International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Final

CONCEPT PAPER

on Revisions of VICH Pharmacovigilance Guidelines (VICH GL24, VICH GL29)

INTRODUCTION/BACKGROUND

VICH GL24 (Pharmacovigilance: Management of Adverse Event Reports) was adopted at Step 6 of the VICH Process on October 18, 2007 and recommended for implementation by 2015, following the development of a harmonised adverse event reporting message and associated technical VICH guidelines GL42, GL35, and GL30. VICH GL29 (Pharmacovigilance: Management of Periodic Summary Update Reports) was recommended at Step 7 of the VICH Process for implementation by June 2007. Over ten years has passed since the managerial concepts (VICH GL 24 and 29) were originally written. During that time, several regions implemented and gained valuable experience with electronic reporting of AERs, and great progress has been made in that area, including the ability in some regions to incorporate data mining/signal detection tools into their pharmacovigilance procedures. In spite of that, not all regions have been successful in implementing all of the pharmacovigilance guidelines.

On January 16, 2015, the IFAH (International Federation of Animal Health, now known as HealthforAnimals) Pharmacovigilance Task Force published and submitted a document (VICH/IN/15001) entitled, "Impact of Disharmonisation on the day-to-day operations in Pharmacovigilance" to the VICH Steering Committee. This document outlined IFAH's perspective on the challenges faced by industry in developing efficient pharmacovigilance systems within their companies. Twelve areas of disharmonisation were identified and described. In 2016, this document was provided to VICH members and two rounds of comments were collected from subject matter experts in each region. Separately, a vision document was submitted to the VICH Steering Committee "by industry partners" as a collaboration between Animal Health Industry (US) and AnimalhealthEurope, originally in May 2014, with an updated version in January 2019.

New veterinary pharmacovigilance legislation (Regulation (EU) 2019/6) in the European Union came into force on January 28, 2019 and will be applied from January 28, 2022 on. An analysis of impact on VICH guidelines was presented to the ESI-EWG in November 2018. Subsequently, HealthforAnimals drafted a new discussion document and presented it to the ESI EWG at the December 2018 meeting. The final version of the HealthforAnimals document, "Vision for a globally harmonised pharmacovigilance system" was presented to the VICH Steering Committee for review in January 2019.

In practice, veterinary pharmacovigilance has matured worldwide through increased awareness and availability of software packages that facilitate the creation/exchange and analysis of the data. Where

the original VICH guidelines were established in the era of 'paper' reporting, veterinary pharmacovigilance has now further evolved while having access to modern databases and analytical systems. Similarly, the age of social media has provided new challenges and opportunities that affect veterinary pharmacovigilance and has contributed to the awareness of this field.

PROBLEM STATEMENT (OVERVIEW)

Given the rapid evolution of veterinary pharmacovigilance and new areas of disharmonisation in VICH regions, revisions of managerial guidelines VICH GL24 and VICH GL29 are likely necessary. Existing issues with these two guidelines are identified below:

VICH GL24:

- Certain *definitions (e.g, serious, unexpected)* in GL24 are less prescriptive than existing definitions in regulations in US FDA, preventing that region from fully implementing that VICH guideline as written without changes to existing regulations.
- USDA has recently implemented the existing VICH GL24 definitions into their regulations.
- Regulation (EU) 2019/6 (to be applied from January 28, 2022 on in the EU) has changed reporting *timelines* for individual adverse drug events (ADEs) now that electronic ADE reporting is available and mandatory in that region. The regulation requires electronic reporting of all adverse events within 30 days, allowing the initial reporter to gather as much information as possible prior to submission of the report. There is no longer a distinction between serious and non-serious, eliminating the need for this region to rely on a definition of "seriousness" or "unexpectedness."

VICH GL29

- Periodic Safety Update Reports (GL29): report formats and regulatory reporting timelines for aggregate reports currently vary amongst regions. Due dates of reports may vary and are set primarily based on approval/authorization date within different regions. For periodic reporting/analysis, it is not clear to the reader of the guideline how to navigate through/harmonize reporting of global products to the international birthdate concept.

