AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

# VETERINARY MEDICINAL PRODUCTS:

## HOW MUCH ENVIRONMENTAL INFORMATION WOULD BE AVAILABLE FOR DEVELOPING A MONOGRAPH?

De la Casa-Resino, I., Haro Castuera, A., Casimiro Elena, R., Rubio Montejano, C., Carapeto-García, R.

MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios


**Agencia Española de Medicamentos**
**y Productos Sanitarios (AEMPS)**

Calle Campezo, 1, Edificio 8 - E-28022 Madrid
https://www.aemps.gob.es
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# SUMMARY

# 1. INTRODUCTION

Regulation (EU) 2019/6 ('new veterinary regulation' [NVR]) addressing the authorisation of veterinary pharmaceuticals in the EU/EEA will be applicable from 2022. It repeals Directive 2001/82/EC and introduce some important procedural updates regarding the Environmental Risk Assessment (ERA) requirements of veterinary medicinal products (VMPs). These changes are specifically related with the type of applications requiring an ERA (article 18.7), the harmonization of the summary of product characteristic (SPC) (Articles 70-72), the authorisation of VMPs containing (very) persistent, (very) bioaccumulative and toxic (PBT and vPvB) substances (article 37.2), the use of VMPs in aquaculture outside the terms of authorisation (article 114.3) and the substance-based assessment or other potential alternatives (article 156). Regarding the last item, although the ERA still follows a product-based approach, the NVR requests to explore the feasibility and usability of an active substance-based review system (i.e. 'monographs system') and any other potential alternatives for improving the ERA of VMPs.

A substance-based ERA would cover some of the shortcomings identified in the NVR (De la Casa-Resino et al., 2021), but it could also imply the generation and assessment of a large amount of environmental studies. On that sense, it is important to remark that for a significant number of active substances included in VMPs currently in the market, a complete ERA data package was provided during the authorization procedure. This environmental information (that belongs to the laboratory that holds the authorisation) could be pulled to produce a monograph on an API without requiring the generation of new environmental data. However, how many APIs are likely to have enough and reliable environmental information? or, what is even more relevant, how many APIs don't have environmental information at all? With such information we would have a clearer view on the burdens (for applicants and authorities) linked to the implementation of a monograph system or other similar alternative.

The main objective of this document is to answer the above-mentioned questions. Analysing the date of authorisation of the VMPs existing in Spain, we will provide an approximation of the number of APIs that would require the generation of ex novo ERA data for the development of a monograph. This is important information that could give indications to estimate the burdens that applicants and regulators will face in a future monograph system.

# 2. TOOLS AND METHODS

## 2.1. VICH GL6 AND VICH GL38: tiered approach for the ERA of VMPs:

The ERA is generally performed using a tiered approach based on two phases according to VICH GL 6 (phase I), VICH GL 38 (phase II) and EMA supporting guideline, that entered into force in July 2000, October 2005 and March 2009, respectively. Generally speaking, if the environmental exposure is expected to be low (e.g. VMPs for pets or applied to individual animals), no phase II assessment is needed (VICH GL6, 2000).

However, if the VMP has a high environmental exposure or if it is an ecto- and/or endoparasiticide indicated for pasture animals or for aquaculture production or if the VMP is indicated for aquatic species reared in open waters a phase II assessment must be performed in line with VICH GL 38. The phase II assessment implies carrying out physico-chemical, fate and ecotoxicity studies needed to characterize the environmental risks (VICH GL38, 2005; EMA, 2009).

## 2.2 APPROACH CONSIDERED

The underlying premise that we followed for carrying out this exercise is that any VMP authorised after March 2009 has an ERA in accordance with the current EMA supporting guidance (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.1; EMA, 2009), that was effective since that date. This date was chosen because the exposure calculation (crucial to define whether a VMPs requires a phase II assessment or not) was not harmonised until then. Therefore, we can infer that we won't have environmental information of those APIs contained in VMPs that were never authorised after 2009. For example, if the API "X" is present in 10 VMPs and all of them have been authorised before 2009, we conclude that there won't be environmental information available according to the current guidelines and that it should be generated for developing a monograph for the API "X". If the API "Y" is present in 20 VMPs, 15 of which were authorised before 2009, we conclude that there is environmental information available according to the current guidelines for that API in 5 VMPs.

