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International harmonisation of regulatory requirements

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Summary

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was formed in April 1996 and is a programme of collaboration between regulatory authorities and the animal health industries of three world regions: the European Union, Japan and the United States of America. Two other regions, Canada and Australia/New Zealand, have observer status.

The principal goal of VICH is to harmonise technical data requirements of participating regulatory authorities before granting marketing authorisation or registration.

VICH has finalised six guidelines on the technical requirements for marketing authorisation/registration of biological products. These guidelines have been fully implemented in the regions. Three more technical guidelines are under development by two expert working groups.

VICH has also finalised a guideline which specifically deals with pharmacovigilance and veterinary medicinal products, including biological products. A further four guidelines relating to pharmacovigilance are under development by an expert working group.

Keywords

Harmonisation – Mycoplasma contamination – Pharmacovigilance – Regulatory requirements – Residual formaldehyde – Residual moisture – Reversion to virulence – Specification – Stability testing – Vaccine – VICH.

Introduction

Under the auspices of the World Organisation for Animal Health (OIE), three main regions (the European Union [EU], the United States of America [USA], Japan) and two observer regions (Canada and Australia/New Zealand) seek to harmonise regulatory data requirements for marketing authorisation for pharmaceutical and biological veterinary medicinal products (VMPs). This article gives an update on the present situation for biologicals and outlines future perspectives.

Many of the world's veterinary authorities require VMPs (biologicals and pharmaceuticals) to be granted marketing authorisation before the products can be distributed in their countries. In some countries the alternate term 'registration' is used. This degree of regulatory control is consistent with one of the missions of the OIE: 'To improve the legal framework and resources of national Veterinary Services'. International harmonisation objectives are consistent with improving this framework.

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

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was formed in April 1996 and

is a programme of collaboration between the regulatory authorities and the animal health industry of the EU, Japan and the USA. Canada and Australia/New Zealand have observer status at VICH, and participate at both the Steering Committee and Expert Working Group levels. The OIE participates as an associate member in the VICH process, and assists by supporting and disseminating the outcomes worldwide.

VICH provides a forum for a constructive dialogue between regulatory authorities and the animal health industry on harmonising the regulatory technical requirements for VMPs within the VICH regions.

The objectives of VICH are to:

– establish and implement harmonised regulatory requirements for VMPs in the VICH regions which meet high quality, safety and efficacy standards and minimise the use of test animals and the costs of product development

– provide a basis for wider international harmonisation of registration requirements

– monitor and maintain existing VICH guidelines, taking particular note of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) work programme, and where necessary, update these VICH guidelines

– ensure efficient processes for maintaining and monitoring consistent interpretation of data requirements following the implementation of VICH guidelines

– provide technical guidance (by means of a constructive dialogue between regulatory authorities and industry) that enables an effective response to be made to significant emerging global issues and scientific developments that impact on regulatory requirements within the VICH regions.

VICH also provides guidance to members on the technical requirements for authorisation/registration of VMPs in order to protect public health, animal health, animal welfare and the environment.

VICH achieves its objectives through the development of guidelines by expert working groups. These groups are composed of recognised experts on the topic and are task-oriented, with their primary objective being the development of a draft guideline that will be released for consultation by the Steering Committee, and subsequently implemented by the regulatory authorities in each of the regions.

Members of expert working groups and the VICH Steering Committee work towards the harmonisation of technical requirements by way of consensus in accordance with established procedures. All guidelines are published on the VICH website (http://www.vichsec.org).

To finalise guidelines, VICH uses a nine-step process which includes:

– formation of an expert working group to prepare drafts of the guideline

– approval by the VICH Steering Committee for public release of draft guidelines for comment

– release of the final guideline to regulatory authorities for implementation

– revision of guidelines.

To date, VICH has finalised 36 guidelines. Eight guidelines are at advanced stages of development and consultation, six guidelines are at an early stage of development and a further five topics are potential future guidelines.

VICH currently categorises its working groups into five broad areas:
– quality
– pharmacovigilance
– target animal safety
– biologicals quality monitoring
– metabolism and residue kinetics.

Each working group may work on one or several VICH guidelines.

Guidelines for veterinary biological products

Five VICH guidelines (GL), all of which are available from the VICH website, are relevant to the technical requirements for marketing authorisation/registration of VMPs that have been developed and implemented in each of the member and observer regions. One more technical guideline is under development by an expert working group.

One guideline relevant to pharmacovigilance has been finalised and an additional four pharmacovigilance guidelines are under development by an expert working group.

Stability testing: GL3 and GL17

The stability of vaccines and biologicals must be determined to ensure that the storage conditions under which they are designed to be held are appropriate.

