PART II

Planning and management of vaccine production

Registration, licensing, controls and practical issues related to veterinary vaccines

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Veterinary vaccines have to be considered as medicinal products and, therefore, should be included in a framework of regulations for marketing. Since these regulations are related to technical requirements, they alone are capable of guaranteeing to potential users the quality, safety and efficacy expected of such products.

Such a guarantee is absolutely necessary for the protection of the livestock population against infectious diseases, and also to ensure, ultimately, the high standards of hygiene required of food products that are to be marketed.

REGULATIONS FRAMEWORK

Regulations relating to veterinary vaccines have to define, as precisely as possible, the conditions required for the registration of veterinary immunobiological products, directions on how to file an application for registration of a product, the conditions under which it is permissible to manufacture a product and the issuing of marketing authorizations (licences).

The conditions under which the inspection of manufacturing premises are to be carried out need to be defined in the regulations relating to immunological veterinary medicinal products (IVMPs).

The regulations should be sufficiently precise to take into account the various standards of manufacture and methods of working with such products throughout the country concerned. Consideration has also to be given to the human and financial resources associated with the industry. If regulations demand standards that are too high – being based on theoretical considerations – and are inappropriate to the socio-economical conditions obtaining in a country, they will very probably never be applied.

Under such circumstances, it would be preferable to formulate regulations of a less demanding nature, which would therefore be more likely be recognized and would lead to improvements in the standard of IVMPs used in that country.

LICENSING AUTHORITIES AND PROCEDURES

It goes without saying that it is necessary to define the conditions and procedures which will be used by the registration authority clearly. Such definitions guarantee to national and foreign manufacturers the independence and impartiality of the registration authority.

Normally the applicant submits to the national authority (which could be the ministry of agriculture or an agency, but is always a government department), an official application to obtain a licence to market a particular IVMP. With the application, several copies of the product's documentation file, giving essential data, are also sent, to enable the authority to compile a dossier relating to that particular product. In addition, samples from typical batches of the product are sent to control laboratories for official testing. Generally, the authority acknowledges receipt of the application and allocates an official registration number to the product. Fees, which vary in amount, have to be paid.

The official registration number will later become the marketing authorization (licence) number of the registered product.

The regulations should define a time period for the examination of the application file by the official technical advisers responsible to the national authority. However, in many countries the authorization to market the product is based on an assessment made by an independent committee, working from the results of an investigation made by technical experts.

The work of the committee should be strictly confidential. Members of the committee should include representatives of the national authority and recognized experts in the field of veterinary immunobiologicals. Impartiality, objectivity, confidentiality, technical assessment and scientific competence are the essential aspects of the procedure to be followed in assessing the suitability of a product for licensing prior to marketing.

DATA TO BE INCLUDED IN AN APPLICATION (REGISTRATION) FILE

The following information is taken from European Commission Directive 81/852 (amended as 92/18 and published on 20 March 1992).

The file is composed of six sections: i) a summary, ii) expert reports, iii) analytical details, iv) descriptions and results of safety and v) efficacy (potency) trials and vi) documentation relating to safety testing and efficacy trials.

Summary of the dossier of information

The IVMP which is the subject of the application should be identified by the names of the active ingredients, together with their pharmaceutical formats and the quantities used in the product, the method and route of administration and a description of the final sales presentation of the product.

The name and address of the applicant should be given together with the name and address of the manufacturer and the sites involved in the different stages of manufacture as well as, where relevant, the name and address of the importer.

Annexed to the administrative data there should be copies of a document (e.g. a licence) showing that the manufacturer is authorized to produce IVMPs. The applicant should submit a list of countries in which such authorization has been granted. The applicant should also submit a summary of the product's characteristics.

Experts' reports

Reports must be provided on all the tests and investigations made. Each report should consist of a critical evaluation of the various tests and/or trials and should present all the relevant data for detailed evaluation. The expert(s) involved should give their opinions as to whether sufficient guarantees have been provided as to the quality, safety and efficacy of the product concerned; a brief summary is not sufficient.

Each report should be prepared by a suitably qualified and experienced person, who may be a company employee. The report should be signed and dated by the expert and should also include brief information about the educational background, training and occupational experience of the expert. The professional relationship of the expert to the applicant (i.e. the company) must be declared.

Analytical section

This section should give descriptions of all the physico-chemical, biological or microbiological tests carried out to characterize the IVMP. All test procedures used should correspond to the most up-to-date scientific methods available and should be validated procedures; results of the validation studies must be provided.

Qualitative and quantitative particulars of constituents. Qualitative particulars of all the constituents of an IVMP should give a complete description of the constituents of the final product, as administered to animals, including the designation or description of: the active ingredients; the composition and constituents of adjuvants, excipients etc. (whatever their nature); and the quantities used, including preservatives, stabilizers, emulsifiers and colouring matter.

