Summary: The author reviews both technical and socio-economic issues in developing nations, in relation to veterinary biologicals. Health risk assessment is a specific process to estimate the likelihood that animals, humans or ecological systems will be affected adversely by a chemical or physical agent, or biological product, under a specific set of conditions. Some technical issues (quality assurance, good manufacturing practice, education of end-users, field monitoring) apply equally well in developed, industrialised and in developing, pre-industrialised nations. Many regions have documented unique diseases (trypanosomosis, tick diseases, theileriosis) or high disease prevalence which may influence risk assessment results. This emphasises the need for scientifically-valid risk assessment methodologies in developing nations.

Developing nations also have various socio-economic concerns, which may not be based on scientific fact but, nonetheless, affect trade in, and use of, veterinary biologicals. These non-scientific but perceived problems and issues are briefly discussed, and possible solutions are presented. The way in which countries deal with such perceived problems and issues in a context of internationally harmonised norms for risk assessment impinges on livestock farmers in developing nations.

Finally, the author presents possible ways to correct the potentially widening cost gap between conventional, proven veterinary biologicals and newly-developed products.

The results of risk assessment of veterinary biologicals influence risk management in both developed and less-developed nations. It is important to agree upon scientifically-based risk management guidelines which may be applied in all countries. The effect of the agreements of the Uruguay Round of the General Agreement on Tariffs and Trade on trade in veterinary biologicals in developing nations is reviewed.


INTRODUCTION

Increased production, quality and safety of both agricultural crops and foods of animal origin are essential in the face of increasing human population and diminishing land resources. Much of the increased production is a result of huge investments in
agricultural technology. These noteworthy improvements are accompanied by increasing concerns for consumer safety and environmental protection. Technical innovations to produce more food are essential; so, too, are safeguards. The broad issues of safety and trade related to veterinary biologicals are the subject of this issue of the *Scientific and Technical Review* of the Office International des Epizooties. For many years, the Food and Agriculture Organisation of the United Nations (FAO) and other development agencies have worked with member nations to increase the quantity and quality of food for human consumption. The FAO Constitution includes a mandate to promote improved efficiency in the production of all foods and agricultural products, and to raise levels of nutrition and standards of living for people in all countries (9).

The progress made to date in increasing food production faces the further challenge of a world-wide human population increasing by 94 million people per year, all requiring adequate nutrition. In ninety-three of the less-developed countries, the average annual population increase is projected to be 2.0%, thus 90% of the new population would be contributed by these countries. The population of sub-Saharan Africa is projected to reach 915 million by 2010, with an average population growth of 3.2% per annum (10). These projections illustrate the challenge ahead in feeding millions more people by the year 2010.

There are clearly unsolved technical issues requiring research and solutions before adequate levels of food production can be achieved, much less sustained, without environmental damage. Clearly, also, new veterinary biologicals will have a major role in improving livestock productivity to feed this increased population.

The animal health inputs required to achieve such levels of food production need to be affordable and accessible to livestock owners. With increasing costs of research, development and registration of new biologicals and pharmaceuticals, it is unlikely that the costs of new products will decrease. Food producers in industrialised nations can probably afford increasing quantities and unit costs of inputs, including newer animal biologicals. However, it is questionable whether livestock raisers in pre-industrialised or so-called ‘developing’ nations can be expected to absorb the increasing cost of newer biologicals and other inputs. Livestock raisers in these countries generally use low levels of inputs, even at current prices. One means of enabling livestock producers in developing nations to afford inputs to increase productivity is to maintain, or even lower, the cost of effective inputs. Recommendations will be made on how to ensure that producers in developing nations have continued access to affordable and effective biologicals in the face of newer, generally higher-priced products which are foreseen for the market.

This discussion will be limited to veterinary biologicals used as vaccines against diseases caused by bacterial, viral, protozoal and other pathogens. Diagnostic reagents also face many of the quality control issues raised for biologicals. However, the risk with diagnostic biologicals lies in interpreting the specificity and sensitivity of results in disease diagnosis. Interpretation creates statistical ‘risks’, which will not be addressed here. In addition, risks associated with animal-derived hormones or diagnostic antigens are considered elsewhere in this issue of the *Review*, and the use of these products in developing nations is generally uncommon.

This paper also addresses issues related to developing nations, and perspectives on the risk assessment of veterinary biologicals in terms of the specific set of conditions found in tropical climates. Public concern about risk and the perception of risk are known to vary between groups within countries and between countries (26, 28).
Consequently, cultural attitudes within developing nations with regard to perceived risks should be taken into account. Ironically, citizens in developing nations may object less than those in industrialised nations to risks associated with the use of veterinary biologicals which increase food production. Ensuring access to sufficient food is a daily concern for millions of people living in ‘low income food deficit’ countries (LIFDC: countries having a per caput income below the level used by the World Bank to determine eligibility for International Development Association credits [gross national product per caput for 1992 less than US$1,305], and with per caput calorie intake below a determined level), and this preoccupation often takes precedence over some food safety issues. Likewise, developing nations may fail to make adequate checks on imported products – biologicals or other goods – which are perceived to be ‘high tech’ and therefore ‘better’ than similar locally-produced products.

