REGISTRATION OF VETERINARY MEDICINAL PRODUCTS
AND BIOLOGICALS

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Summary: The use of Veterinary Medicinal Products and Biologicals has become a fundamental demand for treatment, prevention and control of both infectious and non infectious animal diseases and has warranted official regulations for the registration of these products.

A questionnaire survey carried out in Member Countries (11 responded) of the region has revealed that only two countries do not have a system for the registration of veterinary medicinal products. In four countries, registration falls under the responsibility of the Veterinary Authority, while in the remaining countries, it is the responsibility of the Ministry of Health.

Registration procedures for vaccines to be used in disease control and eradication programmes, should take into consideration whether the vaccine has been produced in compliance with the OIE Manual for Diagnostic Tests and Vaccines for Terrestrial Animals as this is an important issue considered by the OIE when declaring countries or zones that practise vaccination, free from specific diseases.

The establishments where veterinary drugs, vaccines and other medicinal and biological products are stored and distributed play an important role in determining the efficacy, potency and safety of these products. The registration of such establishments is thus as critical an issue as the registration of veterinary medicinal products and biologicals.

Official legislation(s), efficient scientific and technical staff, availability of complete data on animal diseases present in the country, the use of approved testing procedures and criteria are fundamental requirements for the success of a system for registration of Veterinary Medicinal Products and Biologicals.

1. INTRODUCTION

Several animal pathogens were spread in different countries either due to increased urbanisation and the accompanied animal movement, or due to the extension of international trade in livestock and livestock products. Therefore, the use of Veterinary Medicinal Products and Biologicals became a fundamental demand for treatment, prevention and control of all animal diseases including infectious and non infectious diseases. These situations demand official regulations to enforce registration of these products to assure the presence of effective and safe products for combating animal diseases as well as protecting humans and the environment from the risk associated with these products.

The public health impact is an important aspect when inspecting a registration dossier for any veterinary product. It is worthy to note that the Food and Drug Administration (FDA) considers a new animal drug to be “safe” if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals.

A questionnaire was designed in this context and forwarded to the OIE member countries in the Middle East region. Of the 19 countries in the region, 11 have replied. These include: Bahrain, Cyprus, Egypt, Jordan, Kuwait, Oman, Saudi Arabia, Sudan, Syria, Turkey and the United Arab Emirates.

For the purpose of this presentation the Veterinary Medicinal Products and Biologicals include mainly Vaccines, Antisera, Medicinal drugs, Disinfectants, Insecticides, Feed additives, Diagnostic reagents.

This paper will not focus on the laboratory tests and techniques regarding the efficacy, safety, potency and other experimental items in respect of registration of veterinary medicinal products and biologicals. However, it will clarify...
the concept, importance as well as the objectives of registration of veterinary medicinal products and biologicals; and what is the actual situation in the countries of the Middle East region.

1.1. Situation in the countries of the Middle East region

- Of the 19 Member Countries of the Middle East Region, 11 countries replied representing less than 57%.
- Only two countries have no system for registration of Veterinary medicinal products and Biologicals.
- Among the 11 responding countries, the veterinary authority is the sole responsible authority for registration of Veterinary Medicinal products and Biologicals in 4 countries, while in the remaining countries the Ministry of Health share this responsibility with the Ministry of Agriculture concerning the registration of some products. In one country, the environmental authority is responsible for the registration of insecticides.

Figure 1

The authorities responsible for registration of various categories of Veterinary Medicinal Products and Biologicals in the Middle East region

- Vaccines
- Anti-sera
- Medicinal drugs
- Disinfectants
- Insecticides
- Feed additives
- Diagnostic reagents

- V.A Veterinary Authority
- MOH Ministry of Health
- Others Environmental authority, Animal production department as well as Council of Food and Feed
The first registration system in the region started in 1955 in Egypt followed by Sudan in 1966, while the latest system started in 2001 in United Arab of Emirates.

4 countries follow FDA and European Union (EU) regulations as a reference system for registration, 2 countries depend on the expertise of scientific committee as a reference system in this context; while 2 countries have no reference system while one country did not reply.

4 countries follow the international norms of OIE although the OIE has not yet established official international standards in this respect.

