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# Impact of disharmonisation on the day-to-day operations in Pharmocovigilance


Jaume Colomer

IFAH Pharmacovigilance Task Force

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# IMPACT OF DISHARMONISATION ON THE DAY-TO-DAY OPERATIONS IN PHARMACOVIGILANCE

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## I. Background:

The discussion document prepared by the 'RST ad hoc WG on Pharmacovigilance' was submitted in May 2014 to the VICH Steering Committee and was discussed at the Steering Committee (SC) meeting in June 2014.

At the SC meeting industry emphasized that this document provides IFAH's vision for a truly harmonised future pharmacovigilance (PhV) system, including the steps to take to arrive there.

A very good exchange with the regulators followed the presentation of the paper's contents by IFAH-Europe. Industry illustrated the difficulties it faces with the current non-harmonised system and was encouraged by the VICH SC to map out in more detail the issues and their impact. While there was overall strong support at VICH SC for a harmonized vision for global PhV at global level, there was a lack of clarity as to how this could be achieved and who would be responsible for the various elements in such a global system. All parties were encouraged to reflect further on this in preparation for a continued exchange at the next VICH SC meeting in February 2015.

To enable the discussions to move forward it was seen as essential for industry to present in graphic detail the issues and their impact on the daily pharmacovigilance activities in companies. Industry was requested to list each problem and describe in detail what impact this has on their ability to run and efficient pharmacovigilance system within their company, to help the VICH SC to develop a much clearer understanding of what the issues are and how they could be resolved.

An IFAH PhV Task Force identified twelve main areas of disharmonisation and prepared summaries to provide a more detailed description of the issue and what is the impact on day-to-day operations and quantify the extra costs that regional differences implies as well. Please find the description of these issues in the summary table and in the detailed description herein.

## II. <u>Summary table:</u> List of main areas of disharmonisation and their impact on companies

| Description of the area of disharmonisation | % increase of resources | Other potential impacts |
|---|---|---|
| (1) Scope and definition of PhV activities | 20 -30% | Regulatory non-compliance |
| (2) Definitions of PhV reports | 30 – 50% | • Inconsistent serious case counts<br>• Misinterpretation of data<br>• Regulatory non-compliance |
| (3) Seriousness criteria | 10 % | Could lead to different evaluation of the risk |
| (4) Expectedness | 15 – 20% | Could lead to differences on the labels and SPC of the products |
| (5) Reporting timelines for expedited cases | 100% | Could lead to different evaluation of the risk |
| (6) Periodic reporting for same products in different countries | 100% | Could lead to different evaluation of the risk |
| (7) Differing opinions on the meaning and use of various data elements | • 20%<br>• And 50% of annual fees | Regulatory non-compliance |
| (8) Causality assessment criteria | 10% | • Wrong evaluation of the risk<br>• Regulatory non-compliance |
| (9) Scope of reporting | 100% | |
| (10) Content of PSURs | 20 – 25% | Regulatory non-compliance |
| (11) Lack of harmonized product dictionaries | Costs linked to an inspection:<br>• 11 days on average<br>• 5 persons | • Regulatory non-compliance<br>• Trigger a new inspection |
| (12) Requirements for translation | 20 – 30% | Poor quality of translation leading to misinterpretations or errors. |

## III. Detailed description of main areas of disharmonisation:

**(1) Scope and definition of PhV activities:**

*E.g. Definition for veterinary medicines is not equal in the VICH regions; whether the scope includes environmental issues, residues, transmission of infectious agents; withdrawal; periods/residues); differences in adverse events definition between VICH and EU.*

Description of the issue

The definition of 'adverse event' according to VICH is implemented in European Union (EU), Australia and Canada. In the USA, the FDA has published a draft GFI #117 (equivalent to VICH GL24) which is scheduled for implementation by end of Dec 2015. However, although the same definition is used the scope of pharmacovigilance (PhV) is different in the VICH regions. This relates for example to environmental issues which are included in the EU and Australian PhV scope but are not reportable PhV cases in USA and Canada. Regional differences exist also with regard to reports on the validity of the withdrawal periods and whether or not transmission of infectious agents is explicitly mentioned as part of PhV.

Clearly, it is a prerequisite for an international PhV harmonization to have a common understanding of what should be considered part of PhV and what not.

What is the impact on the day-to-day life

Differences in the PhV scope impact the day-to-day life especially in regard to EU 3rd country reporting. Here it needs to be ensured that worldwide reporting obligations are met even though in some 3rd countries the PhV scope is not as broad as in the EU. This could be a regulatory compliance issue.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

Depending on the product portfolio a relevant number of additional Adverse Events reports related to either environmental safety and/ or validity of withdrawal periods have to be processed which induces additional administrative burden and costs.

Furthermore, additional training needs to be provided to ensure compliance within 3rd countries with the broader PhV scope in Europe.

Although there will be large variations from company to company, depending on their product profiles and areas of operation, it has been estimated that this disharmonisation increases the administrative burden and costs to industry by 20 to 30%.

