FEDERATION OF VETERINARIANS OF EUROPE

SPC HARMONISATION REPORT
'Views from veterinary practitioners'
January 2020

Background:

- The majority of the veterinary medicinal products on the market have been authorised under national procedures. As a result, the summary of product characteristics (SPC) of veterinary medicines can differ greatly for similar products, e.g. different withdrawal periods or indications listed in countries, even if they are placed on the market by the same marketing authorisation holder.
- Regulation 2019/6 on veterinary medicinal products lays down the task to an EU coordination group to draw up an annual list of reference veterinary medicinal products which are to be subject to harmonisation of the summary of product characteristics. The new Regulation dictates that it is necessary to harmonise SPCs at least in regard to dosage, uses and warnings of the veterinary medicinal products (ANNEX I).
- IMPORTANT: **SPC harmonisation needs to be done for products which have the same qualitative and quantitative composition of their active substances and the same pharmaceutical form and the same marketing authorisation holder; and for generic and hybrid veterinary medicinal products.**
- EU regulators asked FVE, the Federation of Veterinarians of Europe, for input on the parameters to be harmonised in priority from the veterinary practitioners, the main end users of the products. In the period 6-14th January 2020, FVE reached out to its members for feedback on the following questions:

1) Looking at SPC harmonisation, are there specific types of products for which you believe SPCs should be harmonised?
2) Which main components do you believe should be harmonised?
3) Do you have specific examples of products for which you really think SPC harmonisation is needed?
4) Any other comments you would like to make on SPC harmonisation?

This report was based on 19 responses we received from 3 veterinary colleges and 16 veterinary organisations (ANNEX II). Thank you very much for this input!!!

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Question 1:
Looking at SPC harmonisation, are there specific types of products for which you believe SPCs should be harmonised?

The **main goals** should be:

1. Ensuring and enabling the use of the respective drug in the "best way", meaning a **valid dose range and dosage regimen[1];**
2. Ensuring **consumer safety** by using correct and adequate withdrawal periods (times);
3. Protecting the vet practitioners, public health and animals informing them about **the current knowledge on side effects, precautionary measures during use and related issues.**

It was suggested that the prioritisation of medicines for harmonisation should be '**risk and relevance'-based**, taking into account the following:

- The **volume** of sales/prescriptions; e.g. a product that is used very frequently should be prioritized over a product with a lower sales volume;
- The **disparity** between dosage regimens/withdrawal periods/indications (especially for old products); **Withdrawal period differences** that are particularly important for food producing animals
- **Prioritizing medicines** that are registered & marketed in many (often neighbouring) countries;
- The **benefit** for the animal (i.e. use for life threatening versus non-life threatening diseases).
- The **risk for the animal and human safety** (safety issues of the product) -) urgent cases will go through pharmacovigilance system.

<u>Which products to prioritize?</u>

All respondents agreed that **the first priority for harmonisation should be antibiotics.** Other products to be considered in priority are antiparasitics, analgesics/anaesthetics, all veterinary medicinal products for food producing animals and vaccines.

With regard to harmonisation of SPCs for vaccines, some veterinarians are of the opinion that the key item on the SPC to be harmonised in priority should be the validity of

[1] IMPORTANT NOTICE: Once the new regulation applies, the dose given in the SPC of a VMP will be mandatory to prescribe/use and cannot be legally modified by the veterinarian, unless this is justified in line with the requirements (Article 106/1 of the EU regulation 2019/6) for off-label use (cascade).

revaccination periods. Companion animal veterinarians highlight in particular, the example of Rabies vaccines, where the duration for booster doses for the same product varies between 1 to 3 years in the different countries (sometimes due to governmental regulations). It was indicated however that vaccines may be one of the products that are difficult to harmonised due to the nature of the product, namely the different strains, different methods used for antigen production (inactivated or live viruses), different scheme of immunization and category of animals, etc.

It was also mentioned that the harmonisation of veterinary medicines will facilitate moving towards a single market and can also improve trade and safeguard the public health.