6 countries have systems for registration of diagnostic reagents, although 5 of them did not list the number of the registered diagnostic reagents!!

In 2 countries the regulations for imported products are not the same as locally produced ones, there being additional requirements for imported products.

Responding countries enforcing a system for registration do not approve directly the registered products by other countries except one country (Egypt) where the registered products in EU, United States of America (USA) and New Zealand are approved directly.

6 countries have the facility to produce vaccines locally (Egypt, Jordan, Saudi Arabia, Sudan, Syria and Turkey).

In case of rejection of imported veterinary medicinal products or biologicals the consignment is either re-exported to the country of origin or locally destroyed, while in the Kingdom of Saudi Arabia (KSA) the registration is cancelled.

The documents required for submitting the registration dossier are quite different among member countries of the region.

The validity period of registration for the veterinary medicinal products and biologicals is fixed at 5 years for all categories in 5 countries, at 3 years in one country and 10 years in another one, the remaining two countries have specific validity period for each category of product.

<table>
<thead>
<tr>
<th>Item</th>
<th>Longest validity period/year</th>
<th>Shortest validity period/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Anti-sera</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Medicinal drugs</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Disinfectants</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Insecticides</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Feed additives</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Diagnostic reagents</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Of the 11 responding countries, 6 participate in the international meetings of OIE, 4 participate in the international meetings of CODEX and one participates in the international meetings of VICH. Two countries did not reply to this question.

There was no agreement between any of the responding countries and other countries to obtain vaccines in case of emergency.
- Of the 11 responding countries, 7 test the imported Veterinary Medicinal Products and Biologicals, 1 tests only the imported Veterinary Medicinal Products and 3 do not test the imported Veterinary Medicinal Products and Biologicals.

- All the replying countries enforce ban on certain Veterinary Medicinal Products and Biologicals. There were marked differences between these products among the responding countries.

- The contents of the registration form as well as the banned products are somewhat different.

Table 2

The number of registered Veterinary medicinal products and Biologicals in the responding countries

<table>
<thead>
<tr>
<th>Item</th>
<th>Bahrain</th>
<th>Cyprus</th>
<th>Egypt</th>
<th>Jordan</th>
<th>Kuwait</th>
<th>Oman</th>
<th>Saudi Arabia</th>
<th>Sudan</th>
<th>Syria</th>
<th>Turkey</th>
<th>UAE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>426</td>
<td>24</td>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Anti-sera</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>20</td>
</tr>
<tr>
<td>Medicinal drugs</td>
<td>131</td>
<td>293</td>
<td>400</td>
<td>16</td>
<td></td>
<td></td>
<td>1700</td>
<td>667</td>
<td></td>
<td></td>
<td>186</td>
</tr>
<tr>
<td>Disinfectants</td>
<td>319</td>
<td>MOH</td>
<td>1600</td>
<td>404</td>
<td></td>
<td></td>
<td>220</td>
<td>15</td>
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<td>Insecticides</td>
<td>133</td>
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<td>50</td>
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<td></td>
<td>350</td>
<td>7</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Feed additives</td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td>1300</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic reagents</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>Others (if present)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>1</td>
</tr>
</tbody>
</table>

* UAE=United Arab Emirates

1.2. Importance of Veterinary Medicinal Products and Biologicals

There is a positive feedback between animal health and animal productivity. One of the main fundamentals of veterinary services is the protection and development of animal resources as well as the protection of humans from the risk of zoonoses and veterinary residues in animal products and environment.

At the owner level, drugs, feed additives, growth promoters, insecticides and disinfectants are very essential for the prevention and treatment of bacterial, fungal and parasitic infections as well as feed deficiency and metabolic diseases in order to obtain the maximum animal productivity. At the national level, mandatory vaccines, drugs and diagnostic reagents are very important items in planning and implementing control and eradication programmes for some infectious animal diseases especially those which do not respond to treatment or where treatment is not economical as in the case of some viral diseases and brucellosis.

1.3. What is Registration of Veterinary Medicinal Products and Biologicals?

Registration means the approval of certain concentration of chemical and/or biological substance(s) in a given pharmaceutical form under a unique trade name for a specified period and conditions, for the purpose of use in animal disease treatment, prevention and control.
1.4. Objectives of the registration

- Protecting animal health from any chemical or biological risks which may be associated with the administration of unsuitable or improperly produced medicinal products or biologicals.