**(2) <u>Definitions of PhV reports</u>**:

*E.g. Different regional requirements mandating similar types of reports (different regional content, different methods for reporting (by registration number - NADA or by case), fluctuating local guidance): (a) serious case definitions (EU – serious = expedited report, US – serious and unexpected = expedited report); (b) unexpected sign definitions; (c) divergent reporting routines; (d) definition of lack of efficacy.*

<u>Description of the issue</u>

<u>Divergent serious case definitions</u>**:**

Generally, the EU guidance (i.e. Vol 9B) has been closely aligned with the VICH definition of a "serious" case.

***European Medicines Agency (EMA) Vol 9B* and VICH GL 24 serious definition:***

A serious adverse event is any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event.

However the question and answer document provided by EMA on 18 April 2013[1] regarding reporting rules for serious non-fatal adverse events undermines this alignment because a list of "clinical signs that should automatically lead to classification as serious adverse events as soon as they are reported, regardless of the causality assessment, the outcome, the time to onset etc. (= if it is mentioned, then the adverse event is serious)." This can cause confusion when the overall nature of the case does not fit the standard serious case definition, but happens to include one of the listed clinical signs. Some of the terms are logical choices to assume if reported in a case, the case would be serious, but others are not completely rational such as respiratory distress, collapse, apparent convulsion, blindness or deafness (especially if not medically confirmed) and/or mild severity. Additionally, this introduces a fundamental change to the approach of serious case assessment in the EU, whereby the determination is made at the sign level rather than the overall case level.

The definition of serious adverse event for **cases reportable to the US FDA** is found in 21 C.F.R. 514.3, which states: "Serious adverse drug experience is an adverse event that is fatal, or life-threatening, or **requires professional intervention**, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement." The clause "requires professional intervention" was further defined by FDA in a written communication to AHI (Animal Health Institute) on 7 February 2005 which stated that professional intervention is equal to a veterinary – client – patient relationship, as defined in 21 CFR530.3, where the "practicing veterinarian is readily available for follow up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept". This can be difficult to interpret depending on the quality of information provided by the reporter.

*The key issue is that when these definitions are applied, one case may be assessed as serious in one region and non-serious in other regions. This can lead to different reporting timelines and submission monitoring, significant risks such as misinterpretation of data; inconsistent case counts in different regions, non-compliance and a barrier to further harmonization.*

[1] 18 April 2013 EMA/CVMP/PhVWP/303762/2012 Committee for Medicinal Products for Veterinary Use

* European guideline for Pharmacovigilance of Veterinary Medicinal Products (also referred as Volume 9B)

***The impact to the PhV system is a requirement to have a way to capture, report and monitor two serious classifications for one case and this effectively increases the resources needed by 30-50% to manage the tools and processes associated with compliance.***

Unexpected sign definitions**:**

*Overall, the definitions for unexpected adverse events are aligned among the EMA, FDA and VICH guidelines and this* ***has minimal impact to resources.***

***EMA Vol 9B and VICH GL 24 definition:***

"An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labelling or approved documents describing expected adverse events for a Veterinary Medicinal Product (VMP). Ref. VICH Topic GL 24"

21 C.F.R. 514.3 provides the definition of an unexpected adverse drug experience in the USA, for FDA regulated products and states: "Unexpected adverse drug experience is an adverse event that is not listed in the current labeling for the new animal drug and includes any event that may be symptomatically and pathophysiologic relationship to an event listed on the labeling, but differs from the event because of greater severity or specificity. For example, under this definition hepatic necrosis would be unexpected if the labeling referred only to elevated hepatic enzymes or hepatitis."

Divergent reporting routines (by region):

Expedited reporting requirements are not aligned among VICH regions. First, the term "expedited" is defined as 15-calendar days in the EU, 15-business days by the US FDA, and 30 days in Japan. In addition, the criteria which determines if a case must be expedited is specific to each region, whereby the EU and Japan requires all serious cases (independent of expected-ness), and the US FDA requires only serious and un-expected cases. Expected-ness is a factor for expedited reporting in the USA, however requires one to consider each individual sign rather than the case as a whole. Additionally, cases with multiple reportable products, pharmaceutical or biological are submitted as one case, whereas cases with multiple reportable products in the US FDA must be made under separate submissions.

*This is a moderate impact in that it increases the administrative work to process and monitor submissions for both the manufacturing authorization holder (MAH) and the Health Authority (HA). The ability to submit all cases as single submissions would improve this issue.* ***This effectively increases the resources needed by 30-50% to manage the tools and processes associated with compliance.***

*Submission of all cases to a central global repository according to standard timelines, independent of case content, would significantly improve the current situation*

Divergent suspected lack of efficacy (or lack of expected effect) case definitions**:**

**FDA 21 CFR514.3 and EMA Vol.9B definition:**

FDA definition: Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness (LEE)).

For EMA vol.9B: Lack of expected efficacy (LEE) is defined as the apparent inability of an authorised VMP to have the expected efficacy in an animal, according to the claims of the Summary of Product Characteristics (SPC) and following use of the product in accordance with the SPC.

