CMDv voluntary SPC harmonisation: Report on the pilot phase

1. Context

Several possibilities for harmonisation are provided in Directive 2001/82/EC as amended. Within these possibilities and once the harmonisation exercise proposed by the Directive was refused in 2005 by most of the member states, articles 34 and 35 can be used to achieve harmonisation of a Summary of Product Characteristics (SPC). An Article 35 referral procedure should be justified in the interest of the community whereas an article 34 referral procedure can be initiated following divergent opinions between national competent authorities. Consequently, article 34 referral is to be used for the harmonisation of SPC of nationally authorised products which are not harmonised within the EEA.

In 2009, as an alternative to referral procedures, the veterinary Coordination Group for Mutual Recognition and Decentralised Procedures (CMDv) decided to work on an informal worksharing mechanism to harmonise SPCs and the quality part of the dossier of veterinary medicinal products authorised on a purely national basis.

The **objectives** of the process were:

- To improve the protection of public and animal health and to increase public confidence in product informations.
- To facilitate decisions in MRP and DCP particularly with regards to upcoming generic applications for new marketing authorisations.
- To reduce the number of referrals.
- To help member states to become proactive in the harmonisation of products, using both formal and informal means, rather than simply reacting to a situation as it develops.
- To provide a tool for industry to harmonise SPCs for one product authorised in several member states and consequently to simplify the maintenance of the marketing authorisations.

Within such a procedure there would not be any reassessment of scientific data contained in these old dossiers pursuant to current guidelines. The assessment was to be conducted as for generic applications when information is needed on the reference product: exchanges of assessment reports between member states, based on mutual trust. It was foreseen that the procedure would be beneficial for both the marketing authorisation holders and the authorities. The procedure is of a voluntary nature for both parties and as such not supported by legislation.

This procedure managed by the CMDv without any legal basis was supported by Heads of Medicines Agencies-vet.

A draft procedure was written and the pilot phase was launched in 2010.

2. The pilot procedure

2.1 Choice of the candidate product

The CMDv decided to start the procedure with highly disharmonised older products authorised for more than 10 years

The chosen product for the pilot phase was an enrofloxacin-containing solution for injection for food-producing and companion animal target species. This product was chosen due to the broad level of disharmonisation between the national reference products. The product comprises 3 strengths, not all authorised in each member state. Fortunately, the marketing authorisation holder accepted to participate in the harmonisation pilot phase.

Denmark, and subsequently France, as leader of this project, accepted to be reference member state (RMS) for the pilot phase of the SPC harmonisation procedure.

2.2 Assessment

The first task of the reference member state was to collect all SPCs of products authorised on a purely-national basis. Between 18 to 22 different SPCs were checked. Differences between all these SPCs and the harmonised SPCs proposed by the marketing authorisation holder were checked by the RMS. When information contained in the SPC was not granted by the RMS, the other member states were asked to substantiate this based on their own assessment reports related to the application for marketing authorisation, extensions and variations. The marketing authorisation holder was then asked to provide existing data for some information (claims, indications...) not substantiated by either RMS or other member states.

The majority of the national experts had to return to the dossier submitted during the application for marketing authorisation, especially regarding safety and efficacy data. So, although the harmonisation procedure was only meant harmonise SPCs without the need to re-visit some aspects of the SPC, national competent authorities did check the basis of the major aspects mentioned in the SPC. An unexpected number of issues arose with old data/assessment reports and unavailable data/assessment reports.

The harmonisation concerned the entire SPC as well as the quality part of the dossier. The CMDv agreed upon a defined list of critical pharmaceutical characteristics, essential for granting the marketing authorisation as well as for the control of the veterinary medicinal product.

Participation of the member states and communication between all involved member states and the marketing authorisation holder was of undeniable importance before and during the course of the SPC harmonisation pilot procedure. All member states participated to this harmonisation procedure, even if the veterinary medicinal product was not authorised in their country. Face-to-face and virtual meetings were organised on a regularly basis between member states in the margins of CMDv meetings and led to intensive but productive discussions. Four meetings with the marketing authorisation holder were also organised.

At the latest stage of the procedure, it was really difficult to reach an agreement between member states on specific sections of the SPC, mainly on some target species and specific indications for use.

Finally, in November 2011 after several months, an agreement was reached on a harmonised SPC for the 3 strengths. The harmonisation step of the procedure was successfully finished.

These SPCs were sent to the marketing authorisation holder who asked for justifications on deletions of claims identified as ‘critical’ during the process. The RMS sent its assessment report in return in December 2011.

2.3 Timelines

In its draft procedure the CMDv had fixed a draft timetable based on a Type II-variation timetable (120 days).

