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EudraVigilance Veterinary and Signal Detection

STATUS REPORT TO

EMA MANAGEMENT BOARD / VETJIG[1] / PHVWP-V[2] / CVMP[3] / HMA-V[4] / CMD-V[5]

This document is published on the EVVet Website:
http://eudravigilance.ema.europa.eu/veterinary

Issue/Summary

This document provides a succinct overview on the implementation status and development planning of the European Database for the collection of adverse events related to veterinary medicines; EudraVigilance Veterinary (EVVET).

The updated parts compared to the last publication of the status report on 19 November 2013 are highlighted with the following symbol appearing on the side of the section:

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[1] Veterinary Joint Implementation Group
[2] Veterinary Pharmacovigilance Working Party
[3] Committee for Veterinary Medicinal Products
[4] Heads of Medicines Agencies - Veterinary
[5] The Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary

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1. INTRODUCTION

1.1 Legal and Regulatory framework

"EudraVigilance Veterinary" (EVVET) has been set-up in line with the legal provisions of Regulation 726/2004 (Art. 57) and Directive 2001/82/EC (Art. 73) with the purpose to function as the database to collect and provide access to all adverse event reports that are legally reportable.

Guidelines specific to the electronic exchange of pharmacovigilance information (legally mandatory since November 2005) have been developed by the Veterinary Joint Implementation Group (VetJIG) and the Veterinary Pharmacovigilance Working Party (PhVWP-V) and have been included in the Volume 9B[6]. Relevant guidance is also made available on the dedicated Website: http://eudravigilance.ema.europa.eu/veterinary.

The technical data-elements guideline for the original set-up of EVVET was released by the CVMP in July 2003 and subsequently revised by VetJIG in July 2005. This led to the second major revision of the system; EVVET2, which currently is still in operation.

A project (EVVET 3) that includes a major revision of the current system, was initiated in 2010 and will ensure compliance with VICH[7] Pharmacovigilance guidelines (GL42, GL30, GL24, GL35) as well as making the system more user-friendly with additional functionalities for the surveillance and management of the data. The project was prematurely closed in January 2013 because of a reduction in the budget available and because of the uncertainty that the dependencies of the EVVET3 project on a product and substance database and on a user database could not be met by the foreseen go-live date in 2013. This does not affect the day to day operation and reporting requirements which continue to take place in the current system of EVVET2.

The guideline on the access to the data in EVVet was finalised and adopted by the Member States at the HMA meeting in Antwerp (October 2010) and by the EMA Management Board in December 2010. The technical implementation of the access policy will be stepwise. The initial release foreseen for 2012 of data related to centrally authorised products has been postponed because of budgetary constraints. It is expected that the technical implementation will be achieved together with the release of the next major revision which is foreseen for 2016-2017.

In September 2009, the CVMP initiated the review of the available adverse event data for centrally authorised products directly through specific queries made available. In September 2010, signal detection procedures were put in place to ensure periodic monitoring of all adverse events for all centrally authorised products.

A draft "recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products" was released on 16 December 2013 for public consultation until 30 June 2014. Based on the comments received, the PhVWP-V will be updating the recommendation document, also taking into account the discussions that will take place during the focus group meeting on 19 November 2014 on surveillance and signal detection.

The European Commission released a draft of the revision of the legislation on 10 September 2014, which includes important changes to the overall pharmacovigilance provisions

[6] Volume 9 of "The rules governing medicinal products in the European Union" contains Pharmacovigilance guidelines for medicinal products for both human and veterinary use

[7] International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products - http://www.vichsec.org/

emphasising risk-based surveillance and continuous signal detection using central database systems. These provisions will also influence the future developments of the systems and data described in this document.

1.2 Partners and fora

While the original data elements guideline was released via the PhVWP-V and the CVMP, further releases and all technical discussions related to EudraVigilance Veterinary have been centralised in the Veterinary Joint Implementation Group (VetJIG). VetJIG meets 4 times per year with representatives from all Member States' authorities, IFAH Europe, European Group for Generic Veterinary Products and the Association of Veterinary Consultants.

A new Telematics governance structure between all regulatory agencies including the EMA was introduced in 2014, in order to increase the overall collaboration and to facilitate planning and harmonised implementation of IT systems and infrastructure. The VETJIG group will now become one of the system maintenance groups under this structure with continued participation by industry.