**10 October 2013**

**EMA/CVMP/PhVWP/552/2003 – Rev.1**

**Committee for Medicinal Products for Veterinary Use (CVMP), Annex 3**

Pharmaceutical overdose events are usually exceptions to the requirement that qualifying an event as LEE the VMP needs to be administered according to the claims of the SPC and following use of the product in accordance with the SPC. The information related to the therapeutic indications, the route of administration, the dosage and the target species (age and all other animal characteristics data) should be checked and analysed from a critical point of view before assessing such an event which is identified as LEE by the reporters. The laboratory investigations/post-mortem examinations to confirm the involvement of the product or to establish a differential diagnosis are very important to thoroughly assess these events.

Events should be recorded as LEE after having been administered at a dose higher than that recommended. For instance, if a VMP administered at twice the recommended dose is not efficacious, it is reasonable to assume that it should be non-efficacious when administered at the recommended dose. In certain circumstances, products used at higher doses than those recommended can give rise to cases of LEE, e.g. anthelmintic resistance on a farm.

Discussion**:**

Ideally, it would be most useful for global analysis and reporting to have a harmonized definition. Perhaps the issue is that lack of efficacy and lack of expected effect are actually two different things. Lack of effect is related to the claims and following proper use of the product in accordance with the approved labelling/SPC and lack of expected effect is based more on the opinion of the owner, even if this is not aligned with the approved labelling/SPC. Additionally, the evolving nature of these definitions (i.e. EMA guidance dated Oct 2013) only adds to the confusion and impact on Industry to ensure their current processes are compliant.

<u>What is the impact on the day-to-day life</u>

There is a need to maintain a system and procedures that ensure both types of cases are collected and that they are identified properly and then reported and analysed appropriately. The risk is that as the result of non-harmonized definitions, the results of data analysis may be different depending on what definition is applied.

<u>Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)</u>

***This effectively increases the resources needed by 30-50% to manage the tools and processes associated with compliance.***

**Conclusion/Recommendation:**

Harmonization of lack of efficacy definition or further clarification of two classifications:

- ✓ lack of efficacy
- ✓ lack of expected effect

**(3) <u>Seriousness criteria</u>:**

*E.g. VICH vs. regional definitions*

<u>Description of the issue</u>

Seriousness is a criterion to determine whether an adverse event has to be reported as an expedited report within a legally defined time line or whether it is considered a periodic report only. It is therefore an important aspect with regard to regulatory compliance and the number of expedited reports submitted in time is a key performance indicator for a pharmacovigilance (PhV) system.

In addition, the percentage of 'serious' reports of the total reports for a given product is part of the safety profile.

Although regions like European Union (EU), USA (draft guidance) and Canada implemented the seriousness definition provided in the relevant VICH GL there are still differences between European, Canadian and USA requirements. For example, in the USA 'professional intervention' is included as an additional criterion for seriousness in 21CFR514.3.

<u>What is the impact on the day-to-day life</u>

Differences in the definition of serious are relevant for 3rd country reports, i.e. reports from countries outside the territory of the respective authorities. For example, adverse event reports currently have to be submitted to EU and Canadian authorities worldwide when they are both serious and unexpected. Differences in the understanding of 'serious' are therefore relevant. This is of particular importance in Canada where the authorities, at least for the time being, insist on receiving only 'serious and unexpected' cases according to the Canadian definition. Reports from the USA are often classified locally as serious due to 'professional intervention'. Thus, the same report could be considered 'non-serious' in the EU or Canada. In other words, either the number of 'serious' reports is artificially too high or all relevant USA reports would have to be re-classified according to EU/ CA standards.

Furthermore, the classification 'serious' is used in Periodic Safety Update Reports (PSUR) to group and assess collected adverse event reports for a given product. A different understanding of seriousness complicates this process.

<u>Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)</u>

A precise estimation is very difficult to make and certainly depends on the number of 3rd country reports and the setup of the PhV system. However, it has been estimated that for the Canadian situation alone, that in bigger international companies around 0.25 full time equivalents per year are needed to comply with differences regarding seriousness and expectedness in relation to 3rd country reporting to Canada. This represents a 10% increase in resource needs within a typical company.

(4) **Expectedness:**

*E.g. Reconsider whether expectedness is still useful for a reporting criterion with the worldwide variations of product labelling*

Description of the issue

Countries like USA (21CFR514.80) and Canada have defined expectedness/unexpectedness criteria in their pharmacovigilance (PhV) reporting requirements. VICH guideline 24 also contains the following definition for unexpected adverse event. "An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labelling or approved documents describing expected adverse events for a Veterinary Medicinal Product (VMP)." European guideline for Pharmacovigilance of VMPs (Volume 9B) also stipulates the submission of unexpected adverse events form non-European Economic Area (EEA) region within 15 days.

Due to differences in regulatory guidelines the Summary of Product Characteristics (SPC)/label information for the same product varies in different regions/countries. As a result, the signs which are described and are considered expected in one region/country might not be listed or considered expected in other countries.

