Article @ Virology

Quality control of bovine serum in viral vaccines

*Xiaohuan Zhang[1], Leitai Shi[2],Yongxin Yu**

1.National Vaccine & Serum Institute, Beijing，101111 , P. R. China

2.National Institutes for Food and Drug Control ,Beijing 100050 , P. R. China

ABSTRACT

Residues of bovine serum albumin in viral vaccines can cause allergic reactions. The quality control of bovine serum is a prerequisite for ensuring the safety and reliability of the vaccine. Domestic and foreign regulatory authorities have made clear limits on bovine serum residues.

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Abbreviations: ChP, Chinese pharmacopoeia; EP, European Pharmacopoeia USP, United States Pharmacopeia; EMEA, European Agency for the Evaluation of Medicinal Products

Introduction

Bovine serum has been widely used in cell culture and is one of the important biological materials used in the production of viral vaccines. At present, most viral vaccines are prepared by cell culture. Bovine serum contains a variety of bioactive substances, such as growth factors, hormones, lipids, inorganic salts, which are the sources of growth factors and nutrients for cell proliferation. At the same time, bovine serum is also very easy to contaminate various exogenous factors, if not effectively controlled, it will bring great potential safety hazards to viral vaccines. Therefore, strengthening the quality

*Corresponding author,M.D. , Major in biological product and virology

Tel：86-10-53852130 E-mail: yuyongxin@nifdc.org.cn

control of bovine serum is of great significance for improving the stability and safety of viral vaccine production.

1. Current status of bovine serum quality control

China's drug regulatory authorities also attach great importance to the quality management of bovine serum for the production of biological products. "Quality Control Standards for Major Raw and Auxiliary Materials for Chinese Biological Products" (2000 Edition) clearly stipulates the quality control requirements for bovine serum, providing a basis for the preparation and verification of bovine serum. In order to further standardize the production and quality control of bovine serum in China, the State Food and Drug Administration promulgated the Guiding Principles for the Production and Quality Control of Bovine Serum for Cell Culture in 2008. The Chinese Pharmacopoeia officially included "Blood serum testing requirements", as a mandatory test standard for bovine serum for the production of human biological products in China since 2005.

The quality control of animal-derived biomaterials for the production of human biological products, especially the safety of bovine serum, is attracting more and more attention all over the world.The WHO, EMEA and FDA have formulated relevant guidelines aimed at strengthening the quality control of bovine serum to ensure the safety of human biological products already.

2. Problems in bovine serum quality control

Compared with foreign countries, the following problems still exist in the quality control of bovine serum in China

2.1 Type classification is not clear

Foreign countries not only have corresponding quality standards for different kinds of bovine serum such as fetal calf, newborn calf, calf and adult cattle, but also classify the same kind of bovine serum into different grades such as "standard" and "super grade" through quality evaluation, so as to meet the needs of different uses such as production and research.

At present, all kinds of bovine serum in China are tested according to the requirements of calf serum detection in the third part of the Chinese Pharmacopoeia (2015 edition) [1]. Because the quality control standards of different kinds of bovine serum have not been established separately, it is difficult to evaluate the quality of bovine serum. The quality of bovine serum produced by different production enterprises varies greatly, which makes it difficult for users to choose different kinds and grades of bovine serum.

In addition to the commonly used bovine serum products, foreign bovine serum manufacturers can also provide low IgG antibodies and special bovine serum products treated with dialysis, carbon or

dextran to meet the different needs of users. Domestic enterprises are limited by processing technology, so they are unable to provide these bovine serum products at present.

2.2 Quality standards need to be improved

The current edition of General Principle 3604 of Chinese Pharmacopoeia clearly stipulates the viral examination of newborn bovine serum[1]. The European Pharma--copoeia requires the detection of at least 9 exogenous viruses in bovine serum[2]. The United States Pharmacopoeia imposes stricter requirements on the detection of exogenous viruses. In addition to the nine viruses listed in the table, the following five viruses are also included: akabane, Bovine leukemia, Bovine rotavirus, Foot-and-mouth disease, Rinderpest [3]（Table1）.

There is still a certain gap between China's bovine serum and foreign requirements in the detection of exogenous viruses, which will increase the risk of using bovine serum and bring potential risks to the safety of viral vaccines. In addition, the quality control of bovine serum abroad also includes biochemical detection of protein, lipid, trace elements and vitamin content. However, there is no detection item in the quality standard of bovine serum in China.