Question 2:
Which main components do you believe should be harmonised?

- **Target species**

It would be good to harmonise target species, with a focus on not removing but adding target species.

- **Dosage and dosage regimen**

The dosage and dosage regimen recommendations should be updated according to the newest scientific knowledge[2].

- **Indications**

Indications for use should be harmonized based on existing pharmacological data and the current knowledge for the concerned medicinal product. All possible variable indications should be included while the indications for which a drug is not effective should be removed. Further harmonisation should be discussed on a case to case basis to include alignment of the SPC to the latest scientific knowledge, e.g.

- Older SPC sheets should list indications by using the updated microbiological names (e.g. *Trueperella pyogenes* was formerly known as C*orynebacterium pyogenes*).
- Limited indications of SPCs compared to textbooks and SPCs not always corresponding to textbook references create a medical challenge and a responsibility dilemma for veterinarians.
- Taking into account national science-based guidelines and recommendations

- **Withdrawal periods (food producing animals)**

[2] Many older antimicrobials use the recommendations that may have been considered correct when they were first approved, but are not necessarily considered correct now (e.g. oral amoxicillin should be taken every 8 hours, not every 12 hours as per all of the various veterinary amoxicillin product SPC sheets; the 12 hours regimen has led many times to subminimal inhibitory concentration).

Harmonisation of withdrawal periods is not very significant for companion animals but is extremely important for food producing animals. A small difference in withdrawal times can lead to big economic consequences.
It is vital to take into consideration that any significant extension of withdrawal periods, as it was done for injectables containing Gentamicin (extension from 90 to a maximum of 214 days), may result in confusion for the practicing veterinarians, especially when there are no indications that the implementation of the shorter withdrawal times are insufficient. It also might make the product simply unusable.

- **Safety messages/narrow safety margins/adverse drug reactions**

Most side effects are linked to the active substance and thus should be harmonised across the different products. But some side effects might be linked to ingredients other than the active substances. This has to be considered.
Unless there is evidence that a higher dosage, a shorter withholding period or the absence of a safety warning in one Member State SPC versus another has led to safety issues (as documented in the post-marketing pharmacovigilance of the product) or violative residues (as documented in the residue monitoring programme of each MS) then the **widest range of dosage that's scientifically validated should be harmonised along with the shortest withholding period for that dosage**. Safety warnings may need to be different depending on the distribution category in each MS (for example, if the end user is an animal owner or a veterinarian).

- **Duration of validity of the immune protection for vaccines**

As it was previously mentioned the opinions on this extremely differ. Some consider that it should be harmonised, while others think that it probably should not be harmonised to any great degree since local conditions can vary from region to region, never mind country to country. There is a recommendation to put a one-liner in vaccine SPCs advising that their use can be adjusted based on local need and the judgement of the practitioner.

- **On prescription or over-the-counter**

In some countries a product is on veterinary prescription, while in the neighbouring country it can be bought by animal owners over the counter. This is creating very difficult situations for practitioners. The veterinary profession supports that all Member States should strictly adhere to the criteria laid down in the regulation for the categorisation of POM products.

Question 3:
Do you have specific examples of products for which you really think SPC harmonisation is needed?

Specific examples given include: Bimoxyl inj. (and **amoxycillins** generally), Noromectin inj. (and **ivermectins** generally), Flunixin inj. (and **NSAIDs** generally), Benzylpenicillin-procaine, Tylosin, Fenbendazole, Imizol etc.

There are many examples that prove that harmonisation of SPCs is essential, such as:

- Ampicillin containing medicines for injection approved for horses intended for slaughter. Irish product Ampisol[3] and German product Ampi-Dry 100 mg/ml are similar products that have extremely different withdrawal periods. While for the German product the withdrawal period is 1 day, for the Irish product it is 6 months.

- There are many Amoxicillin containing medicines for different indications approved for cattle in Germany (see Table below). However, it is unknown, whether and which of those medicines are reference products/generic medicines/hybrid medicines.