The primary risks from the use of veterinary biologicals in developing countries lie in their production, importation and delivery. These issues are discussed in turn below.

**TECHNICAL ISSUES CONCERNING VETERINARY BIOLOGICALS**

**Risks arising during the production of veterinary biologicals**

Poor quality, efficacy and/or safety of veterinary biologicals are major concerns in developing nations, as they are in developed nations. The major risks in using substandard biologicals are ineffective control of disease and thus waste of resources. The production of poor quality biologicals in developing nations occurs all too frequently and results from a sequence of the following factors:

- inadequate finance
- lack of appropriate technical knowledge
- deficient production protocols
- defects in quality control (QC)
- lack of ‘good manufacturing practice’ (GMP).

The use of sub-potent or contaminated rinderpest vaccines in African countries is a case in point. From 1988 to November 1991, of 318 batches of rinderpest vaccine produced in countries in East and West Africa, 112 (35%) did not meet international standards. Most disqualified batches (75%) failed due to lack of potency (titre < log 2.5 TCID\(_{50}\) [50% tissue culture infective dose] per cattle dose); 40% failed the test for sterility (some batches failed both tests, consequently the results total more than 100%). For some laboratories, almost 100% of batches consistently passed the test; laboratories for which the results were consistently poor have subsequently ceased producing rinderpest vaccine (24). The use of quality-assured rinderpest vaccine in Africa has made an essential contribution to confining the disease to parts of only two countries on the continent. The FAO has trained numerous scientists from developing countries in the quality assurance of rinderpest vaccine manufacture, and has produced a manual of standard operating procedures for QC (11).

The FAO and the United Nations Development Programme (UNDP), in collaboration with the Organisation of African Unity/Interafrican Bureau for Animal Resources (OAU/IBAR), developed two quality-control laboratories under the Pan-African Veterinary Vaccine Centres (PANVAC) programme. The accomplishments of
these centres in improving the quality of veterinary biologicals in Africa are reported elsewhere in this issue of the *Review* (29).

Tizard (30) has reviewed problems associated with the use of live vaccines in animals, in terms of residual virulence and contamination. Residual virulence occurs in vaccines which are fully attenuated for use in one host species and age group, and under normal conditions, but which can produce various degrees of pathogenicity for another host species (e.g. foot and mouth disease [FMD] virus) or age group, for the fetus of a vaccinated pregnant dam (e.g. bovine virus diarrhea [BVD] virus), or under stressful conditions (capripox virus) (35). Residual virulence and allergic factors causing post-vaccinal reactions are also notorious problems with some live attenuated rabies vaccines (33). Inadvertent contamination with adventitious virus, mycoplasma or pyrogens is known to occur; Tizard cites eight different viruses and mycoplasmas as examples (30).

Examples where live virus vaccines have spread adventitious viruses or bacteria include bluetongue (BT) virus contamination of modified live canine distemper virus vaccine (32). The SV40 virus is known to have contaminated polio vaccines, produced in the 1950s and 1960s, which were administered to millions of people in the United States of America (USA) and Europe (5). Kniazeff *et al.* (15) reviewed the threat of spreading endogenous bovine virus contamination via commercial fetal calf serum used in viral vaccine manufacture. Under the laboratory conditions employed, contamination with bovine viruses occurred in 17 (33%) of 51 commercial bovine fetal calf serum lots from 14 manufacturers. Tests identified BVD virus (BVDV) (12%), parainfluenza type 3-like virus (10%), bovine herpesvirus 1 (6%) and bovine enterovirus type 4 (4%), while one virus remained unidentified. Interestingly, 20 of the 51 serum samples were accompanied by a statement from the manufacturers attesting that the sera had been pre-screened for bovine viruses and found to be negative. Bovine viruses were detected in five (25%) of these pre-screened serum samples. Kniazeff *et al.* (15) state that, 'As long as serum is necessary for cell culture propagation, the threat of endogenous virus contamination will be present'. The high risk inherent in using bovine calf serum indicates the need to develop other manufacturing techniques which avoid this inbuilt hazard.

Blood parasite vaccines against tick-borne diseases present a particular risk of spreading viral and other pathogens, in both developed and developing nations. Some *Babesia* sp. vaccine batches produced in Zimbabwe during 1992 are known to have spread bovine leukaemia virus (BLV) (S.K. Hargreaves, personal communication). Similar spread of BLV occurred in Australia via contaminated bivalent tick fever vaccine (22). The blood donor calf failed to react positively, for an unknown reason, when tested by the agar gel immunodiffusion technique. Contaminated vaccine was subsequently used on 120 livestock properties.

