturer
- It is eligible to request for a testing of the product, its intermediates or other compounds in the National Referent Laboratory (or another laboratory) in in order to check whether the methods that are used by the manufacturer are representative.
- It is eligible to check with the National Referent Laboratory whether the methods used for assessing the residual level presented by the manufacturer have been satisfied.
- It is eligible at any time to ask for additional documentation from the manufacturer.

3.3 Labeling

The Food and Veterinary Agency is responsible for approving the contact and the external packaging of the VMP. The director of the Food and Veterinary Agency is responsible for approving the content of the contact and external packaging. The guidelines for the content and information that must be provided on the labels are given in a separate bylaw that is publicly available on the website of the Agency.
https://doc-14-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/05t2uhdjl4v0d3kh3o5ka9cs0r3cpid4/1582221600000/16614190090344306114/18282805278600029402/1npSz9-qMUlBw4I1l9G0yv_X33wFJ6JRo?e&authuser=0&nonce=d33odsnuea8rk&user=18282805278600029402&hash=hsickk3kkfunj842ns9h8c38ohe5vk6s

3.4 Responsibilities of the authorization holder

The issuing of an authorization for trade of a certain VMP decreases the overall responsibilities towards the manufacturer, and to certain degree the to the authorization holder. The authorization holder is responsible for the validity of all the documents and information that were presented with the request for authorization. After the issuing of the authorization, the authorization holder is responsible in regard to the manufacturing and methods of control, to take into account the scientific and technological advance and to uphold the necessary changes. Hence the production of the VMP has to be in line with the generally accepted scientific

methods. The changes have to be approved by the Food and Veterinary Agency. The Food and Veterinary Agency is allowed to ask from the authorization holder to provide enough substances for analysis for identification of presence of residues of the VMP. The authorization holder is obliged without any delay to inform the Agency of any situation that would lead to the change of the information that were previously provided together with the request for the authorization. The authorization holder is also obliged to inform the Agency right away about every ban or limitation of the drug in a member state or any information that would change the risk-benefit relations of the drug or any unexpected serious adverse effect that that has been discovered in meanwhile. A notification has to be sent to the Agency once the producer is planning to stop manufacturing the drug. For the purpose of pharmacological vigilance, the producer is obliged to deliver to the Agency every information regarding the volume of production and trade and all other information they have regarding the product.

3.5 Refusal on providing an authorization on trade of a VMP

An authorization on trade will not be provided if the request does not have the necessary documents proposed by the Law on Veterinary Medical Products. In addition, an authorization will not be provided if after the analysis of the documents and information it is concluded that:

- The risk-benefit analysis is unfavorable for the health both on the animal and human health;
- The product does not have a therapeutic effect, or the applicant did not provide enough evidence of such effect;
- The quantitative and qualitative composition does not match the information provided in the request;
- The proposed interval between the administration and usage of the animal for food production does not guarantee that the product will not have residues of the drug that may lead to health problems for the human health;
- The labels of the product are not in line with the regulations prescribed by the Law on Veterinary Medical Products;

- The VMP is offered for sale under circumstances that are prohibited by Law;
- Authorization will not be provided if that is necessary in order to preserve the human health, animal health and the environment, even though the VMP upholds the guidelines proposed by the Law on Veterinary Medical Products.

3.6 Authorization on production of a veterinary medical product

The production of the VMP has to be in line with the Good Production Practice and the companies that produce it have to have an authorization for production issued by the Agency even if the product is meant to be exported. Even if the products are being produced abroad, they have to gain an authorization in order to be imported in the country. The products that are being imported in the Republic of North Macedonia have to have a copy of an authorization for production from the country of origin.

3.7 Procedures for acquiring an authorization on production

The Food and Veterinary Agency issues an authorization to the applicant after confirmation that they have all the necessary documents and information provided according to the Law on Veterinary Medical Products. The Agency has to implement the authorization process for a maximum of 90 days after properly receiving the application. If the applicant decides to change come information in the application, then the Agency initiates a procedure for changing the application in a period of 30 days maximum. The Agency is eligible to ask for additional information during the authorization process, in which case the waiting period for issuing the authorization is being stopped. The authorization for production is valid for 5 years from the date of issuing, If the production process does not uphold the guidelines written in the authorization than the authorization is being withdrawn.