Area of application in cattle: **Initiation of a treatment of the following diseases caused by amoxicillin-sensitive bacteria (Gram-positive and Gram-negative):**	**Amoxicillin 15% WDT**	**Amoxisel-TS**	**Aulicin Amoxi LA**	**Belamox**	**Betamox Injection**	**Duphamox**	**Duphamox LA**	**Hostamox LA**	**Synulox RTU**	**Vetrimoxin**	**Veyxyl LA**
Infection of the lung and respiratory tract	×	×	×	×	×	×		×	×		×
Infection of the respiratory tract							×				
Respiratory diseases caused by *Mannheimia haemolytica* and *Pasteurella multocida*										×	
Infection of the digestive tract	×	×	×	×	×	×	×	×			×
Infection of the urogenital tract	×	×	×		×	×	×	×			×
Infections of the ear canal	×	×	×		×	×		×			
General infections and septicemic diseases	×	×	×		×	×	×	×			×
Secondary bacterial infections due to viral infections	×	×	×	×	×	×		×			×
Skin- and wound infections, abscesses, phlegmons	×	×	×		×	×	×	×			
Inflammation of the hoof (Panaritium)	×	×	×		×	×		×			
Infections of the soft tissue (e.g. abcesses, arthritis, umbilical infections, mastitis, panaritium)									×		
Arthritis and umbilical infections in calves and pigs	×	×	×		×	×		×			
Metritis									×		
Acute mastitis in cattle including impaired general condition	×	×	×		×	×		×			
Mastitis, metritis and agalactia (MMA) in sows	×	×	×		×	×		×			
Swine erysipelas (*Erysipelas suis*)	×	×	×		×	×	×	×			×

[3] http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_10976-013-001_18062009020756.pdf

- Another example is Ivermectin oral paste for horses with a concentration of 18.7 mg/g. Irish product QVALAN Oral Paste for Horses 18.7 mg/g has a recommended dose 0.2 mg/kg and withdrawal period of 21 days. Similar German product called Animec 18,7 mg/g oral paste for Horses with the same concentration and recommended dose has a withdrawal period of 34 days. In addition, in the sections regarding interactions with other medicinal products of the SPC, for the German product it says: "Effects of GABA-Agonists might be increased by ivermectin.", while for the Irish product it says "EQVALAN Paste has been used in conjunction with other equine health care products and no interactions have been identified."
- A number of antibiotics used in poultry species in some Member States (MS) have more "liberal" withdrawal periods (e.g. nil withdrawal period for eggs for human consumption) and poultry species indicated than in other MS.
- Rabies vaccines

NOTE: Not all these examples are for products from the same Marketing Authorisation Holder

Question 4:
Any other comments you would like to make on SPC harmonisation?

Other remarks made:

- Ideally a ***single EU market*** for veterinary medicinal products would be created. EU has a single market for animals, animal products, as such it is contra-indicative not to have a single market for veterinary medicines. Importation of medicines is in many cases unnecessarily laborious for practitioners and should be simplified and harmonised in the interest of animal health and welfare. Practitioners working in several countries, especially struggle to comply with the differences between the different implementation of the EU rules in Member States.

- **SPC harmonisation is essential** but should be used as an opportunity to increase availability and **must not in any case negatively impact or lead to loss of availability of veterinary medicinal products**. It is important to consider that the harmonisation of the indications of medicines containing the same active components may negatively affect the motivation of the pharmaceutical industry to initiate or conduct studies. This, in turn, would negatively affect the availability of veterinary medicines.

- In addition to other data, **pharmacovigilance** data should be considered as input for harmonisation. If a product has been on the market for a long time, has been used a lot and almost no adverse events have been reported, this is meaningful information.

- It is acknowledged that the harmonisation of SPCs is a significant task, and that therefore **prioritisation** is needed. **When developing this prioritised listing annually, practitioners' input should be sought**.

- **Specific logo/notification** should be added on boxes of products to make visible to the practitioners that SPC has been (changed) updated.