The regulatory authorities continue to exercise surveillance on the data available in the local databases as well as the data in EVVet to which all EU regulatory authorities have full access. Procedures are under development to strengthen the role of the PhVWP-V in the overall surveillance of the data in accordance with its mandate.

A further partner is the European Surveillance Strategy group (ESS) that was created in 2005 as a subgroup of HMA-V to make recommendations to HMA-V to improve the coordination and efficiency of pharmacovigilance across the EU.

2. IMPLEMENTATION OF ELECTRONIC REPORTING VIA EVVET AND STATUS OF REPORTING

2.1 EVVET Database overall

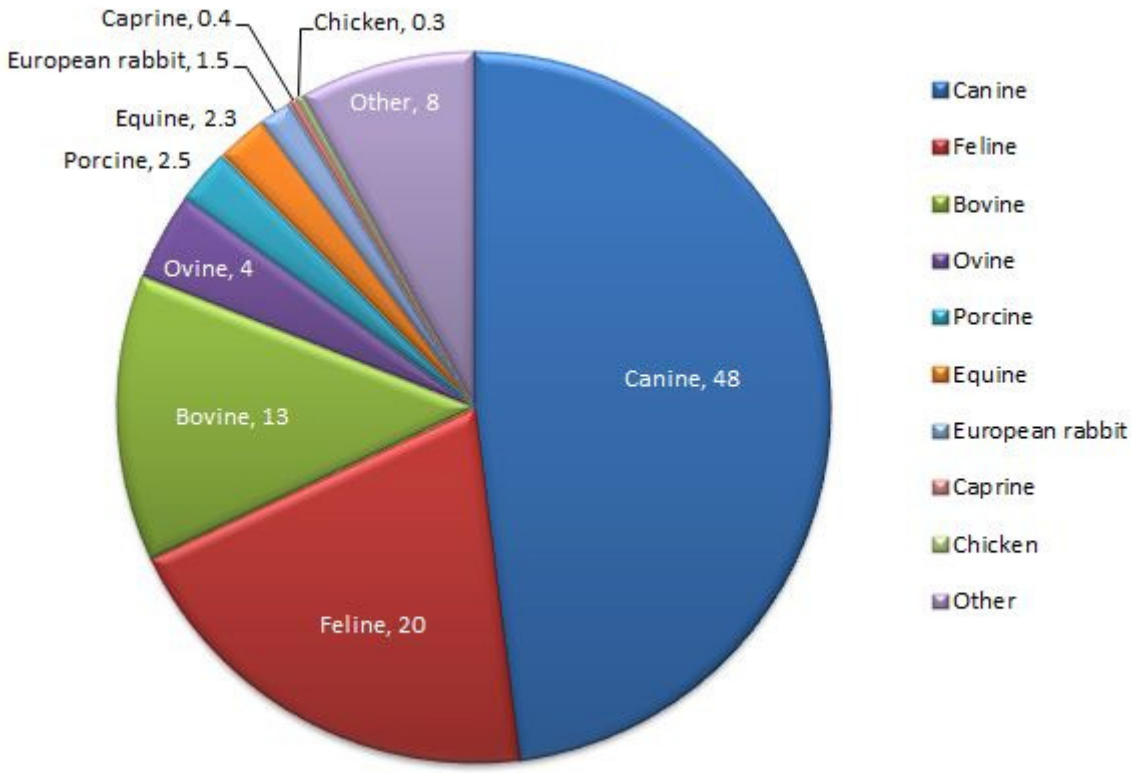
The database contains about 80000 adverse event reports having occurred within the EEA and about 50000 cases from outside the EEA; called third country reports. Eight thousand six hundred of the total reports, concern reactions observed in humans related to the use of a veterinary medicinal product.

