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EudraVigilance Veterinary / Signal Detection and on-going related Veterinary-IT projects

STATUS REPORT TO

EMA MANAGEMENT BOARD / CGVPhS[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 15 September 2015 are highlighted with the following symbol appearing on the side of the section: ⧖

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[1] Consultative Group on Veterinary Pharmacovigilance Systems
[2] Veterinary Pharmacovigilance Working Party
[3] Committee for Veterinary Medicinal Products
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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 to 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. The EVVET3 project is scheduled to be re-initiated in 2017. This does not affect the day to day operation and reporting requirements which continue to take place in the current system of EVVET2.

The updated EVVET3 system is also expected to bring the access capabilities in line with EudraVigilance Human which is currently being developed to allow for increased and direct access for Marketing Authorisation Holders (MAHs) to increase the scope for data analysis by all stakeholders.

In September 2010, signal detection procedures were put in place to ensure periodic monitoring of all adverse events for all centrally authorised products using the Data Warehouse queries that were specifically developed. This has resulted in over 2000 periodic signal analysis reports recorded by the rapporteurs and their experts in the dedicated Veterinary Phamacovigilance surveillance database.

The "Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products" was adopted by CVMP in April 2015 and HMA-V in May 2015.

A pilot on the use of signal detection for the analysis of PSURs (Periodic Safety Update Reports) was successfully conducted for certain centrally authorised products during 2010 up to 2013. The industry has reiterated its interest in participating to combined PSURs and signal detection on the condition that line listing requirements for PSURs can be alleviated for such procedures.

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 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.

[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/

1.2 Partners and fora

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 has now become one of the system maintenance groups under this structure with continued participation by industry and was consequently renamed to Consultative Group for Veterinary Pharmacovigilance Systems (CGVPhS).

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. ESS has now extended its scope of advisory role to the other related veterinary IT Telematics projects.

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

2.1 EVVET Database overall

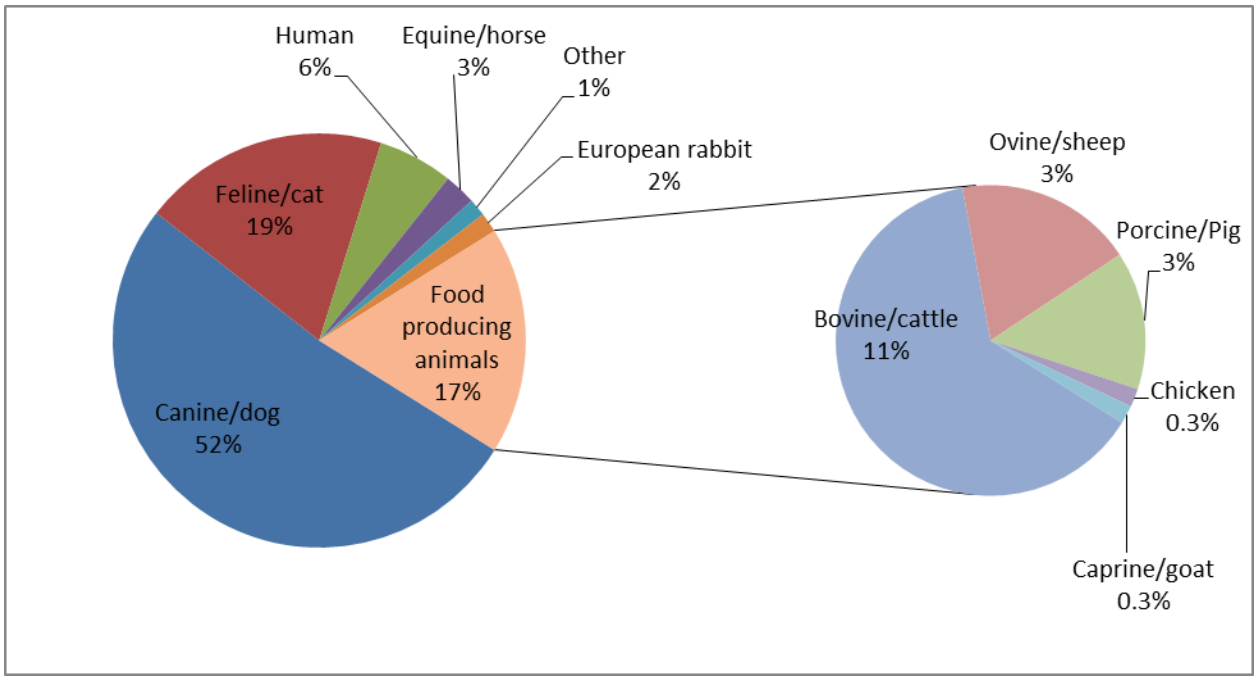
The database contains about 114000 adverse event reports having occurred within the EEA and about 80600 cases from outside the EEA; called third country reports. Eleven thousand five hundred of the total reports, concern reactions observed in humans related to the use of a veterinary medicinal product.