Proteins and lipids are important components of bovine serum, which play an important role in promoting cell growth. Strengthening the control of these components is of great significance for comprehensively evaluating the quality of bovine serum, ensuring the consistency of bovine serum between batches, reducing the effect of differences between batches of bovine serum on cell culture and stabilizing the production of viral vaccines.

3. Suggestions on strengthening the quality control of bovine serum

Compared with foreign countries, China should strengthen the following aspects of bovine serum quality control.

3.1 Strengthen traceability management of bovine serum

Through the traceability management of bovine serum, on the one hand, the processing management of bovine serum can be strengthened from the source to reduce potential safety risks; on the other hand, once problems are found in the production process, it can be traced back to the origin of cattle herds, avoiding the use of bovine serum materials from cattle herds in this area.

Traceability should pay attention to the following aspects: i, Production of bovine serum material should be derived from cattle in areas where there is no report of mad cow disease and foot-and-mouth disease infection; ii, The health status of cattle population, especially the infection of bovine infectious rhinotracheitis virus and bovine diarrhea virus ； iii, Cattle should be vaccinated according to regulations; iv, Feeding conditions and

Table 1: Quality control of newborn bovine serum at home and abroad

Tests	Newborn bovine serum		
	ChP	EP	USP
pH	7.0～8.5	/	7.0～8.0
Protein content(g/L)	35～50	≥35	35～60
Haemoglobin content(mg/L)	≤200	≤4000	≤300
Osmolality(mOsmol/kg)	250～330	240～340	240～340
Bacterial endotoxin test(EU/ml)	≤10	≤100	≤50
Support cell proliferation check	+	/	+
Sterility test	+	+	+
Mycoplasma test	+	+	+
E. coli bacteriophage test	+	/	/
Virus test			
1. Bovine parainfluenza virus 3	+	+	+
2. Bovine herpesvirus 1	-	+	+
3. Bluetongue virus	-	+	+
4. Bovine adenovirus	+	+	+
5. Bovine parvovirus	+	+	+
6. Bovine respiratory syncytial virus	-	+	+
7. Bovine viral diarrhea virus	+	+	+
8. Rabies	+	+	+
9. Reovirus	+	+	+

+：test; /:Not specified

feed management of cattle.

3.2 Detection of Exogenous Viruses

It is known that many viruses can enter fetal bovine blood through placental barrier, such as vaccinia virus, akabane and bovine leukemia. And there may be some zoonotic viruses in bovine serum, such as Japanese encephalitis virus、Forest encephalitis virus and rabies virus. Therefore, the detection of specific exogenous virus in bovine serum should be strengthened.

Existing biological detection techniques, such as cell culture, fluorescent antibody staining or electron microscopy, can be used to detect other unknown foreign viruses that may be contaminated in bovine serum.

3.3 Virus inactivation

The vast majority of vaccines in China use inactivated bovine serum, which brings great potential safety hazards to viral vaccines. The risk of contamination of known or unknown viral exogenous factors in bovine serum can be minimized by using proven virus inactivation process.

The commonly used methods of bovine serum virus inactivation include thermal inactivation and γ ray irradiation. EMEA suggested that the method of inactivation could be used at 37℃ 60 minutes. Many manufacturers also call it thermal inactivation when they treat bovine serum at 56℃ for 30 minutes, but this method can only inactivate the complement in bovine serum at most and has very limited inactivation effect on virus.

γ ray irradiation is also the most commonly used method for inactivating bovine serum virus abroad No matter what method of virus inactivation is adopted, the process should be validated. The virus in bovine serum should be effectively inactivated or removed. At the same time, the activity of various components in bovine serum should be maintained to the greatest extent, and the effect of cell culture affected by the inactivation of various components should be reduced.

4. Peroration

The quality and safety problems of bovine serum for viral vaccines have become increasingly prominent. Despite the rapid development of serum-free medium in China in recent years, the role of bovine serum in cell culture can not be completely replaced in the short term because of the high production cost. Therefore, the quality management of bovine serum for biological products production should be further strengthened. Enterprises should take effective measures to continuously improve the quality of bovine serum and minimize the potential risk of exogenous virus contamination in order to ensure the safety and effectiveness of viral vaccines.

Reference

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