Present systems and future needs for risk assessments of biologicals: the perspective of the regulator in the People’s Republic of China

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Summary: Regulation of veterinary biologicals in the People’s Republic of China is governed by the Animal Drug Administration Regulations issued by the State Council in 1987. These regulations authorise the Ministry of Agriculture to prescribe requirements governing the production and marketing of veterinary biologicals shipped into, within or from China. The goal of the veterinary biologicals programme is to ensure that all veterinary biological products are pure, safe, potent and effective. The programme is based on review, licensing, inspection and post-licensing testing. Risk assessment procedures and requirements for biotechnology-derived veterinary biologicals have been established. China needs international harmonisation of trade in veterinary biologicals and will make a great contribution in this field.


INTRODUCTION

The authority for regulating veterinary biological products in the People’s Republic of China is provided in the Animal Drug Administration Regulations issued by the State Council in 1987 (1). These Regulations authorise the Ministry of Agriculture (MOA) to prescribe requirements, administration methods and standards governing the production and marketing of biological products shipped into, within or from China. The objective of the requirements, administration methods and standards used to implement the Regulations is to ensure the purity, safety, potency and efficacy of veterinary biologicals. The same goal is addressed in different ways by regulatory authorities around the world (3, 4). Although methods may differ from country to country, the purpose is the same: to ensure that veterinary biological products meet accepted standards (3, 4).

The growth and international ownership of the veterinary biologicals industry has resulted in increased interest in the international marketing of these products. International trade has been hampered, however, by the existence of different licensing, production and testing standards in each country (3, 4). It is hoped that the exchange of information on regulations, standards and procedures will aid identification of
requirements which may be harmonised, and recognition of the equivalence of existing standards and procedures. Success in these efforts would facilitate free trade and the international marketing of veterinary biological products. Discussions on risk assessment for veterinary biologicals should also lead to more rapid advancement and improvement of national regulatory programmes for these products. With these goals in mind, the discussion below focuses on the processes of review, licensing, post-licensing testing and inspection for conventional products, and on risk assessment procedures for biotechnology-derived veterinary products in China.

REGULATIONS AND ORGANISATIONS

The Animal Drug Administration Regulations of the People's Republic of China (1) provide the MOA with authority for the regulation of all veterinary biological products shipped into, within or from China. The MOA has issued the following regulatory guidelines:

- detailed rules for implementation of the Animal Drug Administration Regulations
- administration methods for importation of animal drugs
- administration methods for new veterinary biological products
- Chinese veterinary pharmacopoeia
- production outlines and testing procedures for veterinary biological products (2).

The Regulations prohibit the sale or production of worthless, contaminated, dangerous or harmful veterinary biological products. Those engaged in production, distribution, use, research, testing, inspection and administration must observe this requirement and establish administration methods and standards to ensure it is fulfilled. In case of violation, the Regulations permit the MOA to revoke or suspend establishment licences and/or product approval numbers, although the licensee is given the opportunity for a hearing before such action. The MOA also has the authority for detention, seizure and condemnation of products, and injunction against products or an establishment. Criminal action may also be taken against offenders, possibly resulting in a fine or imprisonment.

Under the MOA, four units – each with specific responsibilities – coordinate activities within the veterinary biological products programme. The role of these units is described below.

Veterinary Services

Veterinary Services (VS) is responsible for the following activities:
- management of the veterinary biological products programme
- licensing
- registration of imported veterinary biologicals
- inspection of production establishments
- development and publication of programme policy and regulatory procedures
- standards requirements and notices
- programme planning
- coordination of informal hearings concerning violations.

**Animal Drug Evaluation Committee**

The Animal Drug Evaluation Committee (ADEC) is made up of experts from VS, the National Institute for the Control of Veterinary Bioproducts and Pharmaceuticals (NICVBP), universities, institutes and production establishments. The ADEC is responsible for the following:

- review of new veterinary biologicals
- review of imported products for registration
- re-review of veterinary biologicals produced in establishments.

**Veterinary Biological Products Production Outlines Committee**

The Veterinary Biological Products Production Outlines Committee (VBPPOC) has the responsibility of preparing and revising the *Production outlines and testing procedures for veterinary biological products* (2).

