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Veterinary Medicines Division

Stakeholder Meeting – minutes

Revision of the reflection paper on anthelmintic resistance EMA/CVMP/EWP/573536/2013

13th June 2016, 9.30-16.15, Room 2F

Chairs: G. Hahn and F. Hultén, CVMP Efficacy Working Party

Summary

During the second public consultation of the draft reflection paper on anthelmintic resistance (CVMP/EWP/573536/2013), EMA organised a stakeholder meeting on 13 June 2016. The scope was to facilitate the exchange of views from regulators, industry, academics and veterinarians before the revision of the reflection paper. There were four sessions dealing with different aspects of the anthelmintic resistance: (1) background, (2) prudent use, (3) development and authorisation of anthelmintics, and (4) monitoring tools for resistance development. The following topics were presented and discussed: overview of the anthelmintic resistance in Europe, factors influencing development of anthelmintic resistance, current knowledge of best practices for prudent use, regulatory tools (product information), impact of veterinary medicinal products (VMPs) on resistance development, impact of specific formulations of anthelmintics on resistance development, monitoring methods and systems, and report on lack of efficacy.

The following recommendations for the Committee for Medicinal Products for Veterinary Use (CVMP) were proposed: improve the wording used in guidelines to make it better understandable for the users; restrict the use of long-acting anthelmintics to scenarios where the grazing season is considerably longer than the duration of the effect; develop further guidance on development of “combination products” (multiple actives with similar spectra of activity); harmonise prudent use warnings for similar products.

In addition, further recommendations were proposed, which were however not within the mandate of the CVMP but addressed to other groups: raise awareness in farmers of the risk of anthelmintic resistance development and measures to delay this development; develop better monitoring tools; increase the interest amongst scientists to undertake more research on the topic; encourage national competent authorities to fund systematic monitoring systems at national level or EU-wide; recommend the “SCOPS labelling approach” of VMPs; promote targeted treatment at farm level; make prescriptions of anthelmintics for livestock mandatory; develop more anthelmintics for “MUMS” indications ; better control of (misleading) advertising; encourage veterinarians to report lack of efficacy via the pharmacovigilance system; develop more narrow-spectrum anthelmintics with (reasonably) short withdrawal period; conduct more research on the impact of combination products on resistance development and establish a new EU reference laboratory for anthelmintic resistance.

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First Session- Background

Welcome and introduction.

D. Mackay (EMA) opened the meeting and welcomed the participants. G. Hahn (EWP chair, DE) introduced the topic of the meeting, which aims to help EWP/CVMP to finalise the reflection paper on anthelmintic resistance. A tour de table took place where all participants introduced themselves.

Anthelmintic resistance in Europe

A. Bottger (EWP member, NL), gave an overview of the anthelmintic resistance (AR) situation in Europe in the main target species (cattle, sheep and horses).

In cattle, there are reports from 2006 of ivermectin resistance *(Ostertagia, Cooperia)* in some Member States (BE, SE, DE). In horses, resistance has been reported across Europe in *Parascaris equorum* and *Cyathostominae* against a number of anthelmintic substances. In sheep, resistance against one or more anthelmintic substances/drug classes has been reported all across Europe in most major helminths. Overall, it was noted that resistance can spread very quickly, and changes can happen fairly quickly.

Factors influencing development of anthelmintic resistance.

E. Claerebout (University of Ghent, BE) confirmed that anthelmintic resistance is now present all across Europe, mostly in small ruminants. However, there are not many published reports or clinical studies available about factors promoting resistance.

Selection pressure plays an important role, and the refugia principle is now an established method to reduce anthelmintic resistance development. High frequency of treatments is a significant risk factor of resistance development. Another major factor associated with resistance is routine treatment when environmental *refugia* (i.e. susceptible helminth population) is low e.g. at lambing, during draught period, before move onto clean pasture ('dose and move' practice). Likewise, under-dosing is also associated with development of resistance.

Long-term use of the same class of anthelmintics is suspected to be another contributing factor but there is no scientific evidence. Inappropriate use i.e. not in line with recommendations of the summary of product characteristics (SPC) of a veterinary medicinal product (VMP), use of long-acting drug and pour-on formulation are also risk factors. It is unclear if "mixed-species grazing" contributes or prevents development of resistance, as there are published reports supporting either suggestion. Herd/flock size is not a significant factor of anthelmintic resistance.

