Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

EMA/CMDv/74350/2014
London, 10 July 2014

ANNUAL REPORT 2013

7 Westferry Circus - Canary Wharf - London E14 4HB - United Kingdom

CONTENTS

1 Introduction

The veterinary coordination group (CMDv) for Mutual Recognition (MRP) and Decentralised procedures (DCP) is a platform of the countries in the European Economic Area (EEA) set up to examine any question relating to marketing authorisation of a veterinary medicinal product (VMP) in two or more Member States (MSs).

Focus points for 2013 were:

- Validation phase of MRP/DCP;
- Improving the internal functioning of the CMDv;
- Referrals to the CMDv under Article 13 of Regulation (EC) 1234/2008 and Article 33(1) of Directive 2001/82/EC, as amended;
- Variation worksharing procedures;
- Responding to regulatory queries from industry;
- Review and update of CMDv guidance documents.

2 Organisational issues

2.1 Meetings and membership of the CMDv

The vice-chairperson during the Irish presidency of the Council of the European Union in the first half of 2013 was the Irish CMDv member. In July, the Irish CMDv member continued the role of vice-chair for the second half of 2013 in lieu of Lithuania under their presidency (limited representation at CMDv).

The CMDv members from Finland and Denmark were replaced during the year. Following Croatia's accession to the EU on 1 July 2013, their appointed CMDv member began attending the CMDv meetings.

The European Commission (EC) observed a number of the CMDv meetings throughout the year or participated remotely for specific discussions via telephone link.

On 27-28 June, the Irish Presidency hosted an additional meeting in Dublin with individual and joint sessions for the CMDv and Committee for Medicinal Products for Veterinary Use (CVMP).

On 21-23 October, Lithuania hosted an additional meeting in Vilnius with individual and joint sessions for the CMDv and CVMP.

2.2 Working groups

The following working groups of the CMDv held meetings during 2013 and contributed to the respective policy issues outlined in section 4 below:

- Validation
- Improvement of MRP and DCP
- Packaging
- Document management

Representatives from the CMDv participated on an *ad hoc* basis in the meetings of the joint EMA/CMDh/CMDv variations subgroup and the joint CMD/EMA/EDQM/CVMP/ CHMP/QWP working group on active substance master file procedures.

3 Authorisation procedures

3.1 Initial marketing authorisation applications

A total of 218 MRP/DCP procedures were finalised, relating to 165 products[1]. Table 1 provides an overview of the number of products and procedures that reached the end of the DCP and MRP over the last five years.

Table 1 MRP and DCP products (procedures) finalised

	2013	2012	2011	2010	2009
MRP	66 (83)	63 (74)	72 (89)	42 (57)	50 (57)
DCP	99 (135)	93 (141)	99 (143)	67 (99)	68 (86)
Total	165 (218)	156 (215)	171 (232)	109 (156)	118 (143)

There was little difference in the total number of MR/DC *procedures* compared to the previous year and approximately a 6% decrease in the number of *products* involved in those procedures. Approximately 80% of the total MRPs/DPCs in 2013 were abridged applications under Article 13 of Directive 2001/82/EC, most of them generics.

The Member States taking on the role of RMS per procedure are shown below in table 2.

Table 2 Number of procedures per Reference Member State

AT	BE	CZ	DE	DK	ES	FI	FR	HU	IE	IT	NL	NO	PT	SE	UK
4	1	12	12	1	20	1	20	2	57	1	11	1	6	2	67

As foreseen in the workplan, on a number of occasions during the year, the RMS or a CMS requested a discussion during a CMDv plenary meeting due to potentially serious concerns identified at an earlier stage of the MRP/DCP. This initiative was well-received and found to be beneficial in reaching a common understanding of the underlying issues.

3.2 Referrals to the CMDv

Referrals for initial marketing authorisation applications (MAAs) and line extensions are notified to the CMDv according to Article 33(1) of Directive 2001/82/EC, as amended, and for Type II variations (including worksharing applications) according to Article 13 of Regulation (EC) 1234/2008, as amended. In total 8 referral procedures involving 7 products were finalised by the CMDv in 2013. The procedures referred were 5 initial applications and 3 Type II variations. The disagreement was resolved in 29% of the cases referred to CMDv under the 60-day procedure. For the remaining 71% of the cases there was no resolution and the matter was referred to the CVMP for final arbitration. The CVMP accepted 100% of the procedures referred by the CMDv and the final outcome was that 80% of these referrals were overruled i.e. the concerns of the referring Member State(s) were not upheld or could be managed through risk mitigation measures.

