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Antimicrobial resistance and the guidelines of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)

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Summary

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is an international tripartite cooperation programme that brings together regulatory authorities and industry representatives from the European Union, Japan and the United States, with Australia, New Zealand and Canada as observers.

VICH aims to improve international coordination and cooperation to achieve greater harmonisation of the requirements for veterinary product registration in the regions concerned.

VICH develops harmonised data requirements, i.e. standards for the scientific studies on quality, safety and efficacy that are required to obtain a marketing authorisation for a veterinary medicinal product. It does this by publishing guidelines that provide uniform and consistent guidance for sponsors to follow in developing data for application dossiers as well as for post-marketing safety monitoring of veterinary medicinal products.

Of the 49 VICH guidelines that have been developed so far, two guidelines in particular address issues related to antimicrobial resistance.

Keywords

Cooperation – Data – Guidelines – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Regulatory – Resistance – Safety – Technical.

The background and history of VICH

The initiative to begin the harmonisation process came in 1983 when the first International Technical Consultation on Veterinary Drug Registration (ITCVDR) was held. It was followed by a series of government and industry initiatives which culminated in the formation of VICH.

The Codex Alimentarius Committee (Codex) formed a Committee on Residues of Veterinary Drugs in Foods in 1985.

Standard requirements for veterinary product registration were adopted in Europe in 1981. The United States Food and Drug Administration (FDA) and the European Commission (EC) then held regular bilateral meetings in the following decade to discuss common areas of interest. This has involved a mutual exchange of guidelines for consultation.

The first International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was held in Brussels in November 1991. The meeting brought together regulators and industry representatives from the United States (USA), the European Union (EU) and Japan to address quality, safety and efficacy requirements for human medicines in the three regions.

Meetings on harmonisation of veterinary biologicals were held in Ploufragan, France, in January 1992; in Arlington, USA, in 1994 and in Singapore in 1995, whilst the Global

Harmonisation of Standards (GHOST) discussion document was published by FEDESA (the European Animal Health Industry Association, now called IFAH-Europe) in January 1993. This document set out a programme for the international harmonisation of registration requirements for veterinary pharmaceuticals and biologicals.

The birth of VICH

Following discussions that took place at several ITCVDR and World Organisation for Animal Health (OIE) conferences, the OIE set up an *ad hoc* Group on Harmonisation of Veterinary Medicinal Products in 1994. The preparatory work for the establishment of VICH was carried out by this OIE *ad hoc* Group. Two meetings were held in 1994 and in 1995 at which the scope of veterinary harmonisation was discussed and the membership and objectives of VICH proposed. On the subject of food safety standards, it was decided that VICH should complement the work of Codex and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives. Issues related to good laboratory practice and good manufacturing practices, which were already the subject of mutual agreements, would not normally come within the remit of VICH. Issues related to biologicals were considered appropriate to fall within the scope of VICH. Fundamental to the selection of priority topics for consideration by VICH was the discussion document prepared by COMISA (the Worldwide Confederation of the Animal Health Industry, now called IFAH) for the Steering Committee. This report assessed those ICH guidelines which could be adapted to the VICH programme, defined in detail areas of non-harmonisation between the EU, the USA and Japan and provided a series of 'concept papers' on key topics. It also put forward preliminary suggestions for priority topics.

In April 1996, with all this preliminary work achieved, VICH was officially established by the animal health industry and the regulators from the EU, Japan and the USA, with Australia and New Zealand (which together constitute one region) and Canada joining as observers. The new body brought together regulatory authorities and industry representatives from these countries/regions in a unique discussion forum.

VICH was established under the auspices of the OIE, and the OIE has remained an associate member of VICH.

The scope of VICH

VICH aims to improve the coordination and cooperation in that international process and to achieve greater harmonisation of requirements for veterinary product registration in the regions concerned by:

– reducing/eliminating the need for duplicate testing

– enabling more efficient use of human, animal and material resources while safeguarding the quality, safety and efficacy of veterinary products

– reducing unnecessary delays in global product development

– providing a basis for widening international harmonisation of registration requirements (2).