- Indications for use and dosages vary considerably and many veterinarians across Europe make decisions based on **professional manuals or guidelines e.g. the BSAVA Formulary**. This means that they will sometimes need to use a higher or lower dosage or a product for an indication not on the SPC. Veterinarians should keep the possibility to make science and evidence-based discussion which they can argument on the basis of recognised scientific literature to treat animals in real time.

- Concerning Article 106(1) of the new 2019/6 EU Regulation (ANNEX I) which states the following: „*Veterinary medicinal products shall be used in accordance with the terms of the marketing authorisation*", becoming applicable next year, we consider it to be advisable to make sure that dosage recommendations still reflect the current state of science and meet the challenges of daily practice. Or make it clear that it is possible for **veterinarians to be able to modify the dose/dosage regimen based on scientific evidence, scientific guidance (e.g. BSAVA Manuals) and/or professional judgement and experience.**

ANNEX I: Extract of Regulation 6/2019 on use of medicinal products and SPC harmonisation

Section 3

Use

Article 106

Use of medicinal products

1. Veterinary medicinal products shall be used in accordance with the terms of the marketing authorisation.

2. The use of veterinary medicinal products in accordance with this Section shall be without prejudice to Articles 46 and 47 of Regulation (EU) 2016/429.

3. Member States may lay down any procedures they deem necessary for the implementation of Articles 110 to 114 and 116.

4. Member States may, if duly justified, decide that a veterinary medicinal product shall be administered only by a veterinarian.

5. Inactivated immunological veterinary medicinal products referred to in Article 2(3) shall only be used in the animals referred to therein in exceptional circumstances, in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target animal species and the indication.

6. The Commission shall adopt delegated acts in accordance with Article 147, in order to supplement this Article, as necessary, which establish the rules on appropriate measures to ensure the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration via routes other than medicated feed, such as mixing of water for drinking with a veterinary medicinal product or as manual mixing of a veterinary medicinal product into feed and administered by the animal keeper to food-producing animals. The Commission shall take into account the scientific advice of the Agency, when adopting those delegated acts.

Section 4

Harmonisation of the summaries of product characteristics for nationally authorised products

Article 69

Scope of the harmonisation of summaries of product characteristics of a veterinary medicinal product

A harmonised summary of product characteristics shall be prepared in accordance with the procedure laid down in Articles 70 and 71 for:

(a)

reference veterinary medicinal products which have the same qualitative and quantitative composition of their active substances and the same pharmaceutical form and for which marketing authorisations have been granted in accordance with Article 47 in different Member States for the same marketing authorisation holder;

(b)
generic and hybrid veterinary medicinal products.

Article 70

Procedure for harmonisation of summaries of product characteristics for the reference veterinary medicinal products

1. The competent authorities shall submit annually to the coordination group a list of reference veterinary medicinal products and their summary of product characteristics for which a marketing authorisation has been granted in accordance with Article 47 if, according to the competent authority, they should be subject to the procedure for harmonisation of their summaries of product characteristics.

2. The marketing authorisation holder may apply for the procedure of harmonisation of summaries of product characteristics for a reference veterinary medicinal product by submitting to the coordination group the list of different names of this veterinary medicinal product and the different summaries of product characteristics for which a marketing authorisation has been granted in accordance with Article 47 in different Member States.

3. The coordination group shall, taking into account the lists provided by the Member States in accordance with paragraph 1 or any application received from a marketing authorisation holder in accordance with paragraph 2, draw up annually and publish a list of reference veterinary medicinal products which shall be subject to harmonisation of their summaries of product characteristics and shall appoint a reference Member State for each reference veterinary medicinal product concerned.

4. When drawing up the list of reference veterinary medicinal products which shall be subject to harmonisation of their summaries of product characteristics, the coordination group may decide on prioritising its work on harmonisation of summaries of product characteristics, taking into account the recommendations of the Agency on class or group of reference veterinary medicinal products that shall be harmonised in order to protect human or animal health or the environment, including mitigation measures to prevent the risk to the environment.