Overall the number of referral procedures to the CMDv decreased by 20% between 2012 and 2013. The graphs below illustrate the statistics and motives for the CMDv referrals initiated in 2013.

Figures 1-6 illustrate the statistics behind the referrals to the CMDv in 2013. Six of the seven products referred were indicated for use in food-producing species. Compared to the previous year, the predominant ground for referral shifted from bioequivalence to environmental risk assessment. This may reflect the greater proportion of referred

[1] 1 product includes all strengths and pharmaceutical forms submitted but does not include duplicate applications, which are counted separately

products indicated for use in food-producing species. There was a much narrower range of products and legal bases of MA applications under referral compared to 2012. Notably a greater proportion of the procedures under referral were Type II variations. A significant proportion of the products under referral in 2012 were antimicrobials whereas in 2013 the emphasis shifted onto antiparasitics.

Figure 1

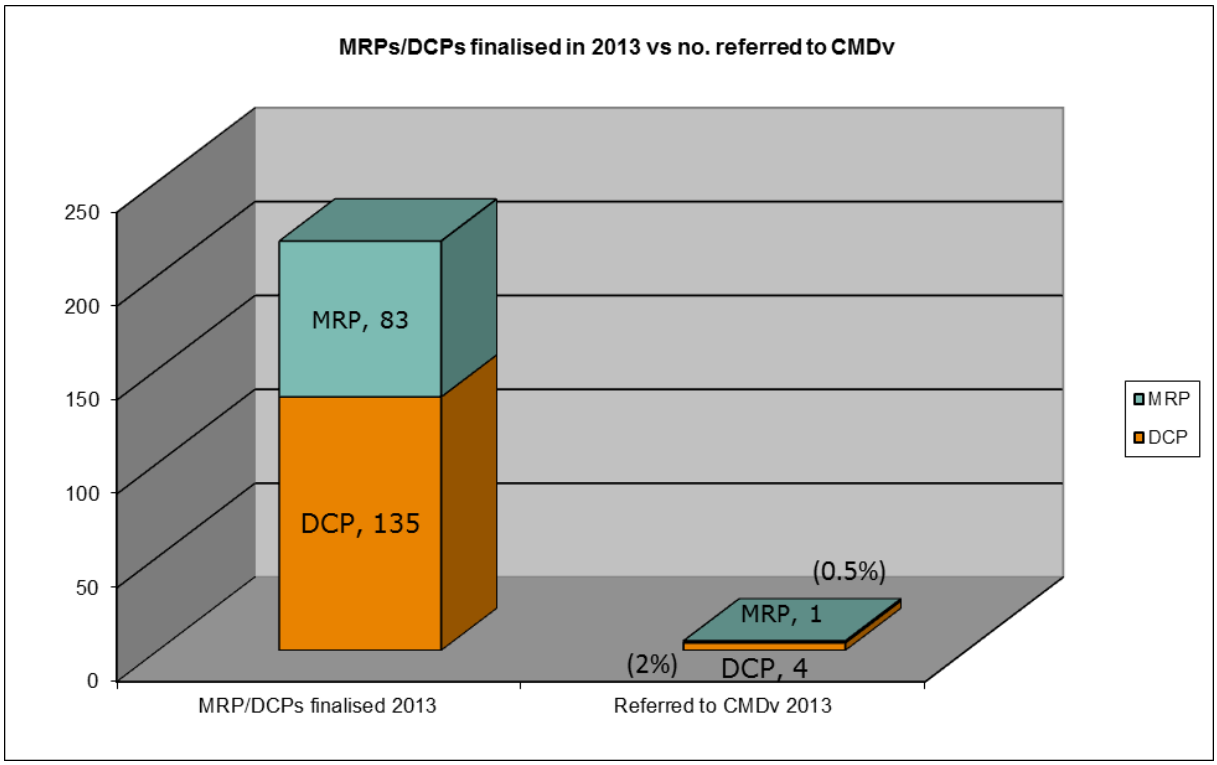