The pilot was launched with this timetable, but was adapted with huge flexibility at each step. The procedure started on 24/09/2010, the final SPC was adopted by member states in November 2011.

Below is an estimation of the time spent within the agencies. The time spent by CMDv members, the EMA secretariat, the chair of the CMDv is not included in this table.

	Min	Max	RMS
Quality experts	0 – 3 H*	20 H	16 H
Safety experts	6 H	35 H	100 H 3 weeks
Efficacy experts	16 H	50 H	140 H 4 weeks
Rapporteur/ Administrative	25 H	46 H	140 H 4 weeks

*hours

2.4 Outcome

In April 2012, although an agreement was reached on SPCs between the marketing authorisation holder and the CMDv, the marketing authorisation holder informed the CMDv by letter that they were not in a position to continue with the pilot phase. The major obstacle cited by the marketing authorisation holder was the lack of a binding procedure for the concomitant implementation of the harmonised SPCs to the generics.

As things stand, the only way to achieve harmonisation of the concerned reference products and their generic products is to initiate a referral procedure.

The article 34[1] referral is usually the one to be used for the harmonisation of SPCs of nationally-authorised products that are not harmonised within the EEA. However it will only include the reference product and not its generics. Concerning the three veterinary medicinal products concerned by the pilot phase, generic products were present on the market in very large numbers. The question is whether it is possible to run an article 35[1] referral procedure with the aim of harmonising the reference and generic products all together? The CMDv will consult with the EMA and the Commission on the best way to go forward.

[1] Directive 2001/82/EC, as amended

3. Results

3.1 Pros

- Even if it was hard and time-consuming due to the nature of the products and the level of disharmonisation, a harmonised SPC was adopted by the different member states and also by the marketing authorisation holder. The harmonisation step of the pilot was successful.

- Discussions within the CMDv (virtual meetings, working group, plenary session) demonstrated the capacity of the CMDv to handle and discuss scientific issues very similarly to an MRP, DCP or pre-arbitration procedure.

- This procedure was the occasion to introduce the concept of standardisation of the quality part of a marketing authorisation application dossier with a list of 10 critical pharmaceutical characteristics. This standardisation was easy and managed with a pragmatic approach.

- During the pilot procedure, the CMDv also clearly clarified and improved the procedure for the implementation of a harmonised SPC via administrative variations for the reference products. There was also a proposal on how to implementation this harmonisation to the generics i.e. via a letter from the CMDv to the marketing authorisation holders of generics asking for the introduction of a variation (C.I.2.a).

- The CMDv has also worked on how to maintain the harmonisation through transfer of the national products into MRP.

- It was also discussed and agreed that member states where the veterinary medicinal product concerned by the harmonisation is not authorised can participate on a voluntary basis in the harmonisation procedure. A repeat-use MRP to officially register the product was also envisaged at the end of the procedure, once the product is transferred to MRP.

3.2 Cons

- The general view was that the time spent was too significant compared to the limited result.

- Moreover, the unpredictable timetable caused difficulties because it was hard to anticipate the forthcoming workload and the actual end of a step (no formal deadline).

- It has to be considered that with a less complex product, a less disharmonised SPC, non-food producing target species and involving fewer member states, the workload would have been lower.

- At the end, the major issue faced was the absence of a legal basis for this harmonisation exercise and the lack of legal basis to enforce the outcome on the generics.

4. CONCLUSION

Three years after the start of the project, the results are rather mixed. However, CMDv members appreciate the collaboration between national competent authorities and also with the cooperation of the marketing authorisation holder. This was confirmed by the marketing authorisation holder.

The CMDv and member states have progressed on the methodology of harmonising national MAs. Possible the CMDv should now try a 'workshared' harmonisation procedure on an 'easier' veterinary medicinal product. But the lack of legal basis and the lack of binding decision will remain a critical limitation.

Therefore, it is proposed that the future revised veterinary legislation would include a legal basis for SPC harmonisation by member states. The legislation should provide adequate flexibility in the process for the harmonisation (e.g. pragmatic vs data-based, prioritisation, timescale), which would allow adaptation of the process over time. With more experience, process improvements and simplifications could possibly also develop. Then, with the subsequent aim of maintaining the harmonisation, the transfer of the national marketing authorisations into a 'European' decision should be mandatory for the marketing authorisation of the reference product and for all related generic MAs. The document "CMDv Recommendation for MRP after art. 34 referral" could be of help for the discussion on the transfer procedure.

Finally, the liaison between the generics and their reference product should also be scrutinised for the future legislation. When the SPC of the reference product is changed, the SPCs of the generic products should also be changed without the need of a substantiated serious risk. This management tool should be binding for all parties. However, applicants could have the opportunity to make an appeal to the CVMP in case the decision is not acceptable.