Several examples are given below of reversion to virulence with the use of modified live virus vaccines. Appel (2) produced reversion of virulence of canine distemper virus after approximately six passages in dogs and ten passages in primary dog lung macrophages. Clinical signs in dogs were mild, no central nervous signs developed, and all dogs recovered clinically after three weeks. Apparent canine distemper was studied by Hartley (12) using certain batches of modified live vaccine against canine distemper virus and canine adenovirus 1. Clark (7) demonstrated reversion of virulence of Flury high egg passage rabies virus after one to five serial passages in murine or human neuroblastoma cells. The virulence acquired was a stable genetic trait retained during subsequent passage in a variety of cell lines. *Babesia bovis* vaccine strains can revert to virulence via passage through ticks. Despite intense investigation in Australia, no
Relative "risk" in using certain veterinary vaccines is associated with the production process. For example, the use of goat spleen tissue rinderpest vaccine carries an inherent risk of spreading numerous adventitious pathogens. This risk can be reduced by producing calf kidney tissue-culture vaccine, but the risk of contamination with BVDV is still a practical concern. Risk of adventitious virus contamination is zero when rinderpest vaccine is produced in Vero cells. The use of some relatively risky biologicals can be significantly reduced by observing improved production methods.

Rabies vaccine produced in adult animal nervous tissue is recognised as dangerous, but is still in use in developing nations. One of the recognised dangers of such vaccine—and the basis for the original recommendation by the World Health Organisation (WHO) (34) to cease using vaccine prepared from nervous tissue from adult animals in favour of tissue or diploid cell-culture vaccines—is the high incidence of neuroparalytic accidents.

A second risk in producing vaccines using sheep brain tissue, even if derived from apparently healthy animals, is possible transmission of the scrapie agent to humans. Consideration should be given to the potential, but undocumented, risk of causing Creutzfeldt-Jakob disease in humans following administration of rabies vaccine made using brain derived from scrapie-infected sheep (3). Srinivas et al. (27) report that fourteen documented cases of Creutzfeldt-Jakob disease had occurred in India up to 1984. Whether there was a history of vaccination with sheep brain-derived rabies vaccine in any of the cases is not stated, and this possibility was probably not examined at the time. In any event, WHO recommendations to cease using this type of vaccine seem justifiably prudent.

**Risks associated with importing veterinary biologicals**

Strain differences among natural (field) pathogens are of concern when vaccines are produced by one laboratory or pharmaceutical firm and sold internationally. The risk of using inappropriate antigenic strains for vaccine production lies in ineffective disease control and the attendant waste of time and money. Detecting failure of protection requires good monitoring in the field, a high degree of suspicion and expensive laboratory facilities. The suggestion that biologicals or diagnostic reagents may be ineffective is usually met with scepticism, and even scorn, by representatives of the manufacturer. An open, inquiring approach to this potential problem on the part of the technical field staff of the manufacturing company would be an asset when the efficacy of a biological has been questioned.

One recent example of strain differences between antigens in different locations concerns bovine rotavirus (BRV) vaccines used on Israeli dairy farms (31). Three strains were isolated in Israel and there appeared to be a complete lack of cross-immunity. The commercial vaccine contained a strain isolated in the United Kingdom which was not protective against the BRV strains causing disease in dairy calves in Israel.

Haemorrhagic septicaemia vaccine is an example where the use of local antigenic strains is vital for adequate immunological protection (18). Effective vaccines must contain Pasteurella multocida strains which are antigenically similar to, or related to, the strains causing disease in the field.

Trypanosomosis is a special case where strain differences or confusion of antigens within the infected vertebrate host complicates production of an effective vaccine.
Isotype switching of variable surface glycoproteins (VSG) in successive generations of trypanosomes is a major technical hurdle. The VSG problem has led researchers to identify protective antigens within the parasite (14).

On numerous occasions, exotic diseases have been introduced to developing nations – all at no extra charge! Smallpox and babesiosis were introduced into the Americas; paratuberculosis was introduced wherever Channel Island cattle breeds moved around the world; East Coast fever (ECF) was introduced into South Africa and Mozambique following repopulation with cattle from Tanzania. The cause of disease spread in these instances was not ‘veterinary biologicals’ in the sense under consideration here, but these examples highlight the historical sensitivity of introducing exotic diseases into developing nations. This sensitivity may not be any less acute than in developed nations.