Figure 2

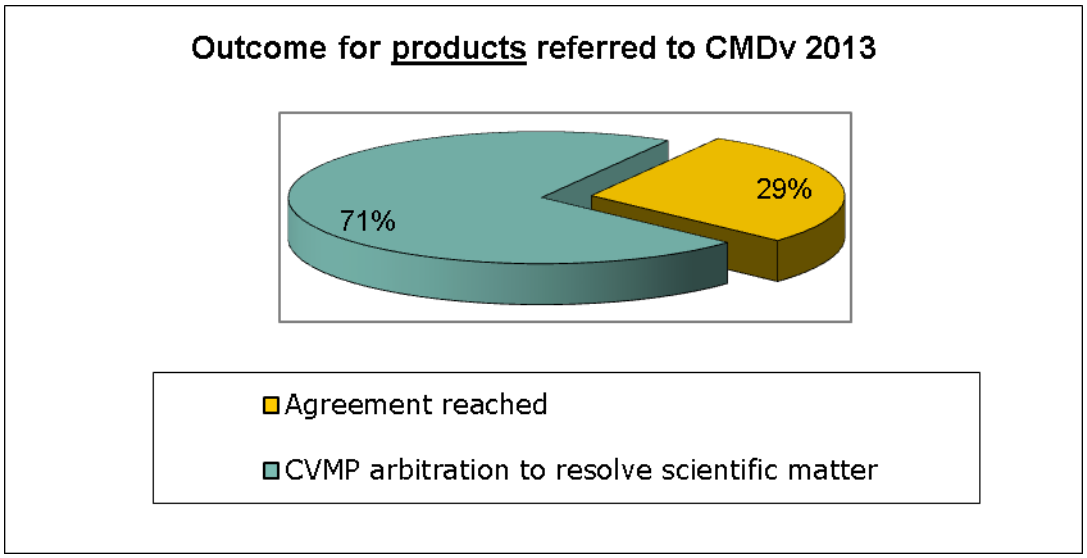


Figure 3

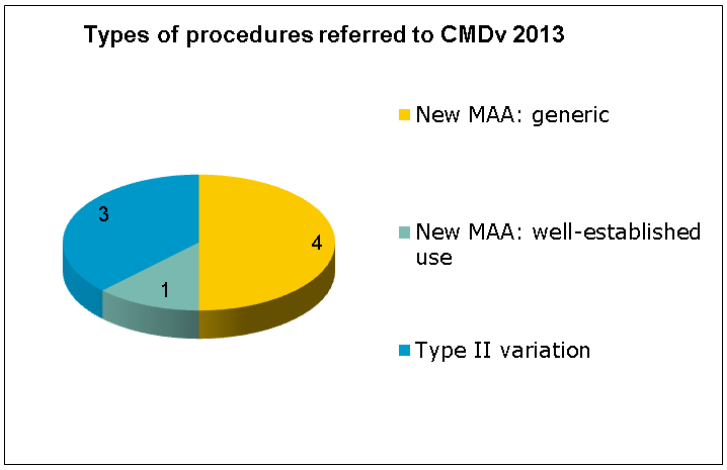


Figure 4

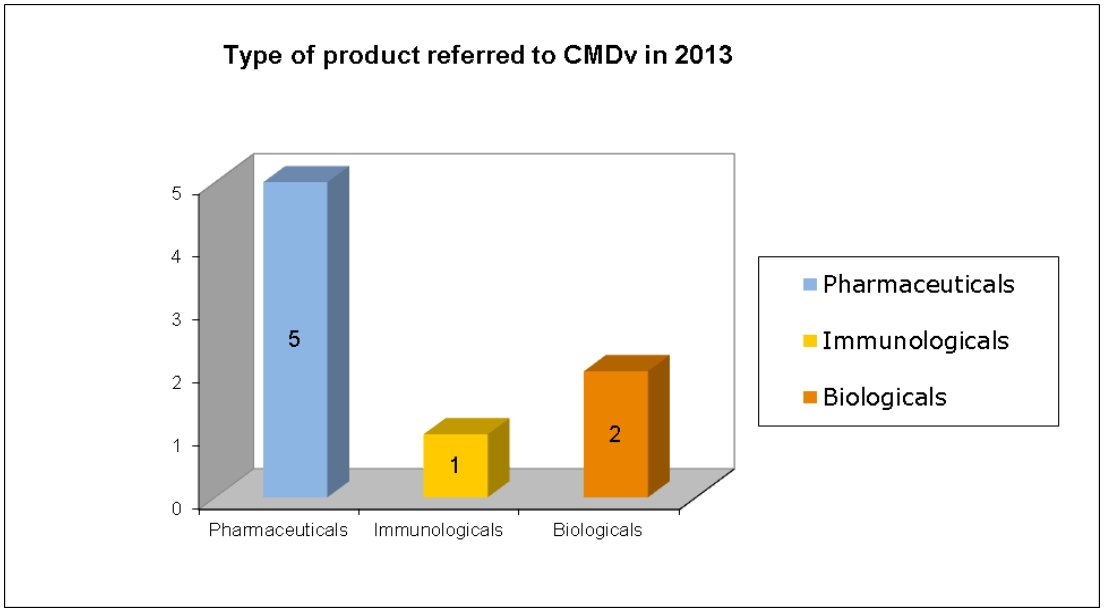


Figure 5 (New MAAs and Type II variation procedures)

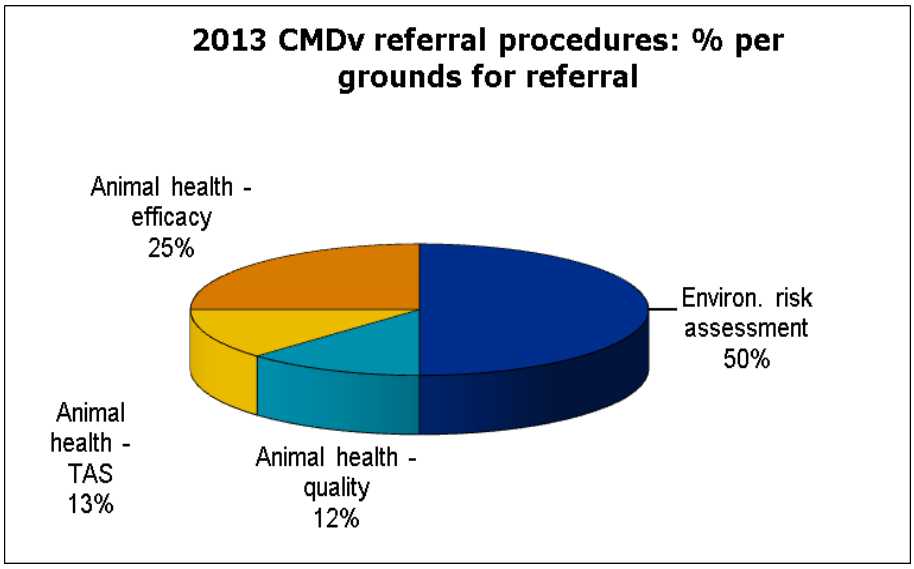
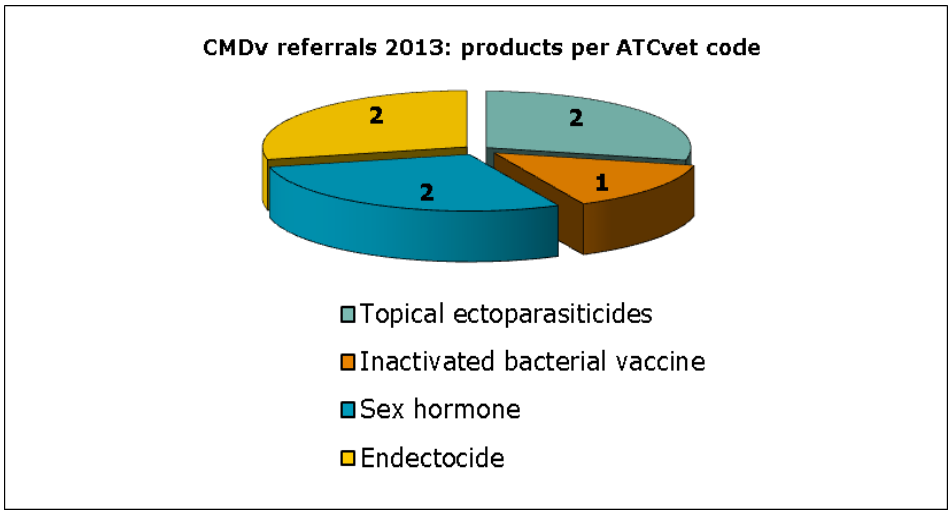


Figure 6



It was stated in the workplan that the list of concerns would be adopted by the CMDv at the start of a referral procedure but on reflection the group considered that the questions should remain under the responsibility of the RMS and objecting CMS(s).