Only one exception was performed to the above-described general rule. VICH GL6 clearly stablish that endo- and/or ectoparasiticides should provide a phase II assessment when they are applied in animals reared in pasture or for aquaculture production. Furthermore, the ecotox information required is clearly defined in VICH GL38. Therefore, it is reasonable to expect that for these antiparasiticides enough environmental information would be available if they were authorized after 1 October 2005, even though the environmental exposure calculations might not be updated.

However, not all VMPs undergo a phase II ERA. The Spanish Medicines Agency and Medical Devices (AEMPS) public database (CIMAVet) of authorised VMPs was used to identify which VMPs would require a phase II assessment. This database allows us to filter all the authorised VMPs in Spain by the date of authorisation, API, target

species, pharmaceutical form, type of authorisation procedure (e.g. generic or hybrid application) and type of VMP (i.e. immunological or pharmaceutical VMP). For data protection reasons, the data provided in the "conclusions" chapter will be bulked with no reference to individual VMPs.

Initially, all pharmaceutical VMPs authorized before 31 December 2019 (including those suspended, i.e. not currently marketed) were considered. That first list was then refined following the tiered approach described in VICH GL6 (2000) in order to guess which of the authorised VMPs needed a phase II assessment. The refinement of the initial list was carried out as follows (figure 1):

1. Those VMPs indicated for companion animals were excluded as phase II assessment is not required according to VICH GL6, GL38 and EMA (2009) guidelines.
2. VMPs indicated for bees were excluded, as phase II assessment is not normally required.
3. The remaining VMPs were divided in 3 main groups: "antimicrobials", "antiparasitics", and "others".
4. Based on the veterinary ERA's team experience it was considered that most of the substances included in the group 'others' will not need a phase II assessment. Therefore, most of them were labelled as "phase I". Two exceptions to this rule were considered: paracetamol and acetylsalicylic acid applied through oral administration in pigs. It is known that a phase II assessment is needed for these substances by considering the exposure. Therefore, these VMPs were labelled as phase II.
5. The antimicrobials were further refined as follows:
   a. antimicrobials likely to be applied to the whole herd (e.g. premixes or solutions for administration in drinking water). Based on the veterinary ERA's team experience, this kind of applications normally need a phase II assessment. Therefore, all VMPs fulfilling this condition were labelled as "phase II".
   b. antimicrobials applied by parenteral route. It could not be reliably determined whether a phase I or phase II assessment is needed in these cases. Therefore, all VMPs fulfilling this condition were labelled as "phase I-II", to indicate that a phase II assessment might be needed in some cases.
   c. Cutaneous, intramammary, local, ophthalmic administrations or antimicrobials used as coccidiostats and fungicides were labelled as "phase I", as a phase II assessment is not normally required.
6. The group "antiparasitics" comprise all APIs included in VMPs with antiparasitic activity. This group was divided in three subgroups:
   a. antiparasitics applied to farm animals reared in pasture or aquaculture production. This group always needs a phase II assessment according to VICH GL6. Therefore, they were labelled as 'phase II'.
   b. antiparasitic applied to farm animals reared indoors. It could not be reliably determined whether a phase I or phase II assessment is needed in these cases as it will depend on the environmental exposure. Therefore, all VMPs fulfilling this condition

were labelled as "phase I-II", to indicate that a phase II might be needed in some cases.

c. Antiparasitics against protozoans were classified as "phase I", as a phase II assessment is not normally required.