- Protect human health from the risk of veterinary harmful residues and/or biological hazards in animal products or in the environment.

- Maintain the success of control and eradication programmes for animal diseases and subsequently maintain the economy of exporting countries from the trade crisis associated with the spread of epidemics and/or OIE listed diseases.

- Setting the obligations of the producers to comply with approved standards and specifications listed by the Competent Authority and customers. This is an essential item for the purpose of evaluation and control of the registered veterinary medicinal products and biologicals.

1.5. Requirements for the success of a system for registration

- The country should have an official legislation(s) enforcing the registration of veterinary medicinal products and biologicals before its local production, importation, and distribution.

- The authority should have efficient scientific and technical staff for the purpose of studying and taking the suitable decisions for the registration of veterinary medicinal products and biologicals. The staff should include veterinary pharmacologists, microbiologists and epidemiologists.

- The competent authority should have a complete data on the animal diseases which are present in the country. These data should include information on the type and distribution of the species and strains of the pathogens.

- Registration of vaccines should be for the purpose of disease control and eradication programmes, the registration procedures should take into consideration whether the vaccine was produced under the conditions listed in the OIE Manual for diagnostic tests and vaccines. This is an important issue for the OIE declaration of disease free country or zones practicing vaccination.

- Testing procedures and testing criteria for the purpose of registration should be according to listed specifications.

- The conditions in establishments where veterinary drugs, vaccines and other medicinal and biological products are stored for distribution or exports are very important as they could affect the efficacy, potency and safety of these products. Therefore the registration of such establishments is as critical an issue as much as the registration of veterinary medicinal products and biologicals to ensure the prohibition of unauthorised prescriptions and safe conditions for the storage and usage of these products.

1.6. What are the specifications for the purpose of registration of veterinary medicinal and biologicals?

These are the list of references to analytical procedures and appropriate acceptance criteria which are numerical ranges, limits or other criteria for the tests described. It establishes the set of criteria to which a drug substance, medicinal products or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.

“Conformance the specifications” means that the drug substance and the medicinal 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 manufacture and approved by regulatory authorities as conditions of approval.

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.
1.7. **What are the reasons for registration of veterinary medicinal products?**

1.7.1. **Control of veterinary residues in animal and human feed**

Veterinary medicine residues are unwanted traces of veterinary medicines that can remain in animal products such as meat, fish, eggs, honey and milk (after slaughter or collection) as a side effect of using veterinary medicines, and so make their way into the food chain.

Most animal products do not contain veterinary medicine residues and where they do occur they are at very low concentrations (measured in parts per billion). Veterinary medicine residues also include any ‘breakdown’ products from the veterinary medicine (the results of the medicine breaking down into its component parts).

Residues of veterinary medicines can remain even when veterinary medicines are administered in the right amount; therefore, withdrawal periods are imposed to ensure that residues have fallen to safe concentrations. The withdrawal period is the waiting time that must elapse before the treated animals can be slaughtered or their products, such as milk and eggs, collected.

People consuming small amounts of veterinary medicine residues in their diet are not at risk, provided that the amount they are consuming is below the safety limit set by the expert committees when the veterinary medicine was authorised. Many scientific studies are carried out to determine the safety limit and its standard practice to include a large safety margin.

Once the safety limit is set, a safety-based legal limit (called a Maximum Residue Limit – MRL) is calculated for each of the animal products. These legal limits represent the maximum amount of the veterinary medicine that is safely and legally permitted in each of the tissues or products.

The use of withdrawal periods (explained above) ensures that residues do not exceed legal limits and provides an assurance of public safety.

The residues of veterinary medicinal products in animal tissues (meat, fat, bone, liver….. etc.) and products (milk and eggs) is one of the main sources of the evolution of drug resistant strains of pathogens either in animals or human consumers.

When evaluating the residual effect for the purpose of registration, it must focus on three items; the type(s) of animal for which the product is intended to be used, the residues in animal tissues (MRL and withdrawal period) and the residues in the environment:

- From the concern of human health; the residues in animal tissues could be of no significance when evaluating a medicinal product intended for the use in inedible animals as dogs, cats, equines and ornamental fish and birds. But from a concern of animal hygiene this could lead to evolution of drug resistant strains of several animal pathogens.

