

## Study of Master Formulas for Animal Use in a Pharmacy

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### Abstract

The main function of the master formulation so far has been to meet the therapeutic needs of humans, but today the animal world also demands greater protection.

**Objective:** To assess the therapeutic needs of animals covered by veterinary master formulations.

**Methods:** All veterinary prescriptions for oral master formulas were recorded in a pharmacy in Leon (Spain), between 2011 and 2016.

**Key finding:** Veterinary formulations represented 0.8% of the total master formulas elaborated in this pharmacy. The most common prescriptions were those related to CNS (59%), followed by those with gastrointestinal activity (20%), immunosuppressive agents (17%), and cardiovascular (3%) and antifungal master formulations (2%). Depending on the dosage form used, capsules were the most commonly formulated (56%), followed by solutions (38%) and suspensions (6%). No significant differences were found in the years studied considering the number of master formulas developed or the season.

**Conclusions:** Veterinary master formulations contributed little to the total production of the master formulation in the pharmacy evaluated. The most prescribed formulations in veterinary medicine were those aimed at CNS diseases, being the capsule the pharmaceutical form with the greatest demand.

**Keywords:** Magistral Formula; Veterinary Prescription; Pharmacy

### Introduction

Master formulation is one of the ancestral activities that still remain useful. Its current task is to fill therapeutic gaps in the pharmaceutical industry. Until now its main role was to cover certain therapeutic needs of human beings, but at present the animal world is also demanding greater protection.

The growing coexistence of pets with humans has made master formulations essential not only for the veterinary profession to safeguard population health by preventing zoonoses, but also to ensure the health and welfare of pets. Currently, this greater concern for the care and quality of life of pets has led to an increase in animal life expectancy and in the number of different animal species considered as companion animals. All these factors may explain the occurrence of pathologies that previously did not exist or were not treated, for which it is not easy to find medicinal products. On the other hand, the large range of weights that may exist within the same animal species is another factor to be considered (e.g. a Great Dane dog may weigh 100 kg and a Chihuahua one only 1 kg). Veterinarians have to take care of certain therapeutic needs not completely covered by the pharmaceutical industry, and as consequence of the legal and economic obligations, they have had to count on the help of the pharmacist to design certain treatment strategies. Thus, master formulation has gained a growing role in animal health.

At present, there is little information on veterinary master formulation, being practically non-existent until before 1988 [1], and there are legislative variations among countries. The Parsemus Foundation conducted in 2015 a legislative review of veterinary drugs in several countries, classifying them as countries “with a strong veterinary regulatory culture” (European Union, Canada, China, South Africa, Australia, and Japan), those “without a strong veterinary regulatory culture” (Nigeria, Trinidad and Tobago, Bangladesh, Fiji, Ghana, Iraq, Kenya, Nepal, Tanzania, and Sierra Leone), and those “with a special situation” regarding veterinary regulatory culture (Mexico, Bolivia, Panama, Colombia, and The United States). Parsemus Foundation stated that the United States generally falls into the group “with a strong veterinary regulatory culture” but there is a great ambiguity “around compounding in the U.S., with nearly all small-animal veterinarians ordering drugs compounded from bulk substances in situations that are technically contrary to FDA regulations” [2].

With regard to the demand and evolution of this type of formulation, few studies have been carried out. The first study on the most popular veterinary master formulas was published in 1999, where the top 10 master formulas at that time were described [3]. A survey was conducted in 2013 by Gargiulo *et al.* with 200 randomized veterinarians in New Zealand, providing information on commonly prescribed formulations and the importance of veterinary-pharmacist collaboration to achieve individualized protocols. In this study only a small percentage of veterinarians worked in collaboration with pharmacists, being positive the relationship between both professionals. The authors concluded that a close collaboration between these two professions could lead to improve veterinary patient care [4]. In another study the use of veterinary master formulas during the years 2014-2015 was analyzed. As explained before, there is a lack of updated data on the needs of veterinary master formulations [5], as well as an increasing need of veterinary high-quality care. So, it is crucial to assess the pattern of use for veterinary master formulations and how this increase is taking place, with the aim of providing the best possible care to our animals.

In Europe, a study carried out in the Czech Republic and published in 2014 described different formulations that can be made instead of industrial preparations [6] but, to the best of our knowledge, no study has evaluated the frequency of prescription for this type of preparations in Europe.