Approximate number of adverse event reports and number of animals per selected species[8]

Species	Number of Reports	Number of Animals
Canine/dog	62500	71400
Feline/cat	26500	37000
Bovine/cattle	17200	226300
Ovine/sheep	5150	185000
Porcine/Pig	3300	494000
Equine/horse	3000	5400
European rabbit	1900	172000
Caprine/goat	470	65000
Chicken	440	16656000
Other	10371	20609000

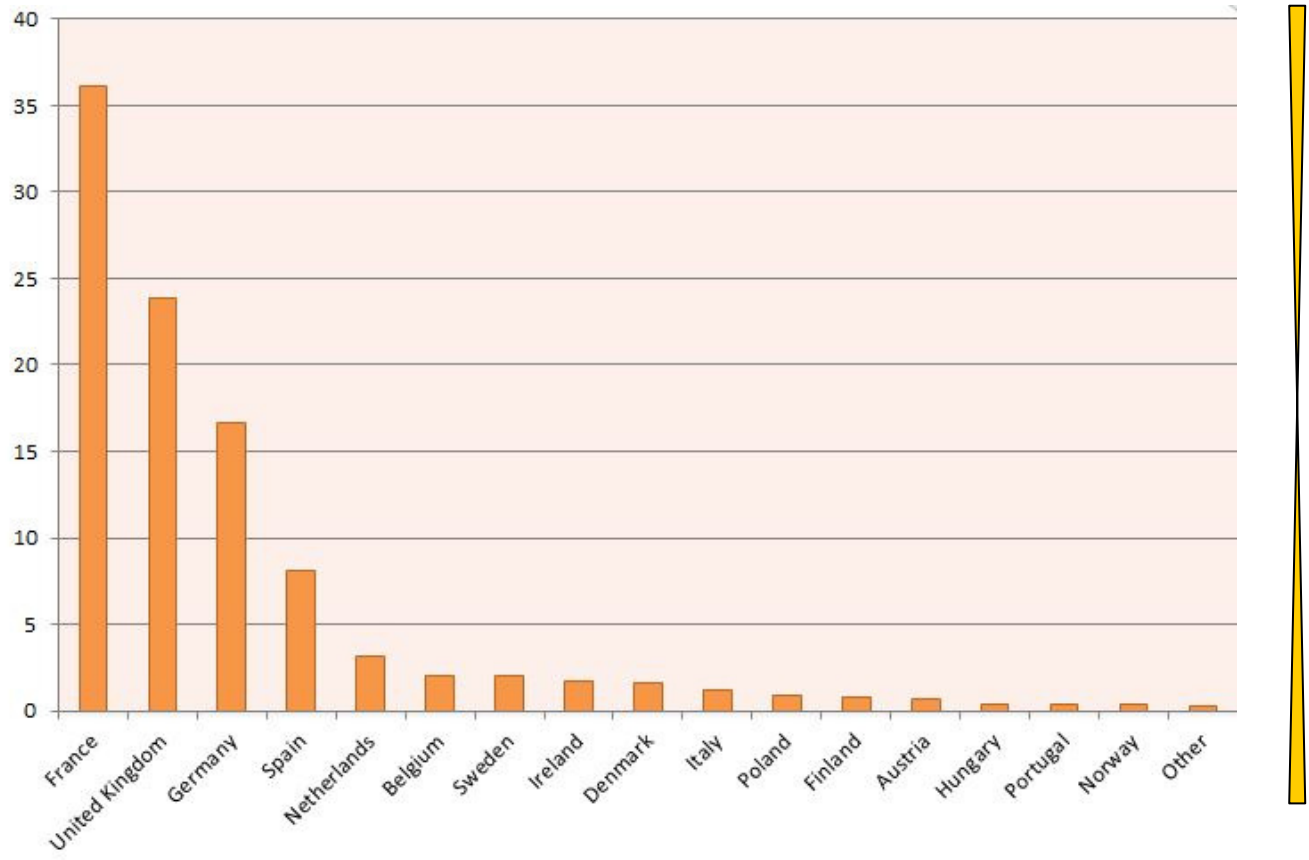
[8] Species with only a few reports were not included in the table.

Relative number of adverse event reports per selected species (%)



The largest portion of reports relates to pet animals however a different picture emerges when considering the number of animals reacted instead of the individual reports, since a single report may contain events related to a group of animals. In particular in relation to food producing species, events tend to be reported when a significant number of animals relative to the production operation are involved. However it is considered that relative underreporting is most significant in relation to food producing animals.

Proportional number of reports by Member State (%)



Reporting differences between Member States depends on the animal population in the country, local reporting practices and reporting practices from the local authorities where some are sending all adverse event reports; cases classified as serious (legally required) as well as cases classified as non-serious.