What is the impact on the day-to-day life

All serious and unexpected cases from third countries have to be reported within 15 days to European Medicines Agency (EMA) database (Eudravigilance).

Marketing Authorisation Holder (MAH) has to fill out additional information to ascertain whether this case is expected or unexpected. Even if the unexpected adverse event is of very mild nature like emesis or local erythema, it still has to be reported within 15 days. In addition in USA, these unexpected case reports require a mandatory 15 days follow up report. Follow up reporting should be based upon the medical merit of the case.

Depending upon the regulatory oversight of different regions an expected case report in one country/region can be an unexpected case report in other country/region. In a number of non-VICH countries, this information is missing altogether (no adverse events are listed on the product label). For lack of efficacy cases depending upon the approved claims in different countries, expected efficacy in one country might not be the expected outcome in another country.

There seems very little use of this criterion to decide the submission of adverse event reports. This criterion does not add much value to signal detection and data analysis where all cases are analyzed regardless of their expectedness criteria. In future, if more countries adopt the EMA and Canada's worldwide reporting requirements of adverse events, then the situation will become more complex.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

Like serious cases, for EEA based companies this depends upon the number of marketing authorizations in third countries (USA, Canada etc.). For a mid to large size companies with affiliates in these countries, it can require additional 10-15 % PV resources around to process these case reports. This is a significant increase in team size and represents significant additional cost.

Recently Canada has also started requesting third country case reports for serious and unexpected cases. This represents an extra 5% add on on already limited PhV resources. In addition, in USA, there is a mandatory follow up submission requirement for all unexpected case reports. This is an additional administrative burden.

**(5) Reporting timelines for expedited cases:**

Description of the issue

The table on next page shows the reporting complexity of a single case involving products approved globally/internationally, as well as the impact.

Example scenario to consider: A case involving a Pharmaceutical, Environmental Protection Agency (EPA) regulated product and a biological applied to a dog per the product label, and experienced a non-serious, non-labeled event, (i.e. isolated, apparent "seizure", from which the pet recovered) in the US. Despite the fact that the event **was non-serious, the pet was examined (+/- treated) by the veterinarian for the event.**

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

Overall, this disharmonisation represents a 100% increase in the resources needed by industry.

| | | Single | | Aggregate | | |
|---|---|---|---|---|---|---|
| | Reportability | Format | Timing | Format | Timing | Assessment |
| FDA | 15-d | HL7 XML (electronic file) | 15 - business days | DER (Drug Experience Reports) | annual | modified Kramer algorithm |
| EPA | quarterly | NA | NA | standard and enhanced | quarterly | EPA severity |
| USDA | NA | NA | NA | NA | NA | NA |
| EMA Reporting | Periodic | NA | NA | PSUR | variable | ABON * |
| JAP Reporting | only required for cases with death, life threatening condition or resulting in sequelae (equivalent to serious) | paper | 30-d | analysis of all cases, standard paper format | annual for first 6 years, ^+ years re-examination | |
| AU | annual | NA | NA | line listing | annual | (numeric) ABON-like |
| NZ | serious = 1 working day, other cases = 20 working days | NA (paper/email) | NA (1 working day for serious) | line listing via email | monthly | ABON-like |
| CAN | 15-d | Electronic line listing | 15-d | CFIA (Canadian Food Inspection Agency) - aggregate | bi-annual | |
| RUS | 2 weeks | electronic and paper | 2 weeks | Country specific format for initial aggregated and renewals | from date of MA - same timing as EMA/vol9B; renewal | |
| Impact | requires systems that can define variations | requires development and maintenance of multiple XML files and paper forms - increases work with little value added | | multiple report formats- may result in misaligned assessments | multiple report time periods- may result in misaligned assessments | variable means to interpret information reported - may result in misaligned assessments |
| Overall impact | **Overall, this disharmonisation represents a 100% increase in the resources needed by industry.** | | | | | |

*Categories of causality: A for probable, B for possible, O1 for inconclusive, O for unclassifiable/unassessable and N for not related

**(6) Periodic reporting for same products in different countries:**

*E.g. Requires creation of different reports with different data sets a few months apart resulting in duplication of efforts with no demonstrated benefit to the end user or better understanding of the product's safety profile.*

Description of the issue

Several countries require periodic reporting of suspected adverse events in the form of aggregated reports. This obligation requires the marketing authorisation holder (MAH) to analyse all cases received during a given period, assess the impact of this information on product safety and efficacy and determine whether there is a need for action. Periodic reporting usually starts from the registration date in a given country and has a periodicity that varies according to different factors, usually country or region specific, such as time from first registration /first putting on the market, legislative requirements or agency requirements. Reporting periodicity may lengthen after several years on the market, but is typically required for as long as the product's licence is valid.

Depending on where the product(s) is (are) registered, such aggregated reports will contain case reports originating from one country, or one region (e.g. European Economic Area (EEA) =31 countries) or worldwide for the same product.