**National Institute for the Control of Veterinary Bioproducts and Pharmaceuticals**

The NICVBP is the authorised laboratory linked to the programme, and is responsible for the following:

- quality control and post-licensing testing
- testing of new veterinary biologicals and imported veterinary biologicals for registration
- preparation, identification, preservation and distribution of master seed, master cell stock and reference standards
- development of new testing methods
- inspection of production facilities (with VS)
- training of manufacturing personnel
- exchange of information within China and abroad.

**REVIEW PROCEDURES**

When research units apply for a new veterinary biological product certificate, the following information must be submitted to VS and ADEC for review:

- application for certificate of the new biological (including name of product, name of developing unit and name of application unit)
- production outlines and testing procedures
- instructions for use (including indications, dosage and administration, storage conditions and precautions)
- explanation of quality standards, i.e. explanation of production outlines and testing procedures (including source and characteristics of master seed and master cell stock; production procedures; purity, safety, potency and efficacy; duration of immunity; duration of storage; stability)
- laboratory study reports
- pilot production reports and field trial reports
- results of field trials.

In accordance with the requirements of the administration methods for new veterinary biological products, ADEC receives and reviews applications and the required supporting materials. Satisfactory review results are sent to VS, which then issues a new veterinary biological products certificate (to be protected for three to five years) to the applicant and notifies the public.

**LICENSING PROCEDURES**

To produce and market a veterinary biological product in China, the producer must obtain two types of licences (i.e. a veterinary biological products establishment license approved by the MOA, and a business licence approved by the local industry and commerce administration) and a product approval number for each product (issued by the MOA), as described in the Regulations.

Procedures for the issue of an establishment licence, a business licence and a product approval number are designed to define and document what is being licensed and who will be responsible for the production and distribution of the product. The procedures are also intended to ensure the purity, safety, potency and efficacy of each product and the accuracy of labelling.

To manufacture a new veterinary biological for which a valid certificate has already been issued, the producer must reach an agreement with the research unit which owns the certificate for the new product. The producer may then apply to VS for a product approval number. This application must be accompanied by the following documents:

- copy of the veterinary product establishment licence
- copy of the new product certificate
- documentation of the technology transfer agreement reached with the owner of the certificate.

**PRODUCTION AND QUALITY CONTROL**

Manufacture and testing of all veterinary biological products must be conducted in accordance with the guidelines issued by the MOA (2). Each batch of product is tested by an accredited quality control laboratory to ensure that the product is pure, safe, potent and effective. For purity testing, final container samples of completed product are tested for contaminating bacteria and fungi; viral products are tested for mycoplasma contamination; viral products of avian origin are further tested for *Salmonella* contamination, lymphoid leukosis, and extraneous haemagglutinating viruses. The safety test employed depends on the product type and the target species. Safety tests on products for use in the poultry industry are conducted in young susceptible birds; for other species, safety tests are conducted in laboratory animals or target animals. Potency tests for all products include a laboratory animal
vaccination/challenge potency test, a target animal vaccination/challenge potency test, or quantification of the virus titre or the number of colony-forming units per dose.

NICVBP is directly affiliated to the MOA, and is the authorised laboratory for the nationwide quality control of veterinary biological products. These quality control activities are described below.

Review of test result reports

Purity, safety and potency tests on all batches of each product are conducted by an accredited quality control laboratory, and the test results are reported to NICVBP. On receipt of the factory test report, the inspector conducts a review in accordance with the MOA guidelines (2). If problems appear in the test report, NICVBP notifies the factory. The factory must identify and resolve problems as soon as possible.

Post-licensing testing

NICVBP takes random samples and tests many batches of product every year, to verify that the quality control testing systems implemented by the accredited laboratory are capable of differentiating products which are pure, safe and potent from those which are not.

Preparation of master seeds and master cell stock

In accordance with the MOA guidelines (2), NICVBP is responsible for the preparation, identification, preservation and distribution of master seeds, master cell stock and reference standards for the production and testing of veterinary biologicals.