3.8 Responsibilities of the manufacturer of the veterinary medical products

The authorization holder is obliged to:

- Inform the Agency regarding every change of the information that was written in the

application for authorization, especially every change in the manufacture before the occurrence of the change;

- Allow entrance to the officials working for the Agency at any time;
- Allow the veterinary doctor to do their job regarding the pharmacological vigilance at any time;
- Stick to the guidelines for good production practice for veterinary medical products and only use raw materials that are in line with the rulebook for good manufacturing practice for making pharmacological active substance.
- Keep record on all the veterinary medical products sold by them, including samples. They are also obliged to keep record for every transaction no matter whether it has been paid for or not.

3.9 Veterinary doctors

The authorization holder, no matter if for trade or for production is obliged to have at any time at least one qualified doctor for veterinary medicine that is going to be responsible for the technical regulations appointed in this law. The veterinary doctor, no matter their relationship with the authorization holder is responsible for:

- Making sure that every series of produced veterinary medical products is manufactured and controlled according to the Law on Veterinary Medical Products;
- Every series of VMPs that are from another country of origin must be tested in detail whether their content is qualitatively and quantitatively consistent with its documentation.
- When the VMP is authorized for manufacturing and sale, the veterinary doctor is obliged to check whether every series of drugs is consistent with the guidelines of the Law on Veterinary Medical Products.
- The records are being updated continuously and they should be available at any time to the Food and Veterinary Agency.

- The Director of the Food and Veterinary Agency prescribes the conditions that the veterinary doctor has to comply. They are publicly available on the website of the Agency (https://drive.google.com/file/d/0B5GXGNKqbR0TWGtvd200SzcyWXJMcHRjWTFkcFAzNUlFTXdv/view).

3.10 Secure disposal of veterinary medical products

The veterinary medical products that have not been used or whose dates have expired must be disposed safely with their contact packaging. The disposing must be done in a way that is not harmful for the human or animal health nor for the environment. The director of the Food and Veterinary Agency prescribes the manners for disposal of the VMPs. Yet, during the production of this report I was not able to find guidelines on the disposal of veterinary medical products.

3.11 Wholesale of veterinary medical products

Wholesale with veterinary medical products includes import, supply, storage, transport, distribution and sale of VMPs. Wholesale can only be conducted by a company that has acquired an authorization for wholesale of VMPs. The veterinary pharmaceutical stores can only buy veterinary medical products from companies that have authorization for wholesale and sell the VMPs only to drugstores that have authorization for wholesale or retail in line with the Law on Veterinary Medical Products. Additionally, companies are allowed to trade only with products that have been authorized by the Food and Veterinary Agency.

3.12 Conditions that have to be fulfilled by the wholesaler

The wholesaler has to fulfill the following conditions:

- It must have appropriate premises, equipment, staff for wholesale, transport, distribution and storing in accordance with the quantity and nature of the veterinary medical products that they are selling;
- To have a Doctor of Veterinary Medicine employed, who is responsible for veterinary and

pharmacological vigilance, reception, storage, distribution, transport and delivery of veterinary medical products, and also control over the documentation for the purpose of keeping record on the sale of VMPs;

- They must keep record on the veterinary medical products and always to be able to withdraw from sale a certain product, and to keep record of the complaints regarding the drug.
- To fulfil all the necessary conditions regarding the legislation on sale;
- The Director of the Food and Veterinary Agency prescribes the conditions that have to be fulfilled by the wholesaler. They are publicly available on the website of the Agency. https://doc-04-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/gj2l1ele55p86i5j16ijoq9sls9fo47m/1582296300000/16614190090344306114/18282805278600029402/1MF4T8yeJ_ZzZEvUy_mj_Qsmj-TKG2wPw?e&authuser=0&nonce=in11bt23st1nm&user=18282805278600029402&hash=40ojdcu401d2jnaukn0399gpu71v2ec0

3.13 Keeping record on the trade with veterinary medical products

The wholesaler is obliged to keep record on the trade with VMPs for every transaction. The wholesaler makes a detailed report for the purpose of input and output of the products in comparison with the current stocks. The records that are being kept have to be available to the Food and Veterinary Agency. The Director of the Food and Veterinary Agency prescribes the guidelines on the record keeping of the wholesale of VMPs.