Reports on "lack of efficacy" are unreliable, as the reasons for insufficient efficacy are often not clear, and confirmatory tests are not routinely done. In addition, incorrect use of the test methods or incorrect timing of sampling might give misleading results (e.g. macrocyclic lactones suppress egg production; faecal egg counts (FEC) should be undertaken after 2 weeks of treatment).

For a sustainable use of anthelmintics, all risk factors of resistance have to be taken into account; and parasite control needs to be integrated in the farm management. Besides alternative treatment methods, the number of treatments has to be reduced and targeted only on individual animals that are most at risk in order to maintain a good level of *refugia* and prevent the development of resistance ('targeted strategic treatment'). This requires appropriate monitoring of infection levels and production levels to decide on the treatment.

Discussion

The participants all agreed that currently not many data on resistance development are available, and that a systematic EU monitoring system would be desirable. Reasons for the lack of data are the difficulties in monitoring systems and monitoring tools (very labour-, cost-and time-consuming), but also a general lack of interest.

Resistance-research and monitoring has problems in funding, and will only be reliable in future if supported by public funding; however, public interest is low at present and awareness would need to be raised. Farmers (except for sheep) are generally not aware or not concerned about resistance development, and do not pay attention to methods that could delay the resistance development. The prevalence of resistance might be low for some animal husbandry systems where the 'all-in all-out system' allows a good disinfection. Currently not much resistance information is available from pig production (*Oesophagostomum*), however, this might change in future after full implementation of the welfare directive with grouped housing and/or outdoor farming.

Anthelmintic treatment should be part of an integrated parasite control system of farm management. While the efficacy level is usually still very high against most anthelmintics, knowledge of the susceptibility level is important to select the products to be used. Also, the choice of pharmaceutical form should be considered (e.g. variable effects of pour-ons due to the lower maximum plasmatic concentration compared to injectables, probably because of factors such as licking and weather…). Inappropriate storage/use of a VMP might also play a role in unsuccessful treatment although this is not considered a major factor for resistance development. Routine treatment should be replaced by targeted treatment taking into account the age of animals, e.g. young lambs might need more frequent treatment than older sheep with better immunity system.

Although little is reported about resistance development in species other than sheep, it was generally agreed that the qualitative observations made in this species could be extrapolated to other species such as the principle of *refugia* and frequency of treatment. However, the extent/quantitative risk level cannot be extrapolated, and therefore monitoring programmes would be useful. When monitoring resistance, the frequency of treatment, but also initial thresholds on a specific farm for each parasite species and active substance, and duration of persistent efficacy need to be considered.

In companion animals (dogs, cats), there are only anecdotal reports on resistance reports available (*Uncinaria, Ancylostoma and Dirofilaria immitis*) mostly from non-EU countries. *Dirofilaria* resistance has been reported from the USA, and although macrocyclic lactones are usually applied at low doses and high frequency, there is still a large *refugium* of heartworm not exposed to treatment due to individual monitoring and treatment of animals. Overall, the anthelmintic resistance is not considered a major concern in companion animals as there is still a large refugia population in untreated pets or stray dogs/cats. In addition, monitoring of an individual animal is better, and spread of resistance is probably less than in livestock.

Recommendations:

- Raise awareness with farmers of the risk of anthelmintic resistance development, and measures to delay this development.
- Support development of better monitoring tools, e.g. user-friendly software/apps that could be routinely used (by farmers) for monitoring.
- Increase the interest in scientists to undertake more research on the topic.

- Encourage National Competent Authorities (NCAs) to fund systematic monitoring system at national level or EU-wide.

Second session –Prudent use

Current knowledge of best practices for prudent use

L. Stubbings (SCOPS, UK), introduced SCOPS (Sustainable control of parasites in sheep) which is a group committed to reducing reliance on anthelmintics. For most farms, early intervention before resistance is detected and targeted selective treatment are key to success. Reliance on anthelmintics only is increasingly avoided e.g. by improved grazing strategies and nutrition, enhancing acquired immunity, breeding selection for immunity/resilience and quarantine protocols to avoid importation of AR.