4 Policy issues

4.1 Harmonisation and worksharing

Communication between NCAs was encouraged to exchange information on significant variations to purely-nationally authorised products with the aim to initiate worksharing, to maximise resources across the network and to ensure a consistent assessment of supporting data.

The Joint CVMP/CMDv Task Force on Harmonisation of SPCs and Referrals (TF) worked further on the development of prioritisation criteria for referrals. A report and recommendations to reflect the considerations of the CVMP and CMDv regarding prioritisation of referrals were prepared by the TF and endorsed by CMDv and CVMP. The document was presented by the EMA to HMAvet. HMA agreed that the Agency should prepare a document summarising the main points that should be considered when submitting a referral in terms of content and procedures. The objective would be to promote 'best practice' without infringing in any way on the rights of Member States to initiate referrals in line with the legal framework and as they see fit.

The lessons learned from the CMDv's pilot voluntary SPC harmonisation procedure were published.

In 2012, a European referral procedure under Article 35 of Directive 2001/82/EC, as amended, concluded on VMPs containing a single flukicidal active ingredient, resulting in changes to the withdrawal periods. In order to encourage a harmonised approach between MSs, the CMDv collected information on products containing a *second* flukicidal active substance. For such combination products authorised on a purely-national basis in several MSs, this allowed NCAs to share the proposed warnings that would be introduced via variation (i.e. in line with the changes recommended by the CVMP for each flukicide component).

4.2 Legislative changes

Since the European Commission's proposals for revision of the European legislation on VMPs and medicated feed was not released in 2013, the CMDv's working group on legislation did not meet. In the context of the review of the regulatory framework, the

CMDv coordinated a questionnaire from the Commission to the Member States to collect information on potential future requirements for NCAs and control laboratories.

4.3 Validation

In 2013, the CMDv formalised its initiative on improving validation. In less than six months, a standard validation checklist was adopted by all CMDv members and published together with an explanatory note on the pilot process. The CMDv's established interested parties were provided with regular updates during the triennial meetings.

The new validation process relies on mutual trust between Member States. The RMS is responsible for completing the validation checklist and sending it to CMS(s) at the start of the validation phase or at day -7 at the latest. The CMS(s) should wait to receive the checklist before making their own comments.

At the beginning of July, the pilot phase was launched to test the validation checklist until the end of the year 2013. During this pilot phase, the NCAs did their best to participate and to compile feedback. The CMDv's interested parties were also asked to collect feedback from their member companies.

4.4 Improvement of MRP and DCP

At the additional CMDv meeting hosted by the Irish Presidency in June 2013, the idea was put forward to create a CMDv working group on the improvement of MRP/DCP. This proposal was formalised towards the end of 2013 with the adoption of a mandate and workplan. The UK CMDv member was appointed as Chair of this new working group. The work began with preparation of a key steps analysis for the DCP, which CMDv members were asked to review in order to identify practical aspects that could be improved upon. The Chair of the WG also organised for a representative from industry to give a presentation to the CMDv on challenges in the area of labelling, which is considered as a major obstacle to overcome by both industry and regulators.

Under the umbrella of this working group, Ireland led an initiative to avoid repeated assessment of the same version of the detailed description of the pharmacovigilance system (DDPS). A template was developed (taking into account a previous CMDh template and EMA guidance documents) for applicants to declare that a DDPS has been previously assessed in the EU. An assessment report template for the DDPS was also developed for optional use by NCAs. A one-year pilot for the declaration template was agreed upon, starting in January 2014.

Consideration was given to procedural improvements within the DCP to ensure that agreement is reached between the RMS and CMS(s) before D210 on the product name to avoid delays in the national phase. This was carried forward into 2014.

4.5 Transfer of purely-national MAs to mutual recognition status after Article 34 referrals

In 2013, the CMDv was not involved in the transfer of any purely-national MAs to mutual-recognition status following Article 34 referral procedures. In general the reasons cited by MAHs for not participating in this initiative are the prerequisite to harmonise the quality part of the dossier, which is considered unpredictable in outcome, as well as the financial and administrative burden of the procedural aspects required by NCAs.

4.6 Role of CMDv in implementation of the HMA Strategy Paper II – key topics

The CMDv's workplan for 2013 included tasks under specific strategy objectives within the HMA Strategy II - key theme 'Further Improving the Operational Efficiency of Medicines Authorisation by the Decentralised and Mutual Recognition Procedures (DCP/MRP)" - work area "Streamlining and harmonisation".

