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ASSISTANCE IN THE PRODUCTION OF VETERINARY DRUGS IN SADCC COUNTRIES

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BOTSWANA

Technical report: The supply of veterinary drugs and vaccines in Botswana*

Prepared for the Government of the Republic of Botswana
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

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INTRODUCTION

Botswana is a landlocked country in the centre of Southern African plateau, extending to some 582,000sq.km. It is bordered by Zimbabwe to the East, South Africa to the South and South-East and Namibia and the Caprivi Strip to the North and North-West.

The climate of the country is dominated by the harsh desert conditions, particularly in the West and South-West, and the periodic droughts.

The human population was estimated at 845,000 in 1984, growing at an annual rate of 3.1% p.a., estimated to reach 1.4million by the year 2000.

1. LIVESTOCK POPULATION AND PRODUCTION TRENDS

In 1984 annual population statistics were:

Cattle	Traditional	2,305,000
	Commercial	308,000
Sheep	Traditional	168,000
	Commercial	23,000
Goats	Traditional	856,000
	Commercial	25,000
Chickens		850,000
Pigs		9,500

The good prices for beef (for export to the EEC) had proved a strong incentive for cattle production and the industry is thus geared to production even in the traditional sector. Cattle farming is extensive and this fact, coupled with the very low rainfall has resulted in the relative lesser importance of infectious animal disease.

2. NATIONAL DISEASE CONTROL STRATEGIES

2.1 Nutritional disease far exceeds the combined effects of all other diseases even to drastic reduction of numbers of livestock in drought years.

2.2 Foot and Mouth Disease is the most serious, not because of its frequency (the last outbreak was in 1980) but because prophylactic vaccination occupies a major proportion of the Veterinary Department's activities, and should an outbreak occur, the meat exports to the EEC would be threatened. This prophylactic vaccination is combined with rigorous supportive zoosanitary measures, the erection of game fences, the establishment of quarantine posts and the control of animal movement.

2.3 Tick-borne Disease. Ticks and tick-borne diseases are much less important than in all the other SADCC countries because of the harsh, dry conditions and dissemination of the cattle, (the others being anaplasmosis and pyroplasmosis) and is controlled by the use of ectoparasiticides and "Vaccine".

2.4 Trypansomiasis and tsetse control. Aerial spraying has limited the distribution of tsetse fly to districts of the country where there are no domestic livestock.

2.5 Anthrax. Few cases are diagnosed each year, but 1.5million doses of vaccine are used prophylactically.

2.6 Rabies. Rabies is increasing and occurs sporadically country-wide. Control is by free compulsory vaccination of dogs and cats, but a sylvatic cycle (in jackals) exists. 71 were cases were confirmed in 1985.

2.7 Otner Diseases. Blue tongue, African Horse Sickness, Newcastle Disease and Brucellosis have all been reported. Brucellosis is wide-spread and compulsory vaccination of female stock is practised.

2.8 Cysticercosis is prevalent and 12% of slaughtered animals are positive.

3. THE ORGANISATION OF VETERINARY SERVICES

The Veterinary Services came under the Director of Veterinary Services and is separate from Livestock Production. The Veterinary Services are sub-divided into tsetse control, disease control (plus district and sub-district Veterinary Officers) Development, Research and Meat Inspection.

4. VETERINARY DRUG AND VACCINE USED (1985/86) AND ESTIMATED FUTURE REQUIREMENTS

4.1 The Veterinary market is dominated by FMD vaccine.

Product Group	Units	Value
FMD Vaccine	Doses (trivalent) 1,200,000	US$ 000's 1080
Acaricides (Amitraz)	Litres 2,000	17
Anthelmintics Dylox	Litres 36,000	50
Antibiotics		75
Rabies	Doses 50,000	25
Anthrax	Doses 1,500,000	67
Black quarter	Doses 1,400,000	136
Brucella	Doses 500,000	75
Botulism	Doses 500,000	36
		$1,500

All drugs and vaccines used in the control of scheduled diseases (FMD, Anthrax, Blackquarter, Rabies and Brucella) are distributed free of charge. A small handling charge is made on the remainder.