The aim of this study was to analyze the use of veterinary master formulations in Leon, a province of Spain, and to compare it with the scarce existing studies. So, despite the fact that each country has its own legislation and different industrially manufactured medicines, the most demanded drugs worldwide as master formulations are the same, and the veterinary pharmaceutical industry does not offer them.

## Materials and Methods

In order to carry out this study, all the requests made by veterinarians for the elaboration of oral master formulas in a pharmacy in Leon (Spain) during the years 2011-2016 were recorded.

The SPSS 24.0 software package was used for statistical analysis. A descriptive Statistics was carried out with the data obtained. Chi-square test was used for qualitative variables. A level of  $p \leq 0.05$  was considered as significant.

## Results and Discussion

In this study, a total of 8396 oral formulas were analyzed from 2011 to 2016. Only 66 of these oral formulations were from veterinary drugs (0.8%).

Figure 1 shows the frequency of the master formulas prescribed for veterinary use in the 6 years under study. In 2013 there was a small decrease in consumption. Nevertheless, consumption remained uniform throughout the years assessed, and no significant differences were found ( $\chi^2 = 7.8182$ ;  $p = 0.0583$ ).

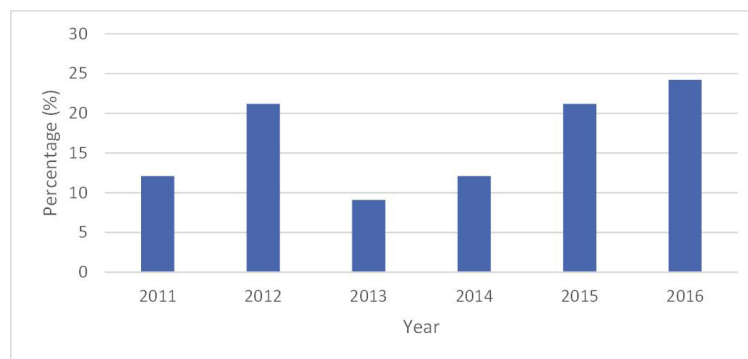


Figure 1: Frequency of prescribed formulas in the period studied (2011-2016)

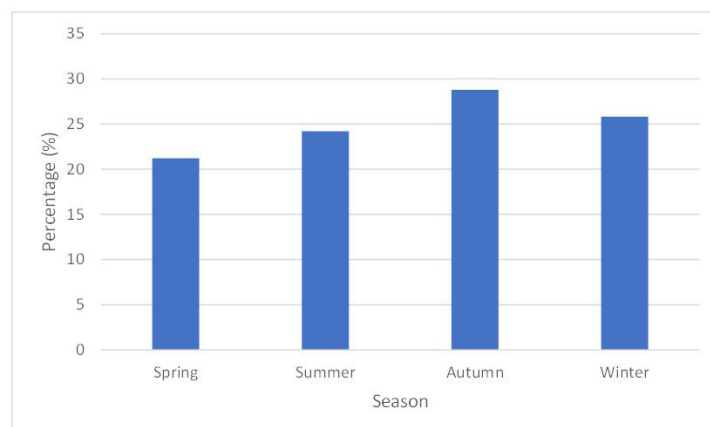


Figure 2: Frequency of formulas prescribed in the different seasons of the year

If data are grouped taking into account the seasons (Figure 2), there was no significant differences among these periods of time ( $\chi^2 = 0.7879$ ;  $p = 0.2388$ ).

All the master formulas requested by the owners of the animals (together with the prescription of the veterinarian, compulsory in Spain) were for oral use. The pharmaceutical forms most used were capsules (56%), followed by solutions (38%), whereas suspensions (6%) were the least employed. Capsules were used with all the active ingredients analyzed except itraconazole. Active ingredients were prescribed in so high doses that made unfeasible its elaboration in a liquid form (solution and suspension), as large volumes are needed to give the adequate dose to the animal, being more comfortable for the owner to administer the medicine to the animal as a capsule. Moreover, capsules have greater stability and do not require refrigeration for storage.

Karara *et al.* [5] employed a wider variety of pharmaceutical forms, as they made topical master formulas. Even so, the most demanded pharmaceutical forms were suspensions (47%), followed by solutions (28%) and capsules (10%). A comparison between our study and that of Karara *et al.* [5] is shown in Figure 3.