In giving the quantitive particulars of the active ingredients of an IVMP, it is necessary to specify, wherever possible, the number of organisms, the specific protein content, the mass, the number of international units (IU) or units of biological activity (either per dosage unit or volume) and, with regard to the adjuvant and the constituents of excipients, the mass or volume of each.

Where an IU of biological activity has been defined, this should be used.

Description of the preparation of the final product. The description of the method of preparation accompanying the application for marketing authorization should be drafted in such a manner as to give an adequate description of the nature of the operation employed. This description should include the various stages of manufacture; in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product; and details of blending, etc.

Production and control of starting materials

The starting materials are all the components used in the production of the IVMP. It is recommended that an official monograph such as the European Pharmacopoeia should be consulted when these substances are listed.

The routine tests carried out on each batch of starting materials must be as stated in the application for a marketing licence. If tests other than those described in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of the pharmacopoeia.

In the application (registration) file, the origin and provenance of starting materials should be described and documented.

For genetically engineered starting materials, the information given should include descriptions of: the starting cells or strains, the construction of the expression vector (name, origin and function of the replicon, promoter enhancer and other regulator elements), the control of the sequence of DNA or RNA which has been inserted, oligonucleotide sequences of the plasmid vectors in cells, the plasmid used for transfection, added or deleted genes, the biological properties of the final construct and the genes expressed, copy number and genetic stability.

Information should also be provided on all the substances of biological origin used at any stage in the manufacturing procedure. Such information should include: details of the source of the materials; details of any processing, purification and inactivation applied, together with data on the validation of these processes and in-process controls; details of any tests for detecting contamination that have been carried out on each batch of the substance.

When the starting materials are not of biological origin, the information should provide a detailed description of the materials, together with their function, methods of identification and purity. A brief description should also be provided of the tests undertaken to establish the purity of each batch of the starting materials.

Control tests during production

Complete information should be provided of the control tests that are carried out on intermediate products, with a view to verifying the consistency of the production process and the final product. For inactivated or detoxified vaccines, inactivation or detoxification should be confirmed during each production run and immediately after the inactivation or detoxification process.

Control tests on the final product

The registration file should list the tests that are carried out on representative samples of each batch of the final product. The frequency of tests which are not routinely carried out on each batch should also be stated and expiry dates should be indicated.

Certain tests of the general characteristics of a product should be included among the tests of the finished product, even if they are only carried out in the course of the manufacturing process.

These tests should, wherever applicable, be concerned with establishing typical values and the maximum deviations to be expected in relation to mechanical, physical, chemical or microbiological characteristics, as well as special physical characteristics such as density, pH and refractive index. For each characteristic, average values, with appropriate confidence limits, should be established by the applicant for each particular product.

For all tests, descriptions of the techniques for assessing the final product should be set out in sufficiently precise detail, such that they can be readily reproduced.

When appropriate testing procedures are available, the quantity and nature of the adjuvant (i.e. its activity) and its constituents should be confirmed by means of tests with the final product and, when necessary, the excipient(s) used should be subject to identification tests described in detail in the file.

Safety tests prior to batch release have to be described in the registration file in addition to appropriate tests to demonstrate the absence of contamination by adventitious agents or other substances and, where applicable, a test to verify complete inactivation should be carried out on the product in its final container and the results given.

Potency tests. Potency tests also have to be described. These tests are carried out to demonstrate conformity with specifications and to ensure that the efficacy of the product is reproducible from batch to batch and is of an acceptable minimum standard.

Stability tests. A description should be given of the tests undertaken to support the shelf-life proposed by the applicant. The results of analyses, justifying the proposed shelf-life under all likely storage conditions, should also be given.

Safety tests. The particulars and documents in the registration file should include a description of all the safety tests carried out on the target species.

Laboratory tests. Trials should be undertaken in which the IVMP is administered at the recommended dose, and by each recommended route of administration, to animals of each species and category in which it is intended for use. The conditions of these trials should be described in detail together with the objective criteria to be used (such as rectal temperature and performance measurements) to assess the safety of a product. Safety tests need to be performed and the results described in terms of possible effects following:

- the administration of one dose;
- the administration of an overdose;
- the repeated administration of one dose;
- the reproducibility of the results of repeated tests.

For live vaccines, special safety tests are required to establish:

- the putative spread of the vaccine strain;
- its dissemination in the vaccinated animal;
- the possibility of reversion to virulence of attenuated vaccines;
- the biological properties of the vaccine strain (e.g. neurotropism);
- the recombination of elements of the genome and the possibility of the emergence of new strains by genomic reassortment.

Field studies. The file should include supportive data from field studies to supplement the results of laboratory studies.

Potency tests

The particulars and documents in the registration file should include descriptions of tests to demonstrate the potency (efficacy) of the product administered to each category of each target species, by the recommended route(s) and using the proposed schedule of administration.