Usually worm infestation is diagnosed based on sheep performance as an indicator (i.e. before clinical signs), and FEC is used as a tool to detect resistance. Monitoring and contamination mapping using FEC is an essential tool to select treatment strategies.

SCOPS promotes a targeted selective treatment approach at farm level. The main selection pressures for resistance are under-dosing and overuse, partly due to the unnecessary use of combination products, e.g. concomitant use of endo- and ectoparasiticides to treat sheep scabies at a time where *refugia* population is low. Feedback from veterinarians (UK) indicated that sheep farmers often lack contact with veterinarians. SCOPS have therefore created five different label types for each anthelmintic class, making it easier for a farmer to select anthelmintics from a specific class. In addition, SCOPS provides sheep farmers with recommendations on the correct use of the different classes, such as reserving some classes/products for certain situations only.

Early research (VMD, UK) comparing SCOPS farms and non-SCOPS farms indicated a significant reduction in the use of anthelmintics on those farms following SCOPS recommendations, without obvious impact on the improvement of the anthelmintic resistance situation.

Regulatory tools (SPC and product information)

S. Steuber (BVL, DE) presented an overview on the dossier requirements for a marketing authorisation of a veterinary anthelmintic product, and the guidance available at present. Guidance on claims for treatment of “resistant endoparasites” is not yet provided by regulatory authorities, and only limited information is available from other organisations (e.g. WAAVP).

If claims are made, information on resistance are either in section 4.2 (indications) or 5.1 (pharmacodynamic properties) of the SPC. The SPC guideline for anthelmintics provides standard warnings in the SPC of anthelmintics.

It was noted that misunderstandings of warning statements of the SPC guidance might arise because of the use of too “technical language”. This might result in non-compliance with SPC recommendations.

Regulatory tools (SPC and product information)

R. van Dobbenburgh (Federation of Veterinarians of Europe, FVE) presented the view of FVE on AR as outlined in their position paper. Their key message is to give to any anthelmintics intended for food-producing animals a veterinary “prescription-only” status and to implement integrated worm control programs at farm level. FVE also promotes the use of alternative products and research

into better monitoring and detection systems.

A recent survey in veterinary practitioners showed that the majority of veterinarians consider the SPC as sufficient and up-to-date. However, off-label use of anthelmintics is common, in particular under the cascade system in some species, where no products are available at all (e.g. goats, donkeys, llamas, alpacas) or where the required indication is not covered by existing products for the species (e.g. *Oxyuris* in horses). Thus lack of efficacy and resistance could result from off-label use e.g. same dose used for sheep and goats.

Many farmers obtain their de-wormers without prescription, and might use these incorrectly. Misleading advertising of anthelmintics might also provide the incentives for incorrect use or overuse.

Discussion

C. Paraud (Anses, FR) provided some information about experience with targeted treatment of cattle and goats. In the absence of any authorised products for goats, many farmers use authorised products for other species, and a recent study showed high resistance levels in goats. In another study, mixed grazing (goats and cattle) showed a significantly lower level of resistance in helminths compared to goats or cattle grazing alone. Use of essential oils (mostly in organic farms) also indicated good results in prevention of anthelmintic resistance. More research is needed in regard to integrated control in small ruminants, in particular the combination of different husbandry and treatment methods.

Participants agreed that targeted treatment at farm level should be the “gold standard”, but is not always possible, and farmers are often not interested. Treatment as early as possible to avoid development and spread of resistance should be promoted. Preventive measures should include (husbandry) management options. “Quarantine” treatment of animals is recommended before they are newly introduced into a herd/flock, using two different anthelmintics, which have the lowest resistance level. Any remaining (resistant) parasites will be “diluted” using the refugia principle. This is currently recommended in sheep (UK, SCOPS) and horses (DE). It would also be desirable to undertake a resistance test prior to introducing new animals into a herd. However, this is often not feasible under practical conditions.

The European Group for Generic Veterinary Products (EGGVP) had undertaken a survey, indicating that apart from the price and availability (prescription status) of a VMP, the main incentive for the choice of a product would be the duration of the withdrawal period.