- The PSUR report, as it currently stands, no longer exists as a concept in Regulation (EU) 2019/6 . Instead, the PSUR aggregate analysis is replaced with the use of continuous signal detection and management as the primary analytical tool. Guidelines will be developed in that region that will clarify this type of analysis. Other VICH regions will likely still require some form of annual report/aggregate ADE analysis from the sponsor.

VICH GL 42, 35 and 30

These three technical guidelines are relatively stable . They have been implemented by US FDA and other regions are actively working on implementation. There is no proposal to change these three guidelines at this time, other than normal maintenance procedures for VICH GL30.
In practice, electronic adverse event reporting seems stable at this time and the group did not identify any areas that were critical to update. The Pharmacovigilance EWG group acknowledges that any changes to these guidelines would potentially require significant investments to change database/schema structure. There does not appear to be a need to change the message structure at this time.

DISCUSSION OF AREAS OF DISHARMONISATION IDENTIFIED IN INITIAL 2015 IFAH DOCUMENT:

The VICH Pharmacovigilance EWG was tasked with identifying and proposing potential solutions for the remaining areas of disharmonisation through guideline revisions, where possible. Many of the areas of disharmonisation identified in the 2015 IFAH document appear to involve VICH GL24 and GL29. These two managerial guidelines address: identifying the scope of PV, providing recommendations for definitions (e.g., adverse event, serious adverse event, unexpected adverse event), and providing recommendations for reporting timelines for individual adverse event reports and aggregate reports (PSURs). Considering the current landscape which includes evolving regulations across regions (EU, LATAM, Asia, etc.) a pragmatic, global approach is needed to achieve harmonisation. This may include updating definitions, eliminating now obsolete classifications, and a redefinition of responsibilities among stakeholders. The following section provides a summary of the Pharmacovigilance EWG discussions related to the remaining areas of disharmonisation described in the 2015 IFAH document.

VICH GL24

Scope of PV

In the current landscape, several VICH regions utilise PV electronic systems to capture case reports outside the existing VICH defined scope of pharmacovigilance, but clearly defined by their respective regional laws and regulations. Depending on the region, these reports may include reports of product/manufacturing defects, reports related to environmental safety/validity of withdrawal period, and/or transmission of infectious agents. Electronic ADE reporting systems and the VICH GL42 message have been designed with the flexibility to allow for submitting these reports electronically as individual cases, potentially to any region willing/needing to receive them. It is recommended that electronic systems for reporting should continue to allow for flexibility to address the needs of all VICH regions. At this time, there is no recommendation to alter the scope of pharmacovigilance in GL24.

PV Definitions

Definitions for both serious adverse event (VICH GL24 III.3) and unexpected adverse event (VICH GL24 III.4) are currently used by some regions to: 1. provide a way for manufacturing authorisation holders and regulators to identify, trend and prioritise analysis and review the most serious ADE cases, and 2. identify reports that require expedited reporting and/or follow up to regulatory authorities in several regions. For regions that define "serious adverse event," a harmonised definition is still desirable; however, the ESI EWG recommends to modify GL24 and acknowledge/allow for regions who choose not to rely on this definition to classify receipt of reports as "expedited."

Serious Adverse Event

- Regions that utilise a definition of "seriousness" in regulation/legislation may or may not have adopted the existing VICH GL24, which has occasionally resulted in confusion for exchange of information for global pharmacovigilance systems and/or analysis and trending of serous AEs. Note: submission of a valid electronic ADE message requires classification of a report in that region as expedited, periodic, follow-up or nullification.
- The definition of serious will no longer be applied in the EU when Regulation (EU) 2019/6 is implemented. Upon implementation, all ADE reports in the EU will be required within 30 days. "Expedited" reports will NOT be dependent on a classification of "seriousness" as they are currently worded in VICH GL24, but "expedited" may need to be independently defined by regional regulatory authorities during this transition period. As is the case now, regulatory authorities may choose to allow "early" submission of any case classified independently in other regions as expedited reports.
- The US FDA regulation describes a definition of seriousness that is broader than the VICH GL24 guideline and includes medical events that "require professional intervention". USDA has adopted the VICH GL 24 definitions in their new regulation. Some regulatory regions outside of the US, who have adopted the existing VICH GL24 definition of serious adverse event, may have subsequently developed additional guidelines or Q&A documents with examples of "serious" adverse events to provide additional clarity to industry. These documents typically specify medical events that should be automatically reported as serious adverse events, even though those events may not appear to fall under the current VICH GL24 definition. One such example related to the current EU system in place is found here: https://www.ema.europa.eu/en/documents/other/questions-answers-serious-non-fatal-adverse-events-reporting-rules_en.pdf.
- Regions still requiring the serious definition do have an opportunity to provide examples of serious events and harmonise "seriousness" concepts in a revised GL24 guideline. A possible proposal is to further harmonise the serious definition by listing examples of medically important events that could be considered "serious" reports in regions that still utilise this definition. While a list is unlikely to be all inclusive, the examples should provide the needed clarity and allow more regions to adopt the guideline as a step toward achieving harmonisation. These lists may at the same time become relevant for prioritising outcomes from signal management (see further).
- The working group acknowledges that reporting timelines for expedited adverse event reporting within VICH regions are mandated by regional regulations and may currently vary. VICH GL24 does *not*