The demonstration of potency should be undertaken under well-controlled laboratory conditions, by challenge, after administration of the IVMP to the target animal according to the recommended conditions of use. So far as possible, the conditions under which the challenge test is carried out should mimic the natural conditions for infection with regard to the number of challenge organisms and the route of administration of the challenge.

In general, detailed results of all safety and potency tests need to be presented in the file and the report of each test should include the test protocol, records of actual data, analysis of recorded results and the conclusions drawn from the data.

Controls must be included in all assays and must be clearly identified in the reports. Bibliographical references should be given where additional scientific data are required to explain some of the arguments put forward by the manufacturer in support of the product.

CONTROLS TO BE UNDERTAKEN BY NATIONAL AUTHORITIES

These controls depend on national policies and on the human and financial resources available in the country.

Controls must be carried out at the national level, by the appropriate authorities both before marketing authorization and before the release of batches.

Controls carried out before marketing authorization are not routine but may be necessary to confirm the data and results obtained by the manufacturer. These controls can be very simple, such as sterility tests and titrations of organisms, but more complex controls, such as efficacy and safety tests on target species, may also be necessary. Obviously, complex controls can only be carried out where the authorities have the technical means sufficient to obtain proper, fully validated results which cannot be contested by the manufacturer.

Efficacy and safety controls may be carried out routinely or not. In most cases, the nature of the control tests undertaken is dependent on the data given in the registration file. If some data appear unclear or insufficient, further tests may be necessary to confirm the results obtained by the manufacturer. Under these circumstances the tests undertaken are, to some extent, determined by the data produced by the manufacturer.

National authority control tests on batches prior to release are carried out on

some vaccines that have strategic importance for specific vaccination or disease eradication programmes, for example rinderpest and foot-and-mouth disease vaccines. Such vaccines are produced by a public or recognized private manufacturer and batches are released only if the results of control tests carried out by the official authorities are satisfactory.

These tests are expensive in time and money and need to be carried out as quickly as possible to avoid delays in marketing the product. Such pressures can contribute to improvements in the quality of the products if the tests are carried out by an efficient and competent organization. In developing countries, it is essential to have a regional policy involving strong cooperation among countries to save resources and to promote the development of more efficient laboratories.

It may not be reasonable or possible to have one national control laboratory per country and it would be more appropriate to avoid duplication by sharing the expenses of maintaining one efficient laboratory among several countries with mutual acceptance of the results obtained by such a laboratory. In practice, however, such an approach has remained, up to now, difficult to achieve.

Official authorities should consider that in many developing countries the national laboratories are themselves producing several vaccines and, in such cases, it is essential that the laboratories in charge of production and those in charge of control tests are completely separate. If not, the independence and impartiality of the control laboratories will be compromised and disputes may arise as to the acceptability of the test results obtained.

INSPECTION

When vaccines are produced locally, the national authorities have to take measures to obtain guarantees concerning the standards of manufacturing practice. Guidelines have been established in various countries and regions such as the United States and Europe to define good manufacturing practices (GMPs). Quality assurance (QA) is increasingly defined as being all the planned and routine actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality (Soulebot, 1992) rather than demanding the overintensive testing of final products. The implication of this is that the quality of the finished product is largely determined by the quality of the raw materials and manufacturing processes used.

If, in addition to the quality of the raw materials, the various stages in the manufacturing process are controlled in an appropriate way, the probability of a defect or contamination in the finished product would be very low. The methods and standards of inspection required may be developed according to this concept.

An authorization to permit production on a trial basis, in the first instance, needs to be made by the official authorities before routine manufacturing of any product can commence and the product receive the appropriate licence. Authorization should only be given if the premises and manufacturing processes meet the technical requirements that will ensure a good-quality product. Technical requirements need to be defined at the national level (even if they have been developed and defined in other countries) and made known to manufacturers as soon as possible.

A compromise has often been made between the minimum standards required to ensure high quality of products and the economic situation of a country. Indeed, in some situations, if the national authorities intend to guarantee the quality of a particular marketed product, it may even be necessary not to authorize its manufacture in the country.

It is essential that manufacturing premises be inspected regularly but at variable and random intervals to check on the consistency of manufacturing practices.

If products are not manufactured locally, the problem becomes a little more complex because the standards required of manufacturing practices have to be the same in the exporting country as in the importing country. Inspection certificates provided by the authorities from the country of origin will be required by the authorities of the importing country and must be included in the registration file. An agreement between countries will often be necessary to ensure that the administrative and technical values of these certificates are the same. Sometimes it may be necessary to harmonize the conditions of inspection in different countries to ensure mutual recognition of certificates issued by different national authorities.

PHARMACO-VIGILANCE

It is important to set up a system which allows an exchange of information on marketed IVMPs between users and official authorities. Such an exchange of information, which may be informal, forms part of a pharmaco-vigilance network and contributes to the detection of problems in relation to the use of a marketed product. Such a system can be very useful, particularly when the economic situation does not permit important controls on finished products or routine and frequent inspections of premises. Very simple systems can be set up by authorities to inform the main users of IVMPs, for example veterinarians, including, for instance, a telephone line connected to a special unit which can give information on problems occurring after the use of certain products. The main difficulty will be to differentiate between real problems that require immediate action and occasional events in which the suspected product plays no role at all.