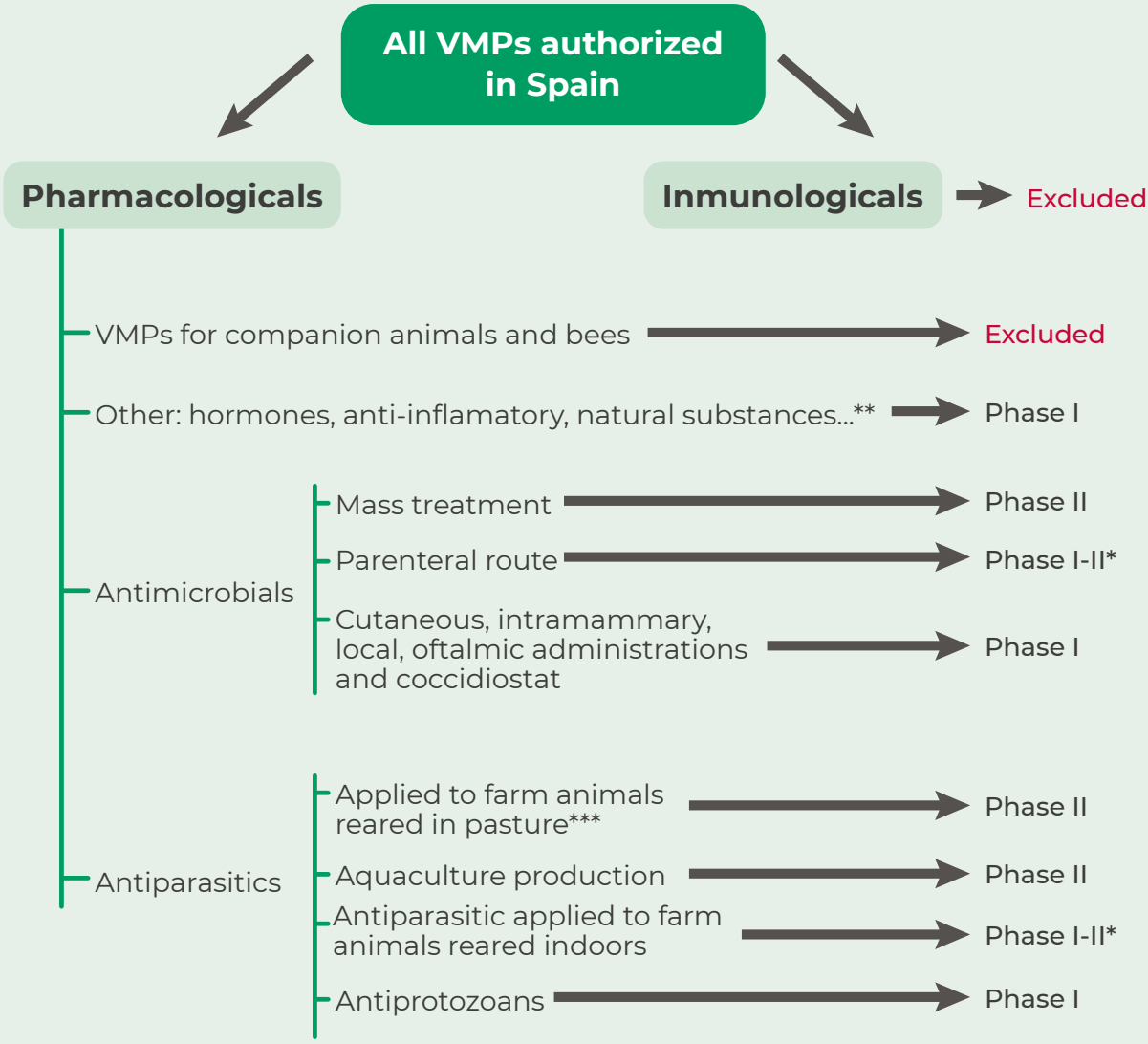


**Figure 1**
Summary of the approach followed to classify all VMPs authorized in Spain.

*A phase II assessment might be needed depending on the exposure.
** Paracetamol and acetylsalicylic acid applied through oral administration in pigs were labelled as phase II.
*** Cattle, sheep, lambs, goats, horse and pony.

Once all VMPs were labelled based on the type of ERA needed, the research focussed on those products classified as "phase II".

In order to determine if reliable environmental information would be available for each API, all substances contained in these VMPs classified as "phase II" were listed by using a Microsoft office Excel® sheet.

The number of products containing each substance were counted and arranged based on its authorization date (Figure 2).

Regarding the authorization date, it was considered that reliable environmental information for an API would be available when the substance has been included in a VMP authorized after March 2009 or in the case of antiparasiticides when it was included in a VMP applied to animals reared in pasture or aquaculture production after October 2005. Consequently, in order to get information on how much environmental information might be available for each API (if any), the authorised VMPS were classified as follows (Figure 2):

- APIs with no VMPs authorized after October 2005 (for antiparasiticides intended for animals reared in pasture or aquaculture production) or March 2009 (for the rest of APIs). No information would be available to develop a monograph for these APIs.
- APIs with only one VMPs authorized after October 2005 (for antiparasiticides intended for animals reared in pasture or aquaculture production) or March 2009 (for the rest of APIs). In these cases, the environmental information that might be available would correspond to only one VMP. The monograph would have been developed based only on this information that might not be completely reliable in some cases. Therefore, new/updated environmental information might be required in some cases.
- APIs with more than two VMPs authorized after October 2005 (for antiparasiticides intended for animals reared in pasture or aquaculuture production) or March 2009 (for the rest of APIs). In these cases, it could be expected that enough environmental information is available to develop a reliable monograph as several products containing the substance have been authorized after October 2005 or March 2009 depending on the case.