Developing nations usually have diseases which are exotic to many developed nations, and therefore biologicals for use in industrialised countries present an increased risk if they are produced in developing countries. Many viruses (e.g. BVDV and BLV) and bacteria are present world-wide, however, and present a real threat to developed and developing nations alike. The consequences of exotic disease introduction are probably much greater in developing nations; they have fewer resources to control or eradicate an introduced disease. Animal depopulation or stamping out policies are unpopular in developed nations, even when indemnities are paid. In developing nations, however, indemnities are often not affordable, movement control is ineffective and depopulation may be politically untenable.

In East and Central African nations where ECF occurs, government officials are concerned with ‘local’ strains of *Theileria parva* and the threat of introducing exotic strains in ‘cocktail’ vaccines. The question of where a domain of so-called local strains starts and ends is difficult to answer; the domain will constantly change with the movement of ticks and animals. This, together with the expense of commercial production from multiple local strains, creates major financial and practical problems. Given the high cost of ECF, the availability of an effective, field-tested cocktail vaccine, the urgency of the problem and the favourable cost/benefit ratio, use of the vaccine in at least some African countries seems prudent at this time. Good QC and follow-up of adverse reactions are particularly important for this cocktail vaccine at the present early stage of its field use. There is no immediate prospect of an alternative vaccine being produced.

Sound, justifiable and scientific judgement is needed to ensure that there are no technical factors suggesting that imported veterinary biologicals may not be safe and effective under the conditions present in the importing country. Regulators must balance the gains to be expected from using new biologicals against the expense of repeated testing which may, in fact, discourage producers from even offering the product for sale. Careful judgement is necessary before demanding re-testing or proof of the efficacy and safety of an imported biological in each nation. Regional co-operation and mutual confidence among regulatory agencies are required.

**Risks arising from inadequate delivery of veterinary biologicals**

In many developing nations, there is a need for better management and funding of veterinary organisations to make them capable of delivering services effectively. State Veterinary Services in some sub-Saharan African nations spend well over 80% of their budgets on staff salaries, with insufficient funds remaining for operating expenses (6).
State veterinary organisations are often the prime supplier of veterinary services, and employees of state Veterinary Services throughout the world do not generally possess the same ‘feeling of urgency’ as does the owner of the livestock or the private practice veterinarian. Breakdowns in delivery of services frequently result from this lack of urgency, inadequate salaries and allowances, and insufficient investment in the repair and maintenance of equipment.

Major donors and development agencies (e.g. World Bank, European Union) have pointed out the detrimental effects that insufficient funds for operating expenses have on the delivery of veterinary services. For over ten years, donors have supported privatisation of some services, including clinical care and mandated vaccinations, and this drive is beginning to pay off. Many governments now encourage private veterinary practitioners and are no longer involved in veterinary drug distribution.

Reports of improper use of pharmaceuticals and biologicals are numerous but rarely documented. Problems result from underdosing of pharmaceuticals and biologicals, the use of chemical sterilents with live vaccines, dilution with inappropriate products, lack of refrigerated storage, and many other errors and shortcomings. The root causes of much of this improper use are a chronic lack of sufficient finances and a lack of knowledge (or a disregard) of proper procedures. Improper use of veterinary biologicals may occur more frequently in developing nations due to financial constraints. Electricity may not be consistently available for refrigerators, freezers or sterilisers; proper diluents may be unavailable; correct needle sizes or syringes may be in short supply. Veterinarians as a group are particularly innovative under adverse conditions. But to be innovative and use proper techniques at the same time, they need sufficient knowledge. In many cases, the situation could be improved by financial commitment to providing technical backup in each country.

Regulatory agencies in many countries mandate post-marketing monitoring of the efficacy and side-effects of new products via reporting systems. Systems for reporting adverse effects of vaccines work reasonably well in situations where a sufficiently well-trained cadre of government and private veterinarians is present throughout the country. In developing nations, human resources are less well developed and supported, and those which are present may be ineffective. An exception is Zimbabwe, where the veterinary field staff detected the spread of BLV from contaminated Babesia vaccine through intensive post-marketing surveillance, thus limiting infections from the vaccine to approximately 350 cattle. Monitoring the efficacy of veterinary biologicals and adverse reactions is a legitimate function of government; the FAO and other development agencies should actively support such monitoring.

**UNIQUE DISEASES AND ENVIRONMENTAL CONDITIONS**

**Risks arising from poor immune response**

Several examples suggest that human populations in developing nations may be particularly at risk due to insufficient protective immunity against infectious disease. Humans immunised in developing nations with potent human diploid cell rabies vaccine develop a lower anti-rabies antibody titre (4). Part of this decreased antibody response can be explained by concurrent use of chloroquine phosphate and/or pyrimethamine-sulfadoxine for malaria prevention (4, 20). These drugs are potentially immunosuppressive at the concentrations administered for malaria prophylaxis.
Simultaneous administration of multiple vaccines, with or without concurrent use of antimalarial drugs, also partly explains the reduced antibody titre to rabies and other antigens (yellow fever) in persons vaccinated while residing in areas where these diseases exist (4).