More complex systems can be used including a computerized database of information from users, inquiries and epidemiological surveys. At present there are very few such systems operational worldwide.

Pharmaco-vigilance is useful in assessing, in the most expeditious way, the real effects of a vaccine in the field. Side-effects and lack of efficacy can often be observed after the introduction of a new product, which may have been used under normal or abnormal field conditions. Occasionally small alterations in the manufacturing process can affect the quality of the finished product and not have been detected by tests carried out by the manufacturer and the official laboratory.

Pharmaco-vigilance is also useful for the collection of data on the effects of vaccines used under conditions that are somewhat different from those described in the registration file. In developing countries, for instance, the number of target species to which a vaccine can be administered may increase considerably. When vaccines are imported or when assays are expensive it is often difficult to carry out tests on particular species, such as camels and game animals for registration purposes and the use of vaccines may, therefore, have to be adapted to very specific and particular conditions. In such cases pharmaco-vigilance can contribute to the data required for registration files, even if it cannot provide it all because the exchange of information is insufficient and the results of serological surveys and/or clinical records are needed to provide objective and quantifiable data. In addition, when products are imported and where local conditions are not totally appropriate for the setting up of regular and important control tests on finished products,

pharmaco-vigilance has an important role to play in assessing the effects of a vaccine in an animal population, particularly with regard to its efficacy.

At present, in several developing countries, there are agreements and contracts between avian and pig production cooperatives and research and control laboratories to carry out field trials for studies of, for example, the development of protective antibodies and clinical results after vaccination. Such trials make possible a better understanding of the performance of vaccines applied under specific conditions.

PRACTICAL ISSUES

To be credible, the organization set up by the national authority has to be founded on technical competence and experience. All of those involved in the different stages of the registration process have to be properly trained in the methods of official inspection, examination of data and laboratory tests. In addition, veterinary immunobiological products have certain specificities and the problems related to the manufacture and control of these products are totally different from those of chemical ones. Specialists and specialized teams are needed to manage the whole registration procedure of IVMPs. To save financial resources, it may sometimes be possible to involve the same people in the administrative procedures for the registration of both chemical and biological products but, in both cases, all technical matters have to be the responsibility of the appropriate specialists.

In developing countries, such problems often become greater because the economic situation does not permit the establishment of an operational, efficient organization. Regional cooperation among countries is therefore needed. Cooperation can include the exchange of test reagents and materials, information about the investigation of new applications for registration and the results of tests and licences which have been granted.

At present, it appears essential to develop a strong collaboration among countries based on good complementary technical competence. The poorer the financial resources of the countries in a region, the greater the need for such collaboration.

It is essential that a licensing system should be both rigorous and demanding and, at the same time, flexible and easily applicable. The system must allow an equitable treatment of all the marketable products which are to be assessed, by using the same technical criteria and standards; this is the sole guarantee for free competition among manufacturers.

If the above conditions are not in place, the system will favour the development of a black market with the opposite results to those desired. The development of a black market becomes more likely when the means and conditions for controlling the distribution of products are weak and inadequate. In all cases, the penalties imposed against those involved in black market activities should be very severe.

The national authorities may have another problem in relation to issuing licences, namely, how to define the threshold of acceptability in regard to quality, safety and efficacy, so as to be able to accept or reject a particular vaccine. In general, a vaccine will be rejected if it appears to be insufficiently safe or lacking in efficacy, there is insufficient scientific data available on file or the qualitative or quantitative composition of the vaccine at the time of testing does not correspond to the data given in the registration file.

It is impossible to generalize about all the possible cases that may justifiy the rejection of a product and, therefore, the refusal of a licence. However, national authorities have to elaborate a policy that

can be properly understood and accepted by manufacturers and this policy should be founded on technical requirements and guidelines developed from present scientific understanding and from the requirements set up in other countries, adapted to local conditions.

Whatever the efforts to develop good technical guidelines, some problems will remain and, at some point, the competence and experience of the official inspectors will be required to intervene to make a decision. Under these circumstances it is essential that the legal requirements of the licensing procedure be such as to limit the subjective element in the interpretation of test results and in the judgement of inspectors on the merits of a particular application for a licence.

BIBLIOGRAPHY

Commission of the European Communities. (1992). *The rules governing medicinal products in the European Community*, Vol. V A. Directorate General for International Market and Industrial Affairs.

International Association of Biological Standardisation. 1992. *Symposium on the First Steps Towards an International Harmonization of Veterinary Biologicals: 1993 and the Free Circulation of Vaccines within the EEC.* Developments in Biological Standardisation, No. 79.