## VMPs classified as phase II

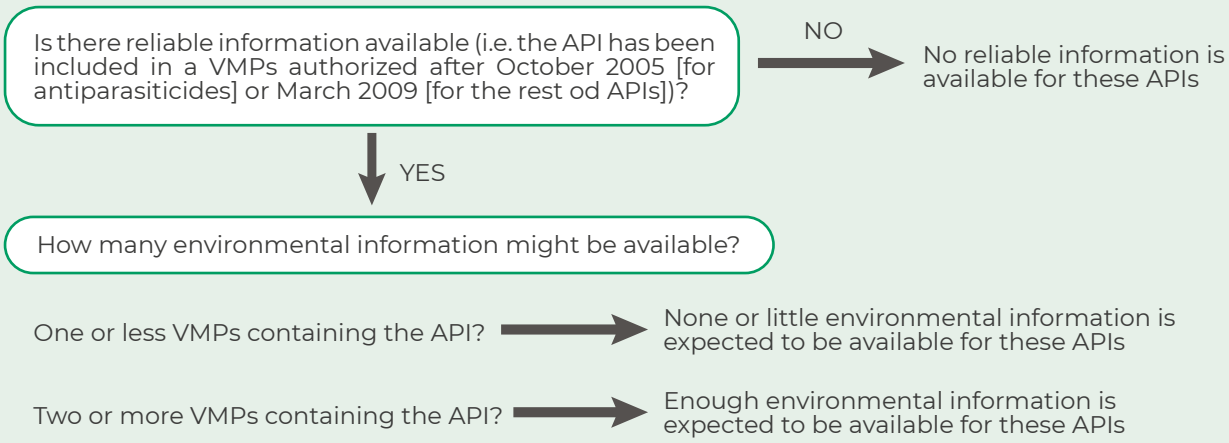


**Figure 2**
Decision tree to determine the environmental information that might be available for each API contained in those VMPs classified as phase II authorized in Spain

### 2.2.1. Remarks:

1. Suspended products were also considered in the assessment as they might have environmental information in their authorization dossiers that could be an additional resource of information.
2. An in deep revision of the dossiers (i.e. technical documentation and ERA assessment) of all VMPs authorized (incl. suspended) in AEMPs was not performed. The above classification was based on the decision tree described in VICH GL6 and the AEMPS' veterinary ERA team experience. Some VMPs might be improperly classified. The aim of this work is to provide a worst case estimate on how many APIs are not expected to have any or few environmental information performed according to VICH GL6, GL38 and EMA guidelines. Actual results might slightly differ.
3. In fixed combination products the combination of API was considered as a new API in order to facilitate the research.
4. When it is concluded in the following sections that "enough environmental information might be available" it does not mean that this information is publicly available. It just means that this information had to be provided for a marketing authorization and thus it might be gathered to produce a monograph without requiring new information. However, whether this information could be used to produce a monograph and the legal procedure that should be developed to share such environmental information is out of the scope of this document.

# 3. RESULTS

## 3.1 GENERAL DATA

A total number of 1130 pharmacological VMPs were analysed, including suspended and excluding VMPs for companion animals and bees (table 1). According to the procedure described under section 2.2, 453 VMPs would require a phase II assessment and 262 were classified as phase I-II to indicate that a phase II assessment might be needed for some of them. In contrast, 416 VMPs are classified as phase I, to indicate that a phase II assessment is not expected to be needed (Table 1 and figure 1).

**TABLE 1** Type of ERA assessment that would be needed for all VMPs authorized in AEMPS

| ERA assessment needed | No. of VMPs |
|---|---|
| Phase I | 416 |
| Phase II | 453 |
| Phase I-II | 262 |
| **Total VMPs** | **1.131** |