For strategy objective 29 (regulation of VMPs) mentioned in the workplan, please see section 4.2 above. Where necessary, the CMDv liaised with the European Commission regarding interpretation of the legislation when updating guidance documents or responding to questions from industry or NCAs.

For strategy objective 33 (borderline products), please see section 4.11 below.

For strategy objective 39 (improving DCP), please see section 4.4 above.

Regarding guidance on requests for access to MAA dossiers, please see section 4.9 below.

Under strategy objective 32 (clinical trials in animals), the CMDv elaborated on a previous questionnaire from 2008 to collect information on how clinical trials are undertaken and managed in the Member States. The aim was to determine the main differences and to submit this to the Commission for consideration within the context of the review of the veterinary legislation. The results of the questionnaire highlighted that, in most of the Member States a well-defined procedure is established; however the requirements and process are not harmonised across the EU.

4.7 Availability

One area continually cited by industry as impacting on the availability of VMPs in the EU is the regulatory/administrative burden of labelling requirements. As a result of discussion during the additional CMDv meeting held under the Irish Presidency, it was agreed to investigate a more flexible approach to labelling within the current legislative framework. This discussion continued at the CMDv meeting held in Vilnius under the Lithuanian Presidency. Particular attention was drawn to the situation whereby the same product has a different prescription status (POM/OTC) in the MSs, which can affect the content of the label and thereby hamper multi-lingual packaging. Additionally MAHs have expressed a preference for a more extended label text for single-language packs whereas minimum text is needed for multi-lingual packs. The CMDv started to consider how these situations can be accommodated in MRP/DCP using the possibilities offered by the QRD product information template (v.8) and within the current legal framework.

As part of an initiative taken by IFAH-Europe, the CMDv was asked to review an early draft of a proposed standard catalogue of pictograms and abbreviations.

Members of the CMDv continued to use the network of colleagues as a resource to collect information about the authorisation status of particular substances.

The CMDv collected up-to-date information on Member States' national requirements in relation to the submission of new marketing authorisation applications. The latest available information was published and it was positive to note that some MSs had removed certain national requirements.

4.8 Question & Answer (Q&A) and miscellaneous regulatory matters

Following queries submitted by Member States or by industry, discussion took place on the topics below in order to establish the CMDv position. The results of the discussion were presented either as a published Q&A on the CMDv website, within the CMDv's public report for release, as a reply directly to the requester or as a questionnaire for internal use by the CMDv.

- Update of published questionnaire on bee products authorised in each MS;
- Requirement for so-called 'textual summaries' as well as detailed and critical summaries (DACS) within Parts 2, 3 and 4 of the MA application dossier;
- Timing of the first variation after initial marketing authorisation procedure;
- Clarification on what constitutes the *name* of a VMP;

- Handling of different pipette sizes for spot-on products as strengths or presentations;
- Acceptability of single package leaflet for multiple strengths of the same product (oral/semi-solid dosage form);
- Prescription status (POM/OTC) in the MSs of products with a claim for flea allergy dermatitis;
- How to handle national patent protection of a new indication for a product authorised via MRP/DCP;
- Various issues related to the application of Article 6(3) of Directive 2001/82/EC;
- Questionnaire on MSs' views regarding future requirements for autogenous vaccines.

At the additional CMDv meeting held under the Lithuanian Presidency, a review began of Q&As published on the CMDv's website to identify those that were obsolete and could be deleted, as well as those that required updating.

4.9 Access to documents

Progress was made by the joint EMA/CMDv group on transparency in developing veterinary guidance on how to handle requests for access to marketing authorisation application dossiers. The need for predictability and proportionality when dealing with requests for access to dossiers on the veterinary side was kept at the forefront of the discussions. However, it was agreed with the EMA to put finalisation of the veterinary guidance on-hold until further experience gained from legal challenges on the human side can be incorporated.

4.10 Variations

The CMDv handled approximately 52 workshared variations, which is an increase of 50% from 2012.

In August 2013 the scope of the Variations' Regulation was expanded (Regulation 712/2012) to include purely-national marketing authorisations and the CMDv's procedures and guidance on variations were updated accordingly. The CMDv worked to improve the handling of worksharing procedures. A new numbering system for workshared variations involving products authorised via MRP/DCP and purely-nationally authorised products was developed and published.