Soulebot, J.P. 1992. Fedesa's point of view: quality – application to IVMPs. *In* International Association of Biological Standardisation. *Symposium on the First Steps Towards an International Harmonisation of Veterinary Biologicals: 1993 and the Free Circulation of Vaccines within the EEC*, p. 201-211. Developments in Biological Standardisation, No. 79.

The role of private industry in the transfer of vaccine technology to developing countries

A.J.B. Haigh

VACCINE TECHNOLOGY EXPERTISE WITHIN PRIVATE INDUSTRY

Commercial vaccine producers

Companies that produce vaccine are in business to generate profit from the sale of licensed products. In certain circumstances some are prepared to sell technology transfer packages to state or parastatal bodies and deals of this nature may be financed by government or agency aid in the form of a soft loan.

In such cases it is very important that a contract is signed which clearly defines the objectives to be met by the company and the performance criteria which must be acheived for the company to discharge its obligation including a defined follow-up period of support consultancy with specified responsibilities.

A feasibility study may be necessary to establish a project outline and broad specification to facilitate a costing and the formulation of a contract that both parties can sign. The cost of the feasibility study may also be funded by government or agency soft loan.

The developing country must be satisfied that the commercial company is capable of meeting the commitments it is proposing to undertake and that it does in fact own the technology it is proposing to sell. The developing country is advised to engage an independent consultant with the appropriate technical background and expertise to advise it and act on the country's behalf in the formative, implementation, handover and support consultancy stages.

Engineering and bioengineering companies

There is a large range of engineering and bioengineering companies available – from manufacturers of equipment (e.g. pressure vessels, filters, process modules) to process development contractors. While these companies are specialists in their own specific fields, their role is really one of support and supply to the existing vaccine production and development industry; they generate solutions to engineering and/or processing problems against specifications defined by the customer.

Consultants

Consultants range from individuals with particular expertise in one or more areas of vaccine technology to consulting companies with teams of specialists constituted to meet the particular technical aspects of a project at various stages. Consulting companies are unlikely to have the required biological process technology expertise but can usually provide the other expert inputs required.

Takeovers and mergers within the pharmaceutical and veterinary biological industry have for some time resulted in the availability of a number of individuals with extensive experience in veterinary biologicals production and control who offer their services as self-employed consultants. These independent consultants have much to offer not only as noted in the section Commercial vaccine producers, above, but also as an alternative to commercial vaccine producers as a source of technology expertise.

THE PROCESS OF ACQUIRING TECHNOLOGY

Prior to contract

Regardless of the size of the proposed business, the stages to be worked through by the purchaser and vendor are similar and differ only in scale and the range of skills and specialized inputs required.

The purchaser must first define his or her needs. Ideally a document should be prepared which sets out the requirements and includes any particular conditions or constraints the purchaser may wish to impose or bring to the attention of prospective vendors. This document may be submitted to potential vendors and/or provide the supplementary information to a published tender invitation. The services and assistance of an expert consultant in preparing the basic terms of reference and in selecting the vendor are advisable.

Potential vendors should submit outline proposals and cost estimates. Then, following further evaluation and negotiation, a detailed contract should be made with a selected vendor. Depending on the size and scope of the project, vendors may need to do extensive detailed work, which may include feasibility studies, both to satisfy the purchaser and to establish detailed costings. This can be both time-consuming and costly and will not be undertaken lightly.

Ultimately the purchaser needs to know what is going to be supplied, how much it will cost and the stages at which payments are due. The vendor must be satisfied that the obligations can be discharged within the agreed time-frame and that the way of doing this has been understood and accepted by the purchaser. These points should be embodied within a contract which clearly states who will do what and by what time, what the acceptance criteria are and what will happen in the event of non-compliance. The contract should provide for binding arbitration in the event of an inability to agree. By and large the clauses in the contract which define the obligations and specify what must happen when either party fails to fulfil its obligations are the most important. While everything is going smoothly the contractual details tend to assume a lesser significance.

Post-contract

Implementation of the contract may demand nothing more than the vendor accepting a number of the purchaser's staff at the vendor's production facility and providing specified training. The terms of the agreement (contract) to do this will state how many staff, how and by whom they will be funded, for how long, the specific techniques they will be trained in, how they will be evaluated, the fee to be charged by the vendor, how many payments are to be made by the purchaser, when they are to be made, etc.

Alternatively, implementation of a contract may involve the erection of a vaccine production unit on a greenfield site and its handover in working order, fully staffed by local personnel. Obviously the scope and scale of this requires a multidisciplinary project team and dedicated project management to ensure definition of, and coordinated adherence to, the critical path.

Even large commercial vaccine companies are unlikely to have the required range of expert staff on hand to implement such an undertaking. Projects of this size are usually implemented by teams composed of experts from more than one company. The contractors may be a consortium of the key technology sources, such as process, civil and mechanical and electrical technicians, and project management may be provided from one or a combination of these, or by a consultancy group. The purchaser should insist that the managing contractor carrying overall responsibility be the

vendor responsible for providing the process technology and that all other inputs, from whatever source, be arranged through subcontracts with that vendor.