currently recommend specific reporting timelines for expedited reporting (immediate, 15 day, or otherwise). The approach being recommended should allow for existing/pending differences, should be adoptable by all regions, and should allow for future regulatory convergence of timelines when possible and practical.

Unexpected adverse event

- "Unexpected adverse events" are defined specifically in regulations of some regions as well, and may differ slightly than the VICH GL24 definition. There does appear to be general agreement within the ESI EWG that if agreement can be reached on the approach to classifying serious adverse events. Some regulatory authorities within VICH regions will likely be able to support reporting serious adverse events as expedited reports, without the additional need for further classifying the event as expected or unexpected.
- A minor revision to GL24 would be necessary to remove the definition of unexpected adverse event, and revise the description of expedited reporting to be associated with serious adverse events (definition clarified with examples) for regulatory regions that continue to utilise this definition. The guidance shall allow for regions not utilising the definition of serious adverse events to consider all ADE reports as "expedited. " Timelines for expedited reports are determined by regional regulations. Currently USDA requires immediate reporting (not to exceed 15 business days), and US FDA requires reporting within 15 business days (approximately 21 calendar days). The EU will be moving to 30 calendar days following implementation of their new veterinary regulation.

VICH GL29

VICH GL29 describes the management of Periodic Safety Update Reports. Regulation (EU) 2019/6 removes the existing requirement to submit routine PSURs, and adopts an alternative signal management approach to aggregate ADE analysis. Timelines for submission of summary information should continue to be based on international birthdates. At the current time, aggregate reporting requirements for FDA CVM are likely to remain in the form of periodic Drug Experience Reports (DERS). Although CVM has not yet implemented VICH GL29, some sponsors have voluntarily submitted DERs in a PSUR-like format that was acceptable to the agency and included the required elements necessary for the DER.

Discussion has ensued about the international birth dates and reporting timelines for PSURs and content. For regions still utilising PSURs, additional approaches in VICH could be considered in the spirit of achieving harmonisation, such as approaches taken in ICH (examples include bridging reports that aim to synchronise reporting due dates with the international birth date), along with continued discussions about harmonising content across regions. Regional requirements for content could be examined and explored if necessary (for example, as stated currently in GL29, the requirement for submission of line listings should be removed if all adverse event reports are submitted electronically). Regulators are likely to need a summary analysis of data for their respective regions, and perhaps a summary analysis of the broader global experience for

comparison. Recommendations for tabular presentation of data and good practices for narrative summaries could be explored. The depth and breadth of these discussions could lead to comprehensive revisions of VICH GL29.

The Pharmacovigilance EWG discussion ultimately found member agreement that content of the *existing* PSUR reports was well understood currently, but the major burden appeared to be the lack of harmonised timelines, and perhaps the method of submitting PSUR reports to agencies. It is unclear if this will remain an issue if the requirements for PSUR submission are relaxed in some regions. At this time, the Pharmacovigilance EWG proposes reopening VICH GL29 to add a description or recommendation for a waiver process (to enable harmonising timelines and allow for submission of PSUR reports as an alternative to other types of periodic ADE summary reports).