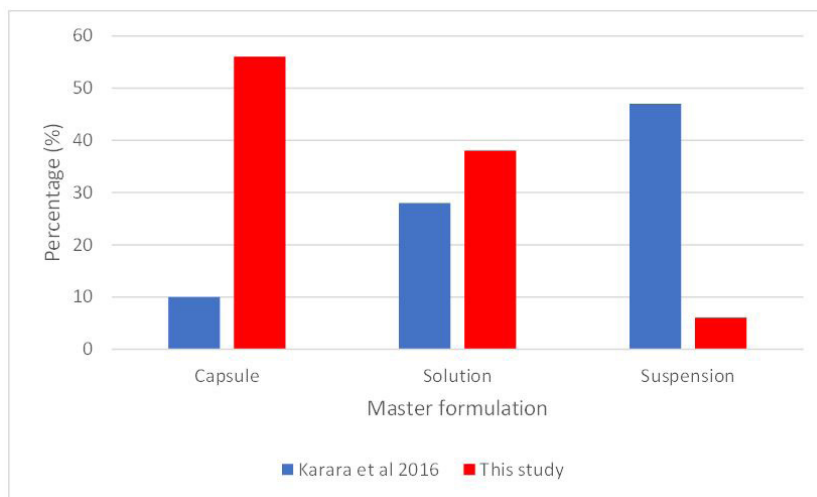


Figure 3: Pharmaceutical forms with the highest prescription in our study vs. Karara et al.

Taking into account the pharmacological activity of active ingredients, we have observed that most of the master formulas were prescribed to treat disorders at the central nervous system (59.1 %), followed by those that exhibited gastrointestinal activity (19.7 %), immunosuppressive (16.7 %), cardiovascular (3 %) and, finally, anti-infective action (1.5 %) (Figure 4).

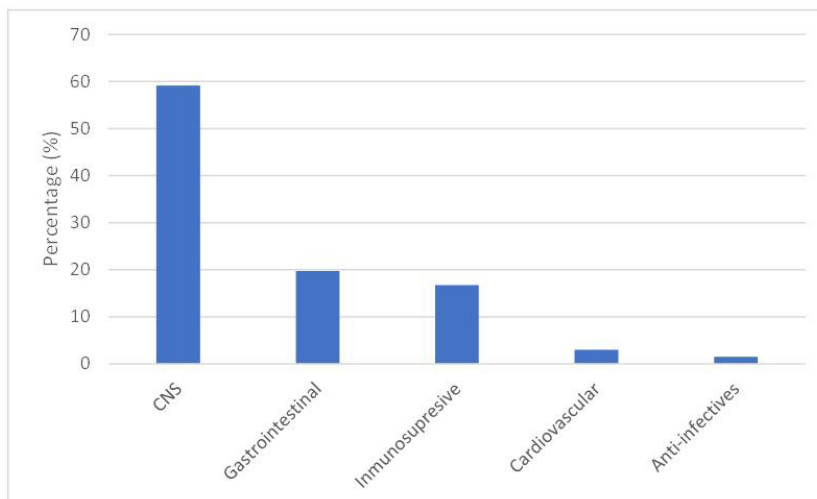


Figure 4: Master formulas prescribed considering their pharmacological activity

### Central Nervous System (CNS)

Among the drugs with activity at Central Nervous System, potassium bromide (KBr) was the active ingredient prescribed in the highest proportion (47% of the total formulas analyzed), with 48% under the form of capsule and 52% as solution. This drug is followed by gabapentin, which represented 12% of the total formulas, with 87.5% as capsules and 12.5% as suspension.

### Gastrointestinal system

Ranitidine represented 20% of the prescribed drugs, and the only one with gastrointestinal activity, being prescribed in greater proportion as solution (69%) and the rest as capsules (31%).

## Immune system

In this category only azathioprine was prescribed, representing 17% of the total formulations. This active ingredient was used in a higher proportion as capsule (82%) than as suspension (18%).

## Cardiovascular system

Among those drugs with cardiovascular action only atenolol was prescribed. It represented 3% of the formulas and was prescribed only as capsules.

## Anti-infectious

Itraconazole represented only 2% of the prescribed compounds, and was formulated only as suspension.

## Most commonly formulated drugs

Table 1 summarized the main drugs present in master formulations in our study and those conducted by Davis [3] and Karara *et al.* [5].