4.2 Estimated requirements for drugs and vaccines
(These are summarised in Annex 1)

Apart from the high probability of at least one serious drought in the next 15 years, the most likely constraint on drug and vaccine usage is the restriction of prophylactic FMD vaccination. There are certain restrictions by the EEC on the importation of meat from cattle which have been vaccinated against FMD. The current policy of fencing, quarantine and vaccination has been so successful that the Department plans to erect further fences and to reduce the number of doses of FMD vaccine used prophyalctically down to about two-thirds of the current offtake.

5. CONSTRAINTS ON DRUG AND VACCINE USAGE

The main constraint is transport and this affects most activities whether the reception of samples for diagnostic purposes or the transport of drugs. However, with the commercial orientation of the livestock owners, it is not considered likely that any great increase in drug or vaccine usage would result from better transport, the over-riding factor always being the climate and the limiting effect of periodic droughts.

6. CONSIDERATIONS FOR LOCAL MANUFACTURE

6.1 Biologicals

6.1.1 Botswana Vaccine Institute (BVI) Gabarone
(for layout see Annex 2)

FMDV PRODUCTION

Introduction

The decision was taken in 1977 to build a vaccine production unit on a piece of land 12,000sq. metres at the Broadhurst Industrial Estate close to the town of Gabarone. The project was implemented by the Government of Botswana in conjunction with Iffa Merieux of France. The method of production elected was the 'FRENKEL' system by which FMD viruses are multiplied on cattle tongue epithelium, inactivated firstly by formalin, recently by ethylenimine, aluminium hydroxide and saponin being added to produce a finished vaccine with a pH of near 8. The finished vaccine is bottled into plastic bottles of 300 x 1 MBR 60 x 5ml doses by modern filling equipment under sterile conditions. Most of the vaccine produced is SAT 1, 2 and 3 strains but types O and A have also been imported from France for incorporation in polyvalent vaccine.

Phasing

The project occurred in two phases, the first phase being to study the different strains of FMD virus and to produce effective vaccine in limited quantities to meet the emergency in the country. The second phase to provide facilities for full scale production of vaccine was approved after all preliminary tests had proved successful.

Phase II started in 1980.

Phase I was achieved by the use of a module laboratory and a guinea pig house air lifted in from France with a design capacity of 3,000,000 doses per annum but which actually produced 8,000,000 doses per annum.

Phase II comprised:

1. Administration building
2. Production laboratory

3. Store on two levels complete with cold store facilities.
4. Animal house and abattoir for isolation of cattle undergoing safety and potency tests.
5. General services including boiler house, emergency generators, engineering workshop, kitchen and canteen facilities.
6. Gatehouse for central security purposes. The buildings have been so arranged as to leave spare space for other buildings should expansion be required or the production of other vaccines considered.

Production

The laboratory has been designed in a novel fashion being split into a virus area and a clean area, effectively providing two buildings under one roof. The advantage being that a corridor is provided around the whole area and double glazed windows are fitted on all the working areas allowing for 'look in' supervision and minimum production interference from visitors to the complex.

Basically there are three areas in the actual production complex as follows:

a) Virus area - where active virus is handled, ie, virus culture filtration, decanting and inactivation.

6) Isolated virus free area - where the vaccine has been inactivated and is harmless but is being tested for safety. This area included concentration and storage in bulk.

c) Virus free area - Under positive pressure handling medium preparation, blending and bottling.

The corridor around the whole area is referred to as the Transit Area.

Entry to the area is controlled by automatic air locks ensuring that only one door can be opened at a time. The lock doors are sealed by inflatable seals. Entry to the virus area is via showers and changing rooms. The company rules are stringent and personnel failing to observe the shower safety system are liable to instant dismissal.

Capacity of PHASE II was said to be 21,000,000 monovalent doses of vaccine per annum.

All materials leaving the virus area are sterilised in a double door entry automatic autoclave. Items too large for the autoclave are sterilised in the automatic lock system.

The virus area is maintained at reduced pressure on a 20% air make-up system the exhaust air being subjected to absolute filtration (0.5 micron).

