Creating Global Harmony in the Regulation of Veterinary Medicinal Products

Setting the Scene
There is an African proverb: if you want to go fast, go alone. If you want to go far, go together. Thus began the opening words from Alice Sigobodhla, Head of Veterinary Medicines Unit, South African Health Products Regulatory Authority, as she opened an inspiring session on "Opportunities from international guidelines and regional collaborations" at the 7th VICH Conference "VICH and a new era."

In fact, the warm and collegial tone of the conference was set from the very first session, as Javier Yugueros-Marcos, Head of Department, Antimicrobial Resistance and Veterinary Products Department at WOAH, introduced the keynote speakers to the conference participants. He commented "This conference brings together a group of people who want to create harmony in this world".

The nearly 200 conference participants seeking harmony had travelled to Amsterdam from 26 countries, from as far away as New Zealand, Australia, India, Brazil, Chile, Korea, and Japan, and from as near as the Netherlands, Belgium, Germany, France and UK. They were roughly split between one third regulatory authorities and two-thirds industry (regulatory affairs professionals from, or servicing, manufacturers of veterinary medicinal products).

A Little Bit About VICH
Before exploring more about the conference, perhaps first a few words about VICH, for those not familiar with the project. VICH was officially launched in April 1996 at the instigation of the World Organisation for Animal Health (WOAH, formerly known as OIE), with Founding Members of the European Union, the USA and Japan. New Zealand, Australia, and Canada came on-board as Standing Members (which participate but do not have a say in final decisions), and were later joined by South Africa and UK. Other countries, fulfilling a set of criteria, can apply to the VICH Steering Committee (SC) to become silent observers at the annual SC meetings.

The two first objectives of the VICH project are:

- Establish and implement harmonised technical requirements for the registration of veterinary medicinal products in the VICH regions, which meet high quality, safety and efficacy standards and minimise the use of test animals and costs of product development.
- Provide a basis for wider international harmonisation of registration requirements.

VICH works by the SC reviewing 'concept papers' proposing the creation or revision of a VICH guideline, and if approved, an expert working group (EWG) on that topic is created. A stipulation of the VICH process is that the EWGs, just like in the steering committee, must contain a balance of experts from both the regulatory authorities and the industry from the VICH countries or regions. All decisions (in SC and the EWGs) are made by consensus. There are currently 9 EWGs working on new guidelines or on updating existing ones.

What is VICH?
VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Its full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

VICH7 Conference
VICH organises public conferences every 4/5 years. The 7th conference was held at the European Medicines Agency in Amsterdam on sponsorship of AnimalhealthEurope.

What has VICH Achieved?
The achievements of the VICH initiative since its launch 28 years ago were elaborated in a conference keynote address from the VICH secretary, Hervé Marion. The principal achievement is the development of 61 internationally harmonised guidelines covering all the main technical requirements of quality and manufacturing, safety and clinical efficacy required for the Registration of Veterinary Medicinal Products.. VICH guidelines also cover in-market safety surveillance (pharmacovigilance).

The harmonisation of data requirements between regions can bring the following benefits:

- Reduction of animal testing
- Reduction of costs of product development
- Increased availability of Veterinary Medicines
- Increased speed to market of Veterinary Medicines
- Increased Product Safety and Consumer Safety

But it is the secondary benefits of the VICH project that really shone out at the VICH7 Public Conference, and these relate to the encouragement of global regulatory convergence. There was palpable enthusiasm in networking to share knowledge and best practice, and in the opportunity to learn from the experience of other regulators.

VICH Underpins Regulatory Convergence
Several speakers during the VICH7 Conference emphasised that VICH has enabled greater international collaboration in the regulatory processes for the market authorisation of veterinary medicinal products. It does this in two ways.

First, by providing a set of international guidelines on technical requirements, regulators from different jurisdictions now have a common language and common standards and expectations. This has created the possibility for joint reviews, shared reviews and simultaneous reviews of dossiers between two or more jurisdictions. It has also underpinned the creation and the operation of regional mutual cooperation systems such as the East African Community and ZAZIBONA regional collaboration project.

Secondly, VICH supports regulatory convergence by being a vibrant international network. It is based on trust, common

interest and cooperation. In addition to the trust to negotiate a common guideline, VICH is about sharing knowledge and building relationships around the world. In 2012 VICH took the decision to reach out to the rest of the world, and created a VICH Forum that other countries could join and become involved. This has been so welcomed that recently VICH had to adapt its structure to reflect its broadening reach and increasing global interest, thus, becoming more inclusive and transparent.

