OIE Regional Workshop on Risk Analysis for Veterinary Vaccines

Practical Application Including Vaccines Related New and Emerging Technologies

(Tokyo, Japan, 1-3 March 2011)

Summary Report

OIE Regional Representation for Asia and the Pacific

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Conclusion and Recommendations of the Workshop

Considering that:

1. The World Organisation for Animal Health (OIE) has been working in the field of veterinary medicinal products and biologicals by organizing a series of regional workshops since 2006.
2. The OIE recognises that the stable and prompt supply of veterinary vaccines and their effective application greatly support disease prevention and control. The OIE also notes the importance of availability of effective vaccines in case of emergencies regarding emerging and re-emerging disease outbreaks.
3. It has been emphasized, at the past workshops in this series, that veterinary vaccines provide satisfactory results when they are manufactured in compliance with internationally accepted standards and properly applied.
4. In order to respond such needs, the most recent workshop focused on risk analysis for veterinary vaccines in reference to the relevant chapter of OIE Terrestrial Manual, where the participants agreed that the Region needs further work for better understanding and application of risk analysis to strengthen vaccine quality and secure effective vaccination within the region.
5. In 2010 the OIE developed a chapter in the Terrestrial Manual on vaccines, "The Application of Biotechnology to the Development of Veterinary Vaccines," to provide technical advice on veterinary vaccines produced by applying new technology in the field of molecular biology and immunology, which have been becoming more popular and important than ever.
6. In May 2010, Japan's National Veterinary Assay Laboratory and National Institute of Animal Health (NVAL/NIAH) were jointly designated as an OIE Collaborating Centre for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia to improve technical competency in this area and to contribute developing networks in the Region.
7. With these developments as background, the OIE Regional Workshop on Risk Analysis for Veterinary Vaccines, "Practical Application including Vaccines related to New and Emerging Technologies," was organized from 1 to 3 March 2011 to help regional members to improve their vaccine policies by actively applying risk analysis procedures, which are essential to promote animal health.
8. The main objectives of the Workshop were to:
    a. review the risk analysis methodologies currently applied to veterinary vaccines (including new and emerging technologies);
    b. develop an understanding of how to apply such methodologies and of what is missing in the current vaccine policies in the Region;
    c. raise awareness of the recent discussions at the OIE ad hoc Group on vaccines in relation to new and emerging technologies and the OIE's work

in relation to vaccines;

d. inform participants of OIE initiatives concerning a vaccine bank; and
e. inform participants of the roles and functions of the relevant OIE Collaborating Centre.

9. The Workshop discussions highlighted the different status of countries in terms of regulatory frameworks, access to and usages of veterinary vaccines, risk analysis capability, in particular, test capability, and information gathering on adverse events.

10. The Workshop touched on important issues related to veterinary vaccines, including:
    a. The quality of vaccines is critical for disease control, and risk analysis is an indispensable tool for quality assurance;
    b. Risk analysis methodologies currently used among leading countries all follow similar principles and OIE guidelines and are applied with only slight variations depending on each case;
    c. The OIE Collaborating Centres have an important role in supporting improvement of test capability in the Region;
    d. Consultation with public health and food safety authorities as well as environmental authorities is becoming more important due to nature of the emerging technologies applied to veterinary biologics;
    e. Organising the next OIE workshop for National Focal Points for Veterinary Products in Cambodia on June 2011.

The Workshop recommends that:

1. National governments should consider prior risk analysis on essential vaccines for emergency use, particularly against threatening transboundary and emerging diseases;
2. Members in the Region should share risk analysis information with the aim to eventually harmonise the risk analysis procedures for emergency vaccines. NVAL should be involved in further discussion of the platform for such information sharing;
3. Members in the Region should consider having access to vaccine stockpiles or other arrangements such as access to rolling stock to meet emergency situations, and such vaccines must satisfy international standards. This may involve exploration of regional or sub-regional vaccine banks;
4. Members in the region should explore, whenever possible, the availability of short term regional training courses or expert exchanging program with the support from international partners;
5. The OIE Collaborating Centres should establish short-term regional training opportunities or expert exchanging program to improve the test capability of member countries;
6. Members in the Region are encouraged, if possible, to publish information on risk analysis conducted for registration of vaccines so that such information can be referred to by other members conducting their own risk analyses; as a long term goal, Members

should work toward harmonisation of technical requirement for registration;

7. The OIE should encourage the adoption of internationally accepted VICH guidelines for an adverse event reporting system for veterinary vaccines, once finalized, including a report format, to allow sharing of reports in a Region using the same vaccines;
8. Members should be encouraged to develop their own websites for sharing information on adverse event reporting, which could be linked to other websites such as the NVAL website for easy access by other members and seek the possibility to expand it into one single web based networking platform;
9. Members should improve cooperation with, and where appropriate learn from, their human health counterparts in such areas as adverse event reporting system and risk analysis procedures, in particular for the safe use of genetically engineered vaccines;
10. Members should be encouraged to share information on strains of transboundary and emerging diseases and the efficacy of vaccines in the field, to facilitate antigen matching; and
11. Members should consider implementing regulatory mechanisms to allow prompt updating of vaccine to protect from field strains.

OIE Regional Workshop on Risk Analysis of Veterinary Vaccines "Practical application including vaccines related to new and emerging technologies" Tokyo, Japan, 1-3 March 2011

Summary Report of the Workshop

Introduction

The OIE Regional Workshop on Risk Analysis for Veterinary Vaccines: "practical application including vaccines related to new and emerging technologies" was held in National Veterinary Assay Laboratory (NVAL), Kokubunji, Tokyo on 1-3 March 2011. The workshop was attended by participants from 15 OIE Members Countries and Territories from the Asia-Pacific Region, Representatives from ASEAN Secretariat and USDA Office in Tokyo. In addition to the speakers from the local institutions in Japan, the workshop also invited overseas resource persons from Australia, Canada and USDA. Observers include representatives from NVAL, NIAH and MAFF. In total 36 representatives participated in the workshop. The workshop was jointly organized by OIE Asia-Pacific and NVAL/ NIAH. The USDA Office in Japan also co-sponsored the workshop.