Countries with registrations occurring much later (for example in emerging/developing markets) than the first ever registration may also require frequent reporting according to their local legislation for "new product" registration. This can occur even when the product is well known and characterised from a safety point of view based upon extensive field experience in the original markets for several years. Periodic reporting at a less frequent basis would be sufficient and appropriate in this situation.

What is the impact on the day-to-day life

For MAHs with the same products registered and commercialised in several countries across a region or the world, this requirement results in many periodic reports being assembled a few months apart to match each registration date and ensuing reporting calendars are based on different start dates (=registration dates). As a consequence, the same data or subset of data are analysed several times but in various time/country combinations.

Examples: Product A is registered in 12 EU countries as a national product; if the reporting date is not harmonised at the EU level, this would result in 12 different periodic reports including third country reports, based on the 12 different national registration dates. This situation is now improved in the EU due to the Periodic Safety Update Report (PSUR) Synchronisation initiative started in 2008. Usually, only one periodic report is now necessary for a product registered in the EEA for all agencies in the EEA.

This product A is also registered in the USA, Israel, Switzerland and Russia. All these countries also require periodic reporting to include their country cases and sometimes third countries as well. Their registration dates will all be different to the authorisations dates in the EEA. This will require another four periodic reports generated for these four countries. Unique datasets including a mixture of EEA or worldwide and local cases reports will need to be compiled, formatted and analysed according to these four countries specific requirements.

Discussion

One analysis of all worldwide case reports aggregated on a periodic basis would bring several advantages, with the report calendar based on the first worldwide registration date (International Birth Date) and provided to all interested agencies. It would provide a consistent and comprehensive review of all pharmacovigilance (PhV) data available to all interested agencies. This would allow agencies to compare their views if necessary based on the same set of data and avoid different analyses that could result in different interpretations/recommendations. Countries in which registration occurs at a later time would have access immediately to worldwide PhV data for these products and would not have to start afresh with new calendars.

Quantitative or semi-quantitative evaluation of the impact on resources (system needed, time spent, money, people)

**This disharmonisation represents a 100% increase in the resources needed by industry.**

The impact of periodic reporting with different calendars within the EEA has been improved with the PSUR harmonisation/synchronised process without a negative effect. However the issue is still very present and impactful for the rest of the world. Each time a MAH creates an aggregated report with part of the data already included in another aggregated report but for another period or a subset of the data (e.g. different countries) this is using people time to reanalyse the "new data" set. This consumes resources for little difference in the overall information (numbers of reports and safety assessment outcome). Calendars of periodic reporting need to be managed for each region /countries and global databases are required. If global databases are not used, more people resource is needed to get all the data together for each of the reports involving more than one country/region. Simply stated, each time a report is done with a different set of data for a similar but different period, **the resources needed are doubled** (Pulling the data, assessing the data, creating the report, distributing and archiving the report).

(**7) Differing opinions on the meaning and use of various data elements:**

*E.g. "date first valid", "alive with sequelea", whether or not one case should contain more than one animal; mandatory vs. non-mandatory data elements, regional configurations; report format (paper vs. electronic); specific requirement based on the interpretation of XML architecture and the letter case (either use of capitals or non-capitals letters authorised).*

Description of the issue**:**

Depending on the region where the case is recorded and has to be submitted, there are some data elements which are non-mandatory and wouldn't be documented by the local staff of a company whereas the same data elements are mandatory in another region where the case will have to submitted as a third country report by other staff of the same company to their local authorities. Amongst the databases of the competent authorities and the pharmaceutical companies, specific requirements may be implemented based on different interpretation of XML architecture, e.g. the letter case (some software authorize the import of XML files where either capitals or non-capitals letters are used, whereas other software don't authorize the use of capitals if the concerned guideline give examples without capitals and the XML is invalid).

What is the impact on the day-to-day life

These sources of disharmonisation force the industry to continuously maintain informatics systems that can address the disharmonised regional requirements. To avoid human error, the system has to be configured to alert the user automatically that some data, that may be not required in the area where the AE occurred, are required in other area and have to be documented accordingly. A continuous monitoring of the regional requirements has to be done to keep the systems up-to-date, with consequences on IT development then testing and validation of the system. Moreover, staff has to be trained to meet local and other area requirements. Internal business rules have to be updated, requiring writing and handling new versions of SOPs. Finally, the quality control must address the continuously evolving practices.

Description of the issue: other system differences

Depending on the region one case should contain more than one animal or not.

Regional requirements for identifying reporters whilst maintaining their confidentiality.

Varying XML architectures require the maintenance of more than one file format (i.e. sending, testing/validating, maintaining code lists, etc.)

What is the impact on the day-to-day life (2)

The differing regional opinions oblige industry to make arbitration in the favor of one of the possible meanings and use, the risk being to be non-compliant towards the other region. In the region where one case can refer to more than one animal, new case records have to be created to meet the requirement of other regions of one case referring to one animal only.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people )

These regional differences generate significant additional costs for companies. Taking into account the additional operations due to disharmonisation (the requirement for regulatory monitoring, testing and validation of IT system, time to prepare and provide training, resources to maintain SOP, the additional time required for Quality Control of data), we may evaluate the supplementary need in terms of people as at least 1 full time person in medium organisations or can be quantified as at least 20% in large companies. The additional costs related to IT system development due to disharmonisation can be evaluated as 50% of the annual fees paid to the editor of the IT system.