The guidelines overseen by VICH provide uniform and consistent guidance for sponsors to follow in developing data for application dossiers as well as for post-marketing safety monitoring. VICH does not generally address issues concerning the assessment of data; with only a few exceptions, that important task is reserved for the regulatory authorities in each of the VICH countries. The overall work of VICH is intended to:

– harmonise regulatory requirements in the VICH regions to ensure high quality, safety and efficacy standards, even as it reduces the number of animals needed for testing and the associated costs

– provide a basis for wider international harmonisation of registration requirements

– monitor and maintain existing VICH guidelines

– ensure the processes operate smoothly, in order to maintain and monitor consistent interpretation of data requirements within VICH guidelines

– encourage constructive technical dialogue between regulators and industry to enable responses to significant emerging global veterinary medical issues.

VICH structure

Fundamental to the existence of VICH is the Steering Committee, which is empowered to drive the harmonisation process.

The VICH Steering Committee is composed of regulatory representatives from the EU (through the European Medicines Agency and the EC), Japan (through the Japanese Ministry of Agriculture, Forestry, and Fisheries), the USA (through the FDA Center for Veterinary Medicine and the United States Department of Agriculture–Center for Veterinary Biologics), Australia and New Zealand (through the Australian Pesticides and Veterinary Medicines Authority and the New Zealand Ministry of Agriculture and Forestry), and Canada (through Health Canada's Veterinary Drug Directorate and the Canadian Centre for Veterinary Biologics of the Canadian Food

Inspection Agency). The representatives from the industry associations come from the Animal Health Institute and the Association of Veterinary Biologics Companies in the USA, the Japanese Veterinary Products Association, IFAH–Europe, the Animal Health Alliance in Australia, and the Agricultural Chemical and Animal Health Remedies Manufacturers' Association of New Zealand.

Two delegates of the regulatory authorities and two delegates of representative industry associations are nominated by the three regions. Australia, New Zealand and Canada have observer status, with one delegate representing government authorities and one delegate representing industry associations from the two countries/regions. The Secretariat of VICH is managed by IFAH.

The Steering Committee is the only structure that is empowered to take decisions on selecting topics, releasing draft guidelines for consultation, and adopting final guidelines for implementation in the three regions. It also monitors the implementation of VICH guidelines by the regulators in the VICH countries/regions as well as overseeing the efficiency of expert working groups (EWGs) and supporting their progress.

The Steering Committee meets at regular intervals, currently every eight to nine months. The location of meetings alternates between Japan, the EU and the USA. All meetings are usually held in English, but participants can bring their own translators.

In order to achieve harmonisation on the selected topics, the VICH Steering Committee appoints EWGs to draft recommendations. VICH EWGs bring together the specific expertise needed for guideline development.

Each EWG normally comprises at least six experts – one representing each VICH full member. Each member may send one additional advisor to participate and the Steering Committee may, depending on the expertise required, decide to allow the appointment of more than one expert per VICH member. Additional experts from observer countries – or even other countries – may also be appointed by the Steering Committee if deemed appropriate.

The Steering Committee appoints a topic leader for each topic. The topic leader is responsible for initiating the EWG and guiding its work. He/she will normally chair the group and be accountable to the Steering Committee for delivering the draft documents.

Related topics may be covered by a single EWG. In this case, a chairperson for the entire group will be assigned in addition to a topic leader for each item. The chairperson has responsibility for driving the EWG and reporting to the Steering Committee.

The EWGs meet regularly to advance their work, which is actively and efficiently prepared by electronic procedures between these meetings.

The VICH EWGs that are currently active are the groups on:
– Quality
– Safety
– Electronic Standards' Implementation
– Metabolism and Residue Kinetics
– Biologicals
– Microbiological Acceptable Daily Intakes (ADIs)
– Bioequivalence.

The VICH process

VICH guidelines are developed by means of a fully transparent process which involves the VICH 9-step procedure, the VICH public website and the VICH public conferences.

The VICH 9-step procedure

Step 1

The VICH 9-step procedure usually starts with the presentation of a Concept Paper on a specific topic by a member of the VICH Steering Committee. The Steering Committee reviews this Concept Paper and amends and refines it until agreement is found for the initiation of the topic. The Steering Committee then establishes an appropriate EWG, if needed, and designates a chairperson. A topic leader in charge of drafting a guideline is appointed and given a clear mandate to do the expected work.