Ad hoc queries relating to variations were discussed e.g. introduction of a new detailed description of the pharmacovigilance system (DDPS) versus an update to an existing version – how this is handled by the MSs in terms of variation classification. Clarification was sought from the Commission on the applicability of variation classification C.II.8 on the veterinary side (as compared to C.I.10 on the human side).

Process improvements were agreed with the CMDv for worksharing procedures where the EMA acts as reference authority.

4.11 Borderline working group

Upon request from the Member States, there were discussions on three borderline products in 2013. All resulted in a recommendation for classification as VMPs, based on their presentation and/or function. The resulting recommendations were based on a majority view with general information on borderline issues being made publicly-available via the CMDv's report for release. An update on the work of this group was presented to the CMDv's interested parties at the beginning of the year.

4.12 Quality issues

The CMDv meetings provided a forum for discussing quality-related issues arising for specific products and to coordinate any necessary follow-up actions. The main such issues arising in 2013 were:

- Notification by a MAH to the CMDv that a previously un-notified component of bovine origin was identified within a vaccine range. The CMDv agreed upon the procedural handling of this matter;
- Adulteration of a component from a particular supplier used in production of human and veterinary vaccines. The CMDv compiled an overview of the affected products and coordinated communication with the respective MAHs;
- Non-GMP compliance of a microbiological testing site affecting both human and veterinary products. The CMDv agreed to share information on any actions taken by NCAs on a national basis.

Following the publication of Commission Implementing Regulation (EU) No 495/2013 of 29 May 2013 amending Implementing Regulation (EU) No 996/2012 imposing special conditions governing the import of feed and food originating in or consigned from Japan following the accident at the Fukushima nuclear power station, the CMDv agreed upon a revision of the communication that was published on the CMDv website in order to keep marketing authorisation holders informed of the updates on monitoring of medicinal products originating from Japan.

The requirement for sterility of products for euthanasia was discussed due to differing interpretation between MSs affecting a decentralised procedure. The conclusion at this time was that there should be no differentiation in sterility requirements for euthanasia products.

In collaboration with the CMDh, the CMDv submitted a request to the CHMP to review the status of sodium hyaluronate as a biological active substance (ongoing).

A Member State initiated a discussion on how to express information on incompatibilities related to premixes within section 6.2 of the SPC (and corresponding section of the package leaflet), with particular focus on the interpretation of the standard phrase ‘none known’. This discussion is ongoing in 2014.

At the beginning of the year, the CMDv noted the pilot report from the HMA’s working group on product testing regarding risk-based selection of medicinal products for laboratory testing. The CMDv Chair reported to HMA on the CMDv’s concerns regarding regulatory burden versus added value on the veterinary side. In December the CMDv appointed a representative to participate in a drafting group set up to develop revised risk identification factors for quality assessors to use in pre-authorisation procedures.

The CMDv followed the development of a pilot worksharing procedure by the joint CMD/CxMP/QWP/EMA/EDQM working group on the ASMF procedure. An update was given to the CMDv’s interested parties at the meeting with them in October.

5 Document management

A document management system is in place to continue promoting the quality, consistency and transparency of decision-making, to ensure a smooth conduct of procedures, to facilitate the access to documents and to respectively define the areas of responsibilities of the MS and the secretarial support provided by the Agency.

5.1 Update of existing documents

The following public documents were revised and re-published on the CMDv's website:

- BPG-001 Mutual recognition procedure
- BPG-002 Decentralised procedure
- BPG-006 Type II variations
- BPG-016 Grouping of variations
- BPG-018 Worksharing of variations
- GUI-003 Management of emails during MRP/DCP
- GUI-22 MSs' requirements on format & no. copies for initial MA applications
- GUI-23 MSs' requirements on format & no. copies for post-authorisation applications
- TEM-018 Covering letter template for new MA applications
- TEM-023e MAH's letter of intent to CMDv for variation worksharing

The following internal documents were revised:

- SOP-003 Allocation of MRP/DCP application number
- TEM-003 Template for public assessment report

Discussion on the CMDv's draft new guidance (GUI-010) on applications for duplicate marketing authorisations continued and was carried over into 2014.

Work began on a full review of the CMDv's SOP-001 on referrals to the CMDv and was carried over into 2014. Progress was delayed whilst the Commission considered a fundamental issue concerning the legal rights of a Member State withdrawn by the applicant from a procedure.