**(08) Causality assessment criteria**:

Description of the issue

In the different regions, even within the VICH countries there is no harmonisation concerning the causality assessment (e.g. ABON coding* versus "confirmed" PhV case or modified Kramer algorithm). This adds extra burden on the companies who have to do multiple causality assessment for the same case. In addition, the companies face difficulties in making sure the correct causality assessment is submitted to the appropriate competent authority.

Within the EU/EEA the ABON coding is used to assess the relation of the product to the signs described in the **entire case**. The guideline EMEA/CVMP/552/03-final "Guideline on harmonising the approach to causality assessment for adverse event reactions to veterinary medicinal products" gives the details. The main aspects to be considered are: the associative connection (in time – including de-challenge or re-challenge; anatomical site), pharmacological and/or immunological explanation (known pharmacology or toxicology of the product; drug concentration in blood; dose-effect relationship), presence of characteristic clinical or pathological phenomena (previous description in literature other SARs), and exclusion of other causes.

The FDA CVM applies the modified Kramer algorithm to determine product relationship with **each individual clinical sign** reported in a case. For the evaluation similar criteria as in the ABON coding are used, i.e. previous experience with the drug, alternative etiologic candidates, timing of events, evidence of overdose, de-challenge, and re-challenge. A causality score for each manifestation is given.

The advantage of performing a causality assessment for adverse event reports is that the time factor and previous experiences as well as the pharmacological / toxicological profile of the product are considered. Product-event combinations using standard data mining algorithms are partitioned at the case level as the main criteria listed above are included in this analysis. Analyses at the product-event level without regard to the case risks reaching false conclusions.

What is the impact on the day-to-day life

Particularly as adverse event are increasingly reported by animal owners and decreasingly reported by veterinary professionals, this may lead to wrong conclusions concerning the product as the medical science and the diagnostic input of the veterinary professional is lacking. Therefore products with higher rates of adverse event reports from animal owners may get a biased assessment of their products.

The consequence of the use of different causality assessment systems, e.g. Kramer for Australia or USA and ABON in other countries, is that a case may potentially have two causality assessments assigned which introduces a significant risk of non-compliance. When using only the ABON system, one is forced to classify cases with potentially variable (i.e. seriousness, unexpectedness, etc.) clinical signs by an extreme. The impact is the potential to over-represent or under-represent product relatedness. Using only the modified Kramer algorithm, there is a high work-load associated with analysing each clinical sign, particularly in cases with numerous signs reported.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

For industry the goal is a single, harmonized approach to causality assessment. Different approaches to causality assessment may lead to differing results for the individual case but not for the overall safety profile of the product. Exchange of data or even reporting of data from foreign countries would be hindered unless re-evaluations are done, which necessitates resources and time without added value for the product safety.

*Categories of causality: A for probable, B for possible, O1 for inconclusive, O for unclassifiable/unassessable and N for not related.

**(9) Scope of reporting:**

*E.g. Scope of reporting to a given agency, e.g. national reports vs. worldwide reports related to a given product and same products registered in third countries. Currently a single case may need to be reported to several agencies with different formats. Each case should be reported only once to a regulatory agency.*

Description of the issue

The EU legislation stipulates that pharmacovigilance (PhV) reports occurring in any third countries (non-European Economic Area (EEA) countries) for products also registered in the EEA must be reported to the European Medicines Agency (EMA). These reports must be expedited for serious cases and also included as part of aggregated periodic reports. For non-EEA countries with pharmacovigilance systems in place such as USA, Canada and Japan, PhV reports also get reported to the country's respective agency so that these agencies can assess the cases in their countries and take any necessary actions locally. Timing of reporting, especially for expedited cases, the extent of the data required, and the format of the information included in these case reports are not harmonised across regions/countries.

This process also creates dual assessment and potential disagreement in recommendations between competent authorities.

Impact on day to day activities

Duplication/multiplication of effort when doing electronic-reporting to different authorities. Reports to different agencies often require customisation due to lack of harmonisation on requirements for PhV reports and reporting or specialisation of agencies. Customisation of reporting includes the following elements:

- type of products (e.g. pharmaceutical product *vs* vaccine *vs* US EPA products)
- where each product is registered,
- what each country/agency wants reported (e.g. serious *vs* serious and unexpected cases),
- data required and format
- format of reporting (paper *vs* electronic)
- timelines for each agency

Complex processes to ensure any new licences worldwide get included in the third country reporting processes for the correct agencies need to be in place.