The Steering Committee ensures that each expert is properly briefed and has a clear mandate enabling him/her to meet the expected outcome in the time frame defined by the Steering Committee, in accordance with established VICH guidance. The Steering Committee ensures that each topic leader has the required competence and interpersonal skills to lead an EWG and achieve its objectives.

Step 2

The appropriate EWG develops a draft guideline, and submits it to the VICH Secretariat with the signatures of all experts.

Step 3

The draft guideline is submitted to the Steering Committee to obtain approval for its release for consultation.

Step 4

Once adopted by the Steering Committee, the draft guideline is circulated by the VICH members to all interested parties for consultation, applying an appropriate consultation period (normally six months). The dissemination of the draft guidelines is formally driven by the regulatory authorities from the VICH participating countries/regions, which publish the draft documents and collect the comments from their country/region. The drafts are also broadly circulated through the OIE to its Member Countries, and are made available on the VICH public website. Regulators and experts in the particular topic from any country in the world therefore have the opportunity to provide their views on the proposals of the VICH experts.

The regulatory coordinators have to inform the VICH Secretariat when the consultation process in their region is delayed.

Step 5

The comments received are directed to the EWG for consideration. At this step, the topic leader must be a representative of a regulatory authority. The 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.

Step 6

The revised draft guideline is submitted to the Steering Committee for approval.

The entire process, including the important official consultation period, takes at least three years, sometimes much more.

Step 7

Once approved by the Steering Committee, the final guideline and a proposed date for its implementation are circulated to the regulatory authorities represented in the Steering Committee.

Step 8

The Steering Committee members report to the Steering Committee on the implementation of the guideline in their respective regions.

Step 9

This step covers the monitoring, maintenance and review of VICH guidelines. The necessity to review adopted guidelines is determined, at least every three years, following the implementation in order to take account of new developments. The Secretariat notifies the Steering Committee of the three-year deadlines.

Any Steering Committee member may propose that an adopted guideline be reviewed at any time, but they must inform the VICH Secretariat well in advance of the next Steering Committee meeting. Such proposals should be accompanied by an abbreviated Concept Paper detailing the rationale and the background for the review.

If the Steering Committee acknowledges the need for a review of the adopted guideline, the Steering Committee designates the appropriate EWG or a topic leader as the reviewer.

The Steering Committee decides on the step at which the revision procedure shall start.

VICH members have committed to implement VICH guidelines in their veterinary product regulatory processes and it is this commitment that is key to the success of the VICH procedure. VICH observers implement the guidelines on a voluntary basis, and have done so for most guidelines.

VICH achievements

VICH has developed and implemented two strategic plans. The First VICH Strategic Plan, also called Phase I, was adopted in November 2000 and covered the period from 2000 to 2005. The main objectives were to implement harmonised guidelines for all regulatory requirements where significant differences existed, to contribute to the global response to significant emerging issues and scientific developments that impacted on regulatory requirements, and to improve consultation and communication mechanisms.

The Second VICH Strategic Plan, adopted in January 2005 and called Phase II, covered the years 2006 to 2010, and, in addition to the objectives from Phase I, aimed to establish and monitor harmonised regulatory requirements for veterinary medicinal products, which meet high quality, safety and efficacy standards and minimise the use of test animals, and importantly, monitor and maintain existing VICH guidelines.

In Phase I, VICH facilitated the increased uniformity of the regulatory process and technical requirements, and generated a global product development approach. VICH greatly contributed to increased product safety and consumer safety.

The first two VICH public conferences were organised in Europe in 1999 and in Japan in 2002.

In Phase II, VICH increased the reduction of animal-based tests and reduced the number of animals used, particularly

in the safety testing of products. These activities are in line with the VICH commitment to the '3 R' rule: reduce – refine – replace whenever possible.

The considerable improvements in the harmonisation of data requirements between regions have enabled further reduction of animal testing and of costs.

The third VICH Conference took place in the USA in 2005 and the fourth Conference at the OIE headquarters in Paris in 2010.

One of the overall major achievements of VICH is the uninterrupted 14 years of confidence-building and collaboration between the participants from the regulatory bodies and the animal health industry, who come from different countries and regions of the globe. This collaboration has considerably enhanced understanding of regulations and concerns in other regions of the world.