The aim is to determine the optimum storage conditions (such as ideal temperature and protection from light) which will maintain the efficacy of the product up to the end of its shelf life.

GL3: Stability testing of new veterinary drug substances and medicinal products

GL3 is a generic guideline for all VMPs. This guideline describes the core stability data package required for new drug substances and products. The guideline provides a general indication of the requirements for stability testing, but leaves sufficient flexibility to encompass the variety of different practical requirements necessary for specific scientific situations and for the particular characteristics of the materials being evaluated.

GL17: Stability testing of new biotechnological/biological veterinary medicinal products

While GL3 applies in general to new biotechnological/biological products, GL17 recognises that specific biotechnological/biological products may have distinguishing characteristics, the stability of which should be evaluated using a well-defined testing programme that can confirm that the product's efficacy would be maintained during the intended storage period. Thus, GL17 covers the generation and submission of stability data for products such as cytokines, growth hormones and growth factors, insulins, monoclonal antibodies, and those vaccines which consist of well-characterised proteins or polypeptides even when chemically synthesised.

GL17 provides guidance on:

– selection of batches for the generation of stability data for submission to the regulatory authority

– selection of the assay or parameter that profiles the stability characteristics of the product

– storage conditions for stability studies, such as temperature and humidity

– studies on stability under conditions of heat stress, such as may occur during transport

– stability after reconstitution and in-use stability of multiple-use vials.

Good clinical practice: GL9

This VICH guideline is intended to be an international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analysing and reporting clinical studies that evaluate veterinary products, including biological products. Adherence to this guideline provides public assurance that the clinical study data are reliable and that due regard has been given to animal welfare and to the protection of the personnel involved in the study, the environment and the human and animal food chains.

Testing for residual formaldehyde: GL25

Many inactivated veterinary vaccines, particularly bacterins, contain residual levels of formaldehyde. It is important to determine the residual level of formaldehyde to:

– help assure product safety

– ensure that the product will not inactivate other products used in combination

– help assure that the product remains active throughout its shelf life

– ensure that any clostridial toxoids will be antigenic and safe.

GL25 is a guideline for the general requirements for residual formaldehyde testing. The guideline allows for flexibility for other testing methods based on specific scientific situations or the characteristics of the target material.

Testing for residual moisture: GL26

Freeze-dried veterinary vaccines always contain some water, commonly known as residual moisture (RM). It is important to determine the level of RM in final products because a satisfactory test gives assurance of an adequate shelf life and that the manufacturer's freeze-dry cycle was properly controlled.

The RM test should confirm that moisture level is consistently within the manufacturer's specification.

GL26 is a guideline on the general requirements for RM testing. The guideline allows for flexibility for other test methods based on specific scientific situations or the characteristics of the target material.

Guidelines relevant to pharmacovigilance: GL24, 29, 30, 35, 42

Pharmacovigilance is the process of monitoring the ongoing safety and efficacy of marketed products after they have received marketing authorisation/registration. Pharmacovigilance provides essential feedback to product manufacturers and also to regulatory authorities.

Manufacturers need pharmacovigilance data for purposes of product warranty, product improvement and future

product development. Regulatory authorities need pharmacovigilance data to provide feedback on the integrity of the regulatory process, and more importantly, to provide ongoing assurance that the products are safe for animals and humans.

Four of these guidelines are currently in the advanced stages of final drafting and consultation before being released for adoption by regulatory authorities. Together, the five guidelines form a suite which provides a comprehensive framework for submitting, receiving and analysing adverse event reports (AERs), using uniform terminology.

Testing for *Mycoplasma* spp. contamination: GL34

It is important that biological products for veterinary use are free of contamination with *Mycoplasma* spp. to help assure consistency of production and final product safety. *Mycoplasma* contaminants may be introduced into cell culture and *in ovo*-origin biological products through the master seeds, the master cell seed (stock) or starting materials of animal origin, and in processing of biological materials during passage and product assembly. Therefore, it is necessary to demonstrate through testing that *Mycoplasma* are not present in the final product, working seeds and cells and harvests, or starting materials such as the master seed, master cell seed, or ingredients of animal origin.

GL34 gives guidance on the stages of manufacture to be tested and test procedures to detect the presence of *Mycoplasma* contamination. GL34 is currently in an advanced stage of final drafting and consultation before being released for adoption by regulatory authorities.

Specifications – test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products: GL40

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria such as numerical limits, ranges, or other criteria for the tests described. A specification establishes the set of criteria to which a veterinary product should conform to be considered acceptable for its intended use. Conformance to specification means that the product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development (upon which many of the specifications are based), adherence to good manufacturing practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and medicinal product rather than to establish full characterisation and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

Examination of live veterinary vaccines in target animals for absence of reversion to virulence: GL41

The absence of reversion to, or increase in, virulence is a fundamental requirement for all live vaccines. Live vaccines replicate in the animal and stimulate a useful immune response. Live vaccines generally cannot be completely characterised by chemical and physical tests alone. For these reasons, a test for absence of reversion to virulence is of critical importance.