Examples:

Third country reporting in the European Union (EU): for all products with at least one registration in the EU and at least one registration in another country outside the EU, all serious and unexpected Adverse Events (AE) reports must be sent electronically within 15 calendar days of first receipt to the EU PhV database (Eudravigilance) and to the relevant national authorities (e.g. to the German authorities if the products are also registered in Germany). All EU licences must be matched to the corresponding licences in third countries and this comprehensive list needs to be constantly updated to include licences being withdrawn in the EU (no third country reporting any more) and new licences getting registered in third countries (third country reporting required for that new licence). Each submission needs to be tracked and checked for acceptance. Depending on the systems in place at the Marketing Authorisation Holder (MAH), as well as the number of products and volume of cases, this requirement gets very complicated to set up and maintain, demanding the use of additional resources and increasing the risk of non-compliance.

Quantitative or semi-quantitative evaluation of the impact on resources (system needed, time spent, money, people)

Every time a report has to be sent to more than one agency, the workload for the MAH increases. Sending duplicate (2 agencies) or multiple (>2 agencies) reports expands the resources needed proportionately, since reporting time ( e.g. 15 calendar days in the EU, 15 business days in the USA), formats and agencies are different. It is difficult to automate the processes completely. Fully automated processes need highly customisable systems which are not currently available “off the shelf”. Human intervention is necessary at most stages. Furthermore, electronic reporting of PhV cases has technical challenges and sending to several agencies increases the risk of issues with a given agency and resources needed to resolve such issues.

In summary, the processes cannot be standardised or automated, so for each additional region/country where the product is registered, the PhV workload is doubled.

**(10) Content of PSUR:**

*E.g. Different format, different content, and different approaches to calculate the number of exposed animals (ratio vs incidence) and duplication of calculations.*

Description of the issue

VICH Guideline 29, "Management of Periodic Safety Update Reports (PSURs)" provides a brief outline on the content of PSURs. In the US Drug Experience Reports (DERs) are submitted according to 21CFR514.80. In Australia the content of a PSUR is quite brief and concise. So far Canada is accepting PSURs prepared according to European Medicines Agency (EMA) format. Lately PSUR submission has also been added to pharmacovigilance (PhV) legislation in many other non VICH regions like Russia.

In the European Union (EU), European guideline for Pharmacovigilance of VMPs (also referred as Volume 9B) provides a detailed guidance on the format and content of PSURs. It also provides the tabular format for the presentation of data. Compared to Australian PSURs and US DERs, EMA PSURs have grown in size and content over the last 10 year period. While they do provide a useful update on the safety profile of the product, they have also contributed to the growing PhV burden on marketing authorisation holders (MAHs). With the ever increasing focus on signal detection activities in future, PSURs serve more as confirmation/duplication of already known information.

What is the impact on the day-to-day life

At the moment, the MAH has to prepare separate PSURs for one product for submission in different regions. For example if the same product is authorized in USA, Canada, Australia and EU, the MAH will have to submit 4 separate PSURs. Not only these PSURs vary in their content, the time schedule for submission of these PSURs also varies. Sometimes, these time schedules differ by few months.

Most often MAHs have to submit these PSURs, even if there are no cases reported during the report period. Due to lack of harmonized global PSURs format and time table, there is additional restrains on PhV resources as well extra administrative burden on part of MAHs.

Regarding the contents of PSURs, as EU PSURs are the most detailed documents, following examples are taken from the preparation of EU PSURs, although some of these examples are also applicable to other regions as well;

- For the calculation of incidence, the breakdown of incidence calculation per each formulation is required. For example if there are 4 presentations (5, 10, 20, 50mg) of an antimicrobial, separate incidence needs to be calculated for each presentation.
- If one product is registered for use in different avian species (turkeys, chicken, ducks) then the breakdown of incidence figure per each species is required. Frequently, despite the best efforts, it is not possible for the MAHs to get exact breakdown sales figures for usage of the product in these species. It is more often an educated guess. Same example is applicable in some other animal species as well.
- Calculation of Ratio/Incidence: ratio is the total number of reported animals (ABON* causality assessment) divided by total number of treated animals (should be the number of doses sold as it is stated in EU guidance (Volume 9B), however, the number of doses is not always easy to determine for all products. Also on some occasions the number of doses is actually the same as the number of animals treated). While percentage incidence is the total number of reported animals (ABO causality assessment) divided by total number of treated animals. Calculation of ratio of animals does not add any value to the PSURs, calculation of incidence should be enough.
- Lack of efficacy incidence is calculated separately; however, many times these cases contain additional Veddra signs in addition to lack of efficacy. As a result sometimes these cases are added to adverse event as well as lack of efficacy incidence calculations.
- Some competent authorities require separate incidence calculation for adverse events from clinical trials. This results in more work for MAHs.