It was noted that for some indications, the lack of narrow-spectrum products might result in unnecessary use. For example, in sheep, the fixed combination of an ectoparasiticide and anthelmintic (or of a combination of a flukicide and a nematodicide) might result in the unnecessary administration of the anthelmintic component. However, timing of treatment is also important: when two treatments are needed at the same time, it makes sense to have a wider-range of indications. It was noted that many (newer) narrow-treatment products have longer withdrawal periods than wide-range products, which would also be an incentive to use the wide-range VMP.

In a recent survey by FVE, 81% of veterinarians indicated that they experienced a lack of efficacy when using anthelmintics; however, regulators do not get that many reports in the pharmacovigilance reporting system. The reason for lack of reporting might be that veterinarians might not be sure if the lack of effect is indeed due to anthelmintic resistance or inappropriate use of the product (e.g. underdosing).

Recommendations:

- Improve language used in guidelines to make it better understandable for the users.
- Use the SPC as an appropriate tool to provide information on prudent use of on anthelmintic products.
- SCOPS (UK) approach (labelling options for the different classes of anthelmintics) could be explored by other NCAs to make it easier for farmers to make an informed choice of VMP.
- Promote targeted treatment at farm level, including quarantine treatment with "reserve anthelmintics" and ideally with post-treatment check-up.
- Mandatory prescription of anthelmintics for livestock.
- Support development of "MUMS" indications for anthelmintics to avoid misuse.
- Better control of advertisement material to avoid misleading information.
- Encourage veterinarians to report lack of efficacy via the pharmacovigilance (PhV) system.
- Develop more narrow-spectrum anthelmintics with (reasonably) short withdrawal period.

Third session - Development and authorisation of anthelmintics

Impact of VMPs on resistance development

T. Geurden (IFAH Europe) presented an overview of the use of "combinations products", i.e. a combination of differently acting substances targeting the same parasite, in delaying resistance development. Such combination therapy was initially used for the control of drug-resistant nematodes in livestock. Early modelling suggested a delay in emergence of resistance for combined insecticides. Models using anthelmintic combination products were developed to delay the development of AR in regions outside Europe (mostly New Zealand) and in UK. The outcome of these models showed that when the initial frequency of resistance alleles is low, and when there is an appropriate *refugia,* using combination products would select more slowly for resistance than mono-products. Leathwick *et al.* (2015) developed a program in in 7 sheep farms using multiactive combinations (but not exclusively) integrated with other management strategies (e.g. refugia). In some farms, there was evidence of some reversion towards susceptibility of *Teladorsagia circumcincta* against ivermectin and levamisole. Calculations based on modelling of annual rotation or the use of combinations indicated that both might reduce the resistance development, when used as part of targeted worm control programme.

Impact of specific formulations of anthelmintics on resistance development

D. Murphy (CVMP member, IE), presented considerations in regard to the impact of different pharmaceutical forms or routes of administration on the resistance development.

Oral use formulations carry the risk of under-dosing, while pour-on formulation might show variable results, as active substances might be absorbed to different extents (differences in absorption between animals), and/or licked off by other animals in the herd. Also other issues such as "tailing off" of active substance into the environment might expose treated animals to sub-therapeutic doses. Extended/prolonged-release formulations might result in prolonged/repeated parasite exposure, which might then have implications on the refugia situation.