- Residues and withdrawal period of products in the tissues of the main producing animals (ruminants, poultry and fish) are fundamental aspects when deciding the acceptance or refusal of a registration dossier for a given medicinal product, high residual titre above the permissible limits or long withdrawal period not compatible economically with the production system should justify the refusal of registration. These conditions are usually encountered when registering antibiotics, anthelmintics, insecticides and feed additives.

- Residues in the environment such as in the air, water and soil are fundamental aspects when evaluating the registration of the veterinary medicinal products especially insecticides and disinfectants. The drug residues in the environment could lead to damage not only for animals and humans but also the risk may extend to plants and aquatic life. Thus recycling of the drug residues could occur if the human consumers or animals eat these products.

1.7.2. **Prevention of falsification**

As any product in the market, the veterinary medicinal products could be subjected to fraud, either by repackaging of expired products or packaging of any mixture or material(s) not belonging to the labelled active ingredient(s).
1.7.3. Minimisation the risk of toxicity and evolution of drug resistant pathogens

- The dose of most veterinary medicinal products differs according to species, age, weight and disease of the animals. Therefore important problems such as toxicity could arise due to over dosage and drug resistant pathogens could result from under dosage. It’s important to assure that the antidote of the product submitted for registration is available (registered) or not.

- Effects of drug residues on human intestinal microflora: Antimicrobial drug residues present in food from food-producing animals may cause adverse effects on the ecology of the intestinal micro flora of consumers. The FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals.

1.7.4. Avoid the side effects and undesirable Interactions

- Some drugs are immune suppressors or immune depressors. This could lead to severe problems when administered with live vaccines. This must be considered when registering any of these medicinal products especially in countries practicing mass or mandatory vaccination with live vaccine(s).

Some medicinal products are teratogenic or abortogenic, others may impair the action of other medicinal products; i.e) use of bacteriostatics and bacteriocidal antibiotics.

2. WHAT ARE THE REASONS FOR THE REGISTRATION OF VETERINARY BIOLOGICALS?

The term veterinary biologicals span the range from fetal calf serum through to genetically modified vaccines.

2.1. Why should vaccines be registered?

- A reliable supply of pure, safe, potent, and effective vaccines is essential for maintenance of animal health and the successful operation of animal health programmes. Immunisation of animals with high quality vaccines is the primary means of control for many animal diseases. In other cases, vaccines are used in conjunction with national disease control or eradication programmes

- Live vaccines are those that replicate in the animal body and stimulate a useful immune response, characterised by stronger and longer immune response rather than killed vaccines. Therefore it is preferred for control of epidemic and endemic diseases in many countries in the region. Rift Valley fever (RVF) vaccines and brucellosis vaccines are examples.

- The absence of reversion to or increase in virulence test is generally an essential requirement for the registration or licensing of live vaccines. The reversion to virulence could lead to epidemics in cases of mass vaccination, the situation getting more complicated if immune suppressant or depressant drugs are used alongside the live vaccine.

- The feasibility of the registration of a biological will be evaluated by the Regulatory Authority to ensure that the use of the product will not introduce an undesired foreign organism into the country (live vaccine) or cause seroconversion in animals that will have a negative impact on serological surveys or animal disease control programmes (inactivated vaccines).

- The purpose of safety data to be submitted for the registration of veterinary biologicals is to prove that the use of the product according to the labels claims (as far as recommended age, route of administration and type of species are concerned), does not pose any danger to the life, general well-being or production potential of the animal to be vaccinated. The evaluation of the safety of the use of the product is also of prime importance to human health to ensure that no harmful residues are present in animals that are destined for human consumption.
2.1.1. Prevent the introduction of new strains:

Cross immunity between the different strains of viral or bacterial pathogens is common except in few cases like foot and mouth disease (FMD) virus. Although most animal diseases (viral/bacterial) in the region were reported or are currently present in the region, different strains exist. Therefore, the importance of protection of the national territories from the introduction of new strains is a logical scientific reason for the refusal of the registration dossier for a given product especially in case of live vaccines.