3.14 Plan for revocation

The wholesaler is obligated to create and implement a plan for revocation of the trade with VMPs that is going to be swift and effective. The order for revocation comes from the director of the Food and Veterinary Agency.

3. 15 Import of veterinary medical products

The import of veterinary medical products and the substances and materials for their manufacturing is done exclusively after obtaining an authorization for their impost issued by the Agency for Food and Veterinary. The director of the Agency is responsible for prescribing the guidelines for authorization on import of veterinary medical products. The guidelines for requesting an authorization for import are publicly available on the website of the Agency.
https://drive.google.com/file/d/0B5GXGNKqbR0Ta3hiOWxGWF9kMXJaNjU0MWRyZElRYTVuSVZj/view

3.16 Retail of veterinary medical products

Retail of veterinary medical products includes supply, storing, keeping and prescribing. Retail can only be conducted by a company that has an authorization for retail (veterinary pharmacy) issued by the Food and Veterinary Agency, and an association that is authorized for conducting veterinary health occupation (veterinary association). The wholesaler is not authorized to do retail. Also, veterinary pharmacies and veterinary associations are forbidden to conduct wholesale of VMPs.

3.17 Conditions that have to be fulfilled by the veterinary pharmacy

The veterinary pharmacy has to have appropriate enclosures, equipment and staff for retail in regards with the quantity and assortment of the VMPS that are up for sale. In addition, there have to be an employed doctor for veterinary medicine that is going to be responsible for reception, storage, sale of veterinary medical products and securing the necessary documentation and keeping track of the sale of VMPs. The director of the Agency for Food and Veterinary prescribes the guidelines that the veterinary pharmacy has to obey. The rulebook for the conditions that have to be fulfilled by the veterinary pharmacy are publicly available on the website of the Agency,
https://doc-0g-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/ut6bijmdvgn2s7j5

bjs2fn2cjsvjnf30/1582544700000/16614190090344306114/18282805278600029402/1sJtv490GRqDlw6XGdEPeTADEL2WCDxSA?e&authuser=0&nonce=44g8d3vh34pda&user=18282805278600029402&hash=ea9ic5ogflinvvnhic468cfp86ckct18

3.18 Means of prescribing veterinary medical products

The veterinary medical products according to their properties and procedures for prescribing and usage are divided in six categories. The categories are proposed for the purpose of protecting the human and animal health and the environment.

- VMPs that are available for unrestricted trade;
- VMPs that can be bought only in veterinary pharmacies;
- VMPs that can be bought in veterinary pharmacies only with prescription;
- VMPs that can be used only by the veterinary associations;
- VMPs that can only be used by doctors for veterinary medicine;
- VMPs with special means of usage and sale.

The categorization of the VMPs is being made with the procedure of authorization for sale. The director of the Food and Veterinary Agency prescribes the guidelines for categorization and the means of prescribing the veterinary medical products. The manufacturer and the authorization holder is eligible to ask the Agency for a change of the methods of prescription. Also, the Agency can ask the authorization holder at any time to change the methods of prescription for the purpose of keeping the health of people and animals and protect the environment. The guidelines for categorization are publicly available on the website of the Agency. However, besides the guidelines for categorization, during the creation of this report we were not able to find the categories in which the VMPs of interest are placed.

https://doc-0c-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/sa01s877scqs5i7o5qgp1l7lf23542od/1582553700000/16614190090344306114/18282805278600029402/1EjFt4q1

UawlUlZ1GUwWus03eXuGFbnJw?e&authuser=0&nonce=s5qqn5insjsdo&user=18282805278600029402&hash=37v3vhqojb0rmf1fu81p6nk5i6v1k2v3

3.19 Special means of trade and usage

The veterinary medical products that possess anabolic, antimicrobial, anti-parasitic, anti-inflammatory, hormonal or psychotropic properties can be used and owned only by veterinary doctors as a part of their professional activities. The Food and Veterinary Agency holds data base for manufacturers and companies who are authorized to keep substances and products with the properties listed above. The companies that are authorized to sell these kinds of products are obliged to keep record on all of the activities with these drugs. The records must be available for the Food and Veterinary Agency at any time for at least five years.