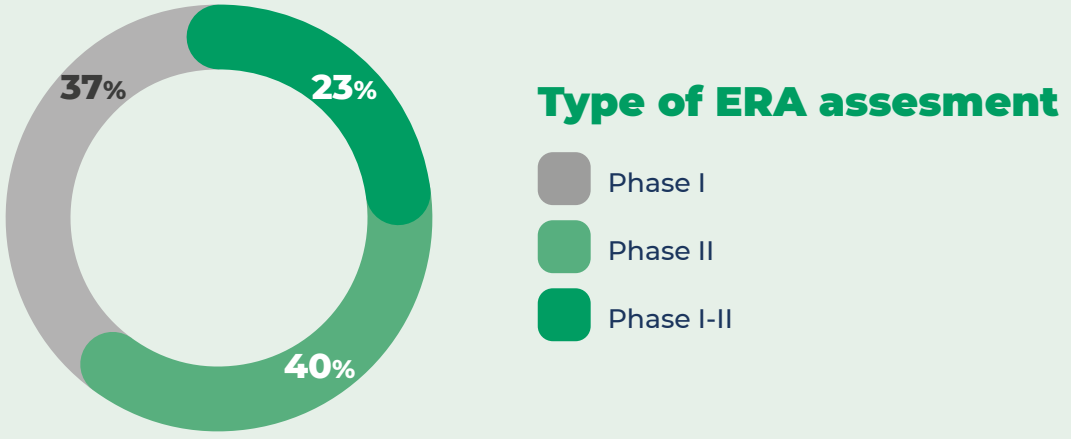


**Figure 1**
Type of ERA assessment (%) required for the VMPs authorized in Spain

### 3.2 ENVIRONMENTAL INFORMATION THAT MIGHT BE AVAILABLE FOR EACH API CONTAINED IN A VMP CLASSIFIED AS "PHASE II".

According to the procedure described under section 2.2, Table 2 and table 3 set out all the APIs contained in VMPs classified as "phase II". Furthermore, the total number of VMPs containing the API, and the number of them authorized before and after October 2005 (for antiparasiticides intended for animals reared in pasture or aquaculture production) or March 2009 (for the rest of APIs) are specified.

Only "phase II" group was considered for analysis as for these VMPs it can reliably conclude that a phase II assessment would be required. If group "phase I-II" would have been considered, the conclusion might slightly vary as more environmental information might be available. However, as this information cannot be quantified (it is known that several APIs included in this group do not need a phase II assessment), it was decided to follow a worst-case approach by considering only the "phase II" group.

Table 2, table 3, table 4 and table 5, summarize the number of APIs, included in VMPs authorized after October 2005 (antiparasiticides intended for animals reared in pasture or aquaculture production) and March 2009 (rest of APIs).

Regarding the APIs included in VMPs authorized after 2009 (excluding antiparasiticides for animals reared in pasture or for aquaculture production), the results indicate that there are 3 out of 33 APIs (9 % of the total) that would not be contained in any VMPs that require a phase II assessment authorized after March 2009. Furthermore, there are 13 out of 33 APIs (39% of the total) for which only 1 VMPs containing the substance have been authorized after 2009. Therefore, it is expected that for 16 out of 33 of the APIs (~ 50 %) included in the VMPs authorized in Spain that require a phase II assessment little or none environmental information according to the current VICH GL6, GL38 and EMA (2016) guidelines would be available (table 3). Instead, there are 17 out of 33 of the APIs (52 %) considered for which enough environmental information according to the afore-mentioned guidelines would be available (table 3 and figure 2).

**TABLE 2** Number of "phase II" VMPs (excluding antiparasiticides intended for animals reared in pasture or aquaculture production) classified per API and authorization date.

| Active Pharmaceutical Ingredient (API) | Total N°. VMP authorized containing the API | No. of VMP authorized before March 2009 | No. of VMP authorized after March 2009 |
|---|---|---|---|
| None VMP containing the API authorized after March 2009 | | | |
| VALNEMULINE | 3 | 3 | 0 |
| SPECTINOMYCIN | 3 | 3 | 0 |
| ERITROMICIN | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Only one VMP containing the API authorized after March 2009 | | | |
| SPECTINOMYCIN; LINCOMYCIN | 2 | 1 | 1 |
| GENTAMYCIN | 2 | 1 | 1 |
| SPIRAMYCIN | 3 | 2 | 1 |
| ACETYLSALICYLIC ACID | 1 | - | 1 |
| AMOXICILLIN; CLAVULANATE | 1 | - | 1 |
| BACITRACIN-ZINC | 2 | 1 | 1 |
| DIHYDRESTREPTOMYCIN | 1 | - | 1 |
| METAMPICILLIN | 1 | - | 1 |
| BROMHEXIN; DOXYCYCLINE | 1 | - | 1 |
| FLUMEQUIN | 6 | 5 | 1 |
| TETRACYCLINE | 5 | 4 | 1 |
| CHLORTETRACYCLINE | 5 | 4 | 1 |
| PHENOXIMETHYLPENICILLIN | 4 | 3 | 1 |
| Two or more VMP containing the API authorized after March 2009 | | | |
| PAROMOMYCIN | 2 | - | 2 |
| SULFAMETOXAZOLE; TRIMETOPRIMA | 2 | - | 2 |
| ZINC OXIDE | 6 | 4 | 2 |
| TILVALOSINE | 2 | - | 2 |
| NEOMYCIN | 10 | 7 | 3 |
| APRAMYCIN | 6 | 3 | 3 |
| THILMICOSIN | 9 | 6 | 3 |
| PARACETAMOL | 6 | 2 | 4 |
| OXYTETRACYCLINE | 16 | 11 | 5 |
| LINCOMYCIN | 17 | 11 | 6 |
| SULFADIAZINE; TRIMETOPRIMA | 9 | 2 | 7 |
| TYLOSIN | 18 | 8 | 10 |
| FLORPHENICOL | 11 | 1 | 10 |
| ENROFLOXACINO | 33 | 22 | 11 |
| THIAMULIN | 28 | 12 | 16 |
| COLISTIN | 30 | 12 | 18 |
| AMOXICILLIN | 39 | 20 | 19 |
| DOXYCYCLINE | 53 | 28 | 25 |
| **Total general** | **338** | **177** | **161** |