AREAS OF DISHARMONISATION NOT CURRENTLY ADDRESSED IN VICH GLS

Comments circulated in response to the 2015 document titled "Impact of Disharmonisation on the day-to-day operations in Pharmacovigilance" referred to differing opinions on the meaning and use of various data elements; however, specific data elements were not identified in the comments. At this time, the Pharmacovigilance EWG believe that the current VICH technical documents provide a solid foundation for definitions of the various data elements, but if areas of confusion still exist, those can be identified and clarified as a revision to GL42. No recommendation at this time until this is further clarified.

Causality Assessment Criteria

This has not been in scope for VICH to date. FDA CVM does not require submission of causality assessments along with ADE reports, but is willing for the ABON causality assessment to be transmitted in the electronic message if available. Newer approaches to signal detection (disproportionality methods/data mining) do not necessarily require a causality assessment at the onset. With newer analytical approaches, assessment of "signaled event" typically occurs through case series analysis occurs after an event (clinical sign) has signaled. USDA has includes the concept of 'product relatedness' in their regulations and will require transmission of a causality score. ABON and possible alternatives to ABON was preliminarily discussed by the group, but no definitive decisions were made. No recommendation for addition to VICH GL at this time.

Lack of harmonised product dictionaries

The VICH Pharmacovigilance EWG members support ongoing work on the development of a global product dictionary and is keeping informed on the progress of the IDMP standard in development. The IDMP approach is exploratory at this stage, and projected to take many years to develop. No recommendations are being made for a new VICH GL at this point; however, the Pharmacovigilance EWG workgroup should continue to explore development, focusing on leveraging existing work and identifying the elements necessary to effectively and efficiently maintain a global product dictionary for veterinary medicinal products.

Requirements for translation – the VICH agreed upon language is English; however, the Pharmacovigilance EWG felt that regional requirements need to remain. No recommendations at this time for changes to VICH GLs.

RECOMMENDATION FOR EXISTING GLs (POINTS TO BE ADDRESSED):

In the short term, the ESI EWG recommends an approach to acknowledge regional differences in the regulations, and provide a guideline that does not constrain, but instead allows for future regulatory convergence when possible and practical.

The following areas could be addressed as minor revisions to existing guideline VICH GL24:

- Propose the following revisions to the description of expedited reporting:
    - Remove the criteria for/definition of unexpected adverse event
    - Relax "seriousness" as a required criteria for determining expedited reporting for regions that do not use it; however, work toward harmonising/clarifying the definition of the term "serious" for the regions that still utilise the definition
    - Add the clarification that expedited reporting is currently defined in regional regulations.

The following could be addressed as a minor revision to existing guideline VICH GL29:

- Add a description or recommendation for a waiver process (to enable harmonising timelines and allow for submission of PSUR reports as an alternative to other types of periodic ADE summary reports).

These minor revisions are editorial in nature, not anticipated to require any software changes to existing pharmacovigilance systems, and could provide needed clarity for marketing authorisation holders and regulatory authorities maintaining/working with global pharmacovigilance systems.

The working group is unable to predict the impact of any new regulations under development. Major revisions could become necessary if regulations diverge significantly from what is currently expected.

TIMETABLE

Submit Concept Paper to Steering Committee: Fall 2019
If approved, ESI EWG develops a draft of minor revisions to VICH GL24 and VICH GL29 submits to Steering Committee: Fall 2020

RESOURCE REQUIREMENTS FOR PREPARATION

Several VICH EWG members with subject matter expertise in the technical requirements of adverse event reporting messages are already working on harmonised acknowledgement message for electronic ADE reports and following development of global harmonised product dictionary.

Minor revisions to GL24 will require draft review of existing documents via email with regular group meetings (virtual)

If major revisions are necessary to either GL24 (AERs) or GL29 (PSURs), a separate working group may need to be formed to address those specific challenges once the impact of pending regulatory changes is known.

IMPACT ASSESSMENT

a. Impact Assessment for Industry (refer to IFAH document from 2015)
b. Impact Assessment for Regulatory Authorities – Minor revisions to GL24 to provide better clarity on definitions are not expected to have significant impact and may permit all regulatory authorities to fully implement VICH GL24. In general, any major revisions to VICH guidelines such as GL24 and/or GL42 may have significant downstream impact and necessitate time and resources devoted to software configuration changes and regional guideline changes.