Immunosuppression and/or immunodepression may occur in humans as a consequence of natural infections with human immunodeficiency virus (HIV) as well as in malaria, and in animals in the case of trypanosomosis (17, 19), tick-borne infections (adult Amblyomma variegatum) (16), BVDV infection, and a variety of other infections and nutritional deficiencies. Administration of modified live virus vaccine against BVD, canine distemper and other diseases also results in measurable immunosuppression. The clinical significance of laboratory-determined humoral or cell-mediated immunosuppression is less clear. Studies in Africa using domestic ruminants infected with trypanosomes demonstrate suppressed humoral immunity to vaccine virus (FMD, rinderpest) or Clostridia sp. Nonetheless, the antibody levels developed are generally considered sufficient for protection against natural exposure (13, 23, 25). It is unknown whether the humoral immunity elicited under these conditions remains as long-lasting or as effective in the face of repeated parasitaemia or challenge from trypanosomes. Additional studies are required before these risks can be assessed.

Some of the above-mentioned diseases causing immunosuppression and/or immunodepression are unique to developing nations, where prevalence may be quite high, while others are distributed universally. The occurrence of immunosuppression or immunodepression is an added cause for concern to decision-makers in developing nations when considering how potential risks may be managed.

An example of the intense scientific interest in immunosuppression is the fear that vaccinia virus-vectored vaccines might cause untoward effects in humans. Evidence shows that this risk is small, but is probably greatest in immunocompromised individuals (e.g. those suffering from T cell depletion as a result of HIV infection) (8, 21). To date, there are no reports suggesting that vectored vaccines are dangerous when used as directed. A recent report (1) confirms that the death of an immunosuppressed man in Germany did not, in fact, result from vaccinia, variola or monkeypox viruses which might have come from vaccine use. In this case, the infection and generalised haemorrhagic variola disease was caused by a cowpox virus.

**Risks due to the determinants of multifactorial diseases**

Animals in tropical regions frequently harbour natural infections with multiple pathogens, and may also have nutritional deficiencies. Concurrent haemoparasite infections are common in animals; indeed, premunition – which induces a chronic carrier state with regard to protozoal parasites – is the goal of many vaccination and strategic tick-control programmes. Clinically-apparent infection with Theileria parva often allows the recrudescence of latent infection with Babesia or Anaplasma (J. de Castro, personal communication). The interactions between the determinants of multifactorial disease should be the focus of laboratory and epidemiological studies to identify the hazards involved.

Safety and efficacy testing in developed nations takes for granted certain ‘background’ environmental conditions and levels of disease exposure. In tropical areas, these and other multifactorial conditions (e.g. mixed natural infections, parasitic infestations and nutritional deficiencies) are significantly different from those in more temperate regions. The unique multifactorial conditions found in developing nations should be respected during risk assessments of all biologicals to be used in these nations.
IMPLICATIONS OF THE URUGUAY ROUND AGREEMENTS

The overall objective of the agreements of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) is to liberalise trade among countries. Liberalisation will result in increased world-wide trade. The World Trade Organisation (successor to GATT) will implement the Agreements and resulting regulations, and will challenge apparently unjustified barriers to trade (including trade in veterinary biologicals).

Some of the barriers to trade in biologicals imposed by both developed and developing nations are scientifically untenable. They will become even more so under the new Uruguay Round agreements and dispute settlement mechanism. The main agreements applying to food safety and veterinary biologicals are the Agreement on the Application of Sanitary and Phytosanitary (SPS) Measures and the Agreement on Technical Barriers to Trade (TBT). Both agreements emphasise, among numerous other things, the use of risk analysis to determine measures which provide the appropriate level of protection in the manner which is the least disruptive to international trade. These agreements also emphasise the need for assistance to developing countries, including the extension of time limits for providing justification indicated under the terms of the TBT agreement.

Clearly, developing nations will be required to strengthen risk analysis capability. Just as clearly, this will require improvements in national veterinary and regulatory services, such as the development of human resources in the theory and application of risk analysis, and in disease monitoring and surveillance, and the development of infrastructures for laboratory testing, quarantine, etc. Such development goals coincide with activities promoted in recent years by the Office International des Epizooties (OIE), the FAO, the World Bank, the European Union and many others, to strengthen the delivery of veterinary services. It is hoped that donor agencies will continue to finance programmes aimed at effecting these improvements, particularly as the Uruguay Round agreements mandate extensive changes in infrastructure and procedures to enhance freer trade.