In general, there is a lack of effective anthelmintics for minor species and resistance in these is particularly wide-spread as dosing levels might differ considerably from effective doses in cattle.
Discussion Risk factors for resistance development resulting from inadequate dose levels for certain formulations when used against certain target pathogens or larval stages, were discussed. While there is little published on anthelmintic resistance development, it is generally agreed that long-acting formulations carry a higher risk of resistance development, although it is unclear if this is only a risk at the end of their duration of effect, when active substance concentrations are expected to decrease. However, it is considered prudent to use long-acting products only in certain situation, e.g. at the start of the grazing season, and only if the grazing season is expected to last considerably longer that the duration of the product effect, in order to facilitate the development of immunity and to establish a healthy refugia. If the grazing season is short, the use of such products is not recommendable. However, there also appear to be species differences, as IFAH Europe conducted a study in cattle demonstrating that the long-acting products showed good efficacy profiles when used in the right scenario, whereas, in sheep the use of long-acting products seemed to promote resistance development. There is demand from farmers for such products, but many farmers might use the products inappropriately. Participants agreed that anthelmintic pour-ons show variable efficacy, as noted for macrocyclic lactones, where efficacy results in the field were very variable, despite successful laboratory trials, probably because of licking. One trial showed that up to 30% of a product was licked-off; however, licking behaviour differs between individual animals and substances, and is not easy to predict. There also are other concerns for pour-ons in regard to their environmental impact, e.g. macrocyclic lactones might be accumulative in the environment. In general the participants indicated that pour-ons might not be recommendable for anthelmintic treatment. Under-dosing for oral in-feed/water medication appears to be less of a problem currently, with the all-in all-out housing situation with thorough disinfection between batches and the relatively short period/lifespan of animals; however, with future changes in animal husbandry systems (increase of free-range animals) this situation might change. Pharmacokinetics of combinations products will need to be carefully considered, and there is currently not much information available on rotation of anthelmintics in a herd/flock, if some are combinations. IFAH EU raised concerns in regard to difficulties in developing combinations, as not much information is published and no guidance is available. It was also agreed that getting such studies is difficult, as studies would need to be very long-term (years) and would need to consider different environmental situations. There are no genetic markers that could indicate resistance development at an early stage. The approach of combining active substances to delay or reverse resistance is increasingly under investigation, but is controversial. The assumption that the use of combination products would delay or even reverse resistance development is currently not supported by field data, but is based on extrapolations from other types of products and modelling calculations. Also, in regard to concerns about the risk of development of multi-resistance against both substances in combination products, no reports are available. In general, the use of combination products should be targeted for the farms, and early intervention would be the best way to address resistance. The use of combination products might be beneficial in case of established resistance and high refugia population. At present such products are only used in rotation with other products (mono-products with a single active substance or combined products).

Concerns were raised on inappropriate advertising, as this might result in wrong user expectations or use of a product. There was agreement that there is a general concern about inappropriate use of anthelmintics and the need for more awareness regarding the proper use of anthelmintics.

Recommendations:

- Long-acting anthelmintics should only be used in scenarios where the grazing season is considerably longer than the duration of the effect.
- Further guidance is needed on development of combination products.
- More research/data are needed on the impact of combination products on resistance development.

Fourth session - Monitoring tools for resistance development

Monitoring methods and systems

G. von Samson-Himmelstjerna (Freie Universität Berlin, DE) presented an overview of available monitoring methods and systems. Resistance in sheep, cattle and horse parasites is reported across the EU, but generally only limited information and no prevalence data are available. There are currently no validated tools/tests or monitoring systems for anthelmintic and routine efficacy tests are needed. In principle, anthelmintic resistance can be investigated using various methods:

In-vivo tests such as worm counts and faecal egg count reduction tests (FECRT), are in principle possible, but unsuitable for monitoring, since necropsy would be needed (worm counts) or costs are too high (FECRT).

There are some *in-vitro* assays, which would be suitable for monitoring, but they are only available for some worm species and/or active substance components (e.g. egg-hatch inhibition test, larval-development inhibition, allele specific molecular tools (PCR, pyrosequencing) or not yet available (e.g. larval migration inhibition assays).

Proposals were made for monitoring systems in small ruminants, cattle and horses, and a feasible monitoring system could be applied using post-treatment testing in 'hot spots', with follow-up monitoring in cases of reported resistance. In general, monitoring of resistance in horses might be easier to achieve than in livestock, since there seems to be more support by horse owners than farmers.

Generally there is a need for an EU reference laboratory across the EU for the establishment and maintenance of reference strains, for the evaluation/validation of monitoring tools and training in resistance detection/monitoring.

Regulatory tools: report on lack of efficacy

P. Ekström (PhVWP chair, SE) informed about the pharmacovigilance system (PhV), which is used to monitor all VMPs post-authorisation. Such monitoring takes account of data which were not available at the time of marketing authorisation, e.g. long-term use for chronic treatment, off-label use, different populations (e.g. age groups, breeds), and use of concomitantly applied products. Reports mostly focus on safety concerns but "lack of expected efficacy" is also part of the PhV reporting.

In regard to antiparasitic products, most lack-of-efficacy-reports concern ectoparasiticides (e.g. remaining ticks), and reports in regard to anthelmintic products are rather rare. Also, the quality of the reports varies greatly, and the best quality reports are usually from academia during clinical

trials. Currently, the PhV system would not be a suitable tool to detect or monitor resistance.