5. On the request of the competent authority in the reference Member State referred to in paragraph 3 of this Article, the marketing authorisation holder shall provide the coordination group with a summary that specifies the differences between the summaries of product characteristics, its proposal for a harmonised summary of product characteristics, package leaflet and labelling in accordance with Article 7, supported by the appropriate existing data submitted in accordance with Article 8 and which are relevant to the proposal for harmonisation concerned.

6. Within 180 days of receipt of the information referred to in paragraph 5, the competent authority in the reference Member State shall examine, in consultation with the marketing authorisation holder, the documents submitted in accordance with paragraph 5, prepare a report and submit it to the coordination group and to the marketing authorisation holder.

7. After receipt of the report, if the coordination group agrees by consensus on the harmonised summary of product characteristics, the competent authority in the reference Member State shall record that there is an agreement, close the procedure, inform the marketing authorisation holder accordingly and transmit to the same marketing authorisation holder the harmonised summary of product characteristics.

8. The marketing authorisation holder shall submit to the competent authorities in each relevant Member State the necessary translations of the summary of product characteristics, package leaflet and labelling in accordance with Article 7, within the time limit set by the coordination group.

9. Following an agreement in accordance with paragraph 7, the competent authorities in each relevant Member State shall amend the marketing authorisation in conformity with the agreement within 30 days of receipt of the translations referred to in paragraph 8.

10. The competent authority in the reference Member State shall take any appropriate steps in order to seek an agreement within the coordination group before the initiation of the procedure referred to in paragraph 11.

11. Where the agreement is not reached because of lack of consensus in favour of a harmonised summary of product characteristics following the efforts referred to in paragraph 10 of this Article, the procedure for a Union interest referral referred to in Articles 83 and 84 shall apply.

12. In order to maintain the level of harmonisation of the summary of product characteristics achieved, any future variation of the marketing authorisations concerned shall follow the mutual recognition procedure.

Article 71

Procedure for harmonisation of summaries of product characteristics for generic and hybrid veterinary medicinal products

1. When the procedure referred to in Article 70 has been closed and a harmonised summary of product characteristics for a reference veterinary medicinal product has been agreed, the marketing authorisation holders of generic veterinary medicinal products shall apply, within 60 days of the decision by the competent authorities in each Member State and in accordance with Article 62, for the harmonisation of the following sections of the summary of product characteristics for the generic veterinary medicinal products concerned, as applicable:

(a)target species;
(b)clinical information referred to in point (c) of Article 35(1);
(c)the withdrawal period.

2. By way of derogation from paragraph 1, in the case of a marketing authorisation for a hybrid veterinary medicinal product supported by additional pre-clinical studies or clinical trials, the relevant sections of the summary of product characteristics referred to in paragraph 1 shall not be considered to be subject to harmonisation.

3. The marketing authorisation holders of generic and hybrid veterinary medicinal products shall ensure that the summaries of products characteristics of their products shall be essentially similar to those of the reference veterinary medicinal products.

ANNEX II: Full list of veterinary colleges and organisations that participated in our questionnaire

- Poultry Veterinary Science (ECPVS)
- Veterinary Parasitology (EVPC)
- Veterinary Internal Medicine of Companion Animals (ECVIM-CA)
- The Society of Swiss Veterinarians - Société des Vétérinaires Suisses (SVS)
- Education, Research & Industry (ERI) Interest Group
- Veterinary Ireland Companion Animal Society (VICAS)
- Veterinary Council of Ireland
- Swedish Veterinary Association (SVF)
- Federation of European Equine Veterinary Associations (FEEVA)
- The European Platform for the Responsible Using of Medicines in Animals (EPRUMA)
- ASV College Veterinaire
- European Veterinarians in Education, Research and Industry (EVERI)
- Latvijas veterinārstu biedrība (LVB)
- Federation of Companion Animal Veterinary Associations (FECAVA)
- Koninklijke Nederlandse Maatschappij voor Diergeneeskunde (KNMvD)
- Medicines Working Group of FVE
- Czech Veterinary Chamber
- Federal Veterinary Surgeons' Association (BTK)
- Les vétérinaires praticiens libéraux (SNVL)