It should be emphasised, for the benefit of developing nations, that the Uruguay Round agreements will intensify trade competition between countries. Developed nations will be in an increasingly favourable position to benefit because they have more products (including veterinary biologicals) to trade, and they have the technology and resources to meet the requirements of the Uruguay Round agreements. Developing nations will be less able to refuse authorisation to import undesirable biologicals. Existing standards cannot legitimately be used by governments as a pretext to bar entry of products which they might wish to exclude but which do not present a risk. Unjustified trade barriers, particularly those which contravene the TBT agreement, will be increasingly challenged. Developing nations must be technically competent and conversant with the regulations of the Uruguay Round agreement, to protect themselves from unwanted imports and to foster trade for their own products.

ENSURING THE AVAILABILITY OF AFFORDABLE AND EFFECTIVE VETERINARY BIOLOGICALS

Improved information on animal disease distribution, prevalence, resulting direct losses and the cost of control is being assembled by the FAO Animal Production and
Health Division. For animal trypanosomosis in sub-Saharan Africa, a geographical information system is being developed to quantify the impact and identify the local areas of disease. Pilot projects in Asia, Latin America and Africa are being implemented to define the distribution of internal parasites, costs of disease and resistance to anthelmintics. Similarly, a module is being initiated in Afghanistan to monitor key indicators of animal production and health in various livestock husbandry systems. The module will be adapted to production systems in other countries. The information gathered by the above projects may well be useful in defining markets for veterinary biologicals in developing nations. The FAO is very interested in establishing co-operating triumvirates involving scientists, institutions and private companies in developing nations, to generate reliable information on animal disease distribution and the attendant losses.

In-country research and market development are seen as two steps which would help ensure the availability of affordable and effective biologicals for livestock owners in developing nations. Field trials and laboratory analysis should be conducted in developing nations, employing national personnel whenever possible. Companies wishing to do business in developing nations over the long-term should pay for and supervise adequate field trials, laboratory analyses, data evaluation, report writing, etc. This is an investment in human capital. Whenever possible, data should be generated which are useful for meeting new international safety and efficacy standards for conventional biologicals in developing nations. This proves efficacy within environments where the biologicals will be used, and also generates market information. When national regulatory agencies in developing nations have the technical competence to conduct their own QC testing, and when this is judged scientifically desirable, the government concerned should not hesitate to charge manufacturers a reasonable fee for this service.

An efficient product distribution network and cold chain are required to ensure delivery of potent biologicals to end-users. Retailers cannot sell what they do not stock. Small-scale local retailers (veterinarians or pharmacies) generally lack the necessary capital to carry a sufficient range of products. An efficient, diversified distribution network capable of delivering orders the same day, or the next day, could continually replenish stocks with long-dated, potent biologicals. Such a distribution system for consumer products and pharmaceuticals functions well throughout Mexico. The remarkable shift to privatisation of clinical services may well be the entry point for providing technical knowledge and efficient distribution. As livestock owners are required to pay for goods and services, the standards of quality and competence demanded will rise.

As conventional veterinary biologicals are replaced by newer products, manufacturers should consider moving production facilities for conventional products to developing nations, or forming joint ventures in these countries, where a market exists for the lower-cost (but still effective) biologicals. Some older conventional products may be cheaper to produce than high technology replacement products. In addition, production costs for conventional products may be even lower in developing nations, particularly where production facilities already exist. The market for conventional products may move to developing nations because markets for such products, as opposed to their newer high-technology replacements, can be maintained relatively inexpensively by local private enterprises.

The above should not be seen as advocating a two-tiered quality standard for veterinary biologicals. Quality and safety standards must remain universally high.
Obtaining the marginal value from improved, high-technology veterinary biologicals may not be cost-effective in the low-input/low-output livestock systems characteristic of many developing nations. Under the conditions described in the preceding paragraph, effective conventional biologicals may well be more cost-effective than some newer replacement products. Local production provides a means of preventing effective conventional biologicals from being entirely eclipsed by newer, more expensive products. As yet, the potential market for older conventional biologicals is insufficiently exploited in developing nations. It is unlikely that manufacturers will invest here to market even more expensive products.

In 1991, the FAO assembled leading scientists for an expert consultation on QC for veterinary vaccines in developing countries (8) to help in the transfer of appropriate technology. The panel made specific recommendations on quality requirements for selected vaccines, standardisation of immunobiologics and international co-operation in this respect. There is an urgent need for the production of veterinary biologicals to employ appropriate technology and recognise the principles of QC and GMP. Livestock owners in developing nations generally cannot afford to invest in expensive, high-technology manufacturing processes. The added value, in terms of increasing the production efficiency of food animals, does not usually justify large investments for small markets. The use of appropriate technology (to reduce the risks associated with producing and delivering veterinary biologicals), together with international standards of QC and GMP, could provide the key to ensure the availability of affordable veterinary biologicals.