3.20 Animal keepers and owners

Owners and keepers of animals that are meant to be used for food production are obliged to keep record on procurements, possession and usage of veterinary medical products. The director of the Food and Veterinary Agency prescribes the guidelines for record keeping on the activities listed above, as well as the categories of the drugs for which keeping record is a responsibility.

3.21 Ban for certain veterinary medical products

The director of the Food and Veterinary Agency can issue a ban on import, possession, trading, supply and/or usage of certain veterinary medical products for certain species of animals. This ban can be issued for the purpose of human and animal health protection and for protecting the environment. When there is an emergency, the Food and Veterinary Agency can issue a temporary ban for trade and usage of certain VMP.

3.22 Veterinary pharmacological vigilance

The Food and Veterinary Agency maintains a system for informing regarding the adverse effects

from the usage of veterinary medical products (system for veterinary pharmacological vigilance). The system includes information that are useful for keeping track of the usage of the VMPs with special attention on the adverse effects for the animals and humans. There is also a respective scientific evaluation on that information. Within the system, there is information on the lack of expected efficacy of the drug, unauthorized usage, period between the administration and the slaughter of the animal and adverse effects on the environment. Veterinary doctors and other technical staff members are obliged to inform the Food and Veterinary Agency if they start to suspect on serious and unexpected adverse effects from the usage of the drug. The Agency prescribes the guidelines on the means of reporting on the serious and unexpected adverse effects from the usage of the VMPs. The director of the Agency issues a program for monitoring of the adverse effects from the usage of the VMPs. The guidelines for reporting of the adverse effects on the animal and human health and on the environment are publicly available on the website of the Food and Veterinary Agency.
https://doc-0o-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/pr6kfegh8m6t4109n4chmfpoq3qn4h6g/1582797450000/16614190090344306114/18282805278600029402/1evfwmjS5OXUG-bL1x0iQ6aXbF1k7eTu7?e&authuser=0

The designated veterinary doctor is obliged to inform the Agency about any unexpected and serious adverse side effect from the usage of the drug. The authorization holder is also obliged to provide a report regarding the safety of the newly issued VMP every six months for the first two years and once per year for the next two years. After that period, the reports are sent every three years or with a request from the Agency. The periodical reports on the safety of the drug are a subject to a risk-benefit analysis. However, the law does not state who performs the analysis. According to the Law on Veterinary Medical Products the authorization holder is obliged to give information from the risk-benefit analysis and this information must be objectively presented and must not be misleading.

3.23 Supervision and control

Supervision and control of the implementation of the Law on Veterinary Medical Products is conducted by the Food and Veterinary Agency. Based on the inspection report on the technical issues, the Agency drafts measures for removing the irregularities and deadlines. The Agency can issue a ban on for conducting work if:

- The safety measures are not implemented within the deadline;
- The identified irregularities are of such nature that proceeding with work can seriously harm the human and animal health and the environment.

If the measures require a specialized organization to conduct the supervision, the Agency can propose such an organization to be engaged. The Food and Veterinary Agency prescribes the means of and conducts the inspections. The guidelines of the publicly available on the website of the Agency.
https://doc-0s-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/ufb3fc31e7rklaldtcfmd53nk9tqahts/1582805475000/16614190090344306114/18282805278600029402/1q-kwK19YDSQy9w49DeXiVmJUc1CnuP46?e&authuser=0&nonce=tc0a4jefc18ui&user=18282805278600029402&hash=gnt796bmdjcce2atgs374poga4gtutd0

The inspection is conducted regularly, systematically and according to plan, but also after a suspected irregularity. The inspection is being conducted without announcement. The Agency provides an annual report to the Government regarding the activities concerning the state of the veterinary medical products with recommendations for removing the gaps and reinforcing the procedures.