2.2 Implementation by EU Veterinary pharmaceutical industry

There are 336 organisations registered (marketing authorisation holders and third parties) with a total of about 865 different users.

Submission of adverse events within the EU is only accepted via electronic means; EVVet (Gateway or EVWEB), the Simplified Reporting form or any other MS specific available electronic reporting system that is compliant with EVVet (see EVVet Website http://eudravigilance.ema.europa.eu/veterinary).

The Simplified Reporting Form (SEF) is compatible with Internet Explorer 6 and 8. SEF is not compatible with Internet Explorer 7 and a specific warning has been added on the Website to clarify this situation prior to accessing the application.

A schematic overview of the reporting procedures to be followed depending on type of product, seriousness of the case, report originating in the EU or in a third country have been published on the EVVet Website (http://eudravigilance.ema.europa.eu/veterinary/reporting.html). A number of practical issues related to reporting have been identified by VetJIG and a corresponding document that specifies "how to avoid common mistakes and inaccuracies when reporting" has been released on the EVVet Website.

3. EVVET AND ITS SYSTEMS – DEVELOPMENT STATUS

3.1 EudraVigilance Veterinary

The current basis of the system, the data elements guideline version 2.2.1., was released on 9 February 2009.

The release notes of in between releases of EVVet (to e.g. ensure bug fixing) can be found on the EVVet Website: (http://eudravigilance.ema.europa.eu/veterinary/documentation.html)

A major new release took place on 19 February 2010 with the update of the combined animal and human Veddra terms and the inclusion of new functionalities that give the Web user direct control on the processing and archiving of messages and acknowledgments in the in and outboxes of the Web application. This release also allows for the sending of automatic acknowledgments for Web users.

Online tutorials are available and allow novel users to get familiar with the application.

EVVET 2 is now in evolutive maintenance with no further major releases being planned. The possible update of some of the standard lists used to the VICH GL30 standard lists is being investigated (for e.g. species). Following the release of Windows 8, new compatibility issues have emerged for both the human as well as the veterinary Eudravigilance system and a document with common browser setting tips has been released. Users are encouraged to report any operational issues with the system (using the dedicated helpdesk email address: Eudravigilance@ema.europa.eu).

EVVET 3.X

A new project was started at the beginning of 2010 for a major update of the EudraVigilance Veterinary system (see project plan in Annex). The vision for this project includes the modernisation and simplification of the data input and distribution tools, harmonisation with international standards, implementation of the access policy to EVVet data and a new tracking facility that will allow to exchange and store results from data analysis performed on the EVVet data. There will also be a focus on making the data more accessible to veterinarians in order to stimulate reporting.

The risks for the projects have been identified and include its dependency on the integration with other systems and databases in particular the single EU product database that at present is not yet available. The international guidelines for harmonisation (VICH) in the field of pharmacovigilance have also come to a close with the finalisation of the electronic message and report definitions in VICH Guideline 35; Pharmacovigilance of veterinary medicinal product: Electronic standards for transfer of data.

The specifications gathering under the second iteration of the inception phase took place within a subgroup of VetJIG; the Technical Advisory Group (EVVET JIG TAG) with participants from regulators as well as industry. Further interviews with representatives of the veterinary profession (FVE) and practice software providers have also taken place in 2011.

A total of 9 Business use cases were developed, mainly by EVVET JIG TAG and were formally adopted by the VETJIG meeting following consultation with the PhVWP-V and following notification of the HMA-V meeting in Budapest (January 2011). There were 13 construction iterations planned until April 2014 with further contingency iterations leading to August 2014. The first release was brought forward to the last quarter of 2013 however due to dependencies on other systems/projects and budget restrictions it was decided to suspend the project at this stage. The project was subsequently prematurely closed following construction iteration 6. At iteration 6, the main revised reporting module has been developed in line with VICH guidance and was ready to go into testing.