Ranking	Davis	Karara <i>et al.</i>	This study
1	KBr capsules	KBr	KBr
2	Metronidazole suspensión	Metimazole	Ranitidine
3	Metimazole solution	Metronidazole	Azathioprine
4	Diethylstilbestrol capsules	Prednisolone	Gabapentin
5	KBr solution	Doxycycline	Atenololol
6	Cyclosporine ophthalmic solution	Piroxicam	Itraconazole
7	Prednisone solution	Diazepam	
8	Amitriptyline solution	Atenolol	
9	Choramphenicol suspensión	Tacrolimus	
10	Protamine zinc insulin	Gabapentin	

**Table 1:** Top 10 drugs present in master formulas. Comparison with other studies

Although in our study a smaller number of formulas were used compared with other studies, some similarities have been observed among these studies. In this sense, potassium bromide (KBr) was the most requested active ingredient in our study and in those carried out by Davis [3] and Karaka *et al.* [5]. It should be noted that this drug is used as an adjuvant to phenobarbital to control refractory cases of epilepsy in dogs.

When comparing the 10 mostly demanded drugs in master formulas, a greater similarity was found with Karara *et al.* [5]. The study of Davis [3] was carried out 19 years ago, and since then several drugs have not already been used. An example of this would be diethylstilbestrol, which was commonly used for urinary incontinence in dogs, but due to its side effects it is no longer in use, and the same occurs with chloramphenicol.

However, compared to the latest study [5], there is greater similarity, as 50% of the drugs studied by us (KBr, gabapentin and atenolol) were also present in the top 10 of Karara *et al.* [5].

On the other hand, in 1999, when Davis [3] carried out his study no drugs were used among animals to treat pain or heart problems, whereas in our study and that of Karara *et al.* [5] atenolol was prescribed for the treatment of heart disease, and gabapentin against neuropathic pain.

Karara *et al.* [5] formulated a greater number of drugs and trained veterinarians took part in this study. In our case, it is not usual to train veterinary professionals on the use of master formulas, and our percentage of veterinary formulas is clearly lower than that of Karara *et al.* [5], probably due to the lack of knowledge that veterinary professionals may have on master formulas, and on the cooperative capacity of this activity, as it can offer a better quality of individual care to veterinary patients. Another factor that may influence the lower number of drugs formulated is the smaller animal population of our geographical region, but even so we have been able to verify that these medicines are in greater demand, and that there are currently pathologies that now are treated and previously did not require any treatment by the veterinarian. An example is feline orofacial pain, a disease diagnosed in the present century, which exhibits exaggerated movements of the jaw, lips and tongue in the animal, with a pain so intense that cats can mutilate themselves with forelimbs. Several studies have shown that this disorder can be resistant to treatment with traditional analgesics. Thus, more recent anticonvulsants such as gabapentin have been used, and pharmaceutical industry does not produce a medicine at the appropriate dose to relieve this pain in these animals [7,8].

Nowadays, knowledge advances faster than the approval of new drugs by the regulatory authorities. This fact, together with the economic interests of the industry, for which disorders with low prevalence could not compensate the initial investment for producing a certain drug, may explain why in some occasions the only solution is master formulation.

In our opinion, master formulation is of potentially enormous value for the veterinarian. It is important that this professional knows the benefits that master formulation can provide. It is necessary to carry out more studies to confirm the demand of master formulas, and their usefulness when treating pathologies not covered by industrially manufactured medicines.

Our study has some limitations. The first one is that our study has been carried out in a small Spanish city, and it could be not very representative. Nevertheless, our study has shown several similarities with other studies developed. All of them help confirm that despite being carried out in different geographical areas, similar results can be concluded, and collaboration between pharmacists and veterinarians allows to provide a high-quality and individualized care to the veterinary patient, when otherwise could not be accomplished.

## Conclusions

Oral veterinary formulations represented 0.8% of the total number of master formulas produced in the pharmacy studied. Veterinary prescriptions were mainly addressed to treat CNS pathologies, and the dosage form with the greatest demand was the capsule.

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This research received no external funding.

## Conflict of interest

The authors declare no conflict of interest. Verónica García worked at this pharmacy when data were obtained, but the pharmacy played no role in the study design, data collection, analysis and interpretation, or in the decision to submit the manuscript for publication.

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