3.24 Measures that the official veterinary doctor is authorized to implement

During the inspection the official veterinary doctor from the Food and Veterinary Agency is authorized and obligated to:

- Issue a temporary or permanent ban for production, testing, trade and use of VMPs if these

actions are against the Law on Veterinary Medical Products;

- Give order to the company to comply its work with the regulations by the Law with a time frame of six months maximum;
- Issue a temporary ban for work if the activities are harmful to the human or animal health or the environment;
- Issue a ban for trade and use of VMPs that are not in line with the prescribed guidelines by the Law on Veterinary Medical Products, harmful, not have therapeutic effect or have unfavorable risk-benefit analysis;
- Confiscate VMPs that have been sold or are up for sale from an unauthorized seller;
- Give order for a VMP to be destroyed if it is defective or unauthorized;
- Ban the import of a drug that does not have an authorization;
- Take samples from a product for the purpose of testing;
- Report a problem to the State Environmental Inspectorate for improper disposal of waste;
- Implement other measures that the Official Veterinary Doctor has authorization under the Law on Veterinary Medical Products or the Law on Veterinary Health.

4 Summary analysis of the procedures for use, import, storage and treatment of VMPs/NSAIDs

North Macedonia has fairly strict regulation on production, storage, trade and usage of VMPs. The way the legislation is designed should have been efficient to ensure food safety and human and animal health. Environmental protection is acknowledged as an objective in broader terms, with emphasis for preventing water pollution, soil and air as well as preventing the spread of diseases. However, biodiversity should have also been taken into consideration, especially in the context of endangered species. Any necessary legal mechanisms to protect biodiversity should be implemented and avoid any loopholes that would threaten the populations of protected species.

Because of the aspiration of North Macedonia to join the European Union, the laws have been synchronized with the legislation of the member states which on one hand is good, since it provides strict regulation and control. On the other hand, if a veterinary drug has been licensed for sale in one member state, this could serve as a justification to be authorized for sale in North Macedonia as well, despite the difference in circumstances that are present in both of the countries, or even if it is banned in all the other EU member states.

In all the procedures relevant stakeholders were required to keep detailed registers of what they have been doing in relation to their activities – production, trade of use of VMPs and treatment of livestock. While the national registers were publicly available, all the other registers at local, farm or company level were not. These registers were available only to the controlling authorities upon their request. In certain cases, especially license issuing or disease control, confidentiality of the information was required by law. In this case the information on local level could have been obtained only directly by the holders, or via the official controlling authorities. Suitable target groups for possible provision of information were the veterinarians, as well as pharmacies, which were obligated to keep very detailed records of the types and quantities of the

used or sold VMPs.

The structure of the coordination, organization and control of use, trade, import and production of VMPs was very centralized and most of the decision-making power was concentrated in a single person – the Director of the FVA. On one hand this very centralized and closed structure could have been very useful for the proper implementation of the law, but on the other hand this concentration of power together with very complex legislation and insufficient transparency of the decision-making process and of the real implementation of the law by the different actors posed a risk for corruption and non-implementation. Lack of sufficient transparency of the in-situ implementation of the law seemed to be a weakness of this very complicated and strict legislation. The key role of implementation of the law, especially as the control body was allocated to the official veterinarians, which were regionally based. They also participated in the border veterinary control in collaboration with representatives of the border police. In fact, there was a special ordinance, which described in detail the procedures of the collaboration between the FVA and the Ministry of Interior.

The legislation related to VMPs was based mainly on license and control mechanisms. There were several levels of control which were related to all the activities, carried out by different bodies - use (treatment), trade (including import) and production of VMPs. At local level (farm, practicing veterinarian, pharmacy, producer of VMP) the control was carried out by the official veterinarians and had access to the detailed documentation kept by the different actors. It is important to note that a significant part of the control mechanisms, apart from documentation examinations, was sampling and examination in the laboratories of FVA. In this respect, it meant that as long as the above mentioned NSAIDs were permitted in a certain dose to be contained in animal products, the relevant laboratories should have the necessary tests to detect them, even if these tests should be applied during the control examinations. Thus, the laboratories should keep an archive of data of these samplings in great detail. Such information, unfortunately, was not publicly available.

5 Gap analysis

The widespread use of antibiotics and other veterinary medicinal products (VMPs), and in particular non-steroidal anti-inflammatory drugs (NSAIDs) in livestock farming pose a serious threat to the health status of vultures (Cuthbert et al., 2006). They can cause serious physical damage such as kidney failure in birds that feed on medicated livestock carrion.