Moreover, VICH is a unique forum for acknowledged worldwide scientific experts from both the regulatory agencies and the animal health companies, and has therefore brought together excellent global scientific expertise. VICH is thus providing a unique opportunity for regulators and industry to discuss topics openly. This has enabled a pooling of expertise that greatly assists in the drafting of joint guidelines on regulatory data requirements and has triggered changes in the regulatory framework in Member Countries and regions.

It is worth noting that in both the VICH Steering Committee and EWGs all decisions are made by consensus only.

VICH has also provided the opportunity to update regional standards and to accelerate the development of veterinary medicinal products for livestock and companion animals, thereby increasing the availability of veterinary medicines.

VICH has encouraged regulatory agencies in the five regions to implement VICH guidelines through official publications and changes of regulatory requirements and legislation.

The four VICH Conferences have provided a unique opportunity for public discussions and exchanges with VICH experts on a broad range of scientific and technical issues, and to influence the strategy of VICH for future years.

As of the end of 2011, 49 VICH guidelines have been finalised and nine more are under development. The full text of all final and draft VICH guidelines is available on the VICH public website at: www.vichsec.org.

VICH guidelines on antimicrobial resistance

The following two VICH guidelines are related to antimicrobial resistance:

VICH GL 27 – 'Pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance', which was implemented in 2004

VICH GL 36 – 'Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI'.

VICH GL 27

The objective of this guideline (1), implemented in December 2004, is to provide harmonised technical guidance in the EU, Japan and the USA for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals. More specifically, it is concerned with characterising the potential for a given antimicrobial agent to select for resistant bacteria of human health concern.

For clarification, this guidance outlines the types of studies and data that are recommended for characterising the potential resistance development that might occur in the food-producing animal under the proposed conditions of use of the product. This includes information that describes attributes of the drug substance, the drug product, the nature of the resistance and the potential exposure of the gut flora in the target animal species. It does not account for post-slaughter factors, such as processing of food products or kitchen hygiene, that affect the potential human health impact.

The guideline further details the basic data that should be provided by the sponsor, including the antimicrobial class, the mechanism and type of antimicrobial action, the spectrum of activity, the antimicrobial resistance mechanisms and genetics, the occurrence and rate of transfer of antimicrobial resistance genes, and the occurrence of cross-resistance and co-resistance as well as pharmacokinetic data.

Pathogen load studies, ecotoxicity studies, the process of risk assessment, the establishment of ADIs, and consideration of residues of antimicrobial agents are not covered by this guideline.

Special consideration may be appropriate for aquaculture products, because of fundamental differences in production systems, bacterial populations present, and potential zoonotic public health threats.

VICH GL 36

This guideline, implemented in May 2005, provides guidance for assessing the human food safety of residues from veterinary antimicrobial drugs with regard to effects on the human intestinal flora (3).

Intestinal flora play a significant role in maintaining and protecting the health of human beings, because they are important for several key processes in the host, such as *(i)* metabolising endogenous and exogenous compounds and dietary components; *(ii)* producing compounds that are later absorbed; and *(iii)* protecting against invasion and colonisation by pathogenic microorganisms.

Ingested antimicrobial drugs can potentially alter the ecology of the intestinal flora. They may reach the colon due to incomplete absorption or may be absorbed, circulated and then excreted *via* bile or secreted through the intestinal mucosa.

If a drug intended for use in food-producing animals has antimicrobial activity, the safety of its residues needs to be addressed with respect to the human intestinal flora. Derivation of a microbiological ADI is only necessary if residues reach the human colon and remain microbiologically active.

The objectives of this guideline are therefore to:

– outline the steps in determining the need for establishing a microbiological ADI

– recommend test systems and methods for determining non-observable adverse effect concentrations and non-observable adverse effect levels for the endpoints of health concern

– recommend a procedure to derive a microbiological ADI; it is recognised that different tests may be useful.

Since further research is needed to confirm the reliability and validity of all test systems discussed in this guideline, it does not recommend any one particular system for use in regulatory decision-making. Neither does it limit the choice of studies that may be performed to establish the safety of residues in human food with respect to adverse effects on human intestinal flora.

Instead, this guideline provides recommendations for a harmonised approach to establishing a microbiological ADI and offers test options rather than specifying a testing regimen.

This guidance does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety. This includes approaches that provide science-based reasons as to why microbiological testing may not be needed.