Some Inspiring Examples

In his presentation of "The view of a VICH Forum member", Yuriy Kosenko, SCIVP, Ukraine, pointed out that international GLs are very important to Ukraine, which has 130 marketing authorisation holders from 33 countries. VICH guidelines have helped Ukraine to identify gaps in their regulatory system and also unnecessary requirements and studies which have now been deleted.

VICH GLs are key references that have supported the creation of the East African Community mutual recognition procedure. Adelaide Ayoyi Ogutu, the MRP Coordinator, reported that 80% of their guidelines are VICH guidelines and they now consider VICH guidelines first. VICH guidelines allow reliance on the work already done by the authority where the product was first registered.

In another example of mutual reliance, Innocent Ravengai, BOMRA (Botswana), described the ZAZIBONA regional collaboration project, which is developing a system for the joint assessments of application dossiers. The project has established a Technical Working Group with active members from 7 countries (Zambia, Zimbabwe, Botswana, Namibia, Malawi, South Africa, and Tanzania). The aim is to share the workload to make better use of limited local resources, including the recognition of Good Manufacturing Practice (GMP) inspections from other trusted jurisdictions, and to establish a platform for capacity building.

The final examples are collaborative review models that were originally enabled through trust and personal relationships built within VICH meetings and through the use of VICH guidelines. Marilena Bassi, Director General, Veterinary Drugs Directorate, Health Canada spoke with enthusiasm of the joint activities of Canada, USA, UK, Australia and New Zealand.

She explained that Canada uses 3 collaborative review models:

1. Simultaneous review model with US; the same dossier is submitted to both jurisdictions at the same time: it allows a phased-review process (a.k.a. rolling review).
2. Simultaneous review model with UK: requires a complete dossier at filing meeting the UK/EU requirements (with a 'crosswalk' to the Canada file structure).
3. Joint review between Australia, New Zealand & Canada: this is a true collaborative work sharing model, where each jurisdiction takes a section of the dossier, does the technical assessment, which is then peer reviewed by the other 2 jurisdictions.

VICH is essential for these collaborative review models. It allows the regulators to meet and develop new ways to collaborate together. Canada is now looking forward to the VICH project developing a common global regulatory dossier framework, which will further facilitate these collaborative review processes.

The key to all these collaborations has been willingness to try something new and to be flexible. To succeed you also need organisational and political will and to find champions within your organisation (both within agencies and within the applicant company). At VICH the relationships between regulators have flourished, bringing a change of mindset, so that these review processes are no longer seen as special submissions but as the way to go.

The Single Dossier

As has been illustrated by these examples, it is now acceptable for a single dossier to be submitted to several jurisdictions. As a result of this VICH now wants to go one step further and in November 2024 the VICH Steering Committee agreed to establish a new Expert Working Group to work on a Global Regulatory Dossier Framework. This has been warmly welcomed by those working in collaborations such a joint reviews or simultaneous reviews.

Some Challenges

The adoption of VICH guidelines by the 'younger' regulatory agencies outside of the VICH Founding Members can present challenges. Perhaps the biggest of these is the need for translations. The conference delegates were reminded that good implementation locally is also a critical step in harmonisation, not just the existence of a guideline.

Adelaide reported that their challenge within the EAC is not how to implement VICH GLs, but how to address the gaps left by VICH GLs. For example, there is currently a gap in VICH guidelines covering GMP for veterinary medicinal products. Hopefully VICH will do more in this space in the near future.

Another challenge is the absence of reference products for bioequivalence work and the absence of local laboratory facilities to conduct bioequivalence studies. This could be a serious issue, as proving the bioequivalence of generic products is very important, to ensure the correct therapeutic dose is delivered particularly to minimise the development of AMR.

In Brazil a long list of VICH GLs has been adopted. The two main challenges Brazil faced were strict regulations constraining what could be adopted and a lack of resources. But the legislation is being changed to make it more flexible, and resources are being allocated for training and raising awareness (*e.g.* a recent seminar on VICH GL9 on Good Clinical Practice).

To overcome the challenges, the recommendation of Health Canada is to focus on 'the game changers' such as aligned assessment timelines, one set of questions, and a single product label.