The following deliverables still need to be implemented and will be re-started at a later stage, the timing has not yet been identified:

- Ability to provide access to the information based on the ownership of the products (including automatic re-routing of the reports to the relevant receivers);
- Integration with some of Agency and European databases (e.g. EudraPharm, Siamed, ECD);
- Possibility to track analysis and establish safety baselines for the products;
- Improve reporting from veterinarians by providing a simpler and more standardise way of report;
- Improve the registration process to avoid duplication of work, e.g. double registration in External Test and Production environments and multiple registration for EV and for other systems;
- Lower maintenance costs by implementing a simpler system, which follows the Agency standards and that, can be handed over to Application Support to maintain it in a more cost effective way.

Veterinary IT/ data strategy roadmap and central product database

The EMA was furthermore requested by the network (HMA-V) in June 2013 to consider initiating specific IT projects, in particular the development of a single EU veterinary product database for which a Business case was adopted by HMA-V at the end of 2012. Such product database would be key to support post-marketing surveillance of all authorised products in the EU and would also allow re-starting the development of EVVET3. In addition, the draft revised legislative proposals includes the provision for a central product database to support the regulatory processes within the EU.

The Agency initiated an initial project in September 2013 as part of the overall EMA IT roadmap to consider the Agency's veterinary data and system needs and to draft the outline of "veterinary roadmap" with particular focus on the need of a centralised veterinary database. IT representatives from the UK, France and Belgium support the project on behalf of the network.

The Veterinary IT and data strategy roadmap was finalised in February 2014 and provides an overall IT and data architectural strategy for a 2-3+ year timeframe focusing on immediate and known business needs as well as anticipating the release of the revised legislation. The roadmap provides the necessary framework to initiate the planned review of the needs of the Agency and the wider EU regulatory Network in relation to IT solutions and data to support the authorisation and surveillance of veterinary medicines in the EU. In particular this document recommends and has resulted in the following 3 project proposals:

1) Re-focus of the Eudrapharm product database to become the single central veterinary medicinal product database. This is a "re-badging" exercise and a confirmation of the Agency's commitment to establish a single central product database as requested by HMA and as required by legislation.

2) Delivery of a "Veterinary product management service". This project will built on the existing "Eudrapharm"- based product database towards an all-inclusive management service model to take into account all business requirements of the full regulatory network.

3) Definition of future implementation projects. Building on the high level recommendations from the roadmap and following on from the new legislative text, this project will identify together with the regulatory network on the detailed needs in terms of IT and Data systems other than the product database.

3.2 Recoding application

The recoding application allows linkage of the adverse reaction reports to the dictionary of the veterinary medicinal products (EVVetMPD) and will allow monitoring of data entry quality issues. Most of the product information in the reports is linked automatically to the product dictionary however because of misspelling or other reasons some information needs to be linked manually through this application. The recoding for reports related to CAPs is ongoing and manual recoding for CAPs is managed at the EMA. The manual recoding process runs efficiently as long as the corresponding product data are available in the EVVetMPD, which is the case for centrally authorised products.

Considering the increased cooperation of several Member States in providing product information for non-centrally authorised products, the Agency has now also engaged in recoding for non-centrally authorised products in support of these Member States. This will

allow the Member States to take full advantage of the Data Warehouse queries for the surveillance of their nationally authorised products. The status is as follows:

Country	Number of products in product database	Recoding status
AT	9	N/A
BE	592	Recoded
BG	1	N/A
CY	0	N/A
CZ	1	N/A
DE BVL	0	N/A
DE PEI	55	N/A
DK	12	N/A
EE	0	N/A
ES	56	N/A
FI	344	Recoded
FR	2593	Recoded
GB	1340	Recoded
GR	5	N/A
HU	37	N/A
IE	1237	Recoded
IT	1612	Recoded
LV	553	Recoded
NL	1246	Recoded
NO	7	N/A
PL	138	Recoded
PT	7	N/A
SE	7	N/A
SK	3	N/A
SI	0	N/A

3.3 Duplicate detection

The first version of the duplicate detection engine is in use. In a novel approach, duplicate reports are linked without the need to create a "master report" and without the need to delete duplicate information. The data analysis tools are adapted to ensure that no double calculation of key data takes place. When a user has performed a query in the data warehouse, the duplicate detection engine allows checking for possible duplicates on the list of cases generated by a query in the data warehouse. The user may then subsequently re-run the same query in the data warehouse that would take into account for any duplicates being identified. Member States have however repeatedly expressed concern that due to privacy law it becomes very difficult to distinguish possible duplicates at Member State level

in the absence of any personal data. An agreement was reached within EVVETJIG that MAHs should endeavour to include the first initial of the first and the last name and the first 2 letters of the zip code unless there is explicit disagreement by the primary source. This would help Member States on a local level with the identification of potential duplicates without the risk of breaching personal data protection.