Excess veterinary vaccine production capacity currently exists in many countries of the developing world; much of this capacity is not financially viable, as production costs are often higher than sales proceeds. In addition, large amounts of the vaccine produced is of poor quality. In many countries of sub-Saharan Africa, the Middle East and Asia, financial constraints – whether due to the government failing to support GMP, the manufacturer lacking sufficient market share, or trade barriers restricting markets – result in the use of poor quality veterinary vaccines. Consequently, there is an increasing realisation that unprofitable, old or small-capacity national vaccine production facilities should be phased out.

A development strategy based on two concepts is emerging, namely regional markets and the specialised production of only a few effective, high-quality vaccines. Regionalised production of biologicals, particularly when undertaken by the private sector, responds better to the needs of developing countries than production on a national scale. As the effective demand for livestock vaccines is often small in any one country, multinational producers are often unwilling to include local strains of pathogens in vaccines. This is particularly true for FMD virus vaccine (S.K. Hargreaves, personal communication). Conversely, the Botswana Vaccine Institute – which is partly state-owned, partly private sector-owned – works closely with neighbouring countries to produce high-quality FMD vaccine containing local strains. It is anticipated that, as these concepts are put into practice, regional manufacturers of veterinary biologicals will become financially capable of producing and marketing consistently high-quality products. The FAO is fully supportive of the current regionalisation of the production of veterinary biologicals.

PANVAC should continue to function as an impartial, independent and scientifically-competent body, providing manufacturers with certification of vaccine quality. This certification service was a distinct asset for manufacturers of rinderpest and
contagious bovine pleuropneumonia vaccines, by providing all biological manufacturers with an internationally-accepted assurance of quality, potency and safety, and thus enhancing the marketability of certified vaccine. Unfortunately, donor support for PANVAC lapsed before a sound cost-recovery basis could be established. However, the service provided to both manufacturers and livestock owners remains essential. It is therefore important to find transitional measures which will eventually lead PANVAC to function in a self-sustaining manner.

Regulators in developing nations should generally recognise the standards adopted in developed nations for licensing new biological products. If a product meets the licensing requirements – in terms of purity, safety, potency and efficacy – in a selected developed nation, regulators should respect these data and license the product for their country. This is particularly true where a developing nation does not yet have the capacity (technical, financial, field monitoring or other) for testing or certifying biological products. Recognising the registration standards of a selected third country is often a practical necessity. It also supports the current trend among OIE Member Countries to evaluate the capability of state veterinary and regulatory services with the aim of developing mutual confidence among nations.

CONCLUSIONS

Quality assurance, GMP and efficient delivery systems are recognised, in both developing and developed nations, as making a major contribution to reducing the risks associated with the use of veterinary biologicals. Daily vigilance by manufacturers is required to ensure that QC and GMP standards are not compromised at any stage in the production process. Appropriate manufacturing techniques for veterinary biologicals, which avoid known risks, require continued research and application. Breakdowns in the delivery system to end-users need to be avoided by increasing investment in cold chain facilities. An efficient ‘just-in-time’ product distribution network to local retailers would solve many technical and marketing problems. An impartial, independent and scientifically competent quality-certifying laboratory can facilitate the marketing of veterinary biologicals produced in developing nations.

Universally-accepted methodology and techniques for risk assessment should be applied equally in both developed and developing nations. The unique environmental conditions and disease exposure present in some developing nations, however, demand that risk assessment and biological product testing be undertaken in these nations. The local capacity of both the state and private sectors to undertake these activities must be improved. Increased investment is needed in developing nations to upgrade diagnostic and testing laboratories, and to develop human resources through training. Post-licensing monitoring for adverse effects from biologicals is one veterinary activity which urgently needs strengthening in many developing nations.

The Uruguay Round agreements will make critical demands on regulatory agencies in developing nations if these countries are to benefit from the liberalisation of international trade while still protecting their legitimate interests. The ability of these agencies to undertake sound risk assessment and risk management urgently needs to be strengthened. The FAO, OIE and donor agencies should anticipate and help to meet training and infrastructure requirements in this regard.

Veterinary biological manufacturers should consider transferring the production of conventional, but still effective, veterinary biologicals to developing nations where
markets for these products already exist. To make increases in production of foods of animal origin in developing nations, more effective and affordable veterinary biologicals must be available. Investment in local production (employing appropriate technology) and marketing (through an efficient distribution system) is seen as a key to the continuing availability of affordable veterinary biologicals.

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ÉVALUATION DES RISQUES LIÉS AUX PRODUITS BIOLOGIQUES À USAGE VÉTÉRINAIRE : PROBLÈMES PROPRES AUX PAYS EN DÉVELOPPEMENT. - D.E. Ward.