The Countries and Territories participated in the workshop consisted of Cambodia, PR China, Chinese Taipei, Hong Kong SAR, Indonesia, Japan, RO Korea, Laos, Malaysia, Mongolia, Myanmar, Philippines, Singapore, Thailand and Vietnam.

The workshop consisted of five plenary sessions and one session of group discussion. The first day plenary sessions included "General Introduction", case study on "Application of Risk Analysis" and the third session on "New and Emerging Technologies of Veterinary Vaccines". The second day sessions consisted of group discussion on "Application of Risk Analysis to Veterinary Vaccines". It was followed by the laboratories tour in the afternoon. During the laboratories tour session, the participants were guided and briefed on the activities and future plan of NVAL and the NIAH as an OIE Collaborating Centre. The third day of the workshop continued with the fourth session on "Presentation of Group Discussion" in which each discussion group presented their group's opinions and suggestions. The fifth session was on "Specific Issues Related to Vaccines" followed by final session for "Conclusions and Recommendations".

After closing of the workshop, there was a special session for the representatives of the ASEAN countries to discuss on the revised draft of "ASEAN Animal Vaccine Laboratory Accreditation".

Opening Session

The Opening Session was moderated by Dr Tomoko Ishibashi, Senior Deputy Regional Representative, OIE Asia-Pacific. Dr Ishibashi invited Heads of the four Organisations: OIE Regional Representation for Asia and the Pacific, National Veterinary Assay Laboratory, National Institute of Animal Health, and Consumer and Food Safety Division of Ministry of Agriculture, Forestry and Fisheries to deliver opening remarks.

Dr Itsuo Shimohira, Regional Representative for OIE Asia-Pacific, welcomed the participants. He mentioned that OIE Asia-Pacific has been organizing several workshops for the improvement of veterinary vaccines under the Japanese Government Trust Fund. He expressed his special appreciation to the guest speakers form USDA, Australia and from the OIE headquarter to come and contribute their knowledge in this workshop. He mentioned that starting from May 2010 NIAH and NVAL had been jointly designated as OIE Collaborating Centre for Animal Disease Diagnosis and Veterinary Vaccine Assessment Centre. He expressed his thanks to the two Japanese Government Institutions for helping in organizing this workshop. He also expressed his appreciation to Dr Kelly Preston, USDA Representative in US Embassy in Tokyo, who has kindly arranged for the co-sponsoring this workshop. Finally he expressed his thanks to ASEAN Secretariat and the ASEAN Member Country Representatives to have this opportunity to work for the improvement of animal vaccine technology in the Region.

Dr Masato Sakai, the Director General of National Veterinary Assay Laboratory in his opening address expressed his appreciation to OIE and the Representatives of Asian Member States for attending this meeting, and the experts from Australia, USDA and OIE for sharing their knowledge in this workshop. NVAL along with NIAH were approved in 2010 May at the OIE General Assembly as the Collaborating Centre for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia. NVAL is the only governmental agency in Japan for testing of veterinary drugs, as the only Asian member of the International Cooperation for Harmonization of Technical Requirements for the Registration of Veterinary Products (VICH) since 1996. NVAL was proud of taking the role of Collaborating Laboratory in order to share the results of the global activities in Asia-Pacific Region.

Dr Kenichi Sakamoto, Research Manger of National Institute of Animal Health speaking on behalf of the Director General Dr Takafumi Hamaoka expressed his sincere greetings to the organizers, guest speakers, participants of the Asian Member Countries and to those

who were concerned in the success of this workshop. NIAH in solidarity with the NVAL were proud of being an OIE Collaborating Centre for Diagnosis and Control of Animal Diseases and Veterinary Products Assessment for Asian countries to help in the improvement of technologies related to the animal health. This task has become more important to counter the ever increasing threat of transboundary animal diseases like HPAI and FMD in order to protect the animal industry for maintaining a sustainable growth.

Dr Kazuki Ikeda, Director of Food Safety Division of Ministry of Agriculture, Forestry and Fisheries, expressed his gratification for being able to invite colleagues from the Asia-Pacific region to this workshop. He reiterated that the main objectives of the workshop were to improve the quality of vaccines and their usage through better risk analysis techniques and to share the information to improve the animal diseases control in the Region. He reminded that with the rapid pace of globalization the movement of people and animals and animal products along with the rapid climatic change is accelerating, as a result animal diseases spread quickly and invade free countries causing huge social economic damages and undermining the productivities of the livestock sector. He stressed that countries in the region need to make more concerted efforts including better improvement of the quality of veterinary medicinal products like disinfectants and biologicals. He stated that vaccines are effective, however to be able to keep ahead of the never ending variant strains of viruses and bacteria, we should be able to produce more potent and efficient products through better technologies, better regulatory procedures and developing mechanisms for rapid supply of safe and effective vaccines. For this purpose, networking of the regional laboratories for information and knowledge sharing will be very essential. He also expressed his appreciation to the OIE Asia-Pacific for providing this platform to work with the veterinary authorities of the Asian countries in the region to address these important issues.

Session I: General Introduction to the Workshop

The Session was chaired by Dr Than Hla, Consultant, OIE Asia-Pacific. Speakers were Dr Sayuri Iwaki Regional Veterinary Officer from OIE-Asia-Pacific; Dr Richard Hill, Director of Centre for Biologics, USDA-APHIS and Dr Asfri W. Ranguti, Technical Officer SPS, Agriculture Industries & Natural Resources Division of ASEAN Secretariat. The three presentations were on the background of each organization's activities in various topics relating to improvement of vaccine technologies.

