VICH Concept Paper for proposing a revision to VICH GL 3 (R)

Outcome of the consultation with the VICH Steering Committee For further discussion at the 29th Steering Committee meeting

Comments to VICH/IN/10014

Comments to VICH/IN/10014, Draft 1 (8 November 2010) were received from the EU (EMA/CVMP/770625/2010, 15 December 2010).

The EU reached the following conclusions:

1. The proposal from IFAH-Europe is very timely to the initiative of VICH Global Outreach.
2. It is necessary to await the outcome of the steering committee discussions VICH Global Outreach before a conclusion on the concept paper can be taken.
3. The support of countries in climatic zones III and IV must be obtained before work starts.
4. Information must be collected on the storage conditions applied in countries in climatic zones III and IV before any work is started.

The EU made the following additional recommendations:

- It is recommended that the storage guidelines for ICH and VICH are kept similar, as almost certainly ICH guidelines will be applied by default if the active substance is used in both human and veterinary sectors.
- The situation should be avoided where more extreme storage conditions, such as those required for climatic zones III and IV, are applied for products used in climatic zones I and II, as this will result in shorter shelf-lives and more stringent storage conditions than necessary for climatic zones I and II.

Additional comments from IFAH-Europe

Information on the storage conditions applied in countries in climatic zones III and IV is already available in Annex 2 of the WHO stability testing guideline (WHO Technical report Series No. 953). This annex has been recently updated on 1st December 2010, and lists the storage conditions required in 196 WHO member countries.

The WHO GL also states that all countries will accept studies done under more extreme conditions. However the experience of IFAH-Europe companies is that this is not always the case. So having a VICH GL would increase predictability and regulatory certainty.

In summary, the intent of a VICH GL would be that:

1) We have guidance for newly developed VMPs,
2) which not only lists standard stability conditions but also discusses the science-driven approaches to exploiting available stability data (e.g. extrapolation, algorithms, technical argumentation),
3) reassurance that if more extreme conditions have been employed in a study (e.g. 30°C/75%RH for zone IVb countries), the results are acceptable also in countries demanding less (e.g. 30°C/65%RH for zone IVa countries).

Introduction:

VICH GL 3(R) Guideline on Stability: *Stability Testing of New Veterinary Drug Substances and Medicinal Products* addresses the stability requirements for Drug Substances and Medicinal products in climatic Zones I and II but not Zones III and IV. As a result there is no "common" document or common consensus addressing the requirements for stability testing for Zones III and IV.

Problem statement, including references to existing technical and legislative requirements in the different regions:

Since VICH GL 3(R) is specific for climatic Zones I and II, there is currently no guideline or common approach for addressing the stability testing requirements of Zones III and IV. As a result authorities in the individual countries of Zones III and IV apply their own criteria with some defaulting to the requirements of the WHO guidance. Some VICH observing countries have regions that fall in these zones and establishing a harmonised guidance would additionally be consistent with the VICH Outreach initiative.

The WHO guideline is specific for human use products and defines individually the stability condition requirement of each member state. Guideline ICH Q1A (R2) *Stability Testing of New Drug Substances and Products* covers climatic Zones I and II only and defaults to the WHO Annex 2 guideline for climatic Zones III and IV. This WHO guideline further delineates Zone IV as Zones IVa (hot & humid, storage conditions 30°C/65%RH) and IVb (hot & very humid, storage conditions 30°C / 75 % RH).

However, within this WHO Annex, guidance is not the same for countries within the same region (some use 30°C/65%RH while others use 30°C/75%RH). Therefore even when the Animal Health industry uses this guidance there is no harmonisation within regions. The WHO GL also states that all countries will accept studies done under more extreme conditions. However the experience of IFAH-Europe companies is that this is not always the case. Thus having a VICH GL would increase predictability and regulatory certainty.

A harmonised guideline would serve to provide a single source, for VICH and non-VICH countries alike, thereby eliminating confusion and requirements for multiple stability studies.

Impact for public health, animal health and animal welfare:

Public health benefits when products are tested to an appropriate standard for the region they are intended and increases the likelihood that storage and handling will not have deleterious effects. In the event of less number of stability conditions required during the stability program this may have the indirect impact to keep cost of goods lower in specific countries.

Without a common approach to stability conditions for veterinary medicinal products intended for all climatic zones, markets of lower commercial value may have fewer medicines available since the cost to conduct additional stability studies is not justified by the expected return on investment.

Alternatively, an Animal Health company may decide to only perform stability at the more extreme conditions of 30°C/75%RH in order to reduce costs, the company then risks the outcome of a shorter than necessary shelf life in the other regions, restrictive packaging options or the addition of a more restrictive storage condition to the label.

In the event of less number of stability conditions required during the stability program this would have a positive impact to animal welfare by reducing any testing requiring the use of animals.

Anticipated benefit to Industry and Other Interested Parties:

By providing the Animal Health industry with a guideline that addresses all climatic zones for stability testing each individual animal health company can provide products to individual regulatory bodies without specific negotiations on storage conditions, specific packaging or performing specific stability studies for that country and still meet appropriate standards.