The objectives of Action A2 were to:

- Explore the use of VMPs with a proven negative effect on vultures with emphasis on NSAIDs aceclofenac, ketoprofen, carprofen, flunixin, diclofenac, and nimesulide. In addition, all medications containing "fenac", as well as metamziole (also known as "analgin"), ibuprofen, mefenamic acid, tolfenamic acid, paracetamol (also known as acetaminophen), phenylbutazone, carprofen and piroxicam would be studied with higher priority, because their impact on vultures was expected to be similar as the VMPs mentioned above;
- Investigate and identify potential alternatives to the dangerous drugs and advocate for their implementation.

This report was compiled thanks to the information gathered from conducting of a desk-based study on national legislation, publicly available information, field study and interviews with local livestock farmers and veterinary doctors.

6 Overview of publicly available information

6.1 Public Registers

On a national level, 4 registers that are related to VMPs are publicly available on the website of the Food and Veterinary Agency. In all the procedures relevant stakeholders were required to keep detailed registers of their activities regarding production, trade and use of VMPs as livestock treatment. However, the law does not oblige them to give regular reports on these procedures and there is no official national register and data base concerning the usage, storage and trade.

6.2 Register of the wholesalers and veterinary pharmacies that are licensed to conduct sale with VMPs

The national register of the wholesalers and veterinary pharmacies, as set by Art. 42(12) of the LVMP, is publicly available on the website of the Food and Veterinary Agency. The list contains information for 26 companies that are licensed to conduct sale of VMPs. The information provided includes type of sealer, address, city, license number, date of issuing, file number within the FVA. However, we could not find an updated list of establishments that are authorized to conduct veterinary practice.

6.3 List of veterinary medical products for which there is approval for trade

(Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18). The list of VMPs in North Macedonia includes information on all the VMPs that are authorized for sale. It contains information on the ID number under which the drug is authorized, name of the VMP, generic name, name of the producer, country of origin, authorization holder, type of usage, number of license and date of expiry of the license.

https://drive.google.com/file/d/1fy12qe7p_aqh9xTHDyqyVJYopgHECT19/view

6.4 List of pharmacological substances that are approved for usage in veterinary medicine

(Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18) The list of pharmacological substances that are authorized for usage in veterinary medicine contains information on: name of the active substance, markers for residues, animal tissue origin, maximum residue limits (MRL), target tissues, other provisions (according to Article 14(7) of Regulation No 470/2009 and pharmacological classification.
https://drive.google.com/file/d/108TtUyfeQatTlfP5cy8NEJADnX5nZxMj/view

6.5 Decision for issue of ban on production, import, possession, trade and/or usage of types of VMPs (Official Gazette no. 42/10)

This document lists all the VMPs, chemicals and substances that are banned for veterinary medical use in the country.
https://doc-0g-4c-docs.googleusercontent.com/docs/securesc/d2fq06hf9i6efuiikfsl6i5ctehh5i3k/6djbu68a8n2bq7jt6kmes3dakpp3t566/1582202700000/16614190090344306114/18282805278600029402/1iJrJqAAGxD3J4QSDE6u02Dd1DXygKcGj?e&authuser=0&nonce=i6d670hjbq95o&user=18282805278600029402&hash=fugofreepcsskf5s7aeqcm496583336d

7 Gap analysis of publicly available information in respect to the relation between the VMPs/NSAIDs and risks for vultures

7.1 Veterinary medicinal products authorized for use in the country

There is a list of the Veterinary Medical products that are authorized for trade and usage in the country. It contains of detailed information on each of the licensed products, including the terms of the validity of the license. Unfortunately, the majority of the NSAIDs that are proven to be dangerous to vultures are authorized to use in veterinary medicine. On the upside, the most dangerous one, Diclofenac is not an active substance in any of the VMPs that are authorized for import, trade and usage. Another visible gap is that although the decisions for authorization should be publicly available on the website of the Agency, they are not. The authorities do not have an available data base of the amount of imported NSAIDs as well. The most major gap is that there is no available information on the amount of traded, possessed and used VMPs. The reason for this is that although the veterinary companies are obliged to keep record on the mentioned activities, they do not provide reports. The only obligation is that they must provide this information only if being asked to do so. Therefore, the amount of used VMPs and treated animals remains unknown.