Project implementation can be considered as a series of phases which overlap. The efficient management of this overlap offers savings in time which can mean a considerable saving in cost. An outline of each of the phases involved follows.

Design. A great deal of design work will have been carried out pre-contract to enable contractors to establish the financial commitments and obligations they are undertaking. This work initiates the preparation of the master design document which lays down criteria and tolerances for all aspects of the project such as technology criteria, operating methods and quality standards. An important aspect of the master design document is the setting of overall design tolerances. Biological systems are, by their nature, relatively unpredictable and very susceptible to operator error. Excess capacity above that specified by the purchaser must be "designed in" to provide the purchaser with a reasonable expectation of meeting specified capacity. This capacity is in addition to that allowed for predictable factors arising from planned maintenance, public and religious holidays, etc.

Design involves detailed drawings, isometrics, models, etc. Models not only assist in three-dimensional design but also facilitate the preliminary validation of the process operating manual. Detailed specifications for the purchase of plant and equipment are issued. The site is usually selected pre-contract since its suitability and availability and the quality of major utilities have an enormous impact on the civil and mechanical and electrical costs. Further visits to the site by design staff may be necessary depending on the quantity and quality of the data acquired previously. Evaluations of locally available equipment, materials and skills (e.g. stainless steel fabricators, welders) will be necessary. Time and money spent at this stage save far heavier costs later.

The design stage includes:

- civil design (buildings, site, etc.): plans and specifications, models;
- mechanical and electrical engineering design (air-handling and treatment, process services, effluent treatment, utilities, etc.): plans, flowsheets, layouts, models, specifications;
- process design (the biological production and handling element): preparation of operating and quality control manuals, plans, flowsheets, layouts, models, specifications;
- spares and spare parts quantification and specification;
- consumables quantification and specification;
- support and ancillaries (refrigerated trucks, regional cold stores, serum processing plants): layouts, specifications, models.

Procurement. Project management in conjunction with design will, so far as it is possible, ensure that the plant and equipment with the longest procurement lead times are specified first and placed on order as soon as possible. These key items and their place in the installation schedule have a major influence on the implemention critical path.

To minimize future problems with importation, vendors should use local sources of supply where possible. However, process plant and equipment and key mechanical and electrical plant will usually have to be imported if the vendor has to guarantee performance; biological processes are quirky and two apparently equivalent pieces of plant may not offer the same biological performances.

Ordering is phased against stated lead times to place equipment on-site adequately in advance of the needs of the installation programme.

Installation. The first element of on-site activity is site preparation and civil construction. Mechanical and electrical installation commences soon after the installation of process plant and equipment installation commences well before completion of mechanical and electrical installation. There should be "milestones" in the contract and critical path at which contractors receive a phased payment. Any training of the purchaser's staff at the vendor's facility should commence at times appropriate to returning them to the site as soon as they can usefully contribute to the completion of the project. The future site maintenance engineer should commence training as soon as the contract is signed so as to be back on-site as soon as installation starts.

Commissioning. Commissioning is the initiation of data collection for justification of handover acceptance. All items of plant and equipment are tested and operated to ensure they perform to specification. Items first undergo engineering commissioning to check that the mechanical and electrical parts function and perform within the criteria specified. These tests are certified and become a cumulative record for handover. All measuring, monitoring and control equipment is tested, calibrated and certified.

Commissioning of the air-handling and filtration system is crucial. This system is the key to biological containment and security. Its capacity to perform reliably to the specified design parameters in the face of both extreme environmental conditions and process loadings must be demonstrated. This should be the responsibility of the specialist contractor.

Finally all plant and equipment with a biological function is tested and certified for performance and, where relevant, sterilizability (e.g. filters, culture vessels, valves, transfer lines, centrifuges, autoclaves). Seed banks are set up with certified stock and scale-up cultures are established. At this point plant is ready to move to the preproduction stage.

Training. Local staff of a suitable background and education are selected very early in the project and subjected to both classroom and practical training in a working environment using the same technology as that of the project. The trainees return to the site to assist in the biological commissioning and to prepare the specific standard operating procedures for the plant to be approved by the vendor.

Preproduction. An agreed series of trial batches are prepared in the new installation by the local staff under the supervision of the vendor, to prove the operability of the plant within the performance criteria specified and, at the same time, to validate the new standard operating procedures.

Handover. The final handover of the plant is dependent on the preproduction batches meeting the target criteria.

Consultancy. Failures of plant, equipment and structures occur even in the most efficiently organized projects. Contractor indemnities for a specified period to cover such events must be written into the contracts/purchasing agreements.