**TABLE 3** Summary table of the number of "phase II" VMPs (excluding antiparasiticides intended for animals reared in pasture or aquaculture production) authorized after 1st March 2009.

| No. VMPs containing the API authorized after March 200 | No. API | % |
|---|---|---|
| None | 3 | 9,09 |
| Only one | 13 | 39,39 |
| More than two | 17 | 51,52 |
| **Total API** | **33** | **100** |

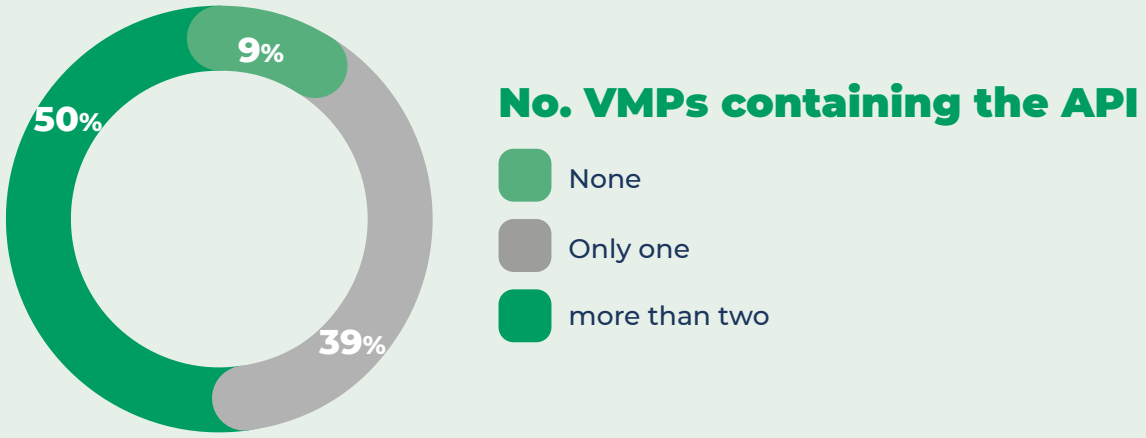


**Figure 2**
Percentage of VMPs (excluding antiparasiticides intended for animals reared in pasture or aquaculture production) authorized after 1st March 2009 containing the API.

When parasiticides for animals reared in pasture or aquaculture production are considered, it is expected that 9 out of 23 APIs (39% of the total) would not be contained in any VMP that requires a phase II assessment authorized after October 2005. Furthermore, 4 out of 23 of the APIs (17% of the total) considered would only have been included in one VMP authorized after October 2005. That would imply that for more than 50% of the antiparasiticides included in VMPs intender for animals reared in pasture of aquaculture production, little or none environmental information according to the current VICH GL6, GL38 and EMA (2016) guidelines would be available (Table 5). In contrast, for 10 out of 23 APIS (43% of the total) enough environmental information according to the previously mentioned guideline is expected to be available (table 5 and figure 3).