3.4 EudraVigilance Veterinary Medicinal Product Dictionary (EVVetMPD)

The availability of product information is crucial to allow recoding (see 3.2) and subsequent analysis of the safety data within EVVet. Product data have been submitted historically via means of excel datasheets by Member States for manual input by the Agency or through direct input in the Web-application. Both methods are very labour intensive and for the last 2 years a number of Member States (UK, France, Ireland, Italy, Latvia, Finland, Holland and Cyprus) have invested in linking their product data directly from the local database into Eudrapharm which is the original application made by the Agency for the creation of a single EU product database. The Netherlands have however suspended, in the second half of 2013, the update of the database through Eudrapharm pending clarification by the Agency on the overall direction regarding a possible single EU product database. Following on to the release of the Veterinary IT roadmap and the confirmation from the Agency to the "Eudrapharm"-model for a single EU veterinary product database, requests have been received from the Spanish, Polish and French authorities for further product data transfers.

The need for a single veterinary EU product database was acknowledged at the level of the HMA-V in 2012 together with a recommendation to build the process and system around the existing Eudrapharm system. Decisions on the actual funding and development policy at the level of the Agency for such veterinary specific system are however still pending and have become part of an on-going project that looks at the overall veterinary IT data and system needs in view of a long-term roadmap (see also under 3.1). Other Member States are encouraged to follow the same route of direct data transfer however some Member States are waiting until the decisions on the actual build of such system have been taken.

An initial cleaning exercise of the available active substance list has taken place between March 2013 and August 2013. About 13000 active substance terms were linked originating from EVVET (6400) and from reference lists used by the French, German and a high quality reference list used by the Swedish regulatory authority. This exercise answered also the need to make available a list of active substance to be used by industry for e-submission.

3.5 Simplified reporting form for MAHs (SEF)

The simplified reporting form is an additional HTML Web based form that allows MAHs with a relative low reporting frequency to report standardised information without the need to get familiar with the more complicated EVWEB application.

Prior to opening SEF on the Website, further information has been added on the Website to indicate in which Member States the form can be used or whether alternative local electronic reporting systems should be used for particular Member States.

There is an increased interest from companies to choose this reporting form, also for companies responsible for CAPs, however the form is still only occasionally accessed from the EVVet Website.

The form was originally built for use with Internet Explorer 6 (IE6). The form is not compliant with IE7 but has now been made compliant and can be used with the latest IE8. SEF is only being used occasionally however there is feedback that this reporting form is indeed being preferred by some users over the current EVVET2 which is considered not user friendly for data-input.

3.6 EudraVigilance Veterinary Data Warehouse (EVVet DWH)

A major milestone was reached in September 2009 when the CVMP started to access EVVet data directly via the DWH for the monthly surveillance of serious reactions related to CAPs.

The information in the SPCs on adverse reactions for centrally authorised products (CAPs) has been coded into the corresponding Veddra terms and linked to the CAPs product information in EVVet so that Veddra terms that are already in the SPC are highlighted automatically in the output of the results of the DWH queries. This allows the expert when performing surveillance queries, to focus on the terms that are not yet in the SPC.

The limiting factor remains the lack of product information for non-centrally authorised products and consequent recoding (see under 3.2.) before EVVet and the DWH queries can be used efficiently for surveillance of all veterinary medicines in the EU. Recently however, good progress was made by several Member States in transferring product data via Eudrapharm to the EVVET product database (see under 3.4.) and some Member States have started using the EVVET DWH for surveillance of nationally authorised products.

A dedicated sub-PhVWP-V group has developed further specific DWH queries for the surveillance of the data that will allow screening the full data set instead of the current approach that involves a monthly review of all individual new reports for CAPs. The new procedure was implemented in August 2011. An additional database for the collection and monitoring of the analysis results by rapporteurs was also made available. Over 1200 analysis results have been recorded in relation to CAPs until now.