7.2 Standard procedures for permits, use and storage of VMP/NSAID

The procedures for use and trade of VMPs, including NSAIDs, were clearly outlined. According to them, every farm, veterinarian, pharmacy, trader and producer had to keep detailed records of their activities, especially retail sales and direct usage of VMPs by veterinarians and in farms. However, this data was kept only locally and were not available in a centralized database, so there was no access to this information. The only possible way to obtain definite information about types and quantities of NSAIDs used locally (at farm or owner level) was to rely on the willingness of the veterinarians/owners to provide this information or though targeted questionnaires distributed by the BFSA to the veterinarians in the study area. Pharmacies could also be questioned in this way.

7.3 Standard procedures for import of VMP/NSAID

The procedures for import of VMPs, including NSAIDs were clearly outlined, but the information on the types and quantities imported VMPs was not publicly available, no statistics were maintained and so far, no clear mechanism of obtaining this information was available. A list of banned VMPs was missing with the assumption that everything was banned, unless it had received a national license. There is a list however of chemicals that are banned for usage However these were mainly highly toxic substances and substances where a maximum permitted level cannot be determent in veterinary medicine.

7.4 Overview of the NSAIDs that pose risks for vultures

- *Aceclofenac.* No substances containing Aceclofenac were licensed in Bulgaria and no data on the use, trade or import of such VMPs existed.
- *Carprofen.* Caprofen is a constituent of 1 VMP (Carprieve 50mg/ml inj.susp) that is authorized for usage and sale in the country.
- *Ketoprofen.* Ketoprofen is a constituent of 2 VMPs that are authorized for trade and usage in the country. The drugs are: Mediprofen inj. sol. and KETOSOL-100 inj. Sol.
- *Flunixin.* Flunixin is a constituent of 1 VMP (Finadyne 50 mg/ml) that is authorized for sale.
- *Diclofenac.* No substances containing Aceclofenac were licensed in Bulgaria and no data on the use, trade or import of such VMPs existed.
- *Meloxicam.* Meloxicam is a constituent of 1 VMP (Meloxidolor 20 mg/ml inj. Sol) that is authorized for usage and trade in the country.
- *Metamizole sodium.* Metamizole sodium is a constituent of six VMPs that are authorized.
- *Phenylbutazone.* Phenylbutazone is a constituent of 1 VMP (PHENYLBUTAZONE 20%

inj. sol.) that is authorized for usage and trade in the country.

Pharmacologically active substance	Marker residue	Animal tissue origin	Maximum residue limits (MRL)	Target Tissues	Other Provisions (according to Article 14(7) of Regulation No 470/2009)	Therapeutic Classification
Carprofen	Sum of carprofen and carprofen glucuronide conjugate	Bovine, Equine	500 µg/kg	Muscle	No entry	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			1 000 µg/kg	Fat		
			1 000 µg/kg	Liver		
			1 000 µg/kg	Kidney		
	N/A	Bovine, Equine	No MRL Require d for milk	N/A		
Diclofenac	Diclofenac	Bovine	5 µg/kg	Muscle	No entry	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			1 µg/kg	Fat		
			5 µg/kg	Liver		
			10 µg/kg	Kidney		
			0,1 µg/kg	Milk		
		Porcine	5 µg/kg	Muscle	Fat MRL refers specifically to 'skin and fat in natural proportions.	
			1 µg/kg	Skin and fat		
			5 µg/kg	Liver		
			10 µg/kg	Kidney		
Flunixin	Flunixin	Bovine	20 µg/kg	Muscle	No entry	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			30 µg/kg	Fat		
			300 µg/kg	Liver		
			100 µg/kg	Kidney		
		Porcine	50 µg/kg	Muscle		

			10 µg/kg	Skin and fat		
			200 µg/kg	Liver		
			30 µg/kg	Kidney		
		Equine	10 µg/kg	Muscle		
			20 µg/kg	Fat		
			100 µg/kg	Liver		
			200 µg/kg	Kidney		
	5-hydroxyflunixin	Bovine	40 µg/kg	Milk		
Ketoprofen	N/A	Bovine, Porcine, Equine	No MRL required	N/A	No entry	No entry
Metamizole	4-Methylaminoantipyrin	Bovine, Porcine, Equine	100 µg/kg	Muscle	For Suinae the fat MRL relates to 'skin and fat in natural proportions'	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			100 µg/kg	Fat		
			100 µg/kg	Liver		
			100 µg/kg	Kidney		
		Bovine	50 µg/kg	Milk		
Tolfenamic acid	Tolfenamic acid	Bovine, Porcine	50 µg/kg	Muscle	No entry	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			400 µg/kg	Liver		
			100 µg/kg	Kidney		
		Bovine	50 µg/kg	Milk		
Paracetamol	N/A	Porcine	No MRL required	N/A	For oral use only.	No entry