Providing clear requirements within the Animal Health industry for each zone will eliminate the current discrepancy within the zones.

Anticipated benefit to Regulatory Authorities:
A more comprehensive guideline including all climatic zones for stability studies for the Animal Health products would provide solid scientifically based criteria readily usable by regulatory agencies.

Discussion:

As there is no guidance addressing Zones III and IV in the Animal Health industry then each country is left to establish their own criteria. This generates inconsistent approaches and additional testing which may pre-empt wider availability of animal health products in certain parts of the world. While, consistent with ICH guideline Q1R2 and WHO some countries allow for "alternative approaches to be used when they are "scientifically justified", not all countries accept the same criteria for "scientific justification", therefore the benefit of a specific VICH guideline that addresses testing requirements for Zones III and IV for newly developed Veterinary Medicinal Products. This would also be consistent with One World One Health approaches and in line with VICH's Global Outreach initiative.

Recommendation (action plan, issues to be addressed, mandate, etc.):

1. Update the current guideline by providing clear definition for all climatic zones on stability testing of veterinary medicinal products including the scientific criteria to be applied for stability evaluation while providing the science-driven approaches to exploiting available stability data (e.g. extrapolation, algorithms, and technical argumentation).
2. Harmonise the global stability requirements to facilitate access to a wider market for veterinary medicines by reducing the number of storage conditions required and allow for acceptance of stricter stability conditions in zones having less strict storage conditions as is currently provided in the guidance.
3. The situation should be avoided where more extreme storage conditions, such as those required for climatic zones III and IV, are applied for products used in climatic zones I and II, as this will result in shorter shelf-lives and more stringent storage conditions than necessary for climatic zones I and II. Thus the less restrictive condition should be extrapolated/justified for use in zones III and IV.
4. Particularly for active substances the storage guidelines for VICH should remain in line with ICH to facilitate those active substances used both in the human and veterinary medicinal products. Reassurance that if more extreme conditions have been employed in a study (e.g.

30°C/75%RH for zone IVb countries), the results are acceptable also in countries demanding less (e.g. 30°C/65%RH for zone IVa countries).

5. Update the Guideline on declaration of storage condition accordingly.

Timetable and Milestones:

Step 1	Submit the Concept Paper to VICH SC and VICH Outreach Forum members with the goal to identify whether there would be broad support for elaborating a guideline. Feedback would be gathered electronically prior to the 3rd VICH Outreach Forum Meeting in November 2013 and could be discussed at the latter.	3 months (August-October 2013)
Step 2	The VICH SC will discuss and take a decision at next SC Meeting. If approved, the SC will discuss the timing of the work, and the procedure to be followed in order to involve and obtain the agreement of OIE member countries in climatic zones III and IV as well as their input into a survey investigating the current situation.	November 2013
Step 3	Conduct survey with OIE Member countries on storage conditions applied to veterinary medicinal products in countries in climatic zones III and IV.	3 months
Step 4	Quality EWG, taking into account the information received from the survey of current requirements, to develop a working draft revised guideline for wide consultation with experts in the VICH regions and OIE member countries.	6-12 months
Step 5	The draft Guideline, as agreed is submitted to the SC for approving its release for public consultation.	3 months
Step 6	Once adopted by the SC, the draft Guideline is circulated to all interested parties for consultation, applying an appropriate consultation period (normally 6 months).	6 months
Step 7	The comments received are directed to the Quality EWG for consideration. At this step, the topic leader must be a representative of a regulatory authority. The Quality EWG prepares a revised draft and submits it to the Secretariat with the signature of all experts. The signatures of industry experts are clearly separated from those of experts representing regulatory authorities.	6 months
Step 8	The revised draft Guideline is submitted to the SC and OIE Regulatory contacts for approval.	3 months
Step 9	Once approved by the SC, the final Guideline and a proposed date for its implementation are circulated to the regulatory authorities represented in the SC and OIE.	12 months
Step 10	The SC members report to the SC on the implementation of the Guidelines in their respective regions.	12 months

Impact assessment for Industry:

1. The guideline will provide clarity on the requirements and therefore reduce the regulatory uncertainty, duplication and development costs.
2. The guideline will provide clarity of the requirements and therefore accelerate the availability of new products in both VICH as well as non-VICH regions.

Impact assessment for Regulatory Authorities:
1. Increase the clarity of the requirements in the regions resulting in more complete applications.
2. Lead to a consistent approach in interpretation and assessment by the competent authorities.
3. Decrease the amount of unacceptable studies.
4. Most importantly, this guideline will allow for global consistency in reviewing stability studies.

References to literature, existing relevant international guidelines or standards (e.g. ICH, OECD, CODEX, JECFA…):
ICH Q1F *Stability Testing of New Drug Substances and Products*
WHO (Technical Report Series No.953, 2009) Annex 2 *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*
VICH GL 3(R) *Stability Testing of New Veterinary Drug Substances and Medicinal Products*