2.1.2. Maintain the condition of disease free country or zone (without practicing vaccination):

The OIE sets through the Terrestrial Animal Health Code, the conditions required for the declaration of disease free country or zone without practicing vaccination in respect of the OIE listed diseases, one of the main aspects of these requirements for viral and bacterial diseases is that the country should not use live and/or dead vaccine for a specified period depending on the disease. So the uncontrolled registration system for veterinary vaccines could lead to loss of disease free status.

2.1.3. Assure the concentration of the standardised biological units per dose:

- Each vaccine has standardised units for the biological content per dose. During the production process, this count could be higher or lower than the standards.

- The higher units may lead to side effects as abortion in case of RVF live vaccine or even could lead to infection. The high antigen concentration either in live or dead vaccines is one of the causes of immune suppression.

- The lower units lead to weak immune response which may be not sufficient enough to protect the animals against infection.

2.1.4. Avoid the improperly produced vaccines:

- Vaccine contamination with other adventitious viruses in tissue cultures used for vaccine passage.

- Risk of over-attenuation of the vaccine strain.

- Risk of improper attenuation.

- Bacterial contamination.

2.1.5. Avoid transmission of diseases via contamination with biological materials:

As a rule any product manufactured from biological agent(s) could be subjected to contamination by bacteria, virus and/or fungi. A limited number of contaminating, non pathogenic bacteria and fungi may be permitted for living virus vaccines for administration through drinking water, spray or skin scarification. So when deciding to register any biological product the dossier must include commitment that the manufactured biological product will be subjected to tests for sterility and freedom from contamination of biological materials. Each batch should be tested by the official veterinary laboratory (ies) in this respect.

Hereunder some important regulations listed in the OIE Manual for diagnostic tests and vaccines regarding the tests for sterility and freedom from contamination of biological materials:

- Each batch of live viral vaccine, each lot of master seed virus (MSV), each lot of primary and master cell stock (MCS), and all ingredients of animal origin not steam sterilised should be tested for the absence of mycoplasmas .

- Each batch of live virus biological made in eggs should be free from contamination with Salmonella.

- Biological materials subject to viral contamination that cannot be sterilised before use, such as ingredients of animal origin (for example, serum), primary cells, line cells or viral seed stocks, should be tested before they are used.
2.2. What are the reasons for registration of diagnostic reagents?

- Detecting the diseased animal is a very important step in the planning of control and eradication programmes for all animal diseases. The diagnostic reagents which are used in this context could lead to false results if they are not titrated or produced under optimal conditions.

- The problem of fallacy of laboratory results due to the use of improper diagnostic reagents could lead to extensive economic and public health losses if this occurs at a national level. If wrongly tested, many diseased animals can be exported or imported. Likewise many healthy animals can be culled leading to high costs of compensation and restocking.

- Some diagnostic reagents are harmful to human beings, for example; 2- Mercaptoethanol is carcinogenic so the registration of such products should take into consideration the availability of the protective measures during handling and use.

3. CONTROL OF ECOTOXICITY

The ability of each live vaccine to shed and persist in the environment and to spread to contact target and non-target animals must be evaluated to provide information for assessing the risk of the vaccine on the environment.

An assessment of the risk to the environment of the use of the product has to be submitted.

The risk assessment should include:

a) Hazard identification
   - Capacity of the live organism to transmit to non-target species
   - Shedding of live product organisms (route, numbers, duration)
   - Capacity to survive, establish and disseminate
   - Pathogenicity to other organisms
   - Potential for other effects of the live product organism
   - Toxic effects of the product components
   - Toxic effects of excreted metabolites

b) Assessment of likelihood of a hazard occurring

c) Assessment of the consequences of a hazard occurring

d) Assessment of level of risk.
4. LABELLING REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS AND BIOLOGICALS

The label enclosed in the product container should include sufficient information on the producer and product as:

- Producing company,
- Registration number,
- Ingredients,
- Pharmaceutical form,
- Dosage,
- Side effects,
- Indications and contraindications,
- Production date and expiry date,
- Storage conditions,
- Batch number, etc.

REFERENCES

1. Efficacy of veterinary Biologicals; Medicine Control Council, South Africa, Jan 04 v1.doc.

2. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, October 23, 2003.