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

Species	Number of Reports	Number of Animals
Canine/dog	101006	114,026
Feline/cat	37693	50,374
Bovine/cattle	21906	349,410
Ovine/sheep	6450	286,715
Porcine/Pig	4986	1,067,432
Equine/horse	4855	8,739
European rabbit	3049	194,386
Other	2682	25,681,866
Chicken	660	70,122,275

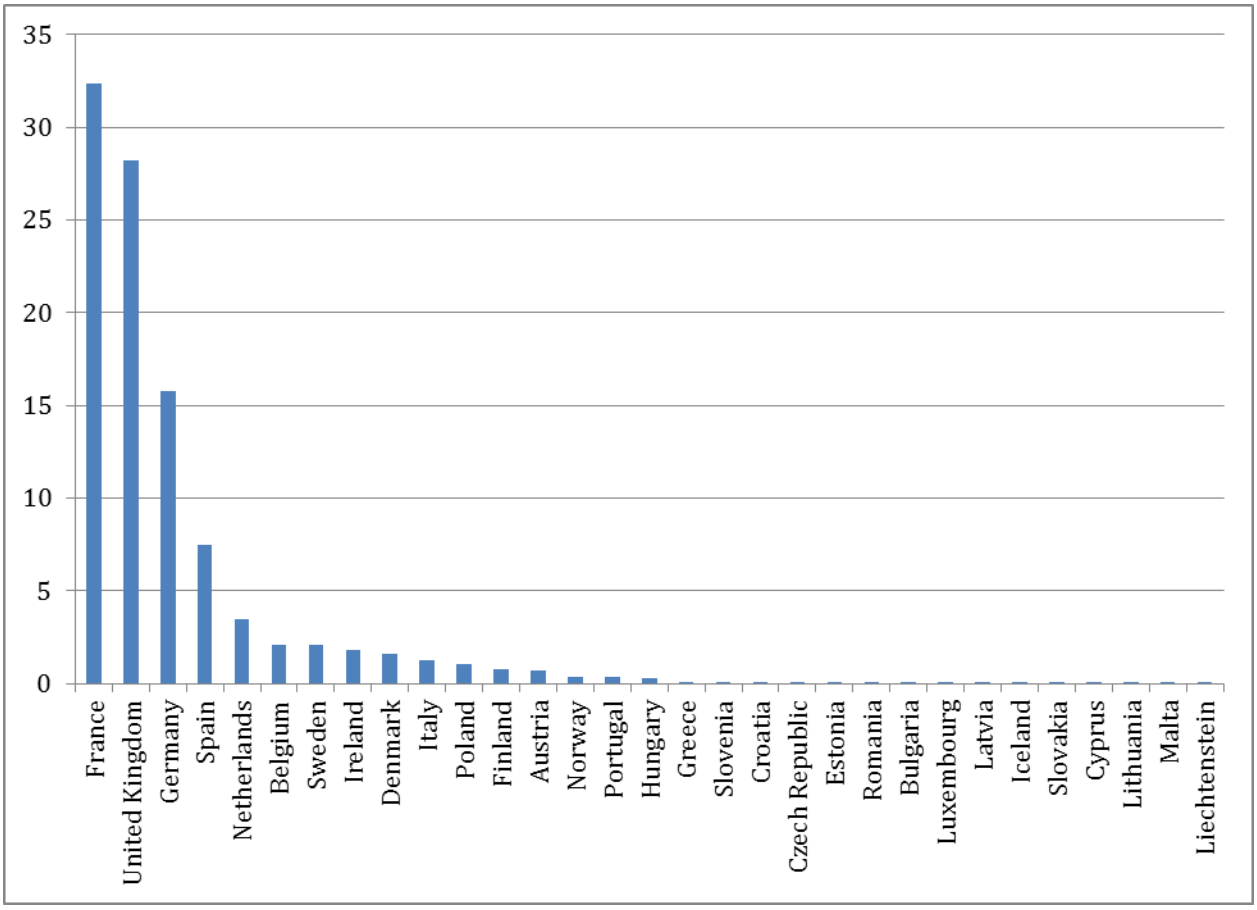
[8] Species with only a few reports were not included in the table.