GL41 is a draft guideline which gives guidance for studies to be conducted on the master seed, by passaging in suitable animals, to check for reversion to virulence. If available data or assessment indicate a substantial risk that the test organism may revert to or increase in virulence, additional studies may be required to provide further information on the organism.

Target animal safety testing for live and inactivated vaccines: GL44

This important guideline is currently under development by an expert working group. It is a contribution towards international harmonisation and standardisation of methods used to evaluate the target animal safety of new veterinary vaccines. The guideline is designed to aid sponsors in preparing protocols for target animal safety studies conducted under laboratory conditions and in related field studies.

Conclusion

The regulation by national veterinary authorities of the quality and safety of veterinary vaccines and biologicals makes a significant contribution to the ongoing usefulness of vaccines and biologicals in the prevention and treatment

of animal disease. However, regulation by itself has limited effect unless the manufacturing companies manufacture product to the highest quality standards, and provide comprehensive data dossiers for evaluation by the regulatory authorities.

The value of the VICH guidelines lies in their joint development by technical experts from industry, academia and regulatory authorities. This collaboration provides guidance documents consistent with current scientific methods, and methods recognised worldwide as the standard for testing and evaluating VMPs. The VICH guidelines have made a significant contribution towards internationally harmonised technical standards for veterinary vaccines and biologicals.

Harmonisation internationale des dispositions réglementaires

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Résumé

La Coopération internationale sur l'harmonisation des exigences techniques applicables à l'enregistrement des médicaments vétérinaires (VICH) a été créée en avril 1996 afin d'organiser la collaboration entre les autorités réglementaires et l'industrie pharmaceutique en santé animale dans trois régions du monde : l'Union européenne, le Japon et les États-Unis d'Amérique. Deux autres régions ont un statut d'observateur : le Canada et l'Australie/Nouvelle-Zélande.

La VICH a pour principal objectif d'harmoniser les cahiers des charges techniques imposés par les autorités réglementaires en vue de l'autorisation de mise sur le marché ou de l'enregistrement d'un médicament vétérinaire.

La VICH a préparé six lignes directrices sur les exigences techniques relatives à l'autorisation de mise sur le marché/enregistrement des produits biologiques. Ces lignes directrices sont intégralement appliquées dans les trois régions. Trois autres lignes directrices sont en préparation, sous la responsabilité de deux groupes de travail spécialisés.

La VICH a également produit une ligne directrice sur la pharmacovigilance et les médicaments vétérinaires, y compris les produits biologiques. Quatre nouvelles lignes directrices liées au thème de la pharmacovigilance sont en préparation sous la conduite d'un groupe d'experts.

Mots-clés

Contamination par Mycoplasma – Dispositions réglementaires – Épreuve de stabilité – Harmonisation – Humidité résiduelle – Pharmacovigilance – Résidu de formaldéhyde – Réversion vers la virulence – Spécification – Vaccin – VICH.

Armonización internacional de los requisitos reglamentarios

M. Holmes & R.E. Hill

Resumen
La Cooperación Internacional para la Armonización de los Requisitos Técnicos para el Registro de Medicamentos Veterinarios (VICH), que echó a andar en abril de 1996, es un programa de colaboración entre las instancias reglamentarias y la industria zoosanitaria de tres regiones del mundo: la Unión Europea, Japón y los Estados Unidos de América, más otras dos regiones, Canadá y Australia/Nueva Zelanda, que participan en calidad de observadoras.
La VICH tiene por objetivo primordial armonizar los requisitos de datos técnicos que imponen las instancias normativas participantes para registrar un producto u otorgar licencia de comercialización.
La VICH ha elaborado seis directrices sobre requisitos técnicos para autorizar la comercialización o registrar productos biológicos, y todas ellas se han aplicado integralmente en las tres regiones citadas. Ahora mismo hay dos grupos de expertos que están elaborando otras tres directrices técnicas.
La VICH también tiene ya ultimada una directriz dedicada específicamente a la farmacovigilancia y los medicamentos veterinarios incluídos los productos biológicos. Un grupo de expertos trabaja actualmente para elaborar otras cuatro directrices sobre farmacovigilancia.

Palabras clave
Armonización – Contaminación por micoplasma – Especificación – Farmacovigilancia – Formaldehído residual – Humedad residual – Prueba de estabilidad – Requisitos reglamentarios – Reversión a la virulencia – Vacuna – VICH.