The combined floor area of the two areas is 1250 sq. meters

Tank sizes for reference

Media Clean Area	2600L
Media Virus Area	2600 x 1500L
Virus Culture	3 x 500L 2600L
Blending	2600L
Concentrate Flasks	25L
Autoclaves	1 x 1 x 1.5ml capacity

40 cm dia-outlet from sensitive virus room to normal virus area

Staff - There are seven expatriates in the production department and ancillary services.

(a) Two Veterinary Surgeons (one of whom is head of laboratory)

(b) Three Lab Technicians (it is a rule of the company that no production facet takes place without one of the technicians being present. This embraces all areas from media production to bottling and distribution of vaccine).

(c) One Chief Engineer

(d) One Deputy Chief Engineer.

Training of local staff takes place on the job but some staff who show outstanding ability are sent to France for in-depth training.

There are 76 people employed which include 21 from site services and maintenance.

Plant and Equipment

Service equipment has mostly been purchased in Sough Africa e.g., steam generators, compressors and cold store compressors. Process equipment is of European origin mainly from ALFA LAVAL who are specialists and other French suppliers. Process pipework is of the Dairy type and supplied by ALFA LAVAL. All tank connections are ALFA LAVAL and so are the control valves of hall type design. Recorders are by Honeywell and vast use has been made of multi channel recorders. A sterile type centrifuge is included in the down-stream filtration system plus absolute plate and pad type filtration. Other centrifuges are used for final clarification.

Safety and Tests

The animal house is in a separate building but is treated as a virus area with a separate air flow system. It contains an abattoir, two large testing stables and shower/change facilities. At the entrance in an area called the transit or corral area cattle are assembled for testing. The test area is under negative pressure with exhaust filters to 0.5micron. It was stated that 58% of total vaccine output is tested in cattle in the animal house. Cattle which have been used are slaughtered, the whole animal is cooked and disintergrated into powder form to provide foodstuff at the company ranch outside the town.

Effluent from the animal house and the virus area is decontaminated as follows:-

(a) Solids - through a double ended autoclave.

(b) Liquids - collected in two by 20000 litre fixed tanks chemically treated (sodium hydroxide), tested and discharged to drain.

Complete records of decontamination and autoclave charts are kept for record purposes.

A stringent system of records in the company are kept, readings being taken every two hours, day and night, every day including holidays of the following:-

(a) Cold rooms temperatures.

(b) Hot rooms temperature

(c) Room temperatures

(d) Other room conditions e.g., humidity

(e) Room air pressures

(f) Recorders on process equipment

(g) Pressure on process equipment

(h) Condition of locks whether or not they are open and on which side

(i) Animal House conditions, pressure and temperature

(j) Autoclaves in use and state of doors

(k) Steam pressure at source and water levels

Costs - This was stated to have been of the order of US $11,000,000 mainly subscribed by EEC. This cost includes buildings, services and process equipment. A 'revolving fund' caters for recurrent expenditure of raw materials, packing materials and overheads due to direct and indirect labour, spares and replacement equipment. This includes purchase of susceptible cattle for test.

Products and Specifications

Foot and Mouth Disease Vaccine - Primary role of this product is to supply Southern African Territories (SAT) type Foot and Mouth Disease vaccine, supported by diagnostic activities and typing of viruses. In addition O/A types of FMD vacine are imported for blending polyvalent vaccine. The institute is able to produce FMD vaccines, equivalent to approximately 0.5×10^6 monovalent doses a week. Altogether $9,314 \times 10^6$ doses were issued in 1986, indicating that about 50% free capacity exists. The production is carried out in a compact, hermetically sealed laboratory with the most advanced equipment, safe to prevent any hazard of contamination.

Rinderpest Vaccine - Using the pre-fabricated building of Phase I to utilise the free manpower/laboratory capacity, this vaccine is produced on a campaign basis using KABETE O STRAIN on rolling cell-culture of Bovine Kidney Cells. As the demand is limited, further free capacity could be considered, this vaccine is potency tested to OIE/FAO standard, on site.