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 389 organisations registered (marketing authorisation holders and third parties) with a total of about 1024 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).

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 "Frequently asked questions & common mistakes in data entry" 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). Compatibility issues with internet browsers and certain Windows operating settings have occurred and specific guidance has been made available to circumvent these issues (http://eudravigilance.ema.europa.eu/veterinary/documentation.html). Users are encouraged to report any operational issues with the system to the new Service Desk Portal: https://servicedesk.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. 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.

Considering the upcoming revision of the legislation and the overall budget restrictions there will now be a strategic review in 2017 to investigate how the new IT requirements and the alignment to the revised international standards can be met.

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 a 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. The Veterinary IT and data strategy roadmap was finalised in February 2014 in collaboration with Member States and provides an overall IT and data architectural strategy 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.

Following on to the recommendations made in the roadmap, a first project was started in October 2014 to create a dedicated single EU product database system for all authorised veterinary medicinal products in the EU. The initial database is entirely based on the existing Eudrapharm database and a dedicated Website was released in March 2015 ("EU Veterinary Medicinal Product Database") that allows to access the veterinary medicinal products available in the Eudrapharm based database. A user group was set up, the consultative group on veterinary medicinal product data systems (CGVPS) which meets bi-monthly.

Five Member States (Finland, France, Ireland, Latvia and the UK) were already using the Eudrapharm database and these data are maintained. Product data from the Netherlands and Italy have also been present but where removed on the request of the Member States in 2014 as a result of the ongoing human "Art. 57" exercise.

For now the database contains the centrally authorised products and the purely nationally authorised products from a number of Member States. The user-group has agreed that all authorised products should be submitted in the local language (including mutual recognition and decentralised procedure products).

The first objective and use of the data is to allow signal detection of safety data (adverse event reports) across all EU Veterinary Medicinal Products. At present signal detection is only in operation for centrally authorised products since many of the nationally authorised products are still missing.

A survey was circulated in September 2015 to all national competent authorities to learn about the planning and product database status within each Member State which would allow the EMA to better plan and provide support for a stepwise implementation and data transfer.

One to one teleconference meetings have been initiated with each Member State to further progress and support the submission of product data. Up to date product data are present for France, Ireland, UK. Spain has been the next Member State to submit the product data in August 2016. A few Member States are expected to submit their data in 2016, some have informed the EMA of their planned submission by Q1 2017.

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	12	N/A
BE	594	Recoded
BG	2	N/A
CY	1	N/A
CZ	2	N/A
DE	34	N/A
DK	14	N/A
EE	1	N/A
ES	59	N/A
FI	346	Recoded
FR	2692	Recoded
GB	1356	Recoded
GR	6	N/A
HU	39	N/A
IE	1345	Recoded
IS	3	
IT	1636	Recoded
LT	8	
LU	6	
LV	554	Recoded
NL	1249	Recoded
NO	10	N/A
PL	142	Recoded
PT	11	N/A
RO	2	

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 in EVVet are stored in the EVVETMPD which is directly fed from the data made available in Eudrapharm which is now renamed to the EU Veterinary Medicinal Product Database (see above under central product database).

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 Internet Explorer. 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 2000 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. In particular, the Data Warehouse allows to create a PSUR comparable “Line Listing” output with the added advantage of having the narrative as well as direct access to the original cases.

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 not be 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.

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.

At the February 2015 VICH Steering Committee, it was agreed to re-start the discussions from the ESI EWG (Electronic Standards Implementation Working Group), in particular to allow for the routine maintenance of the GL30 vocabulary list, to review the industry's paper on the impact of disharmonisation and the finalisation of the validation procedures document. The ESI EWG would also discuss the creation and use of a harmonized xml message to be sent as acknowledgement.

The VICH expert group has initiated the revision of certain GL30 lists, in particular the species list.

4.4 VeDDRA

The yearly Veddra subgroup meeting was successfully held on 20 April 2016. The new version (Veddra 13) will be implemented on 1 October 2016. It has been 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.