The Data Warehouse was migrated from the Microstrategy to an Oracle platform for strategic IT reasons. On the basis of consultation with users there have been further improvements done and queries created as part of this migration exercise. The Oracle platform is expected to be more user-friendly and positive initial feedback has been received.

A policy decision was also taken to allow automatic access to the Data Warehouse for all EVVET users from regulatory authorities where previously separate requests for access were needed.

3.7 EVVet Website

The tutorials section has been completed with multimedia tutorials on the use of EVVet. These tutorials are considered a significant improvement to guide and assist MAHs. Further updates to the tutorials are on-going as well as work on an extended FAQ regarding practical reporting issues.

4. GUIDELINES AND INTERNATIONAL STANDARDISATION

4.1 Volume 9B Part III

Volume 9B of the Rules governing medicinal products in the European Union including a technical Part III on electronic reporting has been published by the Commission in October 2011 (http://ec.europa.eu/health/files/eudralex/vol-9/vol_9b_2011-10.pdf).

4.2 Draft Access Policy

The draft access policies for EVVet data as well as EVHuman data have been endorsed by the HMA (11-12 July 2008). The draft policy was released for consultation in January 2009 for a period of 3 months. A revised access policy document has been finalised during 4th quarter 2010 following discussion at the level of the PhVWP-V, VetJIG, CVMP, and HMA-V. The technical implementation of the access policy will be stepwise. The initial release foreseen for 2012 of data related to centrally authorised products has been postponed because of budgetary constraints. It is now more likely that the technical implementation will be achieved together with the release of EVVET3, which has also been postponed, see above under 3.1.

4.3 VICH / ISO / EUTCT

The development of VICH pharmacovigilance guidance has come to a close. GL30 (Controlled Lists of Terms) and GL42 (Data Elements for Submission of Adverse Event Reports) were already adopted in 2010.

GL35 (Electronic standard for Transfer of Data) was further discussed and finalised by the "Electronic Standards Implementation of Adverse Event Reports Expert Working Group". GL35 will be accompanied by 2 further documents to specify the validation rules and to help implementation through a so-called "step by step" document. The CVM/FDA, being rapporteur for GL35 was not in a position to prolong the discussions and consequently there was no full agreement reached on the documents presented by the CVM/FDA. The CVMP and its pharmacovigilance working party concluded that the GL35 and the step by step document provide a sufficient basis for a harmonised electronic adverse event report and message which was the ultimate goal for these negotiations within VICH. However the CVMP could not endorse the validation rule document since it would lead to the exclusion of a large number of adverse event reports when certain information, e.g. strength or ATC vet code, would be missing. This would be not in compliance with EU legal obligations and practice for reporting and was considered to compromise animal and/or public health. In practice this would mean that the harmonisation of the format of the electronic report has been achieved and that reports can be exchanged between the VICH regions, but that pharmaceutical industry may be faced with reports that would be eligible for submission in the EU while the same reports would technically be rejected by CVM/FDA. In practice the FDA has instructed industry to include the term "not available" in the strength field that is mandatory in the US system. In the EU, this strength field will not become mandatory and an empty field will follow the overall convention of all other empty fields where it is assumed that the requested information is not available.

In addition the VICH expert group is working on an update procedure for the standard list in GL30 as well as in case there are changes needed to GL35. There is also a need to publish a corrigendum of the agreed VICH GL30 lists since the FDA has implemented a previous version in its system compared to the published version and other minor errors require updating. This is still possible since no other system than the FDA is yet using the GL30 lists.

The VICH Steering Committee agreed at its November 2013 meeting in New Zealand for the implementation in all regions of the VICH pharmacovigilance guidelines by the end of 2015.

Following the publication of the draft proposals for the revision of the legislation there is now a need to assess the likely compliance or possible non-compliance of the proposals with the existing VICH guidelines.

4.4 VeDDRA

The yearly Veddra subgroup meeting was successfully held on 23 April 2014. The new version (Veddra 11) will be implemented on 1 October 2014. The EVVETJIG meeting agreed that Member States Authorities using a Gateway system should ensure to always implement the latest Veddra version in order to allow for the submission of reports by marketing authorisation holders.

5. Other

5.1 Upcoming Meeting dates

- VetJIG meeting: 21 October 2014
- Focus group on pharmacovigilance surveillance and signal detection: 19 November 2014