Résumé: L'auteur analyse les problèmes liés aux produits biologiques à usage vétérinaire dans les pays en développement sous leurs aspects techniques et socio-économiques. L'évaluation du risque sanitaire est une procédure spécifique qui consiste à estimer la probabilité de contamination des animaux, des hommes ou des systèmes écologiques par un agent chimique ou physique ou un produit biologique dans un ensemble de conditions déterminées. Certaines questions techniques (garantie de qualité, bonnes pratiques de fabrication, information de l'utilisateur final, surveillance sur le terrain) s'appliquent aussi bien aux pays développés et industrialisés qu'aux nations en développement et pré-industrielles. De nombreuses régions rapportent des cas de maladies qui leur sont propres (trypanosomose, maladies transmises par des tiques, theilériose) ou des niveaux élevés de prévalence, qui peuvent avoir une influence sur les résultats d'une analyse des risques. Il faut donc des méthodes scientifiquement fondées pour l'évaluation de risques dans les pays en développement.

Ces pays se heurtent également à de nombreux problèmes socio-économiques qui peuvent ne pas reposer sur une réalité scientifique mais qui n'en affectent pas moins les échanges et l'usage de produits biologiques vétérinaires. L'auteur aborde tous ces problèmes non scientifiques, mais perçus comme réels, ainsi que leurs solutions possibles. La façon dont les pays traitent ces problèmes dans le contexte de l'harmonisation des normes internationales applicables à l'évaluation des risques se répercute sur les éleveurs des pays en développement.

Enfin, l'auteur indique quelques moyens permettant de corriger l'écart des coûts, qui ira probablement en grandissant, entre les produits biologiques à usage vétérinaire classiques et bien connus, d'une part, et ceux issus des techniques récentes, d'autre part.

Les résultats d'une évaluation des risques portant sur des produits biologiques à usage vétérinaire déterminent la gestion de ces risques dans tous
les pays, développés ou non. Il convient d'adopter des directives scientifiquement fondées sur la gestion des risques pouvant être appliquées dans tous les pays. L'auteur rappelle les conséquences des accords du GATT (Accord général sur les tarifs douaniers et le commerce) dans le cadre de l'Uruguay Round, sur les échanges de produits biologiques à usage vétérinaire dans les pays en développement.


Resumen: El autor examina cuestiones tanto técnicas como socioeconómicas ligadas a los productos biológicos de uso veterinario en las naciones en vías de desarrollo. La evaluación de riesgos sanitarios constituye un proceso específico para estimar la probabilidad de que animales, seres humanos o sistemas ecológicos resulten afectados de forma adversa ya sea por un agente químico o físico o por un producto biológico, dada una serie concreta de circunstancias. Algunas de las cuestiones técnicas (garantía de calidad, buenas prácticas de fabricación, formación de los usuarios finales, monitoreo de campo) conciernen por un igual a las naciones desarrolladas e industrializadas y a los países preindustriales, en vías de desarrollo. En muchas regiones se señalan enfermedades que no existen en otras partes del mundo (tripanosomiasis, enfermedades transmitidas por garrapatas, theileriasis), o tasas elevadas de prevalencia de enfermedades, que pueden influir en los resultados de la evaluación de riesgos. Ello subraya la necesidad de poner a punto metodologías de evaluación de riesgos científicamente válidas en los países en vías de desarrollo.

Varias preocupaciones de índole socioeconómica de los países en vías de desarrollo, aunque no directamente ligadas a las realidades científicas, pueden también afectar el comercio y la utilización de productos biológicos. Estas cuestiones y problemas no científicos son objeto de breve discusión, y se proponen posibles soluciones. La forma en que los países se enfrentan a estas dificultades y problemas percibidos en el momento de armonizar las normas internacionales para la evaluación de riesgos tiene un fuerte impacto sobre los ganaderos de los países en vías de desarrollo.

Finalmente, el autor presenta posibles modos de paliar la desproporción existente entre el coste de los productos biológicos convencionales ya conocidos y el de los productos nuevos, una diferencia susceptible de crecer todavía más.

Los resultados de la evaluación de riesgos de los productos biológicos veterinarios influyen sobre el manejo de los riesgos tanto en las naciones desarrolladas como en las menos desarrolladas. Es importante consensuar una serie de directrices con fundamento científico que puedan ser aplicadas al manejo de los riesgos en todos los países. El autor examina también las consecuencias que los acuerdos de la Ronda Uruguay del Acuerdo General sobre Aranceles Aduaneros y Comercio (GATT) tienen sobre el comercio de productos biológicos de uso veterinario en los países en vías de desarrollo.
PALABRAS CLAVE: Acuerdo SPS (Medidas sanitarias y fitosanitarias) – Acuerdo TBT (Obstáculos técnicos al comercio) – Barreras al comercio – Evaluación de riesgos – Garantía de calidad – Países en vías de desarrollo – Productos biológicos de uso veterinario.

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