Technology - This is based on the Frenkel process (see Annexes 3 and 4)

Communication and Distribution

Based on the requests of the local government the Institute is able to produce the FMD vaccine needed in a short time. This vaccine is filled into sterilisable plastic flasks of 300ml, packed into polystyrene boxes and transported in a cooled form. This procedure relates to the export as well, which is transported by air.

The Rinderpest vaccine (freeze dried) is issued in a protective packing too, to prevent any damages of viability during occasional delays of transport.

Discussion

The high disease security of the laboratories, the advanced technologies, the equipment and the appropriate in-process and final quality tests as well as the high level of knowledge, discipline and strict technical supervision classifies this Institute among the best ones in the world.

6.1.2 Diagnostic Building - Gabarone Botswana

This building with a total floor area of 1800sq.m. on two storeys has been constructed on a site of 8 hectares, 15 kilometres from the town of Gabarone.

The upper storey has been equipped for administration complete with conference rooms and a large library. The ground floor is equipped for diagnostic tests on field samples received and service facilities including five separate air-conditioning systems which effectively separate areas and prevent cross contamination.

A total of 75 people are employed at the complex including four expatriates of various European origins.

The building was completed in 1986 and is not yet fully operational. Some equipment received has yet to be installed. The finishes in the building are excellent, conform to modern thinking and GMP and at a finished cost of US $ 3,000,000 no expense has been spared in either service equipment or laboratory equipment. There is a sophisticated high security area for rabies tests with high efficiency filters and a superb Post Mortem Area complete with its own incinerator system. Effluent from the laboratory is monitored and treated accordingly before discharge into the local sewage system. A quantity of sufficient cold stores and walk in incubator rooms have been installed. Sophisticated autoclaves and freeze-drying equipment have also been provided plus laminar flow systems and high efficiency centrifuges. Full attention has been paid to both safety and security.

Discussion

Although at the time of viewing the laboratory was not fully operational, it is difficult to envisage full utilisation of the facilities except in the case of national or even regional emergencies.

Recommendations

1. All air conditioning servicing is in the hands of local agencies who are an offshoot from the parent company in South Africa, as the complex does not employ an engineer. It would be cheaper to employ such a person and carry out 'in house' maintenance. Day to day maintenance is carried out by the senior laboratory technician detracting him from his more important duties. Employment of an engineer would increase the usefulness of the senior laboratory technician.

2. The -20^{0}C cold store has an entrance directly from the corridor. This is wasteful in energy terms, the normal method being to approach a -20^{0}C cold store via a +4^{0}C cold store. The architect should be consulted to re-arrange the system.

3. The formalin hatch leaks badly into the high security room as the room is under reduced pressure. The windows on the hatch should be replaced with a removable stainless steel sheet and suitable gasket.

4. Sulphuric acid is used in the control of the pH of infected effluent. A safer method would be to use acetic acid.

6.1.3 Veterinary Diagnostic Laboratory

Staff: 5 Veterinary Officers
6 Laboratory Technicians
8 Laboratory Assistants
4 Livestock Officers
5 Clerical Class Staff
17 Industrial Class Staff
3 Veterinarians and 2 Technicians are expatriate experts.

Training - Out of local Technical staff 7 are studying abroad (New Zealand, USA, UK). The Laboratory is unable to recruit young people due to financial

discrepancies. The professional activities are supported by the British Veterinarian Investigation Service, Veterinary Research Institute, Onderustepoort, Animal Virus Research Institute, Pirbright and Royal (Dick) School, Edinburgh.

The Institute consists of the following sections: Bacteriology, Biochemistry, Toxicology, Food Hygiene, Pathology, Hystopathology, Parasitology, Virology and Culture Medium. There is a high security unit for the use of rabies diagnosis. In all 2356 samples were tested during one year, (cattle 950, equine 80, porcine 23, small stock 302, avian 334, pets 611, game 16, humans 2, miscellaneous 38). In the opinion of the directors the most frequent diseases are:

1. Rabies (out of 178 samples 71 were positive).
2. Heartwater (out of 98 samples 72 found positive).
3. Internal parasites.
4. Brucellosis
5. Botulism
6. Deficiency Diseases

Only sporadic evidence of Blackquarter, Haemorrhagic septicaemia and Anthrax were observed.

The Virology and Hystopathology sections were not operating as foreign experts had not arrived, but they are full of sophisticated and expensive equipment.

Due to the long distances in the country, several specimens received were found in a state of decomposition. Very faint signs of activities were observed and the number of samples is 2356 annually.

6.2 Pharmaceuticals

Veterinary pharmaceuticals are not produced in the country.

Discussion

The Botswana Vaccine Institute stands alone in SADCC in the standards of manufacture and quality of the biological products it produces (FMD and rinderpest vaccines). It is already recognised as the Regional FMD Laboratory by FAO/OIE and has been designated by the EEC as an official source of rinderpest vaccine, with the responsibility of maintaining at least 3 million doses of vaccine for strategic reserve purposes.

There is an excellent nucleus of ex-patriate specialists together with local staff trained on site. There is considerable excess capacity in the FMD laboratory and the rinderpest vaccine production facilities can meet the required annual demand in a few weeks per year. Also, there is ample space to construct additional virus vaccine laboratories on the same site.

Considering the demand for the local production of lumpy-skin, sheep-pox, blue tongue, Rift Valley Fever, African horse sickness, Ephemeral Fever and rabies vaccine, among which some are produced in only one plant of this continent, the utilisation of the technical skill and free capacity of this institute, with small additional investment, for these products would result in:

1) The safe regional production basis for the main part of the viral vaccines.
2) The better feasibility of the products being obtainable at the most reasonable price and of the same quality as imported biologicals.

3) Continuous training facilities for the technical staff of the diagnostic network of the SADCC countries, involving the possibility of having skilled staff for expansion even in other countries if the conditions prevail and the need for these biologicals exceeds the maximum capacity of this plant in the future.

7. RECOMMENDATIONS

7.1 That the strategic approach to FMD control within the SADCC region based on the B.V.I. production capability should be developed.

7.2 The the B.V.I. also be built up as the SADCC regional rabies vaccine laboratory and meet the total rabies vaccine requirement of member countries. This should be on a planned increase basis, commencing with imported vials for labelling, followed by both antigen importation for local formulation and testing, and finally complete local production.

7.3 That consideration be given to the production of other viral vaccines, important within the SADCC and with either very limited availability elsewhere or possibly none at all.

These include:

African Horse Sickness Vaccine

Rift Valley Fever

Blue tongue

Sheep-pox

Goat-pox

Lumpy skin disease

Ephemeral Fever

VETERINARY DRUGS AND VACCINES USED AND ESTIMATED FUTURE REQUIREMENTS

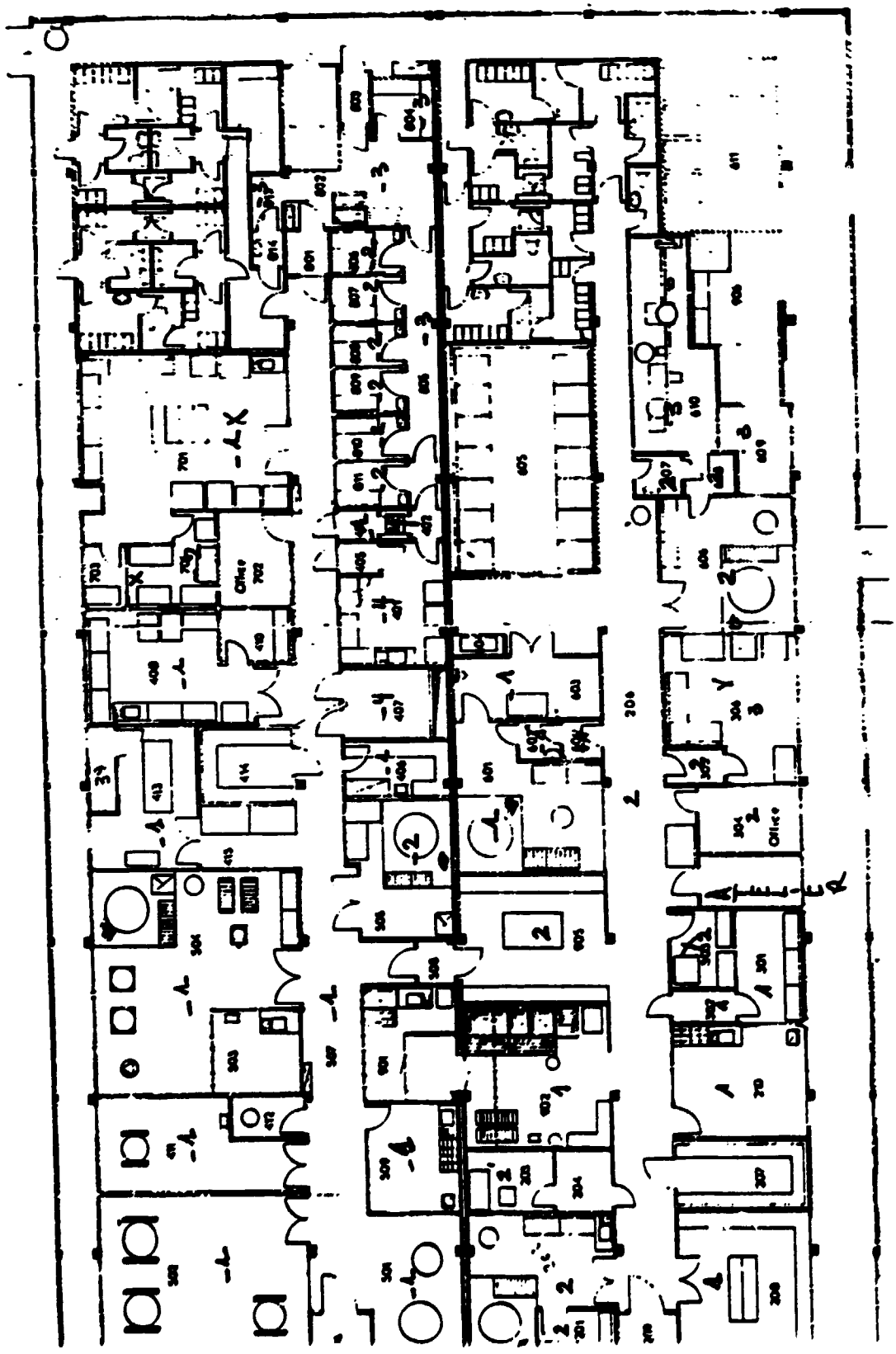
DRUG/BIOLOGICAL	YEAR 1986 UNITS	1986 VALUE US$000's	1990 UNITS	1990 VALUE US$000's	2000 UNITS	2000 VALUE US$000's
Ectoparasiticides						
Amitraz	2,000	17	2,500	21	3.000	26
Anthelmintics	36,000	50	40,000	55	50,000	70
Antibiotics		75		85		100
Antiprotozoons						
Feed Additives		50		50		50
SUB-TOTAL		192		211		246
Biologicals	Mono doses					
FMD*	3,500,000	1,080	2,400,000	960	2,400,000	1,200
Rinderpest+	3,000,000	100	3,000,000	100	3,000,000	100
Rabies**	50,000	25	50,000	25	50,000	25
Poultry vaccines						
Other viral vacc. (Rift Valley Fever African Horse Sickness etc)						
Blackquarter	1,400,000	136	1,000,000	100	1,000,000	100
Anthrax	1,500,000	67	2,500,000	112	2,500,000	112
Brucella	500,000	75	500,000	75	500,000	75
Pastuerella	00,000	14	400,000	14	400,000	14
Botulism						
Others	500,000	36	500,000	36	500,000	36
SUB-TOTAL		1,533		1,423		1,663
TOTAL		1,725		1,634		1,909

* To this must be added exports of some 6.3 million monovalent-equivalent doses for a value of about US$ 2 million

** These figures would change drametically if the regional rabies strategy (See Appendix) were adopted.

\+ These are intended for export

Annex 2



Botswana Vaccine Institute

MANUFACTURE AND CONTROL SCHEME: FMD VACCINE

MANUFACTURE	TESTING at BVI
RAW MATERIALS	
- Tongue epithelia	cells count
- Media	pH / at / sterility
- Virus stock	pH / F'c(N-F) / $TCID_{50}$ UV peak / sterility
VIRUS CULTURE	
1) Minitank	pH / F'c(N-F) / $TCID_{50}$
↓	
2) Small tank (100ℓ). (temp. recorded)	pH / F'c(N-F) / $TCID_{50}$ / UV peak
↓	
3) Large tank (600ℓ). (temp. recorded)	pH / F'c(N-F) / $TCID_{50}$ / UV peak
VIRUS TREATMENT	
4) Centrifuge	
↓	
5) Chloroform treatment	
↓	
6) Centrifuge (high speed)	
↓	
Treated virus	pH / F'c(N-F) / $TCID_{50}$ / UV peak / sterility
INACTIVATION	
Treated virus + Ethylene Imine (EI)	pH / Cinetics of inactivation
7) Inactivator (temp. recorded)	
↓	
8) Centrifuge	
↓	
9) Filtration	
↓	
Inactivated virus	Ultrafiltration - Inactivation tests on cells culture (4 passages) pH / F'c(N-F) / UV peak / Sterility

ADSORPTION

10) + Alumine hydroxide

↓

Monovalent vaccine

→ discard supernatant

Saponine

11) Concentrated monovalent Vaccine (bulk) stored at +4°c (temp. recorded)

pH / Sterility (decantation adsorption test done by Rhone Merieux)

F'c Hemolysis 100% / pH

pH / sterility (Potency done by RM)

pH / sterility

TESTING OF THE CONCENTRATED MONOVALENT VACCINE

In vitro:

- pH
- Sterility

In vivo:

- on all batches → Serum Neutralization Test 3 weeks after vaccination
- On 58% of the volume of vaccine produced in 1985 → Bovine Potency according to the requirements of European Pharmacopea

BLENDING OF MONOVALENT

Vaccine (temp. recorded)

↓ vaccine vials, rubber stoppers

Bottling

↓

Bottled vaccine

Sterility tapes

TESTS PERFORMED ON THE BOTTLED VACCINE

In vitro: → pH, Sterility

In vivo: (on cattle free from FMD antibody) → Safety test according to the requirements of the European Pharmacopea

MANUFACTURE AND CONTROL SCHEME: TISSUE CULTURE RINDERPEST VACCINE

MANUFACTURE	CONTROL (BVI)
- BOVINE KIDNEY CELLS (frozen in liquid nitrogen) thoroughly tested received from Rhône Mérieux (Lyons, FRANCE)	
- CULTURE MEDIUM / Trypsin SERA (received tested from RM)	pH / at / sterility
- VIRUS STOCK (attenuated Kabete O strain) (received from RM and grown at BVI)	lack of exogen contaminant pH, virus yields sterility
1) Multiplication of cells cultured in roller bottles (3 passages)	cells counts, pH sterility
2) Virus production — 1st harvest — 2nd harvest ↓ Storage in -70°c freezer (temperature recorded)	
3) Testing on frozen antigen (on each harvest)	- pH - Sterility (bacteria, fungi and mycoplasms) - Virus yields - Lack of exogen contaminant
4) Freeze drying tested antigen + lyophilization substrate	pH / at / sterility
↓ ——— sample	sterility
bottling	
⋮ ——— sample	sterility - virus yields
lyophilization	
↓	
FREEZE DRIED VACCINE	

5) **Testing on freeze dried vaccine**

In Vitro:

- pH
- Sterility
- Virus yields (bacteria, fungi, mycoplasms)
- Lack of exogen contaminant
- (Stability - survival)

In Vivo:

- Non specific toxicity on mice
- " " " on guinea-pigs
- On cattle (free from Rinderpest antibody)
- Safety (one animal with 100 doses)
- Potency direct challenge with the Caprinised strain on one cattle vaccinated (1/10 of one dose) + 1/100 dose antibody titration 3 weeks after vaccination

} REQUIREMENTS OF OIE, FAO