NICVBP is involved in other aspects of the veterinary biological products programme, including the development of new test methods, and standardisation and expansion of the assay techniques used for quality control testing.

**RISK ASSESSMENT PROCEDURES FOR BIOTECHNOLOGY-DERIVED VETERINARY BIOLOGICAL PRODUCTS IN CHINA**

The advent of biotechnology has required the regulatory agency in China not only to develop new standards and techniques, but also to address public concern that the release of new veterinary biologicals may have an adverse effect on the human environment. The MOA is responding to this challenge by fostering a regulatory climate which encourages innovation, and the development and commercialisation of new biological products, while implementing a responsible regulatory policy. The MOA is also committed to an international harmonisation policy which promotes exchange of regulatory procedures, developments in risk assessment, and practical management experience for biotechnology-derived biological products.

The final MOA policy statement for regulating biotechnology-derived veterinary products has been developed, and will be issued very shortly. This document will consolidate the role of the MOA in the coordinated framework for regulating biotechnology in the People’s Republic of China. The goal of risk assessment procedures for biotechnology-derived products in China is to ensure that these products pose no risk to the human environment.
CONCLUSIONS

Procedures for ensuring the purity, safety, potency and efficacy of veterinary biological products in China are presented above. Review, licensing, inspection and post-licensing testing processes ensure the development of and compliance with programme standards. Although some of the programme procedures employed in China may be similar to those of other nations, many significant differences exist in specific product requirements. Increased interest in the international marketing of veterinary biological products has stimulated further interest in the harmonisation of regulatory requirements to facilitate this trade. It is hoped that the exchange of information on risk assessment for biological products will lead to continuing communication between the participating countries. The goal of the regulatory authorities in the People's Republic of China is to strengthen and update domestic programmes, and also to make a contribution to the international harmonisation of trade in veterinary biological products.

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SYSTÈMES ACTUELS ET BESOINS FUTURS DE L’ÉVALUATION DES RISQUES APPLIQUÉE AUX PRODUITS BIOLOGIQUES : PERSPECTIVES OFFICIELLES EN RÉPUBLIQUE POPULAIRE DE CHINE. - Y. Xia, Z. Zhang et M. Li.

Résumé : En République populaire de Chine, les produits biologiques à usage vétérinaire sont régis par la réglementation Animal Drug Administration, promulguée par le Conseil d'État en 1987. Cette réglementation autorise le ministère de l'Agriculture à édicter des textes réglementaires pour la production et la commercialisation de produits biologiques à usage vétérinaire dans ce pays, ainsi que pour l'importation et l'exportation de tels produits. L'objet du programme relatif aux produits biologiques à usage vétérinaire est de veiller à ce que tous ces produits soient purs, inoffensifs, actifs et efficaces. Ce programme assure l'analyse, la délivrance d'autorisations, l'inspection et le contrôle. Des procédures d'évaluation des risques ainsi que des normes applicables aux produits à usage vétérinaire issus de la biotechnologie ont été établies. Une harmonisation internationale du commerce des produits biologiques à usage vétérinaire s'impose et la Chine est prête à y apporter sa contribution.


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Resumen: En la República Popular de China, la reglamentación de los productos biológicos de uso veterinario se rige por las Normativas de la Agencia de Medicamentos Animales (Animal Drug Administration Regulations) dictadas por el Consejo de Estado en 1987. Estas normas autorizan al Ministerio de Agricultura a establecer los requisitos necesarios
para la producción y comercialización de productos biológicos veterinarios, tanto de importación como destinados a la exportación o al uso interno. El objetivo del programa sobre productos biológicos veterinarios es asegurar que todos los productos de este tipo sean puros, seguros, activos y eficaces. El programa se basa en la realización de estudios, en la concesión de licencias, la práctica de inspecciones y las pruebas de control. Se han establecido asimismo procedimientos y requisitos para los productos biológicos veterinarios derivados de la biotecnología. China necesita la armonización internacional en cuanto al comercio de productos biológicos de uso veterinario, y va a realizar un gran esfuerzo para contribuir en este sentido.

PALABRAS CLAVE: Armonización internacional – China – Evaluación de riesgos – Productos biológicos de uso veterinario.

REFERENCES