A Brief Background and Objectives of the Workshop

Dr Sayuri Iwaki gave a brief background and objectives of the workshop. A series of regional workshops on veterinary products have been conducted by OIE Asia-Pacific primarily started with the requests from ASEAN Member Countries. The first OIE workshop was discussion on Harmonization of Veterinary Products, followed by the workshop on Harmonization of Veterinary Vaccines, the third workshop was on Vaccine Quality and GLP and the most recent workshop addressed the issues of Risk Analysis for Import, Distribution and Handling of Animal Vaccines. Dr Michel Lombard as a resource person recommended by OIE Headquarters, supported the workshop by providing an in depth explanation on the OIE Terrestrial Manual Chapter on Risk Analysis of Veterinary Vaccines.

Dr Syuri Iwaki went on to give an explanation about the purposes for holding this present workshop. The fact that in May 2010, Japan's NIAH and NVAL were jointly designated as an OIE Collaborating Centre for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia was the main driver to initiate this workshop as a contribution to the Region by the new Joint Collaborating Centre. She also added that OIE was also planning for holding a Workshop on 28-30 June 2011 in Cambodia for all OIE Members in the Asia-Pacific Region, inviting all the National Focal Points for Veterinary Products.

Risk Analysis and the Regulation of Veterinary Biologics in the US.

Dr Richard Hill Jr. from Center for Veterinary Biologics of APHIS, USDA presented System of Risk Analysis and the Regulation of Veterinary Biologics in the US. He gave an exhaustive account of risk analysis considerations and scope which covered WTO international consideration, regulatory process and oversight. He also covered the topic of risk analysis with relevant to the recombinant technologies and how it relates to import/export of veterinary biologics.

He put forward that risk analysis is the process of identifying the elements that pose risk. The process involves analyzing their likelihood and impact, and finally communicating the risks to the relevant parties. He stated that no one single method applies to all cases. He also stated that the principles of risk analysis include commitment to WTO and International Trade Agreements, aiming to facilitate safe movement of animal and animal products based on international standards. He said "Risk Assessment needs ongoing participation in the international discussions and collaborations. It is a dynamic process with continuing refining".

He also recommended a fine reference book for risk analysis which is a publication by the OIE Scientific and Technical Review Committee, titled Risk Assessment for Veterinary Biologicals, Vol 14, No 4, 1995. For the Regulatory Requirements and Processes, he stated that the process can be categorized in three parts: Pre-license considerations, quality monitoring and post license activities.

He went on to explain the detailed steps involved in the process of licensing considerations, quality monitoring including manufacturing, inspection, testing, routine post-licensing check testing and serial/batch release testing and the pharmacovigilance measures to fulfill the process. He also touched on the Regulatory aspect of biologics of biotech origin, the regulatory authorities and regulatory measures for the biotech biologics under US system. Key in the biotech product is evaluation of individual product in the Summary Information Format (SIF). USDA testing put great emphasis on SIF. If SIF is satisfactory, Master Seed can be approved for use in production.

The final part of presentation concerned with the import permits for distribution and sale of the biological in the US. In conclusion, he stressed that Animal and Plant Health Inspection Services (APHIS) is committed to participating in international meetings and symposium, exchange standard reference materials, procedures, and results of studies between national control laboratories, a transparent process and risk assessment based marketing of biologics.

ASEAN Veterinary Vaccines Activities

Asfri W. Rangkuti, Technical Officer of SPS, Agriculture Industries and National Resources Division of ASEAN Secretariat gave a presentation on ASEAN Cooperation on Animal Vaccines. He recalled that ASEAN Secretariat and the OIE have signed an MOU in 2007 to enhance partnership arrangement and cooperation. The MOU covered broad area of cooperation in animal health activities, and one of the areas was vaccine regulatory improvement and harmonization of vaccine technologies. ASEAN regional responsible body for vaccine has been set up many years back as ASEAN National Focal Points for Animal Vaccines (AFPAV) under the ASEAN Sectoral Working Group on Livestock. ASEAN has

developed guidelines for Accreditation of ASEAN Vaccine Testing Laboratories. NVDAL in Bogor, Indonesia has been audited and accredited as Regional Vaccine Testing Laboratory. ASEAN has also developed ASEAN Register of Animal Vaccines and ASEAN Standard Requirements for Animal Vaccines. Regional Vaccine Standards and Guidelines are continuingly revised and improved by the Focal Points. The OIE and AFPAV have worked very closely together in organizing several workshops on several areas of animal vaccine technology at the Regional level.

Discussions

Questions were raised by Dr Jarunee from DLD Thailand on how the US Regulatory body set the policies on efficacy and potency tests. Another question was on how to validate the master seed of which detailed history was not known. The answer were that efficacy is the test on host animal at the time of licensing that the product works in the animals at a certain level. Potency test is batch to batch testing during production whether each batch produced throughout time has the same level of efficacy. Concerning Master Seed, he stated that as a mean of mitigating risk associated with the Master Seed, Master Seed should be fully characterized, fully tested to be free from extraneous agents. VICH is currently looking at Master Seed Standards.

Dr Kelly Preston asked "what was the regulator's view on autogenously vaccines?". To this question, Dr Hill answered that one of the most important criteria for autogenous vaccine is not to apply it to other epidemiologically unrelated population and the vaccine must strictly be in inactivated form.

Dr Pujiatmoko asked the question on how to control the master seed which should not exceed X+5 passage like in the case in Avian Influenza master seed. Dr Hill gave a general guidelines on how to test the efficacy of the master seed exceeding passage limit comparing it with the standard one to ensure any shift or drift of the quality of the master seed. On that topic, Dr Jarunee also provided a suggestion of checking the genome of the new passaged seed virus and compared it to that of the standard seed by using the molecular technique to see if there is any difference in genetic sequence.