**TABLE 4** Number of "phase II" antiparasiticides intended for animals reared in pasture or aquaculture production classified per API and authorization date.

| Active Pharmaceutical Ingredient (API) | Total N°. VMP authorized containing the API | No. of VMP authorized before October 2005 | No. of VMP authorized after October 2005 |
|---|---|---|---|
| None VMP containing the API authorized after March 2009 | | | |
| EMAMECTIN BENZOATE | 1 | 1 | 0 |
| CLOSANTEL; OXFENDAZOLE | 1 | 1 | 0 |
| DIMPYLATE (DIAZINON) | 2 | 2 | 0 |
| CLOSANTEL | 4 | 4 | 0 |
| FENBENDAZOLE | 2 | 2 | 0 |
| NITROXINYL | 1 | 1 | 0 |
| LEVAMISOL | 12 | 12 | 0 |
| CLOSANTEL; MEBENDAZOLE | 1 | 1 | 0 |
| NETOBIMIN | 2 | 2 | 0 |
| Only one VMP containing the API authorized after March 2009 | | | |
| OXYCLOZANIDE | 1 | 0 | 1 |
| FOXIMA | 1 | 0 | 1 |
| MONEPANTEL | 1 | 0 | 1 |
| FORMALDEHYDE | 1 | 0 | 1 |
| Two or more VMP containing the API authorized after March 2009 | | | |
| DORAMECTIN | 2 | 0 | 2 |
| MOXIDECTIN; TRICLABENDAZOLE | 2 | 0 | 2 |
| ALBENDAZOLE | 16 | 14 | 2 |
| MOXIDECTIN | 6 | 4 | 2 |
| CYPERMETHRIN | 8 | 5 | 3 |
| CLOSANTEL; IVERMECTIN | 3 | 0 | 3 |
| CLORSULON; IVERMECTIN | 5 | 1 | 4 |
| DELTAMETRIN | 7 | 1 | 6 |
| EPRINOMECTIN | 10 | 1 | 9 |
| IVERMECTIN | 25 | 14 | 11 |
| **Total general** | **114** | **66** | **48** |

**TABLE 5** Summary table of the "phase II" antiparasiticides intended for animals reared in pasture or aquaculture production authorized after October 2005.

| No. VMPs containing the API authorized after October 2005 | No. API | % |
|---|---|---|
| None | 9 | 39,13 |
| Only one | 4 | 17,39 |
| More than two | 10 | 43,48 |
| **Total API** | **23** | **100** |

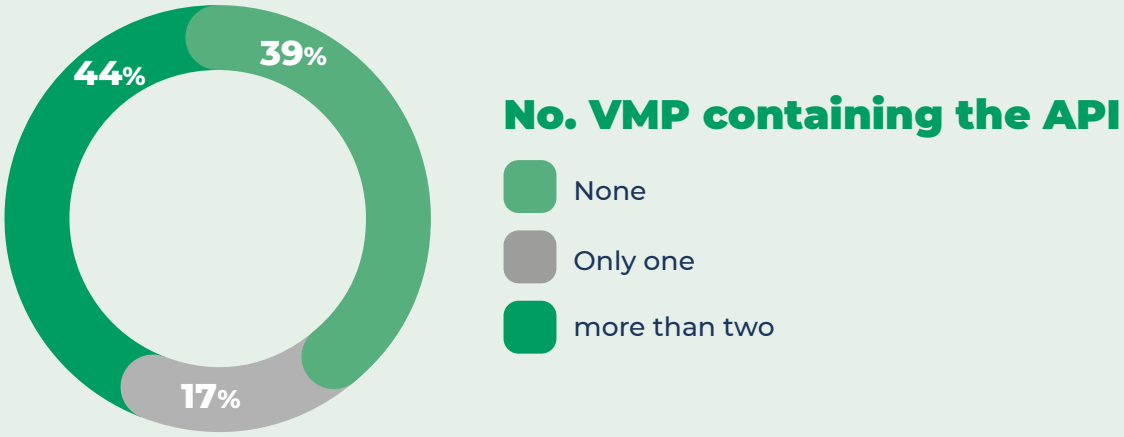


**Figure 3**
Percentage of antiparasiticides intended for animals reared in pasture or aquaculture production authorized after October 2005 containing the API.

In order to draw a global picture, all the APIs and VMPs labelled as "phase II" were compiled and summarized in table 6 and figure 4. There are 12 out of 56 APIs (21 %) that were not included in any VMP that would require a phase II assessment authorized after October 2005 or March 2009. Furthermore, there are 17 out of 56 APIs (30 %) that would only have been included in one VMP authorized after October 2005 or March 2009. Therefore, it can be concluded that for ~ 50 % of the APIs included in VMPs that would require a phase II assessment little o none environmental information according to the current VICH GL6, GL38 and EMA (2016) guidelines would be available (table 6 and figure 4).