Performance problems of a biological nature may be beyond local expertise. The consultancy phase is designed to place the expertise of the vendor at the disposal of the new facility for a specified period, for instance, three years. Biological technology is constantly being improved and it is very important that the original contract clearly

defines the purchaser's rights with respect to improvements in the process technology being purchased, particularly over the period of the follow-up consultancy and any subsequent extension to that period. Ideally, the contract should require the vendor to notify the purchaser of improvements to the technology over this period and the purchaser should have the right of acquisition at a reasonable price.

The vendor should make an annual audit inspection of the facility and provide the purchaser with a written report together with recommendations for implementation. The inspecting team should be appropriately staffed for the target facilities to be properly inspected. Additional vendor support should be available on request. This may be provided at the vendor's facilities or on-site as appropriate for the particular problem. The formal annual inspection and recommendations should command a consultancy fee. Ad hoc support should be available on request on a time charge plus expenses basis.

The purchaser should have the option to extend the consultancy phase against renegotiated rates.

TRADITIONAL TECHNOLOGY ACQUISITION BY DEVELOPING COUNTRIES: POINTS FOR AND AGAINST

The single most quoted justification for technology acquisition by developing countries is self-sufficiency followed closely by a cheaper product which saves hard currency by avoiding the import of commercial vaccine.

Unfortunately the facts do not generally support this justification (although every individual case must be evaluated on its merits). The benefits of scale are lost. The initial capital investment is enormous and the bulk of this investment (about 70 percent) is in civil and mechanical engineering, i.e. the creation of the envelope and environment in which the process plant and associated equipment and resources are located and operated. Most of the process plant and many of the mechanical and electrical plant spares as well as many process liquor components and control reagents must still be imported, requiring hard currency. This is frequently subject to bureaucratic delay. Major utility supplies, especially water and electricity, are unreliable in developing countries, resulting in frequent production crises and disasters. The provision of effective standby sources is expensive both to provide and to operate. Trained staff salaries are rarely competitive, resulting in continuous losses of staff which further endangers production reliability. The need to operate to international good manufacturing practice (GMP), good laboratory practice (GLP), quality and environmental standards adds further to unit costs.

Self-sufficiency requires that certified quality- and potency-tested vaccine meeting the standards (with long lead times in many cases) will be available when the demand arises. The points given above are only a few of the more common causes of failure to achieve this and, unfortunately, the management of vaccine plants in developing countries is rarely sufficiently experienced or powerful in the hierarchy to influence the situation for the better.

A further consideration is that of emerging new technologies. The possibility of multiple antigen vector vaccines administered orally, possibly even via the feed, is quite real. Against such a possibility the validity of investing in traditional vaccine technology, rather than continuing to import until the position clarifies, becomes very doubtful.

The above remarks should not in any way deter those seeking to improve existing production facilities particularly with respect to meeting GMP/GLP standards or upgrading quality assurance.

General design and operating requirements for vaccine manufacturing establishments

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The design and operation of facilities suitable for the manufacture of veterinary vaccines depend on many factors, including the nature of the organisms from which the vaccines are to be prepared, the specific manufacturing processes used and the particular economic, technical and geographical situation in which the facility is to operate.

This chapter will give only a broad outline of the principles which should be borne in mind for the design and construction of new facilities or the upgrading of existing installations. Many of the design features are relatively uncomplicated and should therefore not be prohibitively expensive to incorporate into a new building design although it may be difficult and expensive to make changes to existing buildings which did not take into account these factors at the design stage. Similarly, when facilities are being upgraded or modified for other purposes, it is often appropriate to review basic design and operating parameters to ensure that, wherever possible, improvements which permit the most satisfactory functioning of the plant are incorporated.

The essential requirement for a manufacturing plant is that it should produce a sufficient quantity of good-quality, safe and effective product in an economic manner as required. The objectives of optimum plant design and the concepts of good manufacturing practice and total quality management are intended to ensure that these requirements are met on a routine basis.

In a number of countries, general guidelines for the manufacture of veterinary products have been in place for some time. In particular, manufacture within the United Kingdom has been subject to compliance with published guidelines (Sharp, 1983; Government of the United Kingdom, 1983) and a set of guidelines for the manufacture of veterinary immunological products within the European Union (EU) has also been published (Commission of the European Communities, 1992). These guidelines set out the general requirements for facilities and their operation and are based on an appreciation of the problems that can occur in the manufacture of veterinary vaccines and of how such problems can be avoided.

Although these guidelines are not mandatory in other parts of the world, most of the principles they contain are applicable to any manufacturing situation and, where they can be effectively integrated into the design and operation of other units, it is frequently advantageous to do so. Incorporation of some specific design features at the start of a project may not be practicable or cost-effective, but careful design with thought to future possible needs when setting down the basic design and layout is likely to prove worthwhile and may save expensive modification work as and when these features become important.

The following sections describe the main principles governing the general layout of laboratories, the major factors which need to be considered in their operation and the

specific needs of particular manufacturing areas.