5.2 New documents

- Member States' requirements during national phase of MRP/DCP (EMA/CMDv/133305/2013)

  Published overview on submission of documents during the national phase of MRP/DCP.

- TEM-029 Post-authorisation commitments

  The CMDv published a template for applicants to use in MRP/DCP when making post-authorisation commitments. The rationale behind the development of this template was to harmonise the approach taken between Member States.

- BPG-012 Informed consent applications

- BPG-017 High-quality national translations

  Based on an equivalent CMDh document, with the aim of improving the national translations of the product information submitted during the national phase of MRP/DCP.

6 Cooperation

6.1 Heads of Medicines Agencies

The CMDv chairperson updated HMA on a regular basis at their meetings and, at the request of HMA, set some specific targets and practical priority actions that the CMDv aimed to fulfill during the coming years. The CMDv chairperson also provided the CMDv with feedback from the HMA meetings.

6.2 Committee for Medicinal Products for Veterinary Use

Agendas and minutes were exchanged and monthly verbal reports given to and received from the CVMP. The CMDv Chair participated in the strategic planning group meetings of the CVMP in order to raise issues of common interest between the CMDv and CVMP, as well as to provide relevant updates on topical CMDv activities.

6.3 Pharmacovigilance working party (PhVWP-V)

The CMDv took note of the agendas and minutes of the PhVWP-V. The PhVWP-V chairperson and secretariat presented the latest developments at the CMDv meetings.

6.4 CMDh

Agendas and minutes were exchanged with the CMDh, also monthly verbal reports were given and received.

6.5 The Working Group on the Quality Review of Documents (QRD)

The CMDv took note of developments on the human side regarding the inclusion of quick-response codes on packaging and contributed comments to the QRD group on specific veterinary aspects.

6.6 eSubmission

The CMDv received updates via the EMA from the meetings of the TIGes vet group.

6.7 Representative organisations

Contacts with the established interested parties, IFAH-Europe, EGGVP and AVC have been maintained and meetings were conducted in January, May and October covering a variety of regulatory issues with an emphasis on packaging requirements. The meeting in May was extended to include member companies, as well as the representatives, of these industry associations.

6.8 HMA's Homoeopathic Medicinal Products Working Group

The CMDv contributed to requests for veterinary input from this group, namely information on nationally-approved homeopathic VMPs to obtain an overview for the EU and also comments were provided on the list of terms used in homeopathy.

7 The secretariat

The Agency provides a secretariat to support the CMDv. The secretariat has responsibility for preparing and hosting the plenary meetings in London, as well as coordinating, distributing and archiving meeting papers. Secretariat support is also given to various working groups. For each meeting the secretariat prepares minutes and a report for public release.

The secretariat provides regulatory advice, on request, as well as ensuring that the CMDv is updated on topical matters led by other groups e.g. from Quality Working Party.

For the CMDv referral procedures, the secretariat draws up timetables, liaises with the RMS/referring CMS(s), notifies the applicants, coordinates preparation of the list of concerns, organises the oral hearings and generally plays a facilitating role in supporting the work of the group in this area.

Annex I List of acronyms

The Agency	European Medicines Agency
Adobe connect	System of virtual meetings
ASMF	Active Substance Master File
AVC	Association of Veterinary Consultants
BPG	Best Practice Guide
CMDh	Coordination group for Mutual recognition and Decentralised procedures (human)
CMDv	Coordination group for Mutual recognition and Decentralised procedures (veterinary)
CTS	Communication and Tracking System (database for MRP/DCP)
CVMP	Committee for Medicinal Products for Veterinary use
CVMP-WP	CVMP-Working Party
DCP	Decentralised Procedure
E.C. & EC	European Commission
EEA	European Economic Area (EU+Iceland+Norway+Liechtenstein)
EGGVP	European Group for Generic Veterinary Products
EMA	European Medicines Agency
EUBAN	European Borderline Assessment Network
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
IFAH-Europe	International Federation for Animal Health Europe
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
MS	Member State
NCA	National Competent Authority
NtA	Notice to Applicants
PhVWP	Pharmacovigilance Working Party
Q&A	Question and Answer
QRD	Quality Review of Documents group
RMS	Reference Member State
SMP	Standard Management Procedure
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TIGes vet	Telematics implementation group on e-submissions – vet subgroup
VMRI	Veterinary Mutual Recognition Index