Question asked was on how to make human resource available to cope with a large number of samples for serial batch testing. Dr Hill explained the procedure practiced in the USDA. He said more emphasis was put on the thorough reviewing of the records of testing by the manufacturer. He admitted that many products are tested at 5% level.

Session II: Case study- application of risk analysis

The Session was chaired by Dr Mayumi Kijima, Senior Leader of Bacterial Assay Section of NVAL. Speakers were Dr Shigeyuki Nakamura and Koji Oishi from NVAL; Dr Sam Hamilton, Senior Veterinary Officer from Department of Agriculture, Forestry and Fisheries (DAFF) of Australia; Dr Richard Hill, Director, Centre of Biologics USDA-APHIS. Each one of the speakers presented risk analysis for veterinary vaccines in their respective systems.

Risk Analysis of Veterinary Vaccines in Japan

Dr Shigeyuki Nakamura gave presentation on the outlines of Risk Analysis Process of Vaccines in Japan. He explained the hierarchy of the Pharmaceutical Affairs structure in Japan: the four steps of risk analysis of veterinary vaccines from development of the product to the final evaluation. He explained in detail the requirements of application for marketing approval with the flow chart from application to approval stage. He also explained the standards set for the biological materials, and minimal requirements of biological products. Next he continued with the Overseas Manufacturer License approval system in Japan; the manufacturing stages need to meet the Good Quality Practice, compliance to test methods which are harmonized and designated in the VICH. Finally he discussed about the Good Vigilance Practice. He also stressed that in Japan, use of vaccines are not allowed without prior consultation to a veterinarian. Finally he laid emphasis on Post Marketing Surveillance of Drugs system in Japan which includes re-examination 6 years after approval, re-evaluation which encompasses regular survey of the efficacy and safety of a vaccine which is known as Good Post Marketing Study Practice. He concluded by providing the message that the database of veterinary drugs, adverse event information, responses to user complaints etc., are all disclosed in the information website to the public.

Document Necessary for Risk Assessment of Biological Products in Japan

Dr Koji Oishi gave a detailed steps and documents required for risk assessment of Veterinary Biological Products for marketing approval in Japan. In order to give a more realistic image of the requirements, he assumed an imaginary vaccine being made in response to an outbreak of an imaginary disease named New Newcastle Disease. He showed the official application required for marketing approval of the vaccine. Seven sets

of appendix document are needed as attachments to the application with specific data to verify the contents. He presented in detail what data have to be included in the each appendix. The first appendix was the data concerning the origin and background of the virus discovery. The second appendix was on immunogenicity of Master Seed (MS), which includes the data that immunogenicity of the vaccine to the target animals must not be changed by subculture through the challenge tests. The 4th appendix was on safety to target animal of MS. The 5th appendix was on the absence of reversion to virulence of MS, comparative studies data between primarily MS and 5ht cultured material have to be provided. Appendix 8 was on Standard Test of MS: Working Seed, Production Seed which includes all the test methods for the final product, information for production protocol and also data concerning the stability test to establish the validity of the vaccine. The 9th appendix was on data concerning Target Animal Safety (TAS) test using final product. The 10th appendix was on data concerning efficacy of the vaccine which includes data for determining the minimum effective dose of the vaccine. Appendix 14 was concerning clinical trial which implies evaluation of safety and efficacy of vaccine in the field.

Discussions

Dr Jarunee questioned about vaccines which could not use challenge test for lack of pathogen or lack of facilities, whether it is possible to use other tests for validation of the standards of the materials. Dr Oishi answered that under such condition, other tests like virus content, antibodies titres can substitute the challenge test.

Dr Pujiatmoko asked in the regulation of test for avian influenza, he was informed that in Japan, the final product test for the avian influenza was performed in a company laboratory and the results were validated by NVAL, and what was the minimal requirements for the regulation for such a practice. To this Dr Oishi answered that in practice private company could not do the challenge test because they don't have the high containment facilities. In Avian Influenza case, NIAH did the challenge test and the company attached the data in application for approval. There is no specific regulation for such a practice.

Risk Analysis for Veterinary Vaccines in Australia

Dr Sam Hamilton, Senor Veterinary Office from the Office of the Chief Veterinary Office, Australia gave the presentation on the risk analysis for veterinary vaccines in Australia. He briefly provided Australia Government system for marketing approval of veterinary vaccines. He gave a good example of risk analysis for use of GMO vaccine for equine influenza (EI) in 2007 when EI was confirmed 25 August 2007 in New South Wales (NSW). About 76,000 horses and 10,651 premises were infected in NSW and Queensland. The agreement to use the vaccine occurred 3 weeks after EI was confirmed. Buffered vaccine

zone was used for biosecurity, movement control, zoning and quarantine were used for controlling the disease. Proteqflu (Merial), canary pox vectored vaccine was the vaccine of choice. Over 320,000 doses were administered. He explained how the consultation of stakeholders took place on permits for EI vaccine. The official government bodies included Office of Gene Technology Regulator (OGTR), Australian Quarantine Inspection Services (AQIS)/Bioscurity Australia and the third body was Australian Pesticides and Veterinary Medicines Authority (APVMA). He described briefly the OGTR risk analysis framework.

The process for application to use EI vaccine to OGTR was initiated by Australian CVO who applied for an Emergency Dealing Determination to use the GMO vaccine. He also described the other two bodies: the AQIS/ Biosecurity Australia and APVMA and their roles in the regulation of vaccines for emergency use. The Emergency Dealing Determination was issued for 6 months. He also pointed out that OGTR's role to regulate all GMO use is 'One Health' approach. As a good practice, obtaining necessary permits and developing policies before outbreaks would reduce time to deployment. He added that AUSVETPLAN also outlines the potential use of emergency vaccination in emergencies.

Discussions

Question was raised by Dr Chantanee whether vaccine permitted to use for emergency situation would be valid for use after the outbreak. Dr Hamilton replied that there was strong control on such vaccine. Hence it would not be freely marketed after the outbreak.