Some Science

The progress we have seen in global regulatory convergence would not be possible without the hardwork and commitment of the scientific and regulatory experts from the regulatory agencies and the trade associations who put in the hours in the expert working groups working on developing the harmonised guidelines. VICH is a fantastic forum where scientists from around the world come together sharing knowledge and sharing best practices. One small conversation over coffee can lead to another step towards harmonisation, as misassumptions and misunderstandings melt away.

It is worth noting that VICH is monitoring new developments in therapeutic science, such as novel therapies and novel technologies. But it is critical that sufficient experience is gained with new science before a guideline is written, to avoid stifling innovation. Perhaps VICH could follow the lead of the leading regulatory agencies, and develop "reflection papers,

discussion documents" and consideration documents that describe current regulatory thinking on an active topic, before committing to the elaboration of a guideline.

An interesting trend in drug development in human medicines shows investment in research in small molecules going down and investment in research in biologics going up. The veterinary sector is also at the start of this trend. There are now 6 monoclonal antibody products on the market or under development in veterinary medicine. The availability of veterinary biologics is expanding by the use of new technologies. Regulatory science needs to keep pace with the rapid development and approval of new biologics, for example by the greater use of fast-track procedures for rapid disease response, conditional approvals and the use of 'master files', such as the platform technology master files or vaccine antigen master files.

Another key area of evolving science is the replacement of animal testing for chemical safety with *in vitro* or *in silico* tests. The conference participants heard a strong call for a change in mind set, whereby we stop talking about animal tests as the GOLD standard. They are not. They are the historical standard and they are outdated. *In vitro* tests are more precise and have better discriminating power and remove the inherent variability of animal tests. Our industry is based on good science and we believe animal testing is not good science.

Good progress is being made toward this, particularly in the area of vaccine batch release. Most regulatory authorities no longer require the target animal batch safety test, and *in vitro* tests are often already preferred for vaccine batch potency testing.

For these new areas of science international regulatory collaboration will be key and an important recommendation was to start with clear definitions. That is the first important step in harmonisation – agreeing what you mean and what you are talking about!

More Work Needed – Inspections

As mentioned previously, one area VICH could research further is manufacturing quality control. Internationally agreed GMP standards and inspection standards agreed through the Pharmaceutical Inspection Co-operation Scheme (PIC/S) enable the development of GMP Inspection Reliance Programmes. These can form an important element underpinning the establishment of trade agreements (Mutual Recognition Agreements).

These are also essential to help eliminate the need for multiple inspections of one manufacturing site by different national competent authorities. There is a high cost, in time and resources, of duplicative inspections to both the regulatory authority and the manufacturer.

The Covid pandemic forced regulatory authorities to further refine a risk-based approach, with increased use of remote inspections and inspection reliance. Mutual reliance was shown to be possible and many benefits were described. It increased trust, knowledge efficiency, use of resources, and increased empowerment of smaller regulatory authorities.

Vision for the Future

Continued convergence is the way forward. VICH is a prime enabler but is just one support mechanism. True regulatory convergence is also a combination of:

- Submission of a single dossier in different regions; this would be facilitated by a Global Regulatory Dossier Framework.
- Mutual recognition of (parts of) assessment.
- Harmonised timelines.

It is about having dreams and changing mindsets, because along the way the challenges of different regulatory systems, different maturity of systems and different classifications of products will need to be overcome. This would be best achieved through the creation of an international forum for regulatory agencies and the shared willingness to try something new and be flexible.

That is one of the dreams for the future. The other is a single dossier, and a single assessment leading to a single global authorisation for veterinary medicines.

Rick Clayton

Rick Clayton, Technical Director of HealthforAnimals, has worked for the European industry association since 1997 and comes from a background of product development and registration of veterinary medicinal products. In this role he is in regular dialogue with decision makers within the European institutions and the European medicines regulatory network with the principle aim of supporting the smooth running of regulatory systems. He is also coordinator for the European industry representation to the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ("VICH"). He has a degree in Applied Biology, a diploma in Marketing and is an Honorary Life member of TOPRA. Since recent decades alongside being Technical Director Rick shares his time representing the global animal health industry. His primary interests are in promoting regulatory convergence and standards of good regulatory practices. This includes international harmonisation of technical requirements, including for pharmacovigilance, good manufacturing practice, and the replacement of the use of laboratory animals in the generation of safety data (e.g. batch release of vaccines).