However, the reporting is generally rather low, and veterinarians are encouraged to use the PhV system to make their observations available.

Discussion

As a consequence of PhV assessment, new changes/warnings to the SPC might be requested. However, differences were noted between such warnings on products containing the same active substances e.g. resistance warnings in avermectin-containing products, this is confusing and not clear to the user. It was suggested that in case of data (e.g. PSURs) indicating the need for a warning of a certain VMP, warnings should be harmonised for similar products, if appropriate.

However, as products with the same active substance might nevertheless have different properties, changes can only be done on a case-by-case approach, and might result in differences between SPCs of products.

Information about avermectin resistance is inconsistent across substances in this group, and insufficient information is available about the differences of the different active substances in different animal species, e.g. moxidectin sensitivity in ivermectin-resistant helminths is reported in sheep but resistance is reported in cattle. If ivermectin resistance is noted in a population, it is generally recommended as a precautionary measure, not to use other products for the same class when rotating treatment options, even if resistance might not have been reported in other substances.

The participants supported the proposal to establish a new EU reference laboratory and while this would be outside the EMA scope, EMA/CVMP is asked to promote/support this suggestion. Although some methods could be used for monitoring across Europe, validation and comparison of these monitoring methods is still necessary. An EU reference laboratory could, for example, define "hot spots" across Europe for the monitoring, e.g. areas of intensive rearing conditions for animals with outside access, areas of high animal density, or geographical regions where routine treatment of animals is undertaken after droughts. Clearer recommendations on how to undertake monitoring tests are also needed to avoid misleading results between users of the same test methods.

Recommendations

- Establish a new EU reference laboratory for anthelmintic resistance; i.e. for the establishment and maintenance of reference strains, for the evaluation/validation of monitoring tools and for training in resistance detection/monitoring.
- Veterinarians should be more encouraged to use the PhV system to report “lack of efficacy”.
- Regulators should harmonise prudent use warnings for similar products, as necessary; and phrase such warnings in an unambiguous way to avoid misinterpretations.

Overall conclusions – actions

- Anthelmintic resistance is now present all across Europe, mostly in small ruminants.
- There is currently not much reliable published literature available about factors promoting resistance.
- A targeted selected treatment approach at farm level/integrated worm control programs are recommended to delay the development of resistance.

- In general, there is a lack of effective anthelmintics in minor species.
- The product formulation might have an impact on resistance development.
- There are currently no validated tools/tests or monitoring systems for anthelmintic resistance.
- Currently, there are no systems available to detect or monitor resistance.

Recommendations for CVMP:

- Improve the wording used in guidelines to make it better understandable for the users.
- Restrict the use of long-acting anthelmintics to scenarios where the grazing season is considerably longer than the duration of the effect.
- Develop further guidance on development of "combination products" (targeting the same parasites).
- Harmonise prudent use warnings for similar products, as necessary; and phrase such warning in an unambiguous way to avoid misinterpretations.

Other recommendations:

- Raise awareness of farmers of the risk of anthelmintic resistance development, and propose measures to delay this development.
- Support the development of better monitoring tools, e.g. user-friendly software/application that could be routinely used (by farmers) for monitoring.
- Increase the interest in scientists to undertake more research on the topic.
- Encourage NCAs to fund systematic monitoring system at national level or EU-wide.
- SCOPS (UK) approach (labelling options for the different classes of anthelmintics) could be explored by other NCAs to make it easier for farmers to make an informed choice of VMP.
- Promote targeted treatment at farm level, including quarantine treatment with "reserve anthelmintics" and ideally with post-treatment check-up.
- Mandatory prescription of anthelmintics for livestock.
- Support development of "MUMS" indications for anthelmintics to avoid off-label use.
- Better control of advertising material to avoid misleading information.
- Encourage veterinarians to report lack of efficacy via the PhV system.
- Develop more narrow-spectrum anthelmintics with (reasonably) short withdrawal periods.
- More research/data are needed on the impact of combination products on resistance development.
- Establish a new EU reference laboratory for anthelmintic resistance i.e. for the establishment and maintenance of reference strains, for the evaluation/validation of monitoring tools and for training in resistance detection/monitoring.