Dr Pujiamoto enquired whether in the OGTR risk analysis matrix, the likelihood estimate which was scored as low, medium and high was based on any calculation method to reach the score. The answer was that it is not a quantitative estimate, it is based on qualitative estimate.

Question was raised regarding transgenic vaccine registration; how to investigate for the safety of the vaccine. Dr Hamilton answered that the genetic vaccine is not a matter of food safety when it is used in equine. When it is used in the cattle or any other food animals, the public concern will be different. But the licensing condition did specify the horse meat which could be used for human consumption.

Question was asked that who were responsible for the surveillance of the vaccination and how were the vaccines delivered. Dr Hamilton answered that any registered veterinarian who had undergone training developed by Australian Animal Health can use it. For surveillance, serological test was done for sero-conversion for HA gene after the disease was eradicated.

Risk Analysis for Veterinary Vaccines in USA

Dr Richard Hill presented risk analysis for veterinary biologics under USDA system with reference to several case studies on biotechnology-derived vaccines. He presented two main categories of vaccine as case studies: 1) Vectored vaccines 2) Transgenic plant derived vaccines. In all cases, the process starts with the biologics firm providing the requested information using the pertinent Summary Information Format (SIF). USDA will make risk analysis on the proposed field trials on animal safety, public health and the environmental assessment (EA). If the field trials showed the product to be safe and met all other requirements, the product will be issued with license.

He provided a good example of vaccinia- vectored oral baited rabies vaccine (V-RG) for wildlife. He began with a short account of the history of rabies control in the United State. With the event of tissue cultured rabies vaccine, rabies was quickly eliminated in domesticated animals but many cases of wild life rabies problem remained. In 1983 vaccinia-vectored rabies vaccine was developed by a company as baited oral vaccine for wild life. Extensive studies have to be done in the field including studies on contact with baits in a wide variety of species. Safety tests in various species of wild animals and birds with a view of environmental release in the US were conducted. It was only approved to be used in Raccoon in 1995 on conditional license.

Next he cited examples of canary pox vectored vaccine which serves as a backbone for many vaccines including canine distemper, feline rabies, equine influenza, West Nile virus and feline leukemia. Field trial results in at least 3 different geographical areas for each of these vaccines are required to be submitted for assessment. He briefly mentioned that apart from vectored vaccines other categories of biotech biologics like subunit vaccines, recombinant antigens for diagnostic kits, DNA vaccines are also coming up as a new area of vaccine for the consideration of regulators.

Next he introduced the transgenic plant based biologics. The risk analysis for these products are very different from conventional vaccines. In this case master seeds are plant seeds. Vaccines are fed based for oral mucosal immunization or the vaccine may be used as parenteral subunit or feed additive. He also explained the environment effects are also different from other biologics; it would consider on non-target animals, pollen drift, effect on food crops and wild relative plants etc. Other risk factors include consideration such as accidental release to food/ feed facilities. Next he gave a list of potential biotechnology products like transgenic plant cell subunit vaccine, transgenic plant derived proteins for animal vaccines.

On unique vaccines and emerging issues, Dr Hill stated that because of impact of FMD disease United State is looking forward to the product that is not currently needed in the US. As an example he gave live adenovirus vectored FMD vaccine pending for field trials

and testing in US. In conclusion, he suggested to refer to USDA website on the Compendium of Veterinary Vaccines for Transboundary Diseases www.cfsph.iastate.edu/Vaccines/index.php for the several issues on the emerging new technologies.

Discussion

Question was raised whether there is any regulatory framework for GM vaccines for zoonotic diseases in the US and also in Japan what is the status to this. Dr Hill answered that up to this point the relation with human health had been on consulting basic, there was no formal regulatory framework. In case of rabies vaccine human health worked together as part of the risk analysis for CDC. Within the USDA, consideration is underway for a "One Health coordinating office" for human and animal counterparts for this issue.

Session III: New and Emerging Technologies for Veterinary Vaccines

The session was chaired by Dr Richard Hill, Director, Center of Veterinary Biologics, USDA. The speakers were Dr Donna Hutchings, Senior Veterinary Biologics Evaluator from Canadian Food Inspection Agency, Dr Hideto Sekiguchi, Deputy Director from Animal Products Safety Division of MAFF and Dr Shigeki Inumaru, Team Leader of Research Group for Advanced Biolgicals, NIAH Tsukuba.

Recent Discussion at OIE *ad hoc* Group on Vaccines in relation to New and emerging Technologies

Dr Donna Hutchings who is a member of OIE *ad hoc* Group on Vaccines in Relation to New and Emerging Technologies gave an overview of recent discussions in OIE HQ, particularly Chapter 1.1.7A of the OIE Manual. The first meeting of the group was held in November 2008. The group proposed that OIE Terrestrial Manual "Chapter 1.1.7 Biotechnology in the diagnosis of infectious diseases and vaccine development" be split into two parts: the existing content on diagnostics remains with the same chapter and a new Chapter 1.1.7A "The application of biotechnology to the development of veterinary vaccines" be added to the Manual. The draft chapter was prepared by the summer time in 2009. In November, the *ad hoc* group again reviewed the draft which was then adopted in May 2010 at the General Session. The content of the chapter 1.1.7A was to introduce and describe a range of technologies used to produce vaccine engineered for a specific purpose noting that the technologies were not mutually exclusive. Dr Hutchings also gave a short description to each of the new emerging technologies used to produce genetically engineered vaccines.

Dr Hutchings next went on to present an overview of the OIE/FAO/WHO Meeting on the Assessment of Food Safety Related to the Use of Recombinant Vaccines in Food-Producing Animal. She said that the meeting discussion focused on non-heritable constructs, and the term genetically engineered (GE) vaccines was agreed as a standard term for the discussion. The group discussed the risk assessment of licensed GE vaccines like canarypox vectored influenza vaccine in horse. The group agreed the traits introduced into GE vaccines posed less risk than the GM foods. There is very little likelihood of genetic traits remain in animal at the time of slaughter.