GENERAL ARRANGEMENT OF BUILDINGS

Buildings should be constructed of good-quality materials, with impervious finishes which can be easily cleaned and maintained and constructed in such a way that adjacent areas can be effectively sealed and separated from one another and from the outside. In today's manufacturing environment wood is not regarded as ideal and, where used, needs to be thoroughly painted and regularly maintained.

In many situations it will be necessary or desirable to hold individual areas under an air-pressure differential, which may be negative or positive to the outside and to adjacent areas. The materials and method of construction should be such that this can be achieved easily.

In the construction and fitting out of all manufacturing areas, consideration should be given to the avoidance of ledges and crevices and unnecessary internal protrusions such as surface water downpipes or other architectural features. Wherever possible, windows should be fitted flush to internal wall surfaces and coving used to create smooth, easily cleaned corners.

Areas where the product or its sterile constituents are directly exposed during manufacture will require greater attention to these details than those in which the product is manipulated within totally enclosed containers. However, the principal aim remains to create the cleanest possible manufacturing environment and one which is easily maintained.

Attention paid to the logistics of product and material flow and staff movements during manufacture will ensure that sequential manipulations may be carried out in adjacent areas and will promote an efficient flow of materials into and out of each area.

To maintain cleanliness and the integrity of the manufacturing environment, facilities need to be provided for the transfer of materials into and out of manufacturing areas in such a way that the environment of the room is protected and infectious agents (either to be manufactured or adventitious) are contained. In general these access points should be separate from those used for the entrance and exit of staff.

Materials, in particular live organisms, that are handled in quality control (QC) laboratories are considered by most regulatory authorities to present a risk to the manufacturing operation. Such laboratories should therefore be situated in a building separated from that used for manufacturing. Where this is not practical or feasible there should be at least a solid wall between the two different activities. Again, care taken at the design stage will ensure that features can be accommodated that will make possible the smooth flow of samples from the manufacturing areas to the QC laboratory and of the results of analyses from QC back to manufacturing.

The sizing of manufacturing facilities is a complicated operation. Areas need to be large enough for the operations which will be carried out in them but such facilities are expensive and excess space is unnecessarily costly. Conversely, as will be clear from the above, if logical flow patterns are to be established and maintained, the later expansion of individual areas may be difficult to achieve. In consequence, it is usually prudent to make allowance for any future expansion of activities while the project is still at the design stage.

EQUIPMENT

The detailed equipment requirements for a vaccine manufacturing establishment will depend on the scope and capacity of the particular unit, but some general points can be made.

Many facilities will require stainless steel fermenters, inactivation and blending vessels which may vary in volume from a few to several thousand litres. Many manufacturers can provide fermenters and other vessels of satisfactory design but it should be noted that the control package which accompanies the vessel may be much more sophisticated than is actually required – resulting in unnecessary costs. In most of the situations covered by the scope of this manual, process operations will be essentially hand controlled and, while a degree of automatic environmental control will be required, it would be wise to ensure the vessel manufacturer provides only that which the process needs and not the ultimate of which it is capable.

At the other end of the spectrum, it is sometimes considered appropriate to minimize capital costs by fitting mild steel jackets insulated with cheap lagging instead of using good-quality stainless steel. In many cases this is a false economy since, once installed, such fermenters are frequently required to function over an indefinite lifespan in a hot humid atmosphere, which soon results in deterioration of the lagging and ultimately the jacket. Effecting repairs is then difficult, disruptive and expensive.

Great care needs to be taken at the design stage to ensure that fermentation equipment is installed with due regard to both process and service flows and particularly that drainage from both vessel and pipework during steam sterilization is effective. Open drainage channels in floors are frequently considered undesirable because of the resultant contamination risk and the efficient draining of steam condensate to ensure the sterility of pipework and vessels is made considerably more complicated where valves cannot simply be purged.

In addition to fermentation equipment, the facility will need autoclaves and sterilizing ovens, designed in such a way that the minimum requirements for sterilization can easily be met (Parenteral Drug Association, 1978 and 1981), and a range of other equipment such as freeze-driers, filling machines, centrifuges, filters and antigen concentration equipment. Again, there is a wide range of sophisticated commercial equipment available from which to choose and it is important to balance the right level of sophistication against the needs of the process and the situation in which it is being operated. Simple systems are frequently more labour-intensive but tend to require less maintenance and are easier to put right when they go wrong.

AIR-HANDLING SYSTEMS

Most manufacturing facilities require a fairly sophisticated air-handling system. In the interests of the operators, their efficiency and the product itself, it will be necessary to maintain equitable temperature and humidity levels in the facility. In addition, a principal objective should be to maintain as clean a working environment as possible. This will entail segregation, both internally and externally, from other areas, which may pose some risk to the maintenance of a satisfactory manufacturing environment.

The methods normally employed to promote a clean working environment include the provision of air filtered through sterilizing high-efