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PHILIPPINES PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

DP/PHI/87/019

PHILIPPINES

Technical report: Production of Vaccines and Antisera*

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

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United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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   b) Improve quality control, if necessary.

3. Advice on the development of experienced and trained staff available for the production and advise on the needs in order to develop trained manpower for the production of vaccine and sera.

4. Submit a comprehensive report containing the observations and recomendations which will serve as a basis for the preparation of the overall development plan for the pharmaceutical industry.

Summary

This brief report reviews the three points indicated in my terms of reference.

The demands for vaccines and sera are increasing and diversifying year by year and of the vaccines used in the EPI programme, DPT, BCG, measles, oral polio, the basic vaccines for child-health, only BCG can be produced with confidence at BPS to meet budget demands. Tetanus toxoid, tetanus antitoxins and cobra antivenom can be regularly produced but are not EPI vaccines; DPT cannot reliably be produced. An additional 8 products are imported and sold: hepatitis B, measles, mumps, rubella, rabies and oral polio vaccines, various immunogamma-globulins and gas gangrene antiserum.

The Biological Production Services' prices for BCG, P0.5 per dose and tetanus toxoid, P1.67 per dose compare most favorably with hospital and drugstore prices which go as high as P 288 per dose for hepatitis B vaccine. Nevertheless, BPS costing should be re-examined to ensure the accuracy of these figures.

Several visits to the Alabang site showed that all features of the complex, buildings, grounds and services are quite unacceptable by modern GMP standards. Much good work is being done but physically the site in general is deteriorating. Much needs to be done quickly if production of the range of EPI vaccines and additional products is to be achieved. To expand and improve facilities to GMP standards and increase output rapidly, I recommend that consideration be given to developing a "turnkey" project with a major vaccine manufacturer through a "soft" loan from the World Bank or other funding agency. This will ensure the development of the site and the necessary new construction within 2 years.

Quality Control (QC) is well done within present limitations but more highly qualified and better trained staff, more equipment and better laboratories are needed if the present range of EPI vaccines is to be fully controlled. The development of new vaccines will mean additional responsibilities for QC. New QC laboratories should be a first priority in any new site development at Alabang.

For vaccine production to succeed in the Philippines I have recommended that career prospects and career structure at BPS be reviewed. BPS should have the status of a university department and be able to attract and retain young staff who can see themselves aspiring to be head of the Department. At this level, appointment from outside BPS should stop: the director should come from within. Salaries, too, should be commensurate with the improved status and responsibilities. To young scientist in the west, biotechnology is an exciting topic but bringing its discoveries to fruition depends on the capa- bilities of a production facility like Alabang. Nothing can be achieved if the discoveries cannot be turned into products of the standards recommended by WHO.

Introduction

In gathering the data for this report most of the people I met were located in Manila. In addition I made several visits to the Biological Production Services (BPS) of the Department of Health at Alabang, formerly the Alabang Vaccine Laboratory (Intercare Report) and to the National Institute of Biotechnology and Applied Microbiology (BIOTECH), University of the Philippines at Los Banos.

The following is a list of those who were kind enough to give me a few minutes of their time and to share their thoughts, ideas and experiences. Some were extremely hospitable and to them, all, I say "thank you". In many instances I met members of their departments particularly the production staff at BPS, with whom I spent much time. I hope I was able, in some small way, to help resolve some of their problems and to take some of the seeming "mystery" or "magic" out of the various production processes. As has been said of learning the calculus in mathematics "If one simpleton can do it, so can another."

People Met

Dr. Alfredo R.A. Bengzon, Secretary of Health
Mr. Rhais M. Gamboa, Undersecretary of Health
Dr. Quintin Kintanar, Assistant Secretary of Health
Dr. Bernardo Mora, Director, Biological Production Service,
Atty. Nicassio Tayao, Procurement Service, DOH
Dr. William G. Padolina, Biotech, UP, Los Baños
Dr. Edito Garcia, College of Public Health
Dr. Wilfredo Tiu, College of Public Health
Dr. Augusto L. Lingao, President MED-TEST
Dr. Saturnina C. Halos, Natural Science Research Institute, UP Diliman
Dr. Bernardo Resoso, Director, National Meat Inspection, Commision.
Dr. Thomas Maramba, Undersecretary of Health
Dr. Lui Xiring, WHO representative, Manila.
Dr. Ponciano Aberin, EPI representative.
Mr. Wilfred C. Rivera, President Tryco Corporation
Dr. Antonio Jacalne, College of Public Health
Dr. Benjamin Fontanilla, Bureau of Animal Industry
Dr. Pratima Kale, UNICEF Repesentative to the Philippines
Dr. Jaime Z. Galvez Tan, Programme Officer, UNICEF
Mr. Georges J. Leclerc, Counsellor (Development), Canadian Embassy
Mr. C.V. Campos, Senior Vice President, Cenel Development Corporation
Mr. C.L. Campos, Cenel Development Corporation

Demands for Vaccines and Sera and Costs of Locally Produced and Purchased Products

Immunization figures

With a population of 57,366,150 in the Philippines, the number of eligible for vaccination in the EPI scheme is calculated at 1,721,585 (EPI data, January to December, 1987). The target population to be immunized was set at 50 to 70 % of the eligible population in the 13 scheduled regions. In the great majority of cases this figure was well exceeded, the overall rates being:

DPT, 3 doses	73 % immunized
Oral polio, 3 doses	73 % immunized
BCG, Infants, 1 dose	92 % immunized
Measles, 1 dose	68 % immunized
Fully Immunized	62 % immunized

This is a commendable achievement. It is hoped to extend the level of fully immunized subjects to 90 % by 1990. These data refer to the use of EPI vaccines. There are no comparable data for the use of other vaccines, antisera and immunoglobulins purchased by hospitals and drugstore for non-EPI diseases. These products are reviewed later from the point of view of calculating the total amount spent on human biologicals (excluding Oresol, an oral rehydration salts product for cholera and diarrhoeas) in the Philippines. It should perhaps be pointed out that even if today the sum spent, probably about P50,000,000 is regarded as modest, failing a determined programme by the government of the Philippines to produce its own vaccines, it will face in the future regularly and massively increasing costs. This is inevitable as the cost of EPI vaccines rises, as the planned level of immunization increases and as newer vaccines are introduced.

Demands and Costs

These data were available to me from the BPS production budget estimates for 1989 from EPI usage and from data on private purchases by hospitals and drugstores.

The data given for hospitals' and drugstores' purchases were difficult to interpret. The range of products is much more extensive than that of the EPI and the products, in general, are much more expensive. The following is a list of these products, their total cost in pesos and whether purchased by hospitals or drugstores:

	Costs	
Product	Drugstores	Hospitals
Tetanus antitoxin	1,945,000	857,750
Hepatitis B vaccine	2,034,000	2,708,000
Rubella vaccine	6,000	233,000
Measles vaccine	6,000	292,300
Rabies vaccine	4,460,000	40,000
Oral Poliomyelitis vaccine	267,000	178,000
DPT vaccine	281,000	47,500
Gammaglobulins	3,349,000	2,597,000
(Mixed rabies,tetanus,pertussis, hepatitis gas gangrene antisera)	69,000	---
Totals	12,348,000	6,953,550
	19,301,550	

It will be seen that the total expenditure by hospitals and drugstores combined in 1987 was P 19,301,550: of that total P 6,953,550 was spent by hospitals and P 12,348,000 by drugstores. Since the cost per single dose was not available I have taken the projected WHO cost per dose for three EPI vaccines for 1985 and 1990, namely DPT, oral polio and measles and from the amount spent on these three products by hospitals and drugstores estimated the likely number of doses used:

	WHO/EPI cost ($)		Estimated no. of doses bought	
Product	1985	1990	Hospitals	Drugstore
DPT	0.038	0.047	62,500 to 50,532	369,737 to 298,936
Oral Polio	0.034	0.041	261,765 to 217,703	392,647 to 325,610
Measles	0.144	0.175	101,493 to 83,514	2,083 to 1,714

The budget estimates from BPS for production for 1989 are:

Freeze dried BCG vaccine	5,949,600 doses
Tetanus toxoid	5,284,320 doses
DPT vaccine *	3,718,500 doses
Oral Polio vaccine	7,437,000 doses
Measles vaccine	2,479,000 doses

Taken together with the private sales the estimates of the number of doses for three of the vaccines, namely DPT, oral polio and measles have to be revised upwards:

DPT	7,437,000 + 390,853 (average) = 7,827,853
Oral Polio	7,437,000 + 598,248 (average) = 8,035,248
Measles	2,479,000 + 94,403 (average) = 2,573,403

Of the other vaccines listed, the only other requirement BPS has to meet is for 5,949,600 doses of freeze dried BCG vaccine.

In the Intercare Report the production-estimates for 1989 made by the Department of Health, and allowing for wastage, are as follows:

BCG	3,793,231	to	3,855,177	av.	3,829,204
DPT	5,529,318	to	5,619,615	av.	5,574,467
Tetanus toxoid	4,355,427	to	4,426,552	av.	4,390,990
Oral Polio	5,529,318	to	5,619,615	av.	5,574,467
Measles	1,988,770	to	2,021,248	av.	2,005,009

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* The same amount to be obtained from UNICEF

Whether these are compared with the budget estimates of BPS for 1989 or with the BPS estimates together with the sales to hospitals and drugstores there are considerable discrepancies, except in the case of measles vaccine.

	Ministry Estimates	BPS Budget	BPS Budget + privates sales
BCG	3,829,204	5,949,600	5,949,600
TT	4,390,990	5,284,320	5,284,320
DPT	5,574,467	3,718,500	7,827,853
Oral Polio	5,574,467	7,437,000	8,035,248
Measles	2,005,009	2,479,000	2,573,403

Thus it is difficult to identify clearly the total demand for vaccines and it is perhaps wiser to accept the 1989 figure given for the BPS production budget together with the estimated sales to hospitals and drugstores. Discussions with BPS staff indicate that they have the capacity to produce the DPT, BCG and tetanus toxoid but because of problems with laboratory services (steam, air, water) fermenter maintenance and lack of spare parts it will be wise not to count on the availability of the total DPT budget.

The estimated BPS production costs of freeze-dried BCG vaccine and tetanus toxoid are P 0.505 and P 1.67 per single dose, respectively, thus for these two items, total expenditure will be :

BCG	5,949,600 doses at P 0.505 per dose =	P 3,004,548
Tetanus Toxoid	5,284,320 doses at P 1.67 per dose =	P 8,824,814
		P11,829,362

This figure, P 11,829,362 compares with the estimates total operating budget for BPS of P 27,000,000 for 1988 (Intercare Report). Since no account is taken of the cost of production of the other biologicals produced at BPS, the figures for costs must be regarded with extreme caution and almost certainly revised upwards.

Whilst the budget estimates for the number of doses of the different vaccines may be debatable as to whether they are high or low, it is clear that the costing and accounting system at BPS must be completely overhauled. Without a much more accurate set of costs the true cost of vaccines simply cannot be calculated and the level of subsidy will remain unknown. Equally, if it is the intention eventually that BPS offer products or services, such as diagnostic reagents, veterinary rabies vaccines, engineering maintenance to the public at a charge to yield some income, this is another reason why the accuracy of costing must be greatly improved.

Compared with the BPS costs, the figures given by Doctor Aberin, EPI, per dose of vaccines are as follows:

BCG	P 0.80, 1 dose given cost per child P 0.80
DPT	P 0.60, 3 doses given cost per child P 1.80
Polio	P 0.60, 3 doses given cost per child P 1.80
Measles	P 2.40, 1 dose given cost per child P 2.40
Tetanus toxoid	P 0.80, 2 doses given cost per child P 1.60

Thus of the 11 products listed as bneing bought by hospitals and drugstores, only BCG and tetanus toxoid, not strictly an EPI vaccine, can be produced reliably in the Philippines. Of the others, EPI programme requires, in addition, measles, DPT, polio and possibly rabies. The data "EPI accomplishment, January-December, 1987" show the number of doses of vaccine injected per child to be as follows:

DPT	3,783,330; with 25% wastage becomes 4,729,163
Polio	3,769,458; with 25% wastage becomes 4,711,823
BCG	1,577,384; with 50% wastage becomes 3,154,768
Measles	1,166,829; no figure for wastage

In the case of BCG the field workers want to increase the wastage figure to 75% giving a revised usage of 6,309,536 doses. The wastage is not caused by cold-chain breakdown but by the "dropping out" of children because of families moving and because the economics of production show a 20-dose ampoule to be the most cost-effective method of production at BPS. Yet if only one or two doses

are injected from an ampoule, 18 or 19 doses are lost. At present BPS is looking into ways of reducing these losses by increasing the range of doses per ampoule. Alternatively, production in rubber-stoppered vials may be much more economical. Thus in addition to the cost to hospitals and drugstores, the cost of supplying vaccines to the EPI is as follows:

BCG	6,309,536 doses (75% wastage) at P 0.8 per dose =	P 5,047,629
DPT	4,729,163 doses (25% wastage) at P 0.6 per dose =	P 2,837,498
Polio	4,711,823 doses (25% wastage) at P 0.6 per dose =	P 2,827,094
Measles	1,166,829 (no figure for wastage) P 2.4 per dose =	P 2,800,390
Total		P 13,512,611

The total cost to the Philippines for human biologicals is the sum of these figures:

EPI vaccines (excluding tetanus toxoid)	P 13,512,611
Hospitals	P 6,953,550
Drugstores	P 12,348,000
	P 32,814,161

This estimate is almost certainly low since so many of the figures have been arrived at by extrapolation. A true figure is possibly nearer P 50,000,000. It should be realized that this figure will inevitably continue to increase because demand for the vaccines used will increase with increased coverage by the EPI and because the number of vaccines in use will increase. Two new vaccines at present used in North America, human tissue culture rabies and hepatitis B, cost about P1000 per dose there and about P300 in the Philippines (fig. 1). These prices are artificial and represent the price the manufacturer needs to recover his development costs. The demand in the Philippines will continue to increase, as will the cost, yet the production of such products is well within the ability of a competent vaccine producer. If action is not taken to acquire and develop this ability the Philippines will be faced with the prospect of increasingly expensive yet essential vaccines.

For non-EPI biologicals the production costs at BPS are:

Inactivated typhoid vaccine		P1.92 per dose
Rabies vaccine,	Semple (goad brain, for humans)	P2.07 per dose
	Flury (chick embryo, for dogs)	P8.00 per dose
Tetanus antitoxin		P1.70 per dose
Cobra antivenom		P95.11 per vial
Oresol (oral rehydration salts)		P1.46 per packet

Concerning serum production the prosition, in general, is that many producers in Europe and North America discontinued serum production in the late 1960s because of rising costs and a diminishing market. Inevitably the prices of sera rose. In BPS the serum products are tetanus antitoxin and cobra antivenom. For the latter there is no substitute and its production must continue. It may even be advantageous to conduct a market-survey in South East Asia with a view to exporting this product. The alternative to tetanus antitoxin, prepared in horses, is tetanus antitoxin derived from human blood. This latter is an expensive product and although safer and giving longer lasting protection because it is homologous it is questionable whether its use in the Philippines can be justified except in emergencies. Being homologous it cannot induce a hypersensitivity reaction as can tetanus antitoxin prepared in horses. The real objective should be to immunize the whole population with adsorbed tetanus toxoid. Even in the emergency or casualty departments in hospitals tetanus toxoid should be given. If it appears to be ineffective then immunoglobulin or tetanus antitoxin should be given.

Two diseases of concern in the Philippines are malaria and schistosomiasis. In the case of the latter, much excellent work has been carried out locally by Dr. Garcia and Dr. Tiu at the College of Public Health. A glutathione-S-transferase enzyme has been shown to be both immunogenic and protective in mice. In laboratories elsewhere, especially in the United States, much successful work is also being carried out on malaria. Since, however, neither of these diseases affects Europe or North America to any great degree, any vaccine developed there will be expensive, in the same category as hepatitis B and rabies. It is, therefore, in the interests of the Philippines to pursue this work locally and

to develop preparations which can be made available at reasonable prices. The ideal approach would be through genetic engineering, analogous to the approach used with hepatitis B, where coding for the hepatitis surface antigen was transferred via E. coli to S. cerevisiae. This yeast vector could be produced in quantity in the bacterial vaccines section at BPS.

Examination of Existing Manufacturing Facilities and Programme to:

a. Expand and improve facilities to GMP standards and increase production output to meet the country's needs.
b. Improve quality control if necessary,

Choices for Procurement of Vaccines

The choices facing the authorities are:

1. Purchase of all EPI vaccines supplemented by local production at BPS: this will be an increasing cost.
2. Dependence on donations by international groups: this will become less reliable as time goes on and should be unacceptable to an independent country.
3. A mix of 1 and 2.
4. The use of a long-term, "soft" loan from the World Bank or other funding agency to enable a "turnkey" operation to be established in the Philippines. This will have the effect, once and for all, of establishing vaccine production in the Philippines as a highly developed science with excellent career prospects for young people, both graduates and non-graduates. Such an operation will be my main recommendation and it will be described in more detail later. Essentially, it will mean that, following agreement, site clearance and rehabilitation will start immediately. The order of construction of different laboratories, QC, bacterial vaccines, viral vaccines, small animal breeding and holding unit, will be decided in consultation between the Philippine authorities (BPS) and the contractor who will assume full responsibility for successful construction. Such an operation has been carried out in Pakistan and Indonesia and several are under discussion in China.

Expansion and Improvement of Facilities

It is doubtful that the buildings of the BPS at Alabang can be restored sufficiently well to comply with GMP recommendations. The cost will be too great. Attempts may be made to rehabilitate individual buildings but this is not a wise approach and cannot be recommended. Within some buildings laboratory facilities are good, particularly for pertussis vaccine and diphtheria toxin production. These laboratories should be kept operational until they can be transferred to a new location.

In order for BPS to meet the GMP standard of operation as soon as possible a fast and integrated approach to construction is necessary. Much of this has already been recommended in the excellent Intercare Report "Albang Vaccine Complex: A Medium-Term Development Plan" submited in August 1987. Whilst agreeing in general with the recommendations of the report I should like to give what I consider to be the appropriate construction priorities in order that BPS become a fully functional unit at GMP standards as soon as possible.

Essentially this amounts to a compression and rationalisation of the Intercare Report recommendations.

Phase 1

All activities in phase 1 to take place simultaneously:

a. Decide the location of buildings on the site.
b. Rehabilitate the site: surface roads, establish workshop/maintenance facility for servicing all new construction.
c. Secure services : clean, high-pressure steam, electricity with voltage regulation and emergency generator, oil-free, dry compressed air, pyrogen-free water.
d. Construct a new Quality Control Laboratory including provision of text-books, journals, reprints, and manufacturers' brochures.
e. Construct a new animal breeding and holding unit for mice, rabbits, guinea pigs and monkeys (for neurovirulence-testing of oral-polio vaccines).

Phase 2

a. Construct production laboratories for bacterial and viral vaccines.
b. Construct central washing, sterilising and media-production department.

c. Construct filling, packaging and despatch areas.
d. If possible, rehabilitate older buildings as warehouses. If not possible, construct warehouse for storage of chemicals and spare equipment.

Because of the area covered by the site at Alabang, it should be possible to maintain current production while this reconstruction is taking place. On the other hand, when transferring production to a new department, it is essential to have at least 6 to 9 months stock of product in order to obviate the interruptions which inevitably will arise.

The approximate costs for such a programme, based on estimates already made, are:

Rehabilitation of site	P 25,000,000
Quality Control	P 14,000,000
Animal Accomodation	P 6,000,000
Washing, sterilising, media	P 6,000,000
Filling, Packaging, dispatch	P 15,000,000
	P 66,000,000

The Intercare report suggests that the costs for equipment for the revitalised complex will be about P 116,000,000. This tends to consider possible new vaccine such as tissue culture rabies vaccines, measles-mumps-rubella, hepatitis B, the pneumococcal, meningococcal, and influenza polysaccharide vaccines and oral typhoid as requiring both new equipment and additional laboratory space. This is not necessarily so. If the quality control and bacterial vaccines sections are properly designed and equipped initially, the same staff and same equipment, with modest adjustments, will be adequate to carry out all the production. Already much good, modern equipment is available in the pertussis, diphtheria and tetanus sectors for DPT production. In my opinion, therefore, equipment should cost about P 80,000,000.

Rather than phase the reconstruction plan over 12 years, as envisaged in the Intercare report, I feel there is a much needed urgency to start as soon as possible and to initiate as much as possible so as to maintain momentum.

This will perhaps be most readily achieved by a "turnkey" operation in which the responsibility for construction, equipping and training is undertaken by an outside contractor.

The Intercare report describes the type of development envisaged for BPS over 12 years moving from today's readily made EPI bacterial vaccines, such as BCG and DTP, through the more difficult to produce EPI vaccines, such as oral polio and measles to the current sophisticated, genetically-engineered hepatitis B vaccine. This is a daunting programme for a well developed and equipped facility. It is quite unrealistic for BPS in the near future.

Many factors are contributing to this situation: the condition of buildings, the unsatisfactory supply of basic services, poor quality steam lacking pressure, insufficiently pure water and unreliable electricity. In viral vaccine production, failure of electricity leading to a rise in temperature in freezers may lead to the loss of valuable seed cultures with the consequent time factor needed for their replacement. As a matter of principle, valuable seeds should be kept in freezers in two separate locations, served by different sources of electricity. Until such basic needs are secured, attempts to sustain even present production levels, before aspiring to new and highly sophisticated products, are likely to be subject to great uncertainty.

With regard to equipment at present available, a 40-litre fermenter operating 40 times per year, the average for a well running production laboratory, will produce per run about 84,000 doses of pertussis vaccine at 60 OU and 70% recovery or 140,000 doses of diphtheria toxoid at 250 Lf and 50% recovery. The maximum annual requirement I have been able to estimate for DTP is 7,827,853 doses. This is equivalent to 7,827,853 / 84,000 = 94 fermenter runs for pertussis and 56 for diphtheria. It is thus not possible to meet such a budget with the present fermenters. If we assume 40 runs per year for both units, the maximum attainable production, balancing diphtheria and pertussis, is approximately 4.2 million doses. Because of unreliability of services, lack of spare parts and non availability of maintenance at Alabang this figure is clearly unattainable. Both 40 litres fermenters should be replaced by a 250 litres unit with a working capacity of 180 to 200 litres. At 180 litres of medium, the target of 8,000,000 doses of DTP can be achieved in 40 runs under ideal conditions, 15 runs for diphtheria and 25 for pertussis yielding

10.63 million doses of each. It should always be remembered that you can put 100 litres into a 250-litre fermenter but you cannot put 250 litres into a 100-litre fermenter. No new skills are needed in operating the larger fermentors but, in terms of the flow diagram for equipment, the capacity to produce large volumes of medium and to process large volumes of end product must also be in available.

Similarly, in tetanus toxin production: the present 140-litre fermenter gives only a marginal economic benefit over bottle culture in terms of cost effectiveness. A 250-litre unit with a working volume of 200 litres is a much more realistic approach. Such units today, fully instrumented, cost about P3-4,000,000.

I am emphasizing this equipment as the major means of increasing production capacity. The staff at BPS have already mastered the technology and no new skills are necessary; if the fermenter comes from a new supplier, a short course in order to become familiar with its operation will be helpful. This can usually be arranged in another laboratory already using the same type of unit. It is not necessary to arrange this through WHO. It is clear, however, that to meet the increasing demands of the EPI budget, including production losses and field wastage, thought must be given to increasing the scale of production at BPS, not only in terms of the size of buildings but also in the size of equipment. This can be done while site improvement is going on because the laboratories for diphtheria, pertussis and tetanus are at present in reasonably good condition.

Concerning the type of equipment which can, with benefit, be offered to a Third World country such as the Philippines, advice should take better cognisance of the practicalities of operation in such countries. Firstly, it is somewhat misleading to talk of a 250-litre fermenter without further qualification: more important is the fact that the maximum working volume in such a vessel is 180 to 200 litres. Again, in the case of pertussis vaccine and diphtheria toxoid, such a vessel, in a well run laboratory in Europe or North America, is generally used, at most, once per week, and 40 times per year. The growth of both diphtheria and pertussis takes 48 to 72 hours; the rest of the week represents "down time": cleaning, maintenance, sterilising and refilling

with medium. A highly proficient production unit, too, will only likely operate a fermenter 40 times per year because of staff holidays, extended maintenance and unforeseen problems. On this basis with a working volume of 180 litres in a "250 litre" fermenter, each run for diphtheria toxin/toxoid production, yielding on average 180 Lf per ml and allowing for 50% processing losses, will give 648,000 doses of toxoid at 25 Lf per dose. Similarly for pertussis vaccine at 40 OU per ml, 20 OU per dose and allowing for 30% processing losses, each run will yield 252,000 doses. These yields, the average in developed countries, have not yet been achieved at BPS. If the same fermenter is used for both products, the ratio of runs should be 3 or 4 of pertussis to 1 of diphtheria to maintain a balance between the two for DTP production. With the 2 x 40 litre fermenters a Alabang maximum attainable output under ideal conditions about 5 million doses of pertussis and diptheria, insufficient to meet the 1989 estimated budget forecasts. Again I emphasize that these figures are calculated on optimum production capability in developed countries.

Similarly, other equipment, upstream for preparation of media and downstream, centrifuges, metafilter, ultrafilters, filter presses, for processing of product should have the capacity to process output within a reasonable time, certainly within 4 hours in the absence of a preservative e.g. diphtheria toxins.

Tables 1 - 3 gives data on the number of doses of diphtheria and tetanus toxoids and of pertussis vaccine obtainable with different rates of production and yield and with growth vessels of different capacities. Under optimum conditions, in a well organised department in a developed country, 40 runs per fermenter per year can be anticipated. Since few, if any, Third World countries routinely operate large fermenters 100 l or greater, their production problems are evident. Thus at BPS, with 2 x 40-litre Bilthoven fermenters for diphtheria toxoid and pertussis vaccine production, maximum output, based on the standards of developed countries is about 5 x 10^6 doses. It is clear from these data for fermenter yields that more thought should be given to the types of equipment given to or requested by Third World countries. Account should be taken of both anticipated budget demands, with projected increases over a period of 10 years, and technical ability to use and service such equipment. Similarly, table 4 shows the growth surface available for the growth of tissue cells for virus vaccine production given by different cell

culture systems. The great advantage of the multiple tube and perfused microcarrier systems over earlier systems is obvious.

Much more thought must also be given to the type of assistance requested through the services of consultants. Apart from the major strengthening of basic services already mentioned all production work with modern equipment needs two types of consultant, the one skilled in the technical or engineering aspects of the equipment who can sustain it in operation, and who will have a basic knowledge of the biological implications of the work, the other a skilled fermenter microbiologist whose orientation is mainly production microbiology, which also includes downstream processing, and with a basic knowledge of fermenter engineering. It is both pointless and unfair to expect the highly complex maintenance of modern equipment to be carried out either by normal maintenance engineers or by the production staff. These comments do not apply to modern electronic equipment which needs highly specialised servicing preferably replacement of non operating modules.

This dual form of technical support, if properly developed, will have a number of consequences:

1. Local expertise will be available at BPS to maintain modern biological production equipment.
2. This expertise can be offered as a service to organizations outside BPS as a source of revenue.
3. The use of fermenters and all downstream processing equipment will become continuous, production will be uninterrupted and serious thought can be given to the products requiring new sophisticated technology such as tissue culture measles and rabies vaccines, yeast (or tissue culture) derived hepatitis B vaccine and the polysaccharide vaccines.

Reference is not made here to viral vaccine production. This should not be undertaken until new premises are available or until there has been training in the latest technologies which carry a much lower risk of contamination and which may be carried out in some of the existing buildings.

With regard to bacterial and viral-vaccine production, the construction of these units need not be sequential. The present laboratories for pertussis vaccine and diphtheria and tetanus toxins can maintain current production while

new construction is underway. The new section, however, should be for bacterial vaccines in general: it will handle, pertussis, diphtheria, yeast-derived hepatitis B, polysaccharide vaccines, attenuated typhoid vaccine, as and when it is decided to undertake these projects. The laboratories should be constructed as to make the most rational use of shared equipment. All of these products are compatible with one another. The basic starting material, the bacteria, can be produced by a group of well trained fermenter technologists. The downstream processing, thereafter, is a matter of the extent of a team's technical ability.

In the case of viral vaccine production there seems to be pressure from the vaccine donating agencies that this activity should be developed as soon as possible as a step towards self sufficiency in the Philippines. For this reason, construction of the necessary facilities should begin in parallel with the construction of the bacterial vaccines section, possibly even earlier if so decided. The main targets would be oral polio, measles and rabies vaccines. The basic technology needed for all of these is training in modern methods of tissue culture, either in multiple tube units (Fig. 2 and 3) or on microcarrier beads. Bottle culture should not be contemplated. Table 4 gives the cell yield from different cell culture systems.

The number of Third World countries undertaking viral vaccine production is limited. There are a number of reasons for this, but the main difficulty is in the number of bottles needed in the original, basic, cell culture stage, the procurement of bottles, either because of high cost or poor availability, and the maintenance of purity (absence of contamination) throughout the process. These problems can be largely obviated today by the use of the microcarrier system for cell culture. In this, the tissue cells grow on the surface of polymer beads (Cytodex) rather than on the surface of culture medium. Because of the small size of the beads (100-200u) there is a large surface for the growth of cells. The latest development in this system is to increase the original concentration of beads from 2-3% to 25-50%. This is accompanied by continuous perfusion of medium but the growth vessel need be no larger than 5 litres. The system closely resembles the steady state growth of bacteria in a fermenter. In the improved system, in a 5-litre growth vessel, 1.5 million doses of inactivated (Salk) polio can be produced. The growth vessel itself can be accommodated in a laminar flow cabinet thus reducing further risk of contamination. For the first time viral vaccine production may well be within

the reach of Third World countries. This seeming "quantum leap" in production technology should enable these countries to avoid the frustration and disappointments of the commoner bottle culture method of production. Also, in this context, when "technology transfer" is being discussed for Third World countries, this should be the technology of choice for viral vaccine production. Bottle culture should become a thing of the past.

Type of new technology recommended for BPS

It is important that any new technology acquired for vaccine production, bacterial or viral, be 1988 technology and be evaluated in conjunction with existing equipment in order to ensure a smooth production flow. For example, a large fermenter followed by a small centrifuge for recovery of bacteria defeats the cost-benefit of large scale fermenter production. Fermenter design has changed little in 20 years except for more automation and computer control. The stirring or drive mechanism may be conventional motor drive through a shaft seal or magnetic. Because of difficult maintenance problems with shaft seals a magnetic drive is to be preferred.

The most useful type of centrifuge for general large scale separation of bacteria is a Sharples. It is much cheaper than any of the sterilisable, continuous rated models and bacteria can be readily recovered aseptically from its collecting bowl in a laminar flow cabinet. A number of spare collecting bowls should be available, commensurate with the volume to be processed: maintenance is simple.

The ultrafilter is a relatively new, multi purpose unit: it can be used for dialysis (removal of ammonium sulphate in toxin/toxoid purification), concentration and purification of proteins, separation of bacteria from culture fluid (an alternative to centrifugation), concentration of bacteria together with high molecular weight extracellular molecules in versatility lies in the judicious selection of membranes which are autoclavable and which, if carefully handled, can last up to 2 years. There are no moving parts and only the high pressure pump which feeds the unit needs maintenance. Such units are made by Millipore, Gelman, Satorius and New Brunswick. A different type of unit, a hollow fibre unit made by Amicon is also useful but not so versatile.

Multi-membrane filtration technology is developing fast and in Europe, Japan and North America has largely replaced pad filtration. It is expensive, however, and the correct time must be chosen when to change from pad filtration. The housings for the filters are of stainless steel, and the whole unit is much easier to assemble than a pad filter. In order to remove all fibres from products, where pad filtration is still used, the final filtration step in manufacture where possible should be through a membrane filter. No maintenance is needed.

Column-chromotographic methods for protein and virus-purification are becoming common. Again they are simpler, usually automated and need no major mechanical expertise for maintenance.

In viral-vaccine production it is essential that either multiple-tube or advanced microcarrier-bead technology be adopted. The bottle-culture technology of a few years ago is too susceptible to contamination to be considered for use today in a Third World country. Furthermore, to master the use of one of these technologies for the production of a single viral-vaccine is to master the ability to produce all viral-vaccines.

Turnkey Operation

This kind of operation is the most dependable means of bringing a unit into production as quickly as possible. The preliminary stages are usually an evaluation of the existing infrastructure (roads, estate management, buildings, necessary site preparation) followed by recommendations for engineering design (general services such as steam, water, air, electricity), project-management and costing. Process design may be included at this stage: in the case of viral vaccine production it should be discussed but in the case of QC and bacterial vaccine production it may be better to talk of process improvement. Such an operation is expensive and the details of what is needed should be carefully discussed before entering into any agreement. If considered, staff will be trained in the contractor's facility abroad with language training too, where needed. There, they will produce and test, firstly under supervision

then by themselves so that on return to the new facility they are able to initiate and control production. The new facility is finally accepted only when the local group (BPS) is fully satisfied that construction is to GMP recommendations and training is of the standard to enable them to produce vaccines routinely to WHO recommendations of purity, safety and efficacy. Such an operation, depending on its scope, may be expected to take 2 to 3 years to complete.

Veterinary Vaccine Production

Emphasis throughout this report has been on the production of human vaccines for use in the EPI programme. Some veterinary vaccines are also produced in the Philippines and I was able to talk with staff in the production laboratory at BIOTECH, Los Banos, with Mr. Wilfredo Rivera of Tryco Corporation which manufactures a number of veterinary vaccines and who is keen to expand his facility, with Messrs. C.V. and C.L. Campos of Cenel Development Corporation which is considering entering the vaccine field and with Dr. Benjamin Fontanilla, Head of the Bureau Animal Industry, of the Department of Agriculture which produces some vaccines and controls imported products (Table 5).

BIOTECH manufactures two vaccines against *Pasteurella multocida:* these are used in carabao, cattle and swine. Tryco Corporation also manufactures a number of vaccines, but neither BIOTECH nor Tryco vaccines appear in the approved list of vaccines of April 1988 issued by the Bureau of Animal Industry. The BAI produces pasteurella vaccine, anthrax spore vaccine, brucella antigen and a number of pharmaceutical preparation. Its production facility is in poor condition. One of its main activities is monitoring imported vaccines, mainly sterility and safety testing, less frequently potency testing which is expensive.

The quality control laboratories are clean, well-equipped and well designed. Dr. Fontanilla hopes to expand his bacterial vaccine production section and has just taken delivery of a 150-litre New Brunswich Scientific fermenter to increase the output of pasteurella vaccines.

In most developed countries commercial manufacturers produce human and veterinary vaccines in the same facility, except where there are known incompatibilities. Where government laboratories are involved in production there are usually separate production units as is the case in the Philippines. There is little or no contact between BPS and BAI and it does not seem productive, at present, to discuss a common production facility in spite of the obvious benefits and economics.

The lack of recognition in the Philippines of the "national herd", the basic livestock population of a country, is surprising. In most Third World countries the national herd is considered to be a such great economic importance that major programme for its sustenance are usually undertaken, often with the help of the Food and Agricultural Organization (FAO) of the United Nations. This is not the case in the Philippines. Veterinary vaccine production, as a consequence, is not well organised. Government production at the Bureau of Animal Industry is poor but quality control of imported vaccines, particularly for safety and sterility, seems to be regularly carried out. Private interests in the veterinary field find controls irksome and their failure to co-operate makes the job of the BAI more difficult. Recognition of the importance of the national herd could mean, initially, input from FAO. Thus strengthened, BAI would be in a better position to control local (Philippines) production and aim at more effective control than is at present exercised. Eventually the private sector would come to acknowledge the necessary role played by BAI and this could lead to better overall organization of the production of veterinary biologicals in the Philippines. Any consideration of joint production of human and veterinary vaccines at say BPS must await the development of veterinary production. From a scientific point of view there is no valid reason why production cannot be organized in a single, well designed laboratory. There is much compatibility between human and veterinary bacterial vaccines. Where incompatibilities are recognised it is not because a product is human or veterinary but because a product presents a potential hazard to the end user. Tetanus toxin production is segregated because of the potential risk of viable tetanus spores findings their way into other products were tetanus toxin produced in the same facility. Since tetanus toxoid is used in both humans and horses, it is clearly illogical to designate separate production areas for human and veterinary tetanus toxoid.

Involvement of Private Industry

Vaccine manufacture in Western Europe and North America is carried out mainly by companies which have several other areas of interest in the pharmaceutical industry e.g. Burroughs Wellcome, Merieux, Behringwerke, Swiss Serum Laboratories, Connaught Laboratories, Smith Kline-RIT. As a result, these companies have their own large pool of scientific manpower. In addition they offer attractive salaries and good career prospects for young people graduating from university. Such a structure and career prospects are not available to any great degree in the Philippines. Were private industry to become involved in the production of biologicals it would result in a drain of staff, principally from Alabang, possibly also from other university groups attempting to develop some degree of competence in vaccine production. Thus, the very objective that is intended to be achieved, the establishment of a viable vaccine production capability in the Philippines, would not be achieved and simultaneously the existing capability would be badly damaged if not destroyed. At some later date, were private industry to wish to cease production because of low profitability, the government would be faced with the choice either of subsidising the industry or of trying to re-establish what had been destroyed: its own production capability. Either way it would be faced with massive increases in costs and also as a threat to supplies. It takes a long time to develop a private industry because of the businessman's dislike of the controls which are essential. This can also lead to poor relationships between the national control laboratory, operating in the public interest and the private producer. For these reasons I cannot see any case for the involvement of private business in the human vaccine field.

Complementary to this, my discussions with members of the private sector show that their first concern is profitability. They seem to prefer joint-ventures with overseas companies in order to give themselves a "name" to attach to their product so that it will sell. Their view is that locally produced products sold under local proprietorship have a poor image with the public. This is sad indeed but is another reason why the private sector cannot be considered as a potential, viable partner in the field of human vaccines in the foreseeable future.

Staff and Training

The requirements for the production and control of products to meet WHO recommendations are well understood but the seems to be a degree of temerity in insisting on their application. The role of QC is not passive. It should be in the forefront, as a collaborative partner, in assisting the production department with the development of their quality assurance programmes and it should, by right, insist on the importance of aiming at all times at GMP standards. Whilst this insistence is hardly feasible at present, the awareness is the responsibility of both the head of QC and the director of BPS. Thus QC must be aware at all times of these two main responsibilities, apart from the routine testing for which it is responsible. These three functions should be constantly performed whether QC at Alabang remains in its present physically unacceptable and underequipped laboratories or moves to new premises. Its responsibilities remain the same. In the event of a new building programme being undertaken, e.g. a turnkey operation, it will then become the responsibility of QC to ensure that the new laboratories are maintained at GMP levels. This will also need the vigorous support of the director.

The new laboratory will serve initially both as the BPS production QC laboratory and as the national control laboratory. Additional training should consist of regular upgrading in the national QC laboratories of recognized stature outside the Philippines e.g. London, Copenhagen, Belgrade, Budapest, Utrecht, Canberra. It is also essential that the laboratory be on the WHO mailing list so that it receives regular updating of the WHO recommendations pertaining to the products in which BPS has an interest, not just those it produces at present.

By testing products coming from outside the Philippines, and this should be extended the included vaccines purchased by hospitals and drugstores, the QC laboratory will achieve several important ends:

1. It will become familiar with a wide and increasing range of test methods.

2. It will ensure the quality of products from abroad being used in the Philippines.

3. It will be in a position to monitor the production and quality of new products as they are developed at BPS.

4. It will develop a knowledgeable and highly skilled staff.

Quality of staffing is most important. In all BPS departments the present staff is of high quality and does an excellent job within its capabilities of training, facilities and equipment. The staff, however, is aging and provision must be made for a career structure to attract and retain young people. The requirements are academic training, career prospects and respectable salaries: these points will be discussed in detail later (section 3).

Space and Equipment

Two other important factors are space and equipment. A QC facility to monitor vaccine-production for a population of 50 million should ideally cover an area of about 400 square metres with further 300 sq.m. for small animal accomodation. The recommendations in the Intercare report appear to be over generous but at a building cost of P8000 per sq.m. a new QC laboratory will still cost about P3,200,000 and animal accomodation should be separate from the breeding facility.

Without commenting on the present equipment position at BPS, the following is a list of the minimum needs for a good QC laboratory testing to WHO recommendations. It is assumed that electricity, gas, water (hot and cold), clean steam, dry, oil-free air and washing up facilities will be available. Other specific equipment should include:

For chemical biochemical and immunochemical controls

Glassware, chemicals, pH meters, Kjedahl equipment, spectrophotometers, balances, centrifuges, electrophoresis equipment, waterbaths, refrigerator,

freezer, homogeniser, shakers, filters.

Where testing for DNA and RNA is undertaken additional needs are provision for handling, storage and disposal of radioactive material, dark room, scintillation counter, equipment for monitoring radioactivity, high speed centrifuge, spectrophotometer, UV photography equipment, controlled-environment incubator shaker, refrigerator, deep-freezes ($-20^{o}C$,$-70^{o}C$), mixers, balances and other general equipment.

For microbiological testing

Laminar-flow cabinets, incubators, refrigerator, deep-freezes ($-20^{o}C$,$-70^{o}C$), microscope (including fluorescent attachment for mycoplasma testing), anaerobic equipment, centrifuges.

For viral-vaccine testing

Laminar-flow safety cabinets, refrigerators, deep-freezes ($-20^{o}C$,$-70^{o}C$), liquid nitrogen containers, freezing equipment for cell-cultures, centrifuges, incubators, egg incubator, waterbaths, microscope (in- cluding fluorescence), microtitration equipment.

Much of the equipment for chemical biochemical, immunochemical and microbiological testing will already be available. Little of the viral-vaccine testing equipment will be. These are meant to be basic check-lists and the necessary item should be obtained as needed.

The use of some of this equipment may call for specialized training. This should from part of the programme for staffs visiting and working in overseas QC laboratories.

Small animal accomodation

It has already been stated that about 300 sq.m. is necessary for the establishment of a QC small-animal house meeting GMP standard. A further 100sq.m. is necessary for breeding.

Good biological science cannot be performed with poor animals. No matter how good one's basic stock is of mice, guinea pigs and rabbits, it cannot retain its genetic vigour if it is not well housed and well fed. The establishment of both a breeding and working facility is essential for the successful operation of the QC laboratory and for the provision of animals to the different production areas. Nothing of the present facility should be retained: in spite of the best efforts of the staff to maintain a good level of hygiene, this is not possible. I do not consider it an advantage here to go into details of building plans. The general principles, building standards and materials of construction are well described in a number of readily available publications cited in the references.

Literature

One of the weakest points I have found at BPS and at other laboratories in the Manila area is the lack of literature: text-books, journals, current reprints and manufacturers' brochures. It should be realised that even today there are few text books available on vaccine production: the publication by WHO (BLG/UNDP/77.1-3 and the manual provided by RIVM are possibly the most useful). Vaccine-production, however, is a young and growing science and should be continually in search of new ideas for the development of new products and the improvement of current product and methods of production. In these contents, text-books, which should be continuously updated, are essential for basic knowledge in bacteriology, virology, tissue-culture, biochemistry, chemistry and other related sciences involved in the development and production and QC of biological products. Journals are essential for the flow of ideas necessary to improve existing products and to develop new ones.

Manufacture's brochures are useful as a guide to improvements taking place in equipment e.g. membrane filtration (ultrafiltration), laminar flow equipment, magnetic drives for fermenters (which minimize needs for servicing), micro-carrier technology for virus vaccine production. It is essential to understand the vaccine production is dynamic, not static, and that new or improved equipment, with knowledgeable costing of the equipment, can result in cheaper and more efficient processes. Perhaps the best example today is the improved micro carrier technology for cell culture & vaccine production developed at the

Institute Armand Frappier in Laval, Quebec, Canada. With this technology 1.5 million doses of inactivated (Salk) polio vaccine can be produced in a 5-litre vessel, costing P200,000, which can be placed in a laminar-flow cabinet Thus, for the first time viral vaccine production becomes possible in Third World countries without the earlier major problem of contamination. Such a development was made possible by careful examination of manufacturers' brochures and the recognition that appropriate equipement was available although not at that time being used for this purpose.

An early and essential part of development at BPS, therefore, is the creation of a well stocked and continuously updated library. Since QC should be the first department to be reconstructed it should also be responsible for initiating the collection of literature. Separate accomodation, where staff can set quietly and read, should be an ultimate objective but temporary accomodation is acceptable at present. The main concern should be the collection and sharing among department of current literature.

A further additional responsibility of the library should be that of obtaining reprints from colleagues in other parts of the world on topics of interest, on alternatively photocopies of necessary publication. There seems to be great reluctance on the part of the staff to request reprints by writing yet this is standard practice in North America, Europe and Japan. It is also how colleagues working in the same field keep in contact and exchange information. Most important of all, it is a cheaper and better method of staying up-to-date in a particular field than either by text-books or journals. Acquisition of reprints and international correspondence must be encouraged and greatly increased.

Eventually the whole question of literature should be the responsibility of individual departments. However, because of the existing good inter departmental relationships at BPS it is better that this be centrally organized in the beginning. At a later date any desired fragmentation consider benificial can take place. Thus, I recommend that QC be given this responsibility.

Development of Experienced and Trained Staff

The most important need in vaccine production in the Philippines today is a clear indication from the government that it is ready and willing to suport fully the extensive upgrading of buildings and personel needed to turn BPS, into a modern facility producing both the full range of EPI vaccines and other vaccines currently imported at high prices. If there is any doubt that this can be done I suggest that reference be made to Biofarma, Bandung, Indonesia, which has a superb production facility. In April 1988 it made application to UNICEF to be recognized as a supplier of bacterial vaccines of WHO quality. If this can be achieved in Indonesia surely it can also be achieved in the Philippines

Concerning the upgrading of staff it must first be understood that there is no substitute for experience. It should become standard practice that the production director of BPS be either someone of long experience in vaccine production, either from outside BPS or promoted from within, preferably the latter. Where experience is lacking, the production director is obliged to accept advice from technical staff yet still be responsible for decision making. This is an unenviable position and not likely to result in good or meaningful decisions. The position of production director at BPS should also be seen as of major importance in the production of biologicals in the Philippines and in the academic community in general: it should be so recognized at the highest levels of government, should be strongly supported there and the production director should be expected to grow with the organization over a period of 5 to 10 years. If, however, being a director of BPS is to be regarded as a stepping stone to a more senior appointment the succesful production of biologicals cannot be achieved: nor will it be held in high regard in the academic community or become a profession which will attract good, enthusiastic, young scientist, a profession in which one can take pride. The present duration, if it is possible, will benefit greatly from 6 to 12 months leave of absence for intensive orientation in good production and QC laboratories in different parts of the world. Should the Philippine authority decide to choose a turnkey operation to revitalize BPS, this might be the time for the production director's leave of absence. He should be replaced temporarily by a consultant as acting director.

It is necessary also to appoint a deputy director. The production director at present has many responsibilities other than that of director of BPS and this too, tends to downgrade the position. Being director is a full time job. Equally a deputy, preferably a member of the production staff, should be fully qualified, capable of running BPS in the director's absence and the person of choice to succeed him in the event of his promotion. This feature of organization should become permanent: a head and a deputy head.

With the main body of the production staff, there is also a serious problem in that they are aging: four, at least, are grandmothers, others are just about to retire. The heads of sections, Q.C., bacterial vaccines, viral vaccines should be of Ph.D. level and in each section there should be one or two BScs or equivalent together with appropriate technical staffs. These senior qualifications are necessary in order to emphasize the importance of the individual positions and of vaccine production as a young, dynamic and highly respected science. The position of director need not necessarily be filled by a medical graduate which in turn makes it possible for a head of section to become the director. Nevertheless, there must always be access to medical advice where the situation warrants.

Small animal breeding should be under the direct control of a veterinarian or, as a minimum, the staff should have access to the advice of a veterinarian. Because of the mix of animals (and reptiles) at Alabang, which includes mice, rabbits, guinea pigs, goats, horses, sheep and ducks, the preferred course will be to have a veterinarian in charge.

The salaries paid to staff reflect their position in the community. I cannot comment on salaries in the Philippines but from the Intercare report and other sources it seems clear the inadequate salaries are a major factor in the inability to attract young, ambitious staff. Salary is not the only factor in generating staff-satisfaction. It seems that for too long there has been a tendency to count on the loyalty of staff at Alabang rather than to reward them with better salaries and with respect. The whole operation should be upgraded to the status of a university department, with commensurate increases in salary, so that staff will wish to remain at BPS and develop their talents.

In this way the Philippines will develop a biologicals industry of which it can be proud.

Overall, what appears to be lacking at BPS is active, knowledgeable initiative. Too much seems to be passive. This is understandable with the frequent change of director but in this situation morale suffers and initiative shrinks. To remedy this situation, stability is needed at the level of director. The director, too, should have professional advice on organization, budget and production planning, general management and costing. All of this should contribute to an atmosphere of high efficiency and anticipated achievement. No scientist can accept an inefficient way of working and efficiency certainly can and should be improved at BPS. There is no need to want for new building programmes to set such changes in motion, but a word of caution. Valuable as input may be from professional business advisers it must be remembered that the final decisions should be taken by the scientific staff. Advisers should be "on tap", not "on top".

The difficulty in sustaining a high and continuing level of expertise in vaccine production in the Philippines arises from the small number of people involved. In the West and in Japan with many more people involved, the opportunities for contact and exchange of ideas are much more numerous. One step which could be taken locally would be to arrange meetings of those engaged in production, from meetings of those engaged in production, from BIOTECH, BAI, BPS, the private sector if necessary, for exchanges of ideas and experiences.

Overseas training is useful, but, as a rule too infrequent for regular updating of activities. Care must be exercised in the choice of candidates for such training. The optimum period should be 3 to 6 months and candidates should be, preferably, senior members of staff. They will be in positions of authority so that on return they can begin to implement what they have learned. Younger members of staff generally lack this authority so that their enthusiasm is dampened when not too much attention is paid to their recommendations. Occassionally they may be even resented because of their good fortune to be trained abroad and this, in turn, is bad for departmental morale.

Recommended Reading

Biosafety in Microbiological and Biomedical Laboratories. CDC-NIH, US Government Printing Office, Washington, D.C. 1984.

Manual of details of tests required on final vaccines used in the WHO expanded programme of immunization. BLG/UNDP/82.1 Rev. 1 1982 and September 1985. WHO, Geneva 1985.

Manual for the design, equipping and staffing of facilities for production and quality control of bacterial vaccines. BLG/UNDP/78.1. WHO, Geneva 1978.

Manuals for the production and control of vaccines. Diphtheria toxoid, tetanus toxoid, pertussis vaccine. BLG/UNDP/77.1-3. WHO, Geneva 1977.

Prospects for production of vaccines and other immunizing agents in developing countries. Sectoral Studies Series No. 4 UNIDO/15.402, 1983.

The challenge of biological technology transfer to developing countries. UNIDO secretariat. ID/WG.466/10 (Spec) 1987.

Technology tranfer of production, control and application of vaccines. R.H. Tiesjema. Regional meeting on production and distribvution of biologi- cals for human and veterinary use in Dakar, Africa. September-October 1987.

Production of biologicals (phase 1) a survey. Technical report: the supply of EPI vaccines in the ASEAN countries UNIDO 10/R.17 1987.

Alabang Vaccine Complex: a medium-term development plan. Intercare: Integrate Health Care Services Inc. Manila, 1987.

Hepatitis B & Liver Cancer

Hepatitis B is an incurable disease. It may progress to chronic liver disease, cirrhosis or liver cancer.*

Hepatitis B infection can be prevented through vaccination. Three doses are necessary for proper immunization.

See your doctor for the schedule of the three doses. Prevent hepatitis B.

P290 PER DOSE!

A public service by
SmithKline Biologicals

*WHO Technical Report Series 691, 1983, pp. 1-30.

Figure 1. Availability of hepatitis B vaccine in the private market.

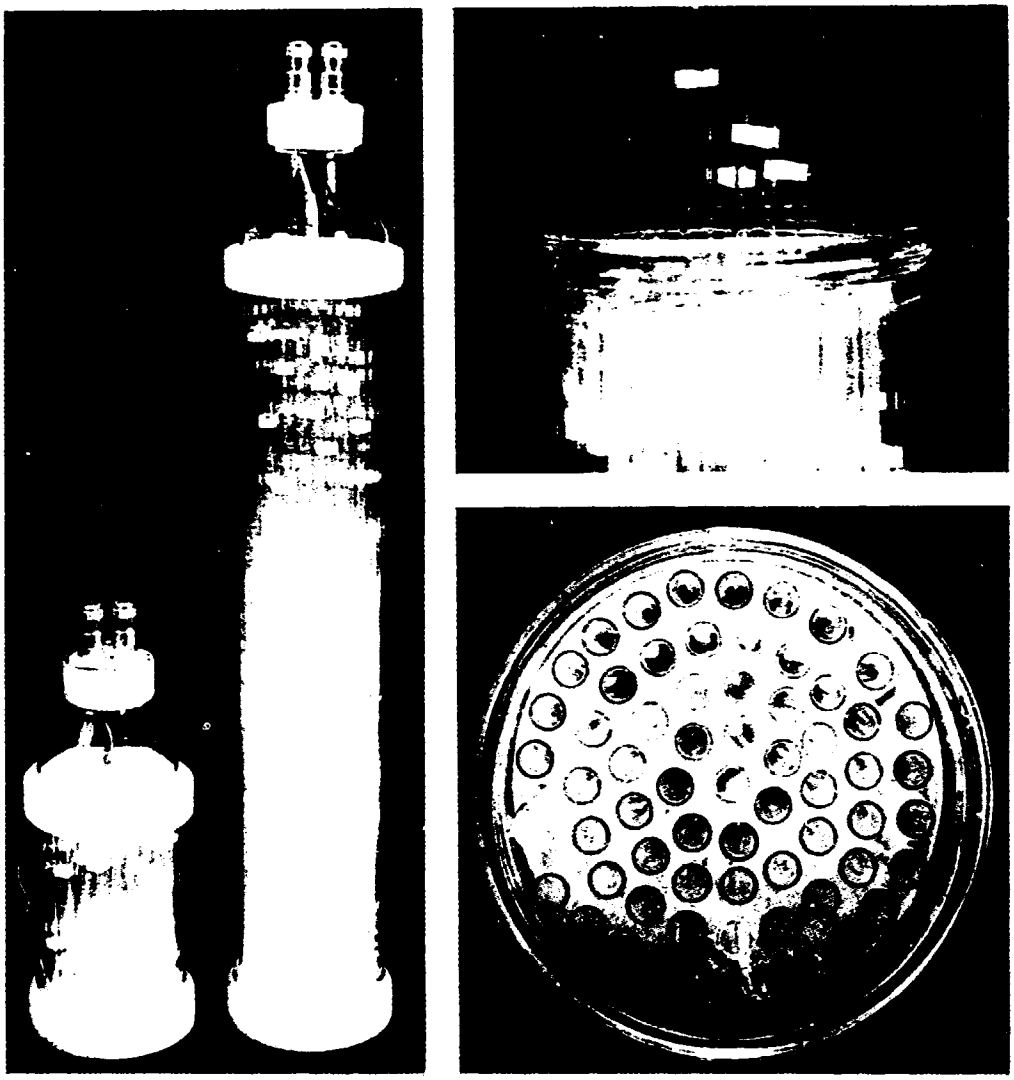
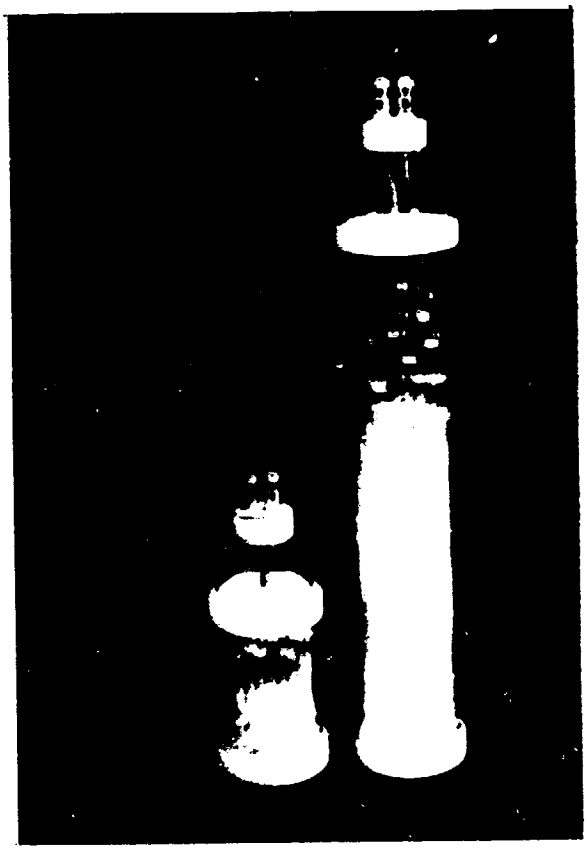
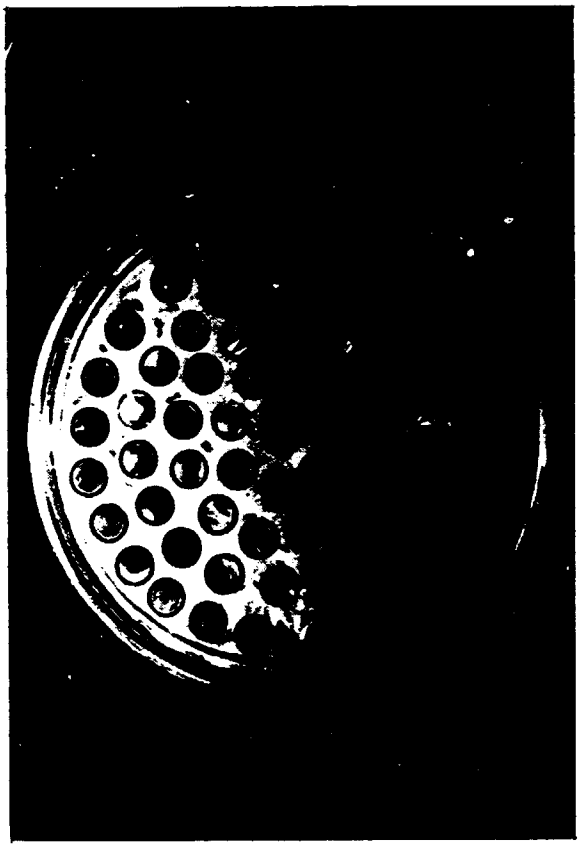


Figure 2. Section and plan of single unit of multiple tube tissue culture apparatus.





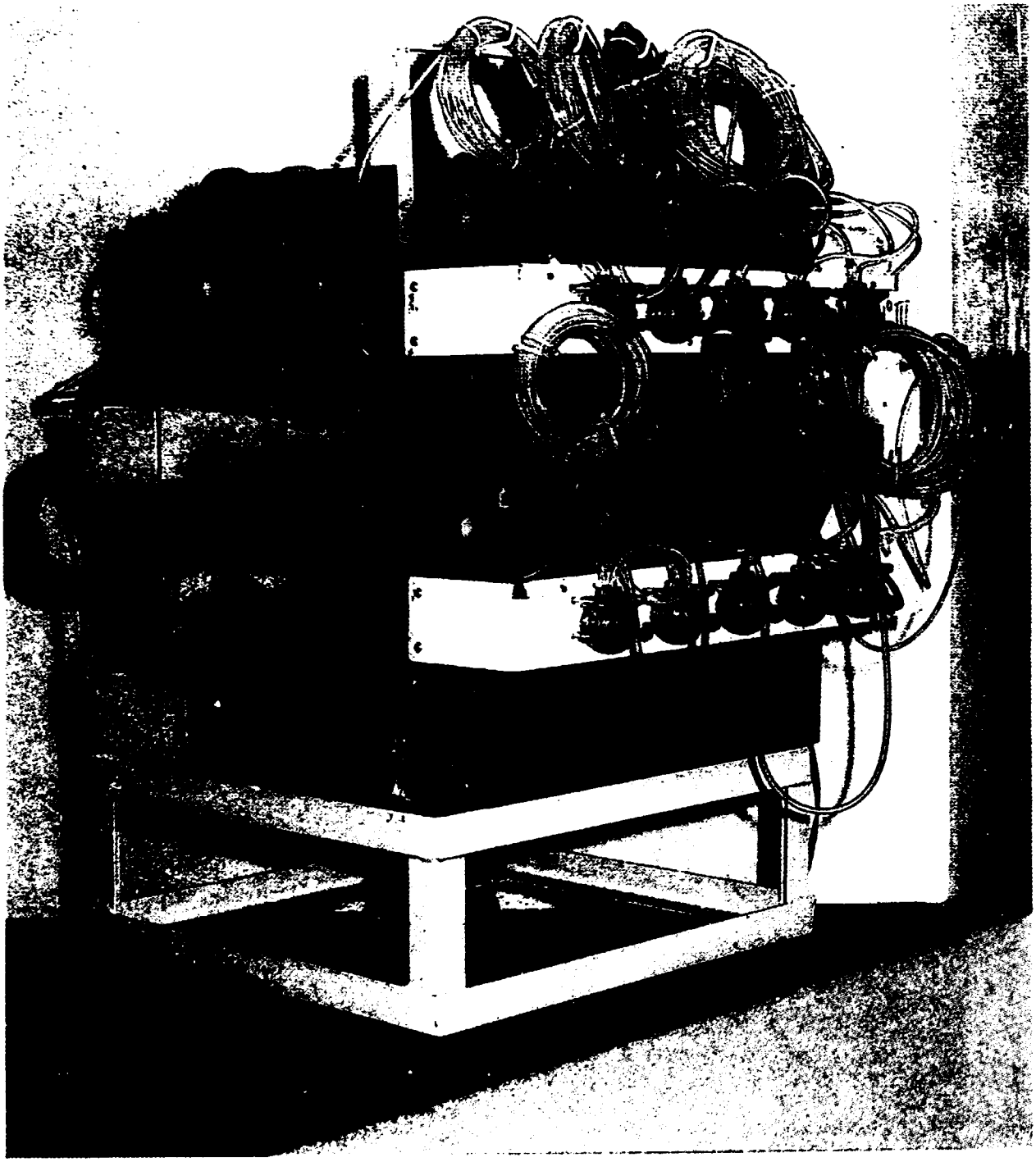


Figure 3. Module containing 15 multiple tube tissue culture units.

Yield from 10 litres of culture medium

Lf per ml of medium	Total (Lf x 10^4)	With 50% processing losses (Lf x 10^4)	No. of doses at 25Lf per/dose
100	1.0	0.5	20,000
150	1.5	0.75	30,000
200	2.0	1.0	40,000
250	2.5	1.5	50,000

Fermenter yield: 100Lf per ml of culture medium

No. of production runs per year	No. of doses (x10^4) at 25Lf per given volume of culure medium (L)				
	10	20	40	80	150
1	0.02	0.04	0.08	0.16	0.32
5	0.10	0.20	0.40	0.80	1.60
10	0.20	0.40	0.80	1.60	3.20
20	0.40	0.80	1.60	3.20	6.40
40	0.80	1.60	3.20	6.40	12.80

Fermenter volume (L)	50	150	250
Correction factor for improved yield	150 Lf per ml : x 1.5 200 Lf per ml : x 2.0 250 Lf per ml : x 2.5		

Table 1. Diphtheria toxin/toxoic production: number of doses of 25 Lf from different size fermenters at different rates of production.

Yield from 10 litres of culture medium

Lf per ml of medium	Total (Lf x 10^4)	With 50% processing losses (Lf x 10^4)	No. of doses at 25Lf per/dose
25	0.25	0.125	25,000
50	0.50	0.25	50,000
75	0.75	0.375	75,000
100	1.00	0.50	100,000

Process yield: 25 Lf per ml of culture medium

No. of production runs per year	No. of doses ($\times 10^4$) at 5Lf per given volume of culure medium (L)				
	10	20	40	80	160
1	0.025	0.05	0.10	0.20	0.40
5	0.125	0.25	0.50	1.00	1.00
10	0.25	0.50	1.00	2.00	4.00
20	0.50	1.00	2.00	4.00	8.00
40	1.00	2.00	4.00	8.00	16.00
Fermenter volume (L)	10	50	150	250	

Correction factor for improved yield	
50 Lf per ml	: x 2
75 Lf per ml	: x 3
100 Lf per ml	: x 4

Table 2. Tetanus toxin/toxoid production: number of doses of 5 Lf from different size growth vessels (glass jars or fermenters) at different rates of production.

Yield from 10 litres of culture medium

OU* per ml of medium per/dose	Total (OU x 10^4)	With 30% processing losses (OU x 10^4)	No. of doses at 20 OU
20	0.20	0.14	7,000
40	0.40	0.28	14,000
60	0.60	0.42	21,000

*OU: opacity units

Fermenter yield: 200U per ml of culture medium

No. of production runs per year	No. of doses (x10^4) at 20 ou per given volume of culure medium (L)				
	10	20	40	80	150
1	0.007	0.014	0.028	0.056	0.112
5	0.035	0.07	0.14	0.28	0.56
10	0.07	0.14	0.28	0.56	1.12
20	0.14	0.28	0.56	1.12	2.24
40	0.28	0.56	1.12	2.24	4.48

Fermenter volume (L)	40	150	250	250
Correction factor for improved yield	40 OU per ml : x 2.0 60 OU per ml : x 3.0			

Table 3. Pertussis vaccine production: number of doses of 20 OU (4 PU) from different size fermenters with different process yields and different rates of production.

SYSTEM	AVAILABLE GROWTH SURFACE	REMARKS
Roller Bottle	7.000 sq cm/10 bottles (standard unit)	5.000 sq cm floor space
Multiple tube (TM)	150.000 sq cm/10 bottles (standard unit)	5000 sq cm floor space
Microcarrier non-perfused	18.000 sq cm/3 g microcarrier/l of medium (maximum microcarrier concentration)	Large capital investment, much floor space as scale of production increase (100l and more)
Mircrocarrier, perfused	150.000 sq cm/25 g microcarrier/l (maximum microcarrier concentration)	Modest capital investment, 4000 sq cm bench space

Table 4. Comparison of different cell culture systems.

Table 5

Republic of the Philippines
Department of Agriculture
BUREAU OF ANIMAL INDUSTRY
Visayas Avenue, Diliman
Quezon City

April 13, 1988

BIOLOGICS NOTICE # 7

To : Staff Veterinarians
Veterinary Practitioners
Regional Director

Subject : Issuance of License/Permits

The purpose of this notice is to bring to the attention of the interested parties the list of license/permits issued to biologics importers and manufacturers as of the first quarter of 1988.

Please take note of the following permit nos.;

(a) those preceded with Letter R are on regular basis, meaning a particular company is allowed to sell such product commercially;

(b) those preceded with Letter S are on special basis and the usage of such product is limited to a particular farm or farms only. Selling to other farm owners is therefore prohibited.

This office will issue updated biological notices and guidelines to all parties concerned from time to time.

ROMEO N. ALCASID
Director

BIOLOGICS NOTICE # 7

NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
SMITH KLINE & FRENCH OVERSEAS	R-001-88	VANGUARD DA_2PL	Canine Distemper Adenovirus type 2 Parainfluenza Vaccine + Leptospira Bacterin
	R-002-88	FELOCELL	Feline Infectious Enteritis Vaccine (live virus)
	R-003-88	RABGUARD-TC	Rabies Vaccine (killed virus)
	R-004-88	MARIMUNE	Marek's Disease Vaccine (live virus)
	R-005-88	EVA	Erysipelothrix Rhusiopathiae
	R-006-88	LEPTOFERM 5	Leptospira Bacterin
	R-007-88	EVA-LEPTOFERM 5	Erysipelothrix rhusiopathiae/ Leptospira Bacterin
	R-075-88	NCD B_1 (Belgium)	Newcastle Disease Vaccine (live virus)
	R-076-88	VANGUARD 5/L	Canine Distemper Adenovirus Type 2 Parainfluenza Vaccine + Leptospira Bacterin
RHONE-POULENC	R-008-88	PESTOVAX	Hog Cholera Vaccine (Modified Live virus)
	R-009-88	IMOPEST	Newcastle Disease Vaccine (killed virus)
	R-010-88	PESTOS	Newcastle Disease Vaccine-Hitchner B_1 (live virus)
	R-011-88	SOTASEC	Newcastle Disease Vaccine-La Sota (live virus)
	R-012-88	LYOMAREK	Marek's Disease Vaccine (live virus)
	R-013-88	RABISIN	Rabies Vaccine (killed virus)
	R-014-88	CANIFFA	Canine Distemper-Hepatitis-Leptospira Vaccine (live virus)
	R-015-88	PARVODOG	Canine Parvovirus Vaccine (Modified live virus)
	R-016-88	LEPTODOG	Canine Leptospira Bacterin
	R-017-88	TETRADOG	Canine Parvovirus, Distemper-Hepatitis (live virus) & Leptospira (killed) Vaccine
	R-018-88	LYSENTERO	Escherichia Coli, Pasteurella multocida, Salmonella Typhi Bacterin

BIOLOGICS NOTICE # 7

NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
RHONE-POULENC	R-019-83	GUMBORAL CT	Gumboro Disease Vaccine (live virus)
	R-067-83	HAEMOVAX	Hemophilus Paragallinarum Bacterin
	R-120-82	BIORAL H120	Infectious Bronchitis Vaccine (live virus)
DALTON CORPORATION	R-020-83	MIXED BACTERIN	Pasteurellosis, Salmonellosis, Pneumonia and Escherichia Coli Bacterin
	R-021-83	TRUEVAC TC	Hog Cholera Vaccine (live virus)
	R-022-83	TRIPLE BACTERIN	Pasteurellosis, Pneumonia, Malignant Edema ' Blackleg Bacterin
	R-023-83	RIEMSER	Hog Cholera Vaccine (live virus)
	R-024-83	NEWCAVAC NOBILIS	Newcastle Disease Vaccine (killed virus)
	R-025-82	GUMBORO D-78	Gumboro Vaccine (live virus)
	R-026-83	VP VACCINE NOBILIS H-120	Infectious Bronchitis Vaccine (live virus)
	R-027-82	VP VACCINE NOBILIS CLONE 30	Newcastle Disease Vaccine (live virus)
	R-028-83	OVO-DIPTHERIN FORTE	Fowl Pox/Diptherin (live virus)
	R-029-83	NOBI-VAC GUMBORO INACTIVATED	Gumboro Vaccine (killed virus)
	R-030-83	VP VACCINE NOBILIS LA SOTA	Newcastle Disease Vaccine (live virus)
	R-031-83	VP VACCINE NOBILIS HITCHNER B_1	Newcastle Disease Vaccine (live virus)
	R-032-83	A.E. VACCINE NOBILIS	Avian Encephalomyelitis (live virus)
	R-033-83	M.S. ANTIGEN NOBILIS	Mycoplasma Synoviae Antigen
	R-034-83	M.G. ANTIGEN NOBILIS	Mycoplasma Gallisepticum Antigen
	R-035-83	NOBIVAC IB + ND	Infectious Bronchitis + Newcastle Disease (killed virus)
	R-036-83	NOBIVAC IB + G + ND	Infectious Bronchitis + Gumboro + Newcastle Disease (killed virus)
	R-037-83	RISHAVAC NOBILIS	Marek's Disease Vaccine (live virus)

BIOLOGICS NOTICE # 7

NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
[illegible] CORPORATION	R-038-88	MOBIVAC PORCOLI	Escherichia Coli Toxoid
	R-039-88	DILUENT FOR NCD VACCINE	
	R-069-88	ND BROILER	Newcastle Disease Vaccine (killed virus)
	R-112-88	MOBILIS H-52	Infectious Bronchitis Vaccine (live virus)
	R-113-88	MAREKINE CA	Marek's Disease Vaccine (live virus)
	R-114-88	MAREKINE SB1	Marek's Disease Vaccine (live virus)
ENERVET, INC.	R-042-88	CLONE SELECTED LA SOTA	Newcastle Disease Vaccine (live virus)
	R-043-88	NCD LA SOTA (A34)	Newcastle Disease Vaccine (live virus)
	R-044-88	NCD B1B1 (A33)	Newcastle Disease Vaccine (live virus)
	R-045-88	INACTIVAC-ND	Newcastle Disease Vaccine (killed virus)
	R-046-88	INACTIVAC-GD	Gumboro Vaccine (killed virus)
	R-047-88	NCD LA SOTA IH	Newcastle Disease Vaccine A-42 (live virus)
	R-048-88	FOWL POX E 102	Fowl Pox Vaccine (live virus)
	R-049-88	MAREK'S HVT	Marek's Disease Vaccine (live virus)
	R-050-88	NCD LA. BRON B1B1	Newcastle Disease & Infectious Bronchitis (live virus)
	R-077-88	MAREK'S VACCINE	Marek's Disease Vaccine (live virus)
	R-092-88	CORYZA VACCINE	Infectious Coryza Bacterin
	R-110-88	HOG CHOLERA VACCINE	Hog Cholera Vaccine (live virus)
INPHILCO, INC.	R-041-88	BIO NEW	Newcastle Disease Vaccine (killed virus)
	R-069-88	BIO B1	Newcastle Disease Vaccine (live virus)
	R-070-88	BIO BRONCHITE	Infectious Bronchitis (live virus)

BIOLOGICS NOTICE #7

NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
INPHILCO, INC.	R-071-88	BIO H120	Infectious Bronchitis (live virus)
	R-072-88	BIO GUMBORO	Gumboro Vaccine (live virus)
	R-073-88	BIO HVT	Marek's Disease Vaccine (live virus)
	R-109-88	BIO MYCO	Mycoplasma Gallisepticum (killed virus)
PREMIER AGROVET, INC.	R-062-88	MD VAC + SB1	Marek's Disease Vaccine (live virus)
	R-078-88	NCD B1B1	Newcastle Disease B1B1 strain (live virus)
	R-079-88	NCD B1 La Sota	Newcastle Disease Vaccine (live virus)
	R-080-88	M.G. ANTIGEN	Mycoplasma Gallisepticum Antigen
	R-082-88	CORYZA VAC	Haemophilus Paragallinarum Bacterin
	R-083-88	M.G. VAC	Mycoplasma Gallisepticum Bacterin
	R-084-88	M.S. ANTIGEN	Mycoplasma Synoviae Antigen
	R-085-88	RABVAC	Rabies Vaccine (killed virus)
	R-086-88	LEPTOVAC 5	Leptospira Bacterin
	R-087-88	P.S. ANTIGEN	Pollorum Stained Antigen K
	R-088-88	GALAXY DA$_2$L	Canine Distemper-Parainfluenza (live virus) + Leptospira Bacterin
	R-089-88	POXINE	Fowl Pox Vaccine (live virus)
	R-090-88	NCD-K	Newcastle Disease Vaccine (killed virus)
	R-091-88	ECOBAC	Escherichia Coli Bacterin
	R-093-88	A.E. POXINE	Avian Encephalomyelitis-Fowl Pox Vaccine (live virus)
	R-094-88	BURSINE K	Gumboro Vaccine (killed virus)
	R-095-88	MD VAC	Marek's Disease Vaccine (live virus)
	R-096-88	NCD LA SOTA BRON	Newcastle Disease Vaccine + Infectious Bronchitis (live virus)
	R-097-88	GALAXY 6 MPVL	Canine Distemper, Parainfluenza, and Parvovirus (live virus) + Leptospira Bacterin

BIOLOGICS NOTICE # 7

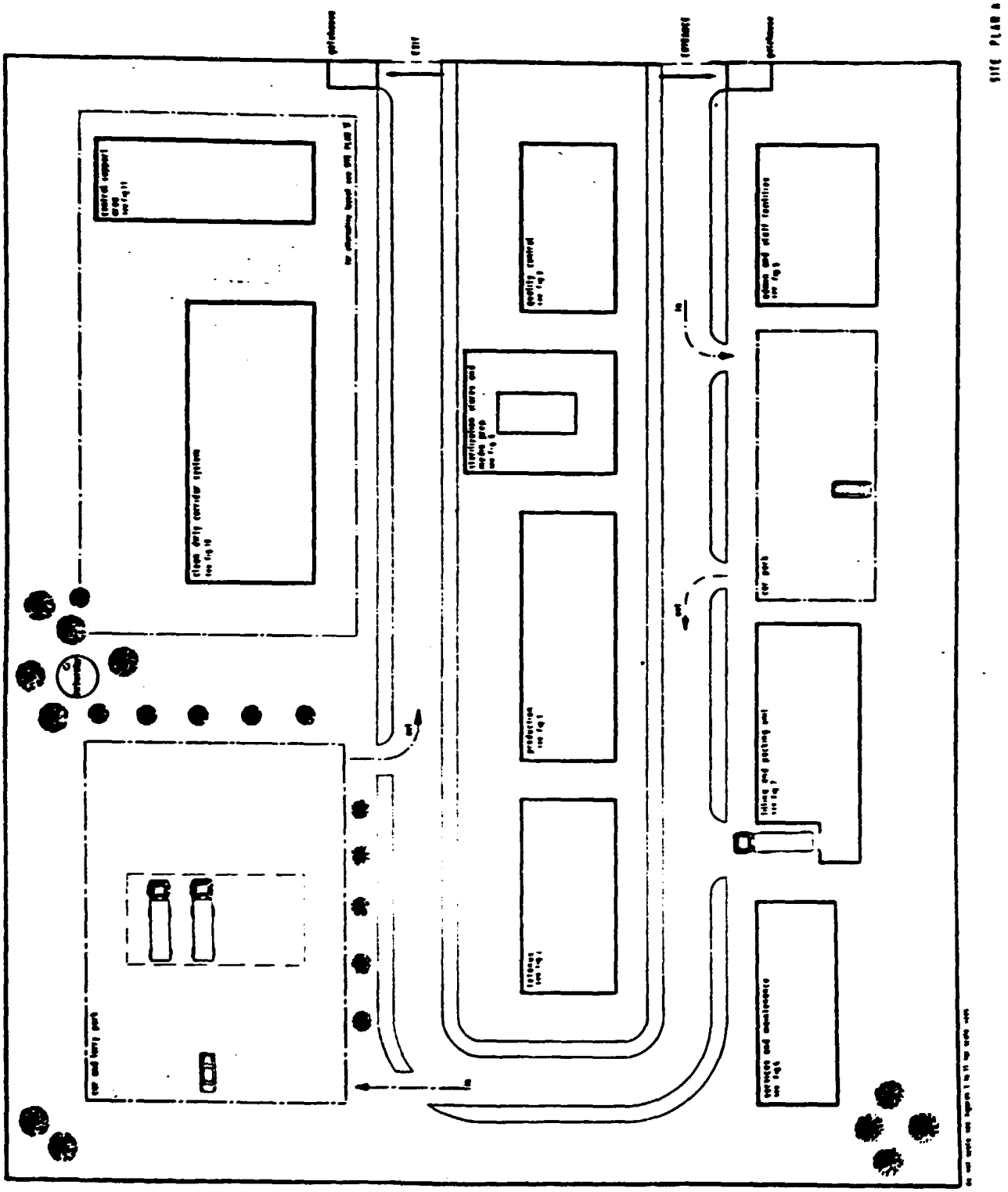
NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
PREMIUM AGROVET, INC.	R-115-83	IB MASS	Infectious Bronchitis (live virus)
	R-116-83	BURSINE 2	Gumboro Vaccine (live virus)
	R-118-83	NEW BRONZ	Newcastle Disease + Infectious Bronchitis (killed virus)
COOPERS ANIMAL HEALTH	R-057-82	SUVAC	Hog Cholera Vaccine (live virus)
	R-058-83	NOVALEP 5	Leptospira Bacterin
	R-059-83	RABDOMUN	Rabies Vaccine (killed virus)
SANOFI, PHILS., INC.	R-063-28	UNI-BLEN	Newcastle Disease B1B1 Strain (live virus)
	R-064-28	FP-BLEN	Fowl Pox Vaccine (live virus)
	R-065-83	MAR-BLEN	Marek's Disease Vaccine (live virus)
	R-066-83	COCLAPEST	Hog Cholera Vaccine (live virus)
	R-117-83	NEW BLEN	Newcastle Disease B1 La Sota Strain (live virus)
J. M. MENDOZA ENTERPRISES	R-093-83	TAD NCD B1B1	Newcastle Disease Vaccine (live virus)
	R-095-83	TAD ND Vac La Sota	Newcastle Disease Vaccine (live virus)
	R-100-83	TAD GUMBORO VAC	Gumboro Vaccine (live virus)
	R-104-83	TAD IB	Infectious Bronchitis (live virus)
	R-102-83	IC VAX	Infectious Bronchitis + Coryza Bacterin
	R-103-83	MG VAX	Mycoplasma Gallisepticum (killed virus)
	R-104-83	LENTOGEN B1B1	Newcastle Disease Vaccine (live virus)
	R-105-83	LENTOGEN LA SOTA	Newcastle Disease Vaccine (live virus)
	R-106-83	FP VAX	Fowl Pox Vaccine (live virus)
	R-107-83	LAYERPLUS	Newcastle Disease Vaccine (live virus)
	R-108-83	IB VAX	Infectious Bronchitis Vaccine (live virus)

BIOLOGICS NOTICE # 7

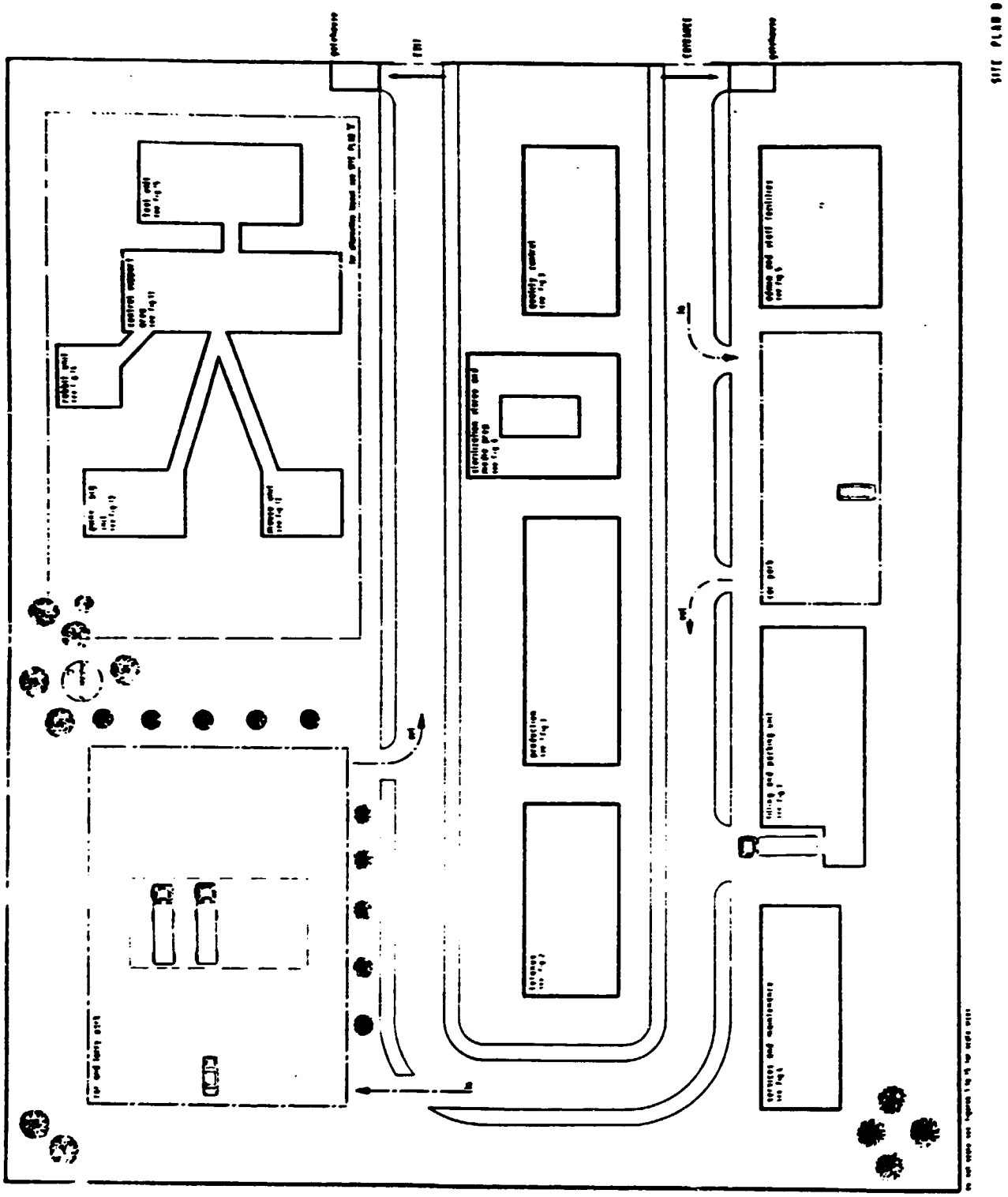
NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
RODELL CHEMICLAS CORP.	R-051-88	PORKIRIN	Hog Cholera Vaccine (live virus)
	R-052-88	DOG VAC RABIA	Rabies Vaccine (killed virus)
ANCOVET	R-053-88	NDV4	Newcastle Disease Vaccine (live virus)
	R-054-88	FOWL POX 19	Fowl Pox Vaccine (live virus)
	R-055-88	MAREK'S HVT	Marek's Disease Vaccine (live virus)
	R-111-88	BURSAVAC	Gumboro Disease Vaccine (live virus)
PFIZER, INC.	R-040-88	SUVOSTAM	Hog Cholera Vaccine (live virus)
BOEHRINGER INGELHEIM	R-061-88	LEPTO 5	Leptospira Bacterin
PASCUAL LABORATORIES	R-056-88	CORYZA	Coryza Bacterin, Kitasato Strain
ZUELLIG DISTRIBUTOR	R-074-88	NEOGARD	Escherichia Coli Bacterin
SPECIAL PERMITS			
DALTON CORPORATION	S-001-88 S-014-88	NOBIVAC AUJESZKY	Pseudorabies Vaccine (killed virus)
	S-008-88	TRIPLE GME	Gumboro, Newcastle Disease and EDS vaccine (killed virus)
	S-009-88	SUCOVET	Anti-Hog Cholera Serum
	S-010-88	GUMBORO + ND	Gumboro and Newcastle Disease Vaccine (killed virus)
	S-015-88	NOBIVAC REO	Avian Reovirus (killed virus)
HOME-POULENC PHILS., INC.	S-002-88	TRIAFTHPOR	Foot and Mouth Disease Vaccine (killed virus)
	S-003-88	BINEWVAXIDROP	Gumboro, Newcastle Disease, + EDS (killed virus)
	S-011-88	GESKYPUR	Pseudorabies Vaccine (killed virus)
	S-012-88	PARVOJECT	Swine Parvovirus Vaccine (killed virus)
	S-018-88	NEWVAXIDROP + EDS	Newcastle Disease + EDS (killed virus)

BIOLOGICS NOTICE #7

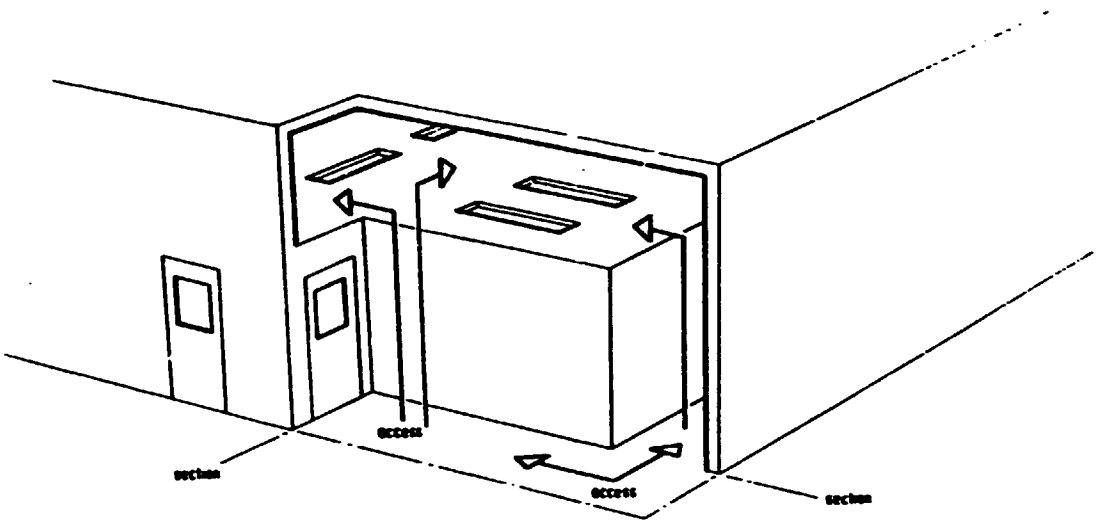
NAME OF AUTHORIZED IMPORTER	IMPORT PERMIT NO.	BRAND NAME	BRIEF DESCRIPTION OF THE BIOLOGICS
NATIVIDAD FARMS	S-019-88	NCD/IB (killed) NCD Clone Type (live virus) IBH-120 (live virus) FOWL POX (live) GUMBORO (live)	Intervet Brand
FOREMOST FARMS	S-004-88 S-016-88 S-017-88	HOG CHOLERA VACCINE	
UNITED PIGGERY FARM	S-005-88	Foot and Mouth Disease Vaccine (killed virus)	
LIBERTY'S FLOUR HILLS	S-006-88	Foot and Mouth Disease Vaccine (killed virus)	
SKF	S-007-88	FIRST DOSE	Canine Parvovirus Vaccine (live virus)
HL. GENETICS INC.	S-013-88	Antigen for Blue Tongue, Brucellosis, & Leptospira	
MONTEREY FRM	S-020-88	ANAPLAZ	Anaplasmosis Vaccine (Inactivated)
BAI-RCD	S-021-88	NCD V4	NCD Vaccine as feed
HOLIDAY HILLS	S-022-88	Foot and Mouth Disease Vaccine (killed virus)	
PREMIUM AGROVET	S-023-88	PSEUDORABIES Vaccine (killed virus) Salsbury	
	S-024-88	PARVO-PRO Swine Parvovirus Vaccine (killed virus)	



Bacterial vaccine production: site plan A



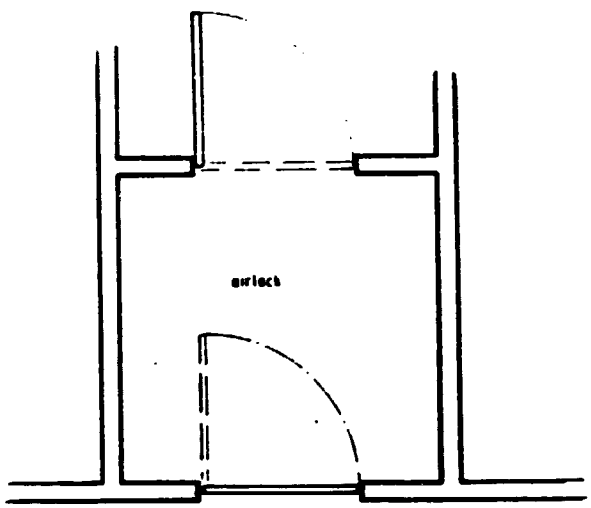
Bacterial vaccine production: site plan B



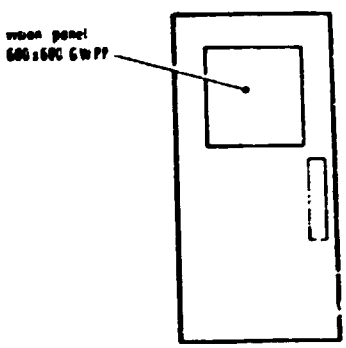
not to scale

ACCESS FOR MAINTENANCE

Fig 18



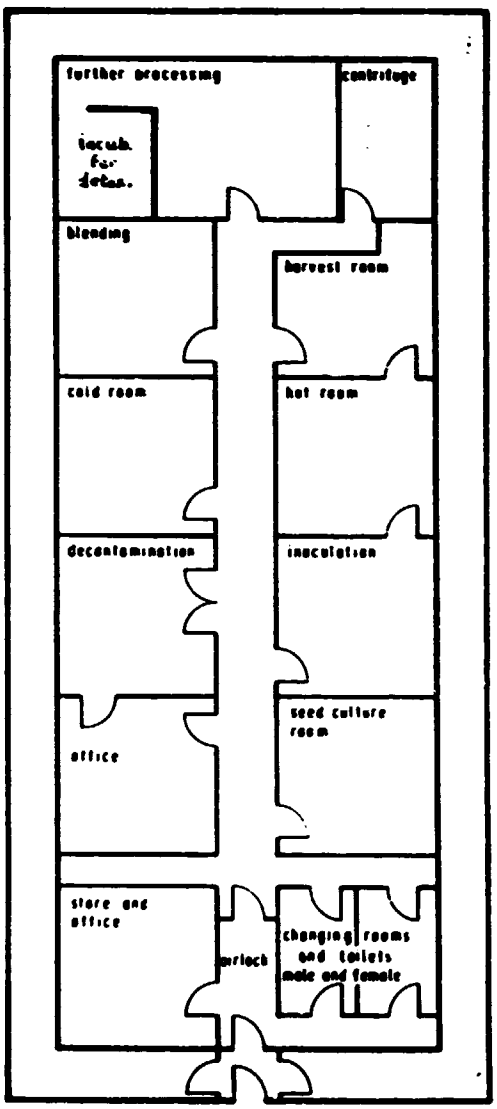
airlock to be achieved by electrical switching
to ensure that only one door opens at any time



door detail

scale 1:40

AIRLOCK and DOOR DETAIL



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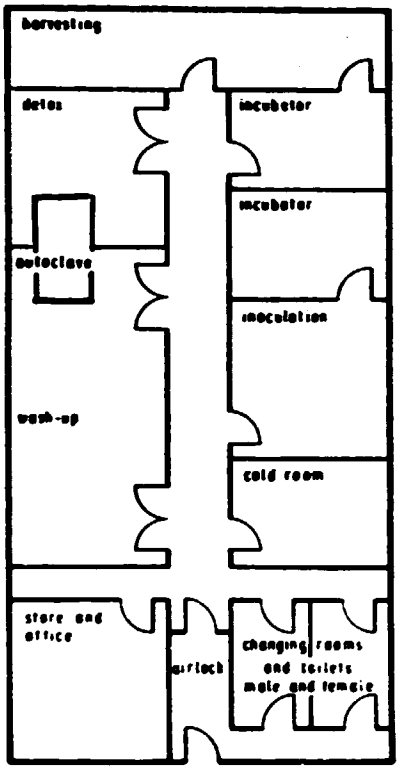
PRODUCTION



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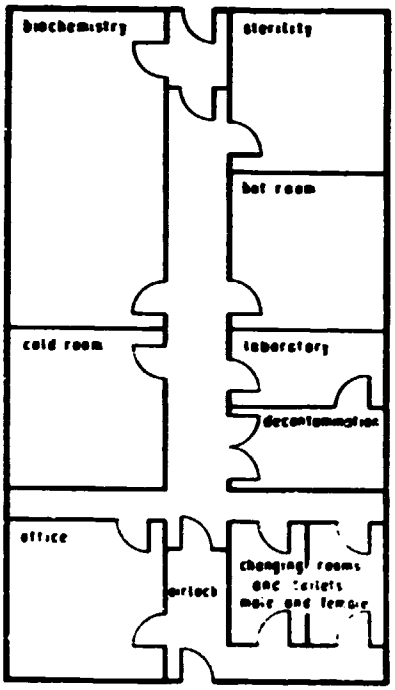
TETANUS



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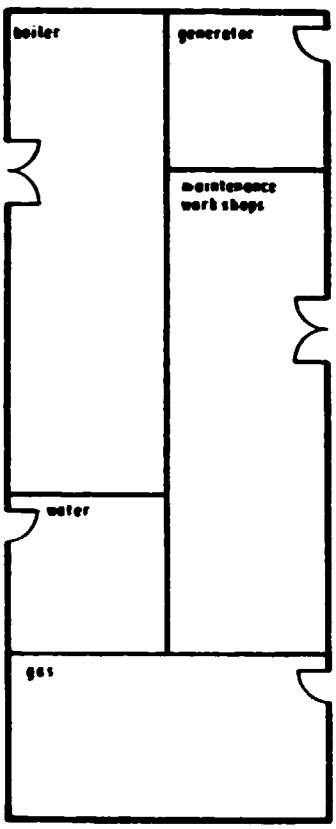
QUALITY CONTROL



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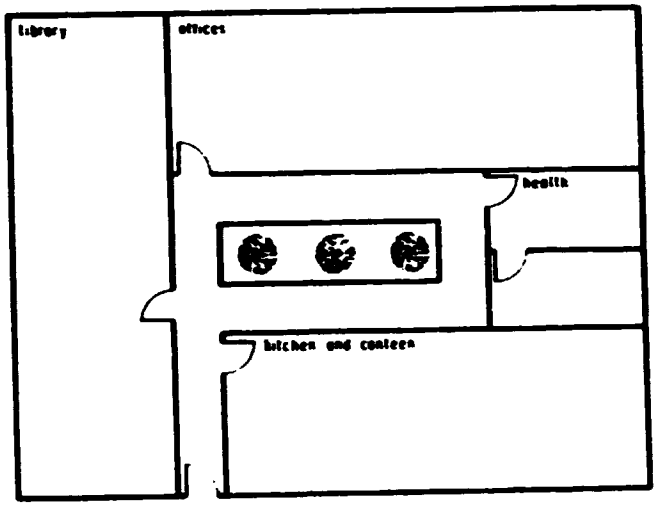
SERVICES and MAINTENANCE AREA



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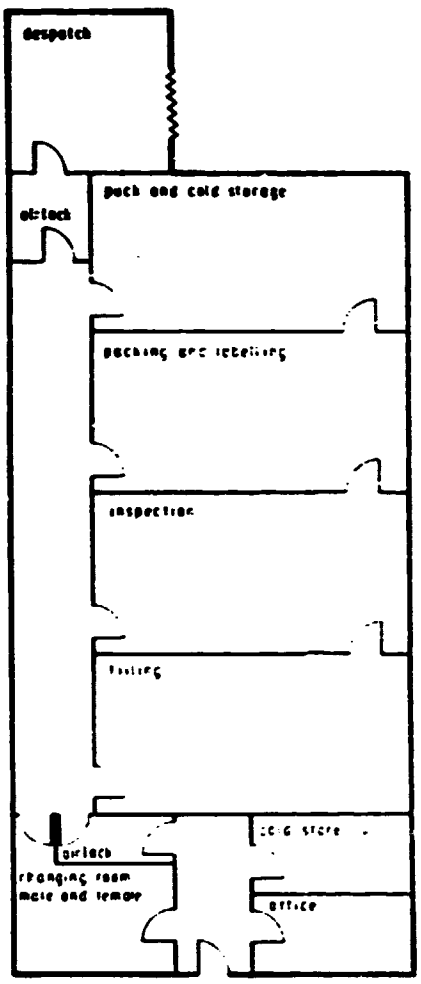
ADMIN and STAFF FACILITIES (Part of Central Services'



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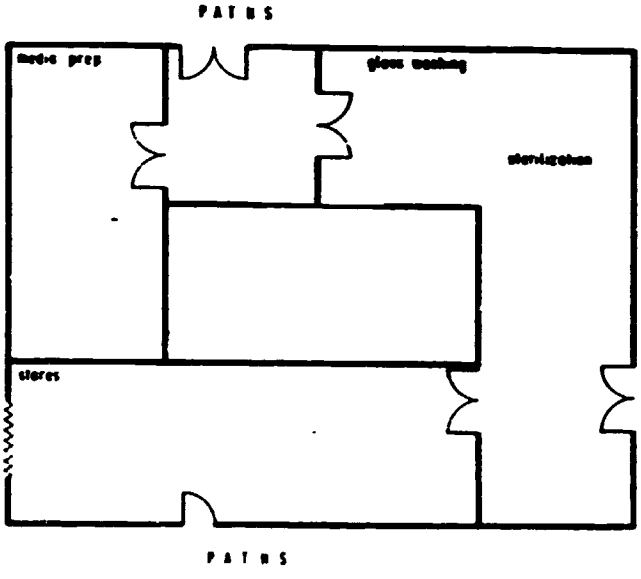
FILLING and PACKING UNIT (Part of Central Services)



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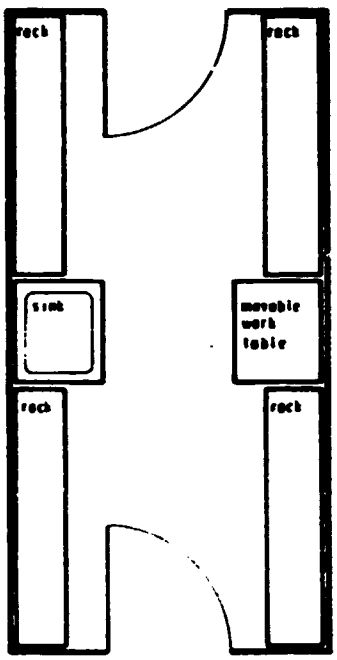
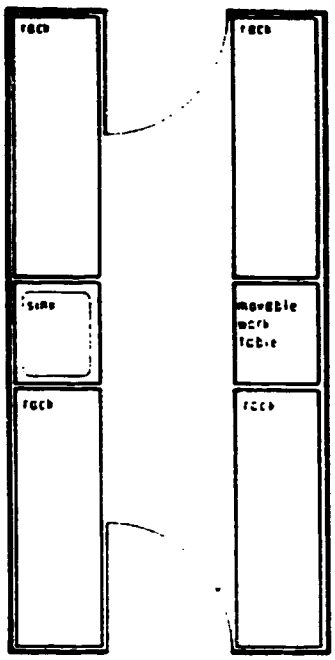
STERILIZATION STORES and MEDIA PREP. (Part of Central Services)



For clean-dirty / corridor
single building system

Scale 1:55

TYPICAL MOUSE ROOM



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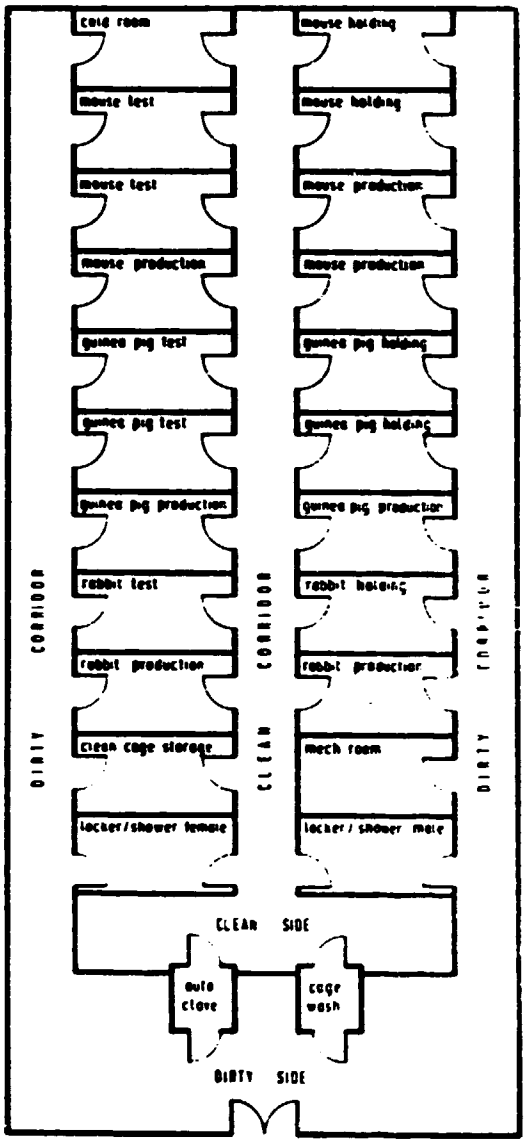
TYPICAL GUINEA PIG or RABBIT ROOM



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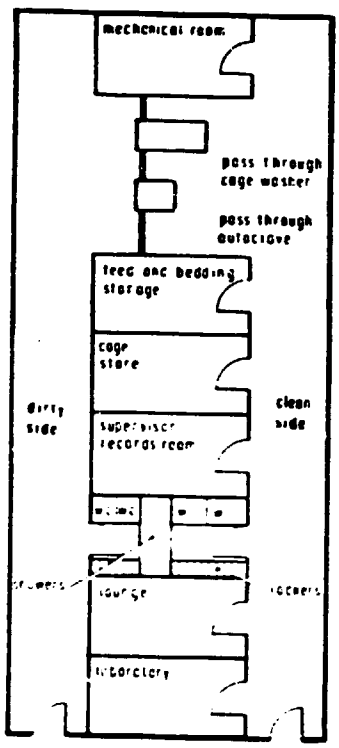
SINGLE BUILDING CLEAN DIRTY CORRIDOR SYSTEM



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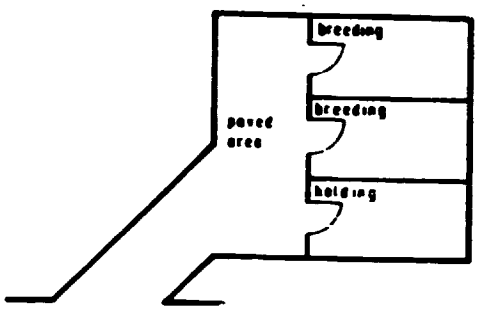
CENTRAL SUPPORT AREA



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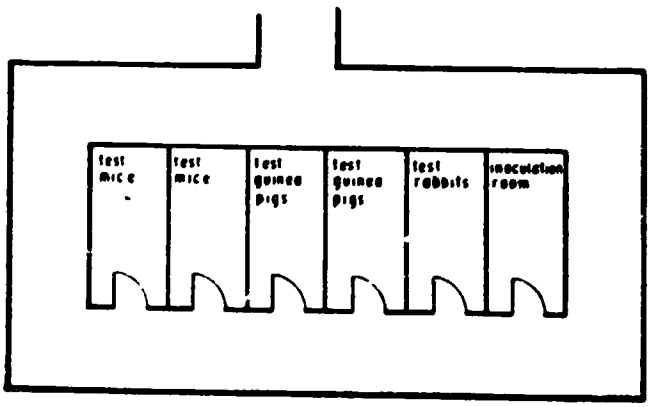
RABBIT UNIT



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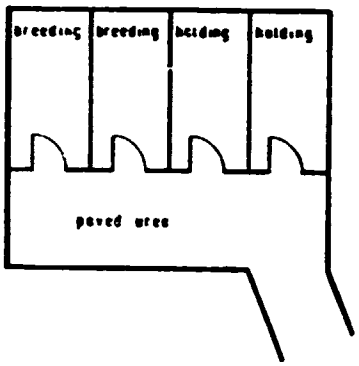
TEST UNIT



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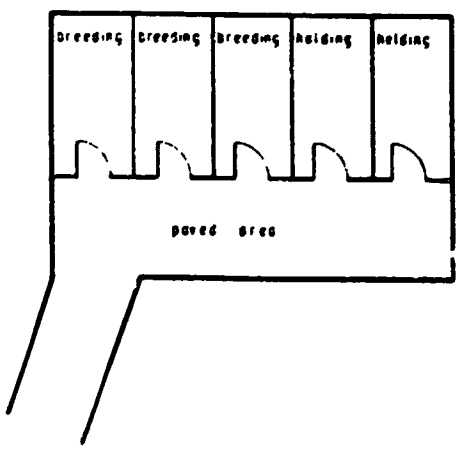
MOUSE UNIT



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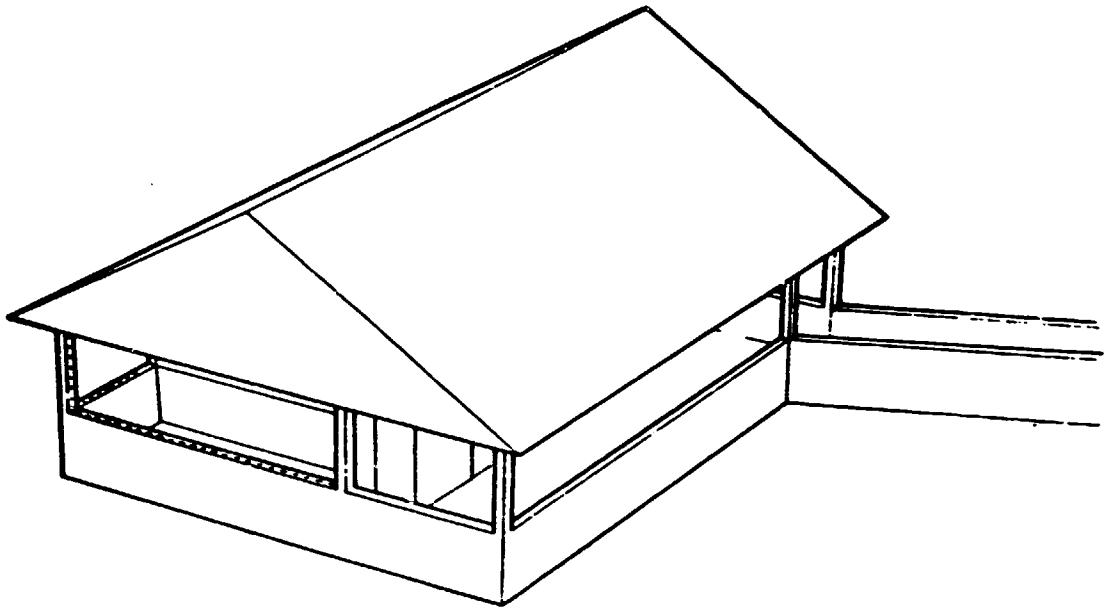
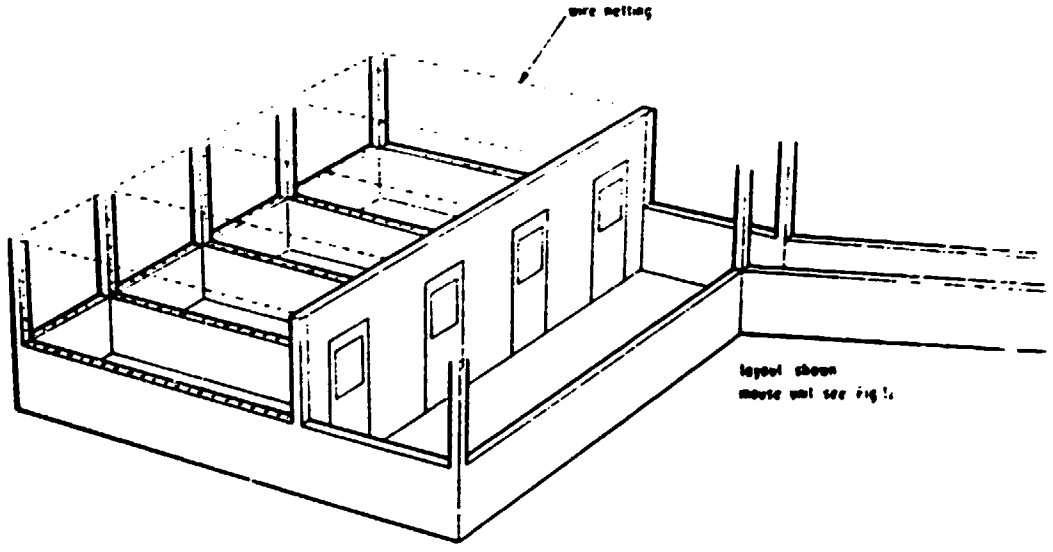
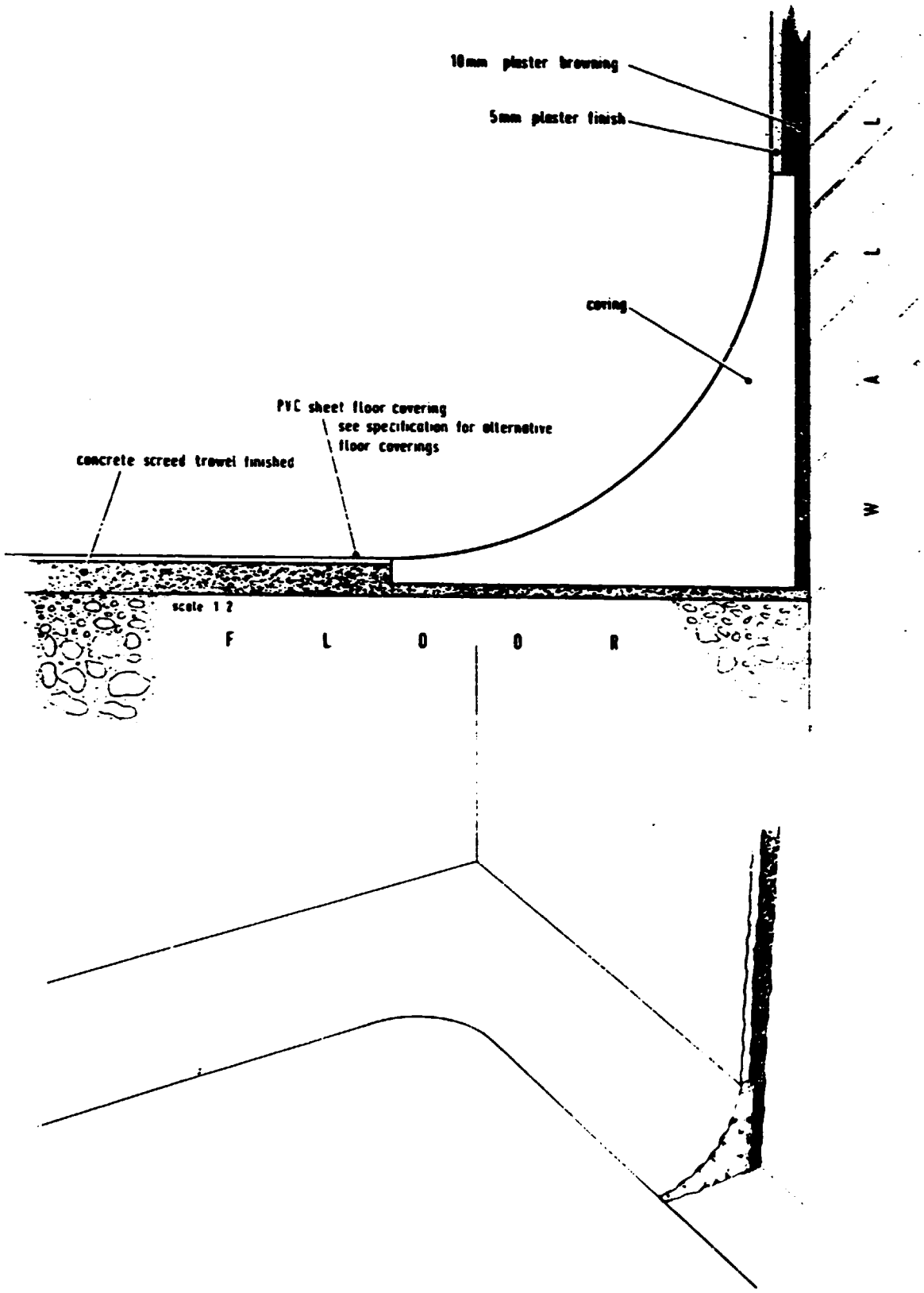
GUINEA PIG UNIT



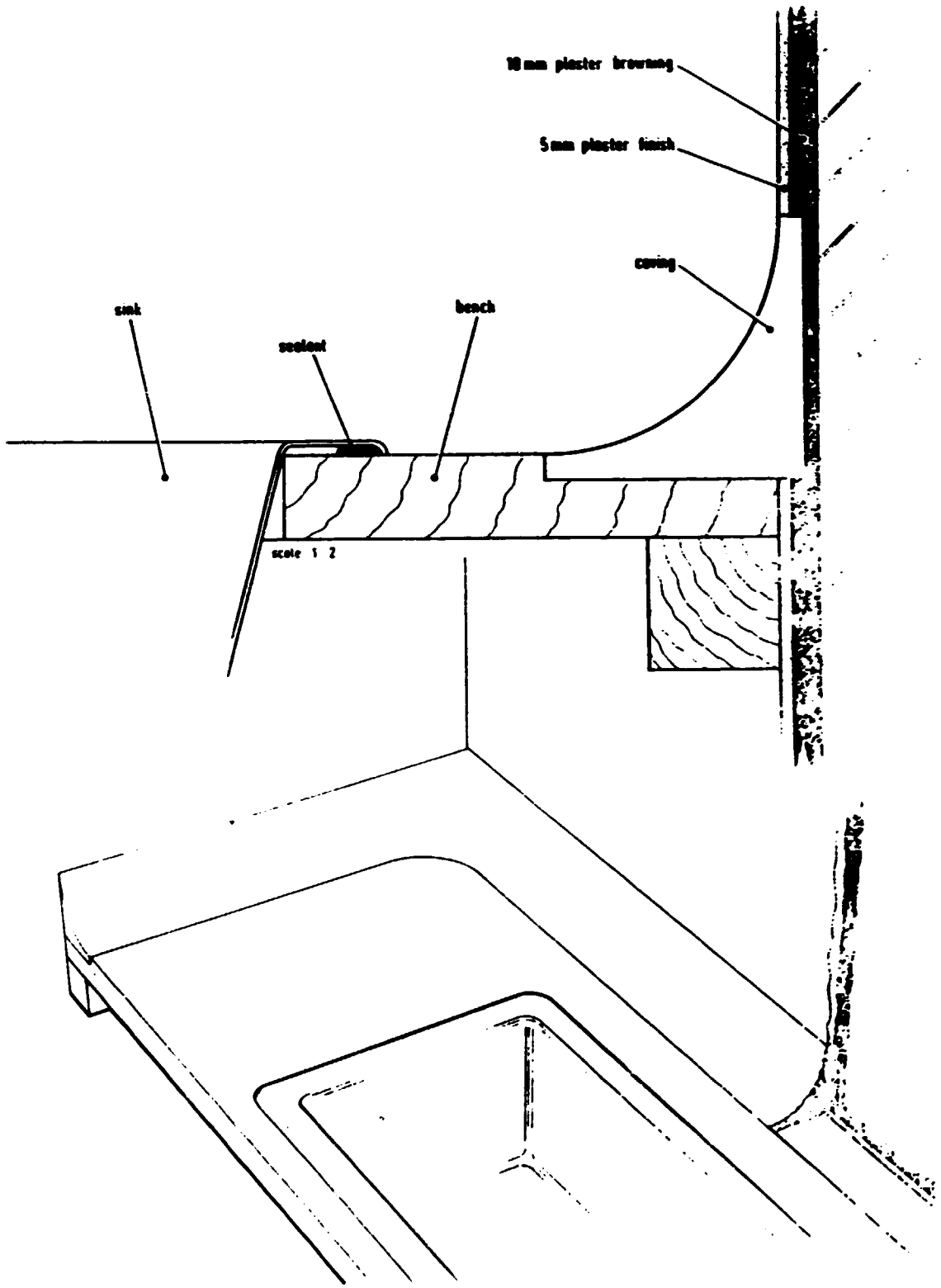


not to scale

TYPICAL ANIMAL UNIT



FLOOR TO WALL



BENCH TO WALL