Discussion

There was discussion about the vectored vaccine. The strong immunity response to the vector could be a problem when boosting for the desired antigen carried by the

vector. Some prefer combining vector vaccine with DNA vaccine; one alternative is to start with the vectored and boosted with the DNA vaccine.

Comments were given by Dr Zhigao Bu (PR China) that in the case of Newcastle vaccine which is heavily used everywhere in the world, the maternal antibodies to the Newcastle disease is usually very high. The high serum antibodies level does not always protect the chicken from infection. Mucosa antibodies contribute high protection to the disease. Because of very short duration of immunity, mucosa immunity needs frequent boosting. Hence in endemic areas, there is a need to repeat every two months.

One question was asked about the use or application of virus-like particle vaccine in the field. Dr Hutchings mentioned that West Nile virus, Yellow fever and Baculovirus porcine circuvirus type 2 are a few examples of such type of vaccine and the OIE is promoting the Blue Tongue vaccine based on virus-like particle. She emphasized that the closer the particle to the antigen the better will be the immune response. For virus-like particle vaccine, testing in the target animal for real benefit will be needed on case by case basic. One benefit is that there is no risk of producing disease from it.

Additional Assessment Required of Recombinant Vaccine under Pharmaceutical Affairs law and Cartagena Protocol in Japan

The topic was presented by Dr Hideto Sekiguchi from MAFF. He described that Cartagena Protocol is an international rules governing the safe transfer and handling of Living Modified Organism (LMO) which involves 6 Ministries in Japan namely, Health; Agriculture, Forestry and Fisheries; Environment; Education and Culture; Science and Technology; Trade and Finance. Japan is one of the 160 countries which ratified the protocol. However, main producer countries of GM crops such as US, Canada and Australia have not ratified it. Dr Sekiguchi explained some of important articles of the Protocol concerning export of LMO, risk assessment of LMO and regulations on the liability and remedies if damages occurred. Two main clauses of the Catagena Law are the Type 1 Use and Type 2 Use. Type 1 Use refers to open air use of GM. Type 2 Use refers to use under containment measures like factory use of LMO. Commercial use of Vaccines falls under the Type 1 Use. He explained by flow charts the approval of 2 items of vaccines for Type 1 Use under the Regulation of LMOs concerning use of veterinary medicinal products. The two items were: Canary virus ALVAC vectored feline leukemia virus vaccine and Marek's disease virus serotype 1 vectored NDV-F, Herpesvirus2 Marek's disease vaccine approved under the Ministry of Agriculture, Forest and Fisheries. He gave a few examples of veterinary medicinal products using LMOs. In Japan, there were 43 approvals under the

Type 2 Use for veterinary medicinal products. For references on Cartagena, he listed a few website on related matters on Cartagena Protocol like Japan Biosafety Clearing House and MAFF related notices and list of approved LMOs.

Discussion

One fundamental query was made on why Japan has ratified the Cartagena Law and US refrained from ratifying it. The chair expressed his regret that he was not a specialist in that area. Question was also raised on how the two laws, Catagena Law and the Pharmacological Affairs Law, control the LMO veterinary medicines. The speaker pointed out that the purpose of the two laws are completely different. Catagena Law measures MLO effects on environment and Pharmaco Law is for safety and efficiency of LMO vaccines on animals.

Development of Veterinary Biologicals Using New Vaccine Technologies

The topic was represented by Dr Shigeki Inumaru from NIAH, Tsukuba. He said the trend of veterinary vaccine has changed from the conventional vaccines (attenuated live vaccine and inactivated vaccines) to vaccines produced by new technologies such as Subunit vaccines, Gene deletion vaccines, Chimera vaccines, Vectored vaccines and DNA vaccines. He also mentioned mucosal immunization via oral or nasal spray which activate mucosal immunity as well as systemic immune response, administered with milk, water or forage will be labor saving and meets the animal welfare standards. The new vaccine technologies could be a very useful tools against new challenges in veterinary field such as emerging and reemerging diseases.

He gave a clear comprehensible explanation about each of the new vaccine technologies providing some practical works of new vaccine technologies developed in NIAH. He also emphasized new possibilities and advantages derived from the new techniques. GE vaccines are generally safer as they do not involve the real pathogen. GE vaccines generally can be constructed as marker vaccines to differentiate vaccinated animals against infected animals.

He gave an example of oral vaccine against Mycoplasma hyopneumoniae of swine developed in NIAH produced via capsule negative *Erysipelothrix rhusiopathiae* bacteria as vector. He also gave an example of application of reverse genetics to develop avian influenza vaccine. Avian Influenza virus could be modified by reverse genetics to become low pathogenic virus. Similarly Paramyxo virus was modified by using the reverse genetic technique inserting the avian influenza virus antigen. Another technique was recombinant protein production by DNA expression system. Examples were given like Baculovirus/Insert cell system, Baculosvirus/Silk Worm system, Transgenic Silkworm and Transgenic Plants

system. Transgenic Plant systems are becoming very popular method in Japan. Tokyo University group has produced rice which has Avian Influenza antigen. NIAH has produced biological active substance (canine interferon) using strawberry. Baculosvirus system is a very efficient system for producing proteins. Using insect cell and serum free media, Baculovirus has been used to produce GM-CSF for various species. Similarly, Baculovirus could be injected into silkworm and cytokines are produced. Silk worm serves as a factory for the cytokine production. Recombinant cytokines production by Baculovirus/Silkworm gene expression system has been commercially used for Feline Interferon and Canine interferon production in Japan. Another recombinant technique is production of porcine lysozyme through the silk worm cocoon. He concluded that emerging technologies open the gateway for development of novel agents never before possible, therefore new rules and guidelines are required to evaluate efficiency and safety of those biological products which in terms will greatly improve animal health and animal industry.