Since the implementation of this guideline in 2005, the experience gained with the recommended tests has led to modifications to the guideline and its recommendations. As of December 2011, the revision of Guideline 36 at step 9 of the VICH process has reached the end of the public consultation phase at step 4 of the process. The revised guideline should therefore be adopted by the Steering Committee in the course of 2012 for implementation in 2013.

Conclusion

VICH has the potential to eliminate duplications, to reduce timelines and to ensure a more efficient usage of available human material and animal resources, whilst safeguarding the quality, safety and efficiency of products on a global level.

Consensus and mutual understanding between all VICH members are the keys to the success of VICH's development over the past 15 years.

By developing Guidelines 27 and 36, VICH encourages a harmonised approach in the VICH regions and countries to addressing antimicrobial resistance issues during the registration phase of antimicrobial veterinary medicinal products.

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L'antibiorésistance et les lignes directrices de la Coopération internationale pour l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH)

H. Marion

Résumé

La Coopération internationale pour l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH) est un programme trilatéral de coopération réunissant les autorités en charge de la réglementation et les représentants de l'industrie pharmaceutique de l'Union européenne, du Japon et des États-Unis ; trois autres pays y participent en qualité d'observateurs : l'Australie, la Nouvelle-Zélande et le Canada.

Le VICH a pour objectif de renforcer la concertation et la coopération internationales en vue d'une meilleure harmonisation des exigences applicables à l'enregistrement des produits vétérinaires dans les régions concernées.

Le VICH élabore des exigences harmonisées concernant les données à fournir, ce qui signifie que ses directives portent sur les études techniques de qualité, de sécurité et d'efficacité des produits pharmaceutiques vétérinaires préalables à l'obtention d'une autorisation de mise sur le marché. Ces directives, que le VICH publie sous forme de lignes directrices, offrent aux sponsors des orientations cohérentes pour préparer les données à fournir lors des demandes d'autorisation de mise sur le marché et lors du suivi de la sécurité post-commercialisation des produits pharmaceutiques vétérinaires.

Parmi les 49 lignes directrices que le VICH a publiées jusqu'à présent, deux sont spécifiquement consacrées aux problèmes liés à l'antibiorésistance.

Mots-clés

Coopération – Coopération internationale pour l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH) – Données – Étude technique – Lignes directrices – Réglementation – Résistance – Sécurité.

Resistencia a los agentes antimicrobianos y directrices de la Cooperación Internacional para la Armonización de los Requisitos Técnicos para el Registro de Medicamentos Veterinarios (VICH)

H. Marion

Resumen

La Cooperación Internacional para la Armonización de los Requisitos Técnicos para el Registro de Medicamentos Veterinarios (VICH) es un programa de cooperación internacional tripartita que agrupa a organismos de reglamentación y representantes de la industria farmacéutica de la Unión

Europea, Japón y los Estados Unidos, más Australia, Nueva Zelanda y el Canadá en calidad de observadores.
La VICH tiene por objetivo mejorar la coordinación y cooperación internacionales para lograr un mayor de grado de armonización de los requisitos exigidos en las regiones participantes para registrar productos veterinarios.
La VICH define requisitos de datos armonizados, esto es, normas relativas a los estudios científicos sobre calidad, seguridad y eficacia que se exigen al fabricante para conceder la licencia de comercialización de un medicamento veterinario. A tal efecto, publica directrices en las que se marcan pautas coherentes que los fabricantes deben seguir al preparar los datos de los expedientes de registro y al efectuar el seguimiento de la seguridad de un producto una vez comercializado.
De las 49 directrices elaboradas hasta la fecha por la VICH, dos versan en particular sobre temas ligados a la resistencia a los antimicrobianos.

Palabras clave
Cooperación – Datos – Directrices – Evaluación técnica – Reglamentación – Resistencia – Seguridad – VICH.

References

1. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (2004). – Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance. Available at: www.vichsec.org/pdf/01_2004/gl27_st7f.pdf (accessed on 10 January 2012).

2. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (2011). – Harmonising the global processes for authorising veterinary medicines. VICH leaflet. Available at: www.vichsec.org/en/VICHleaflet.pdf (accessed on 10 January 2012).

3. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (2011). – VICH official text of revised draft guideline 36. Available at: www.vichsec.org/en/guidelines3.htm.