- According to volume 9B, cases with off -label use should also be included in incidence calculations. Off -label use does provide useful information about the marketed product, however, inclusion of off- label use cases in incidence calculation is questionable. It can result in (erroneously) higher incidence rates resulting in changes to product literature even though the product is perfectly safe if used with label instructions.
- To describe case reports in PSURs, MAHs have to repeat the case information already provided in the line listings.
- Recently for antimicrobials, some competent authorities also ask for the inclusion of antimicrobial resistance data in PSURs.
- Selection of relevant search terms and databases used for bibliographic search are also a cause of concern. This becomes more problematic for long established antimicrobials or generic versions of antimicrobials. Some competent authorities ask for the provision of full length published articles in PSURs.
- Line Listings; normally these are provided in Adobe/Word format or in Excel format for long ones. Some competent authorities want to receive these in disc format.
- Some competent authorities want to receive PSURs in hard copies with physical signatures, and electronic signatures are not acceptable. For large PSURs with many cases it is a major logistical task for the MAH.

*Differences in the PhV scope impact the day-to-day life especially in regard to EU 3rd country reporting. Here it needs to be ensured that worldwide reporting obligations are met even though in some 3rd countries the PhV scope is not as broad as in the EU.* ***This could be a regulatory compliance issue****.*

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

Harmonization of PSURs content and submission schedule at global level will lead to reduced administrative burden for MAHs. It is not easy to quantify the task precisely, however, in future the signal detection management activities where PSURs could be replaced by short safety summary statements, could lead to an estimated 20 to 25% reduction in PhV personnel and time costs. In EU regions, many competent authorities also levy PSUR assessment fees. Once a harmonized and risk based approach will be adopted, this fees cost will also be reduced.

Additionally, the impact on resources could be cut further without compromising safety analysis by moving to global reporting using one PhV system and a risk based approach to regulatory reporting. This way, all of the data would be available to the National Competent Authority (NCA) for review at any time, and periodic summaries of the pharmacovigilance profile of marketed products would be provided aligned with their risk level (i.e. low risk products require surveillance reporting less frequently than new products or those with existing safety issues).

*Categories of causality: A for probable, B for possible, O1 for inconclusive, O for unclassifiable/unassessable and N for not related.

**(11) Lack of harmonized product dictionaries:**

Description of the issue

Due to the absence of harmonized product dictionaries, industry needs to change the reported product name to fit with their own systems at the reception of Adverse Events reports originating from competent authorities.

What is the impact on the day-to-day life

When submitting a follow-up to the originating authority, revised information concerning the product name is sent to the agency's database creating some confusion on their side. Remarks received from the agency need to be addressed, the concerned company is at risk of being found non-compliant as they modify the information originally received from the authorities which may on a longer term trigger regulatory actions, even inspections. Another approach in order to avoid the feed-back from the authorities is that companies using the web-trader access may modify again the product name to indicate the original product name from the authority when they validate the case within Eudravigilance. This is requiring an additional operation.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, and people)

There is a regulatory risk of being non-compliant which could end up in supplementary regulatory actions or even trigger new inspections. An inspection can create on average 11 days (1/2 full month) work for 5 people.

Extra resources in manpower are required even if it is very difficult to quantify.

This added work load could concern up to 15 % of cases handled by a company (around 3 cases out of 10 are received via Eudravigilance from a National Competent Authority (NCA) and out of these, 50% could result into a follow-up to be sent to the NCA by the company).

**(12) Requirements for translation:**

Description of the issue

Requirements for translation into national language even for adverse event occurring and reported in foreign countries (world-wide reporting) as well as translation of Periodic Safety Update Reports (PSURs) including the line listing of world-wide case reports has been proposed in draft pharmacovigilance legislation or has been already implemented in some countries.

Within the VICH regions it has been agreed that for animal health pharmacovigilance the common language is English. However, in some non-VICH countries legislation is prepared or already implemented requesting reporting of adverse event reports and PSURs in national language (other than English).

What is the impact on the day-to-day life

The major burden for companies with regard to cost and resources for translation from English to other national languages is based on the fact, that the vast majority (approx. >80%) of the world-wide cases are usually reported in the other countries, particularly the VICH countries were the cases are reported in English.

Sufficient qualified translation capacity is not available as medical writing and translations for animal health is not as common as for human medicine. Thus, generally no or only limited qualified translation capacity is available.

The timelines of reporting also need specific attention. A single adverse event report can be translated in time. However, with world-wide reporting for expedited cases the picture looks completely different as hundreds of reports need to be translated within short time frames. Particularly for the PSURs containing world-wide data the problem becomes even more important, as those may contain several thousands of adverse event reports in the line listing and contained in several hundreds of pages. In general the short time frames requested for the submission of PSUR cannot be met particularly for PSURs with a higher number of cases. So this is a threat for compliance or in fact will lead in most circumstances to noncompliance when world-wide data reporting is required.

Quantitative or semi-quantitative evaluation of the impact on resources (systems needed, time spent, money, people)

For industry there is no added value as the translation does not offer new insight in the safety profile of products. The goal should be to agree on English as the common language for pharmacovigilance in animal health. If this is not achievable, at least the request for translation of world-wide data from English into national language should be omitted. National cases may then be submitted in either English or the national language. However, the foreign country cases and the PSUR data would not need to be translated.

As the legislation requests the world-wide reporting of expedited adverse events and of all adverse events world-wide in the PSURs, this creates a major burden for companies for resources, cost, quality and timeliness of reporting.