Discussion

Question was raised whether the expressed cytokine will behave in the same way as the natural cytokine activities in the system. The speaker answered that commercially produced cytokine is usually expressed in *E. coli* system, and they show biological activities look very similar to natural cytokine. Baculovirus expressed cytokine is as efficient as the commercially available cytokine which is expressed by *E. coli.*

Session IV: Group Discussion

Summary of Paper Based Country Reports Concerning Risk Analysis of Veterinary Vaccines (including Recombinant Vaccine)

Dr Shoko Iwamoto from NVAL presented the summary of country reports on "present state of veterinary vaccines" from 15 countries and territories which participated in the workshop. The countries/territories participated were: Cambodia, PR China, Chinese Taipei, Hong Kong SAR, Indonesia, Japan, RO Korea, Laos PDR, Malaysia, Mongolia, Myanmar, Philippines, Singapore, Thailand and Vietnam. All the country reports followed the guidelines which were circulated to the participants before the workshop. The report described the country situation with relevant to regulation and system of administration of the veterinary vaccines and the usage of vaccines in each country.

Dr Iwamoto tried to summarise and took out some outstanding points from the reports, especially from the item 8 to item 12 of the guidelines. Countries vary in their capacity for acquisition of technology, and budget support from the government. Countries also vary in the monitoring system of adverse events of veterinary vaccines. Some countries complained about the illegal and unlawful import of veterinary medicinal products. A few countries have emergency vaccine supply against important diseases while some countries say they need outside help for such facility.

After the presentation of Summary of Country Reports, the participants were divided into three groups to discuss on three major issues. The three headings were as follows:

1. Factors for rapid supply of veterinary vaccines against emerging and re-emerging disease outbreaks?
2. How to improve test capacity in the Region?
3. How to respond rapidly and adequately to Adverse Events (AE) of veterinary vaccines?

[PowerPoint Reports of the three group discussions were included in the meeting document CD Rom].

The following salient points could be extracted from each group discussion.

- Group 1 suggested that for rapid supply of veterinary vaccines, prior risk analysis of vaccine should be established to allow rapid importation of vaccines in time of emergency. Also emergency procedure for approval of vaccine in case of exotic disease outbreak should be in place. Contingency plan should be prepared in advance for the government to decide whether to vaccinate or not to vaccinate. Regional vaccine bank was recommended. Regional surveillance focusing on the antigen changes and for emergence of new disease in the area should be also considered.

- Group 2 discussed that most ASEAN countries except Thailand do not have capacity to test new and emergence disease vaccine. More trainings for vaccine quality control with the OIE Reference Lab were recommended. A Regional Training Center for vaccine should be set up. More frequent Vaccine Conference for the developing countries should be organised to guide the developing countries for introduction of new techniques like molecular technique in place of the conventional techniques. USDA, NVAL and French Collaboration Centre and VBAD were considered as centers for technical resources.
- Group 3 discussion on AE concluded that many ASEAN countries do not have good Adverse Event Reporting. There were no major AE recorded or failed to record in most countries. It was suggested that post market Adverse Drug Reaction (ADR) system should be established. Inclusion of ADR letter advice from vaccine producing company to farmers and users along with the vaccines is one way to promote more reporting. Good traceability system and farm records are also essential for a good AE Monitoring.

Session V: Specific Topics Related To Vaccines

VICH Global Outreach Activities

The session was moderated by Dr Masatoshi Ishimaru, Head of Virus Assay Section 1, NVAL. The speakers were Dr Hirotaka Makie, Senior Veterinary Officer for Veterinary Medical Products, Food Safety and Consumer Affairs Bureau, Dr Kenichi Sakamoto, Research Manager, NIAH and Dr Tomoko Ishibashi who presented the topic on EU-HPED Vaccine Bank on behalf of Dr Alexandre Bouchot.

VICH: To a Wider International Harmonization of Registration Requirements

Dr Makie gave an introduction of VICH. The international prgramme was launched in 1996 for trilateral (EU-Japan-USA) harmonization of Technical Requirements for Registration of Veterinary Medical Products. He explained briefly the working process for harmonization of guidelines. So far 49 guidelines had been finalized. There were 11 new guidelines under consultation/discussion. One new initiative of VICH Strategy Phase III (2011-2015) is to expand VICH Global Outreach to become a basis for wider international harmonization of registration requirements. VICH aimed for global regulatory of governance of veterinary medicinal products to be progressed by the OIE- reference to VICH guidelines as a final step.

> Question was raised by ASEAN Secretariat Dr Asfri Rangukti whether ASEAN could participate in the Steering Committee Meeting Outreach. To this Dr Markie answered that VICH certainly wants to invite more participations if they are interested.

Diagnosis and Control of FMD Outbreak in Japan 2010- from the viewpoint of using vaccine

Dr Kenichi Sakamoto gave a very comprehensive description of 2010 Outbreak of Type O FMD in Japan. Japan has enjoyed a long history of FMD disease status since 1902 for almost a century and faced an outbreak in year 2000. Fortunately the PanAsia Topotype O was not very virulent and the disease was controlled by stamping out of a few hundreds animals. The 2010 SE Asian Topotype O Mya-98 FMD virus was a virulent one. Many countries including PR China, RO Korea, Russia, Chinese Taipei and Mongolia were struggling with this virus infection in their countries. Regarding Japan 2010 FMD outbreak, he gave a detailed account of how the disease was first diagnosed on 20 April 2010 in Miyazaki Prefecture by NIAH. In Japan, only the NIAH high containment BSL-3 laboratory can handle the FMD virus. The outbreaks started to spread to cattle and pig farms within Miyazaki prefecture. The disease epidemic was not easily controlled despite strict control

measures of movement and stamping out of animals in the infected and suspected farms. In total 292 farms mostly cattle and pigs farms were affected. Total number of animals stamping out reached 211,608 heads. The number of outbreaks reached its peak around mid-May. The veterinary authorities could not cope with the stamping out of animals. In order to allow time for stamping out animals within the control zone, vaccination measure was implemented.