4. Specifications: Test procedures and acceptance criteria for new biotechnological/biological veterinary Medicinal Products, recommended for consultation at Step 4 of the VICH process by VICH steering committee.

5. Test for Sterility and freedom from Contamination of Biological Materials; cited in the OIE Manual for diagnostic tests and vaccines for terrestrial animals, Chapter 1.1.5.

6. Veterinary medicines: your questions answered; Veterinary Medicines Directorate, United Kingdom.
DATA REQUIRED TO ASSESS THE SAFETY OF VETERINARY BIOLOGICALS

A. GENERAL DATA

1. Basic information on the product:
   a) Strain(s) present in the product
   b) History of strain
   c) Manipulation of strain (number of passages)
   d) Composition of final product.

2. Manufacture:
   a) Outline of Production:
   b) Starting materials (reference or proof of quality):
      ✓ Starting materials listed in a pharmacopoeia
      ✓ Materials of biological origin.
      ✓ Starting materials of non-biological origin, not listed in a pharmacopoeia
      ✓ In-house preparation of media

3. Quality assurance during production (Quality control procedures)

4. Control tests on finished product:
   a) Description of tests
   b) Results of tests on 3 consecutive batches

5. Stability/shelf life:
   a) Storage conditions
   b) Proposed shelf life
   c) Justification of proposed shelf life of finished product and reconstituted product (if applicable).

B. SPECIFIC SAFETY DATA

1. Biological properties of the organism(s) used in the vaccine.

2. Proof of the safety of the product with the exact composition. This would include the specific strain of virus or bacterium, at the passage level as stated, with the exact same type and volume of excipients in the final product. These would be inclusive of (but not exclusively) any stabilizer, traces of cell culture medium etc

3. Proof of the safety of the exact product to be registered for the minimum recommended age of administration.

4. Proof of the safety of the exact product to be registered for each species on the label.

5. Proof of the safety of the exact product to be registered for each route of administration as mentioned on the label in each of the species mentioned.
   ✓ Note: Different intramuscular injection sites require separate safety data.

6. Safety data should include the following:
   a) Safety data for the administration of a single dose
b) Safety data for the administration of an overdose (x10 for live and x2 for inactivated products).

c) Revaccination:

If revaccination is recommended on the label, proof of the safety of a repeated administration has to be submitted.

✓ Note: This requirement is not applicable if a single administration is recommended only.

7. Field safety tests:

All veterinary biological products destined for use in production animals should be tested for safety in the field. Field safety studies are destined to detect unexpected reactions, including mortality that may not have been observed during the development of the product. The tests should be done in the target species, preferably at a variety of geographical locations, using a large number of susceptible animals. The test animals should represent all the ages and husbandry practices for which the product is indicated. A protocol should be developed indicating the observation methods and recording methods. Field safety tests could be combined with field efficacy tests.

8. Safety data for a multi-component biological may be used to prove the safety of a biological that only contains one or more of the components, provided that the composition of the biologicals apart from the active ingredient (s) are identical.

9. Autogenous biologicals:

a) Autogenous vaccines may only consist of micro-organisms either proven to be safe or rendered safe by inactivation.

b) The safety of an autogenous vaccine should be satisfactorily proven prior to authorisation for use in the case of poultry vaccines or where possible. In the case of a vaccine for use in large animals if testing in the applicable species is not practical prior to authorisation, the lack of safety testing should be indicated on the label and the user advised. The user should also be advised that the vaccine is to be initially administered to five animals on the farm and these animals monitored for adverse reactions.

C. ADDITIONAL SAFETY DATA

- Examination of reproductive functions: Safety data is not required if the product is not indicated for use in animals of a reproductive age.

- Examination of immunological function.

- Spread of the vaccine strain: Data has to be submitted to prove the safety of the product as far as the excretion by and the spread of the vaccine strain by the most sensitive category of the target species.

- Data has to be submitted to prove the safety of the unintended spread of the vaccine strain to susceptible animals of a non-target species that is also susceptible to infection by the organism (s) in the vaccine.

- Dissemination in the vaccinated animal: data has to be submitted for the most sensitive category of the target species.

- Reversion to virulence.

- Recombination or genomic reassortment: An evaluation of the possibility of recombination or genomic reassortment should be submitted.

- Residues.

- Interactions.