**TABLE 6** Summary table of the total number of "phase II" VMPs authorized after October 2005 and March 2009.

| No. VMPs containing the API authorized after October 2005 and March 2009 | No. API | % |
|---|---|---|
| None | 12 | 21,43 |
| Only one | 17 | 30,36 |
| More than two | 27 | 48,21 |
| **Total API** | **56** | **100** |

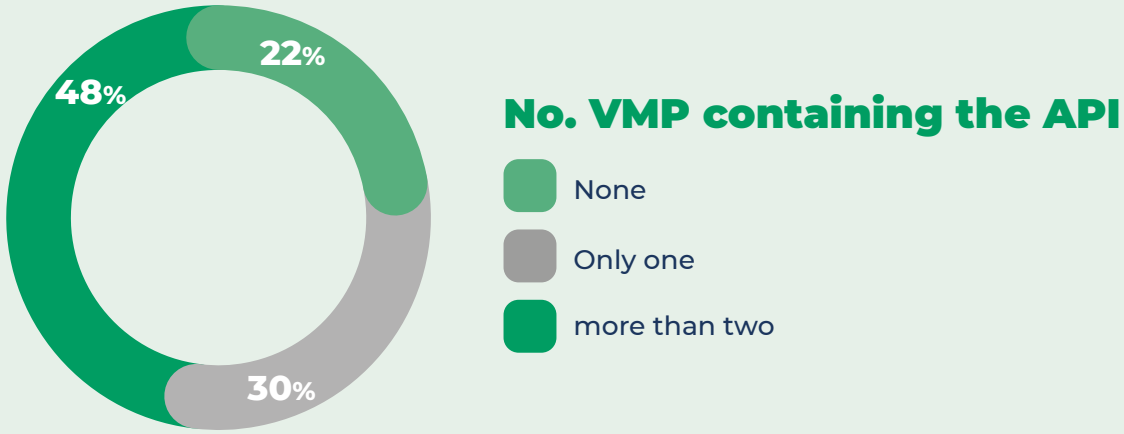


**Figure 4**
Percentage of antiparasiticides intended for animals reared in pasture or aquaculture production authorized after October 2005 containing the API.

On the other hand, it is expected that for 27 out of 56 APIs (48 %) enough environmental information is available as there are at least two VMPs authorized containing the substance after October 2005 or March 2009 (table 6 and figure 4). This information (with the consent of its owner) could be gathered for the development of a monograph for each substance without requiring the generation of new environmental information.

When mixtures are excluded (because more environmental information might be available from the use of the independent substances), there is still 17 out of 56 APIs not included or only contained in one VMPs authorized after October 2005 or March 2009. That would suppose 36 % of the total APIs (excl. fixed combinations) included in VMPs that require a phase II.

# 4. CONCLUSIONS

Approximately, 21 % of the APIs (i.e. 12) included in VMPs authorized in Spain and potentially requiring a phase II ERA assessment were not included in any VMPs authorized after October 2005 or March 2009. That would imply that no environmental information would be available and therefore new tests should be performed to be included in a monograph. This information is relevant for organizational purposes. In case a monograph system for VMPs is finally implemented, it will be important to know the potential burdens that applicants and regulators will be facing, as for at least 12 APIs a complete new ERA might be needed to be performed by and required to the applicants. Furthermore, it should be noted that for those APIs not included in VMPs authorized after October 2005 or March 2009, the applicants might not find economically interesting to perform a complete new ERA. This could have an impact on the availability of VMPs that should be carefully considered.

In contrast, for 48 % (i.e. 27) of the APIs included in VMPs authorized in Spain and potentially requiring a phase II ERA assessment several environmental information would have been already performed for a marketing authorization. For these substances, a monograph development would suppose a huge advance in terms of harmonization of the ERA and reliability of the conclusions.

Nevertheless, we admit that this exercise has got an important bias. All the data comes for the VMPs authorised in Spain solely. We admit that those API identified as not having environmental information might have it available in other EU countries. On the other hand, it is important to remark that Spain is one of the most important livestock producers across the EU. According to Eurostat, (2020), 22% of EU's pigs, 9% of EU's bovines, 25% of EU's sheep and 23 % of EU's goats are produced in Spain. In relation to poultry almost 11% of the poultry meat in the EU-28 was produced in Spain (Eurostat, 2019). Considering the livestock productions, it can be assumed that Spain is a significant market for VMPs and that the results presented above are an important source of information.

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