Table 1. Technical guidelines for usage of veterinary drugs

8 Suggestions for better implementation

- It is very important that besides the obligation for the veterinarians to keep record on the applied VMPs, they should also report this information to the public authorities in order to have an insight on the amount of VMPs being used on national and regional level.
- Authorization of a VMP in a EU member state should not be enough by itself for the drug to be authorized in North Macedonia. Different circumstances in countries mean that additional analyses of the outcomes should be conducted.
- Biodiversity protection should be taken into account when authorizing a certain drug. NSAIDs should especially be reconsidered when authorizing.

9 Conclusions

North Macedonia has a pretty solid legislation that regulates the production, use, trade, and import on VMPs use, well as on livestock welfare and breeding. The legislation was also designed to ensure animal and human food safety and health, resulting in a limitation on food for the vulture population in the country. Although the legislation is approximated to the European Union directives and regulations, it seems to be very distant to the actual requirements.

One positive thing about the law that seems to work properly is the fact that the licensing of drugs in the country goes through a State Commission.

However, biodiversity should have also been taken into consideration, especially in the context of endangered species. Any necessary legal mechanisms to protect biodiversity should be implemented and avoid any loopholes that would threaten the populations of protected species.

Because of the aspiration of North Macedonia to join the European Union, the laws have been synchronized with the legislation of the member states which on one hand is good, since it provides strict regulation and control. On the other hand, if a veterinary drug has been licensed

for sale in one member state, this could serve as a justification to be authorized for sale in North Macedonia as well, despite the difference in circumstances that are present in both of the countries, or even if it is banned in all the other EU member states.

9 Sources of information

- Food and Veterinary Agency of the Republic of Macedonia
- List of veterinary medicine products for which there is approval for trade (Official Gazette no. 42/10, 136/11, 149/15, 53/16, 241/18, 268/19) https://drive.google.com/file/d/1fy12qe7p_aqh9xTHDyqyVJYopgHECT19/view
- Guidelines on keeping record trade of VMPs (Official Gazette no. 21/98) – here are explained the guidelines for record keeping that every seller of VMPs has to take.
- Rulebook on the information that have to be incorporated in the report for assessment of the veterinary medical products (Official Gazette no. 42/10 and 136/11) – for a product to approved for import or trade, first it has to be assessed. This document gives guidelines for which types of information have to be provided in that report.
- Rulebook for how a VMP can be approved for import (Official Gazette no. 42/10 and 136/11) – this document gives guidelines for how a VMP can be authorized for import in the country.
- Rulebook for keeping record on trade, storage, use and negative side effects of VMPs (Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18) – this document gives ground rules for keeping record on trade, storage, usage and negative side effects that has to be updated by the veterinary associations, livestock keepers. It also describes the procedures for record keeping for every type of VMP and depending on the type of animals that are being kept.
- List of pharmacological substances that are approved for usage in veterinary medicine (Official Gazette no. 42/10, 136/11, 149/15, 53/16, 241/18, 258/19) https://drive.google.com/file/d/108TtUyfeQatTlfP5cy8NEJADnX5nZxMj/view
- Rulebook for the format of the template of the request for approval of a VMP (Official Gazette no. 42/10 and 136/11) – This document gives guidelines for the format of the

request for approval of trade of the veterinary medical product, and the conditions that the product has to meet in order to approved.

- Rulebook for the means of conducting a formal assessment of the approval of VMP (Official Gazette no. 42/10, 136/11, 149/15, 53/16 and 241/18)
- Rulebook for classification of the types of VMPs and guidelines for prescribing VMPs (Official Gazette no. 42/10 and 136/11) – this document sets guidelines for classification of the types of VMPs and determines which can be freely sold and which are under more strict control

Decision for issue of ban on production, import, possession, trade and/or usage of types of VMPs (Official Gazette no. 42/10) – this document lists all the VMPs, chemicals and substances that are banned for veterinary medical use in the country.