Dr Sakamoto continued to give an epidemiological analysis of the outbreak from the very first observation on 9 April of a single doubtful case of water buffalo, and subsequent cases a week after were finalized diagnosed and confirmed on 20 April. He explained how the disease spread quickly to the neighboring cattle and pig farms in Miyazaki. He also explained how a few spilled over outbreaks outside the controlled zone were eventually epidemiologically traced back to vehicles used for animal transport. The outbreaks took nearly 3 months to control. The movement ban was lifted on 2 July when there was no more outbreak 3 weeks after the last case with surveillance within the control zones,

He further explained some of the key points when considering FMD vaccination as a control measure. A good matching vaccine is of upmost importance. Good quality vaccine is also essential to enable differentiation between infection and vaccination antibodies. He mentioned also some research works done by NIAH on developing GE vaccine which will contain only virus capsid without virus genome. He also mentioned the research work on administration of antiviral to pigs as a means of controlling virus multiplication and disease spread during outbreak. He warned it is very difficult to control FMD by vaccine because of many antigenic variances of the virus. Vaccine has to be matched with the field virus for which calculation of R value of vaccine against field virus is very important.

> Question was asked on the type O virus used for vaccinating animal in Japan 2010 outbreak control. Dr Sakamoto answered it was O Manisa virus a popular vaccine seed, the R value against the field virus tested to be 0.5. Dr Sakamoto added that R value of 0.3 is sufficient for protection. Another question inquired that after antiviral treated group of pigs were continuously challenged by FMD virus whether the pigs were tested for residue of virus. The answer was that the pigs were slaughtered after the test, no such test was performed.

Regional Cooperation Programme on Highly Pathogenic Emerging and Re-emerging Diseases (HPED)

The presentation on EU-HPED Vaccine Bank was given by Dr Tomoko Ishibashi on behalf of Dr Alex Bouchot. She explained that the topic was actually to be presented by Dr Alex Bouchot who is Manager of the OIE component of EU-HPED project in SRR Bangkok. Dr Bouchot was not able to participate in the workshop because of an emergency mission. Dr

Ishibashi continued to inform the Workshop that OIE Component of HPED Project covered 18 countries particularly from ASEAN and SAARC regions. The OIE component composed of three major activities. One of the activities was to set up functional Vaccine Bank. The funding for Vaccine Bank allocates 40% for Avian Influenza vaccine, 30% for FMD vaccine and 20% for Rabies. The allocation of budget for FMD Vaccine Bank estimated to be around 1.4 million EUR. The aims for the Vaccine Bank in the context of FMD vaccine were to protect the FMD free zones in the region by buffer vaccination; to avoid loss of free zone status. Another purpose was to be used in endemic areas when new strain appears. Detailed requirements for a country to request emergency vaccine bank were furthered explained by Dr Ishibashi. The request should be for high risk situation, it should include the strategies of the country and plan for delivery and implementation subjected to the assessment by the project committee.

Question was raised who were the members of the project committee to assess the eligibility of country request for the vaccine bank. Dr Ishibashi explained that the OIE project was operated by SRR in Bangkok and Dr Alex Bouchot is the Project Manager. She advised the questioner to contact SRR for details of the member composition.

Dr Yamato Atagi for MAFF who has formerly worked in the OIE discussed on one issue regarding the Vaccine Bank. In the Vaccine Bank Programme with an African country, there was no good cold-chain for vaccine delivery from the airport to the field. He suggested that any country which wants to apply for vaccines from the Vaccine Bank should make sure that they have a good cold chain system for delivery. Anther aspect he reminded about the vaccine bank was information exchange like how many doses and what type of vaccines were used in each region. Activities information exchange should be made available for all the countries in the region in order to be effective in the disease control.

Session VI: Discussion and Adoption of Conclusion and Recommendations

The last session was chaired by Dr Itsuo Shimohira, Regional Representative, OIE Asia-Pacific. He invited Dr Tomoko Ishibashi to present the draft Conclusions and Recommendations of the workshop. After discussion and suggestion from the floor the draft Conclusions and Recommendations were tentatively approved by the Workshop. The document was further circulated to all the participants for further suggestions and comments. The final approved version came out as per print on the first part of this report.

Closing Session

The Closing Session was moderated by Dr Tomoko Ishibashi. Dr Ishibashi invited Dr Masato Sakai Director General of National Veterinary Assay laboratory and Dr Itsuo Shimohira, Regional Representative of OIE Asia-Pacific to deliver the closing remarks of the workshop.

Dr Masato Sakai in his closing remarks pointed out that Japan and many countries in Asia and the Pacific Region are still threatened by disastrous transboundary animal diseases like HPAI and Foot and Mouth disease. In order to control the diseases, countries in this region need to establish closer collaboration and try to establish good system for producing and assessing the effective veterinary products including high quality vaccines. This workshop has achieved some of the expectations of this goal. He wished the veterinary authorities of the countries in this Region to broaden the contact among themselves at all levels to realize the goal of regional collaboration. He informed the participants that NVAL is going to expand with new facilities in the next few years. He wished that NVAL would be able to invite the participants again for the future workshops with great confidence to the new facilities.

Dr Itsuo Shimohira expressed his sincere gratitude to all for the contributions they made to this workshop. He is confident that this workshop has provided a lot of information to the participants and also provided an opportunity for the participants and the expert resource persons to form a network. He wished the participants to share the knowledge gained form this workshop with their country colleagues, so as to derive upmost benefit out of it. It is also critical for the participants to share what recommendations have been adopted in this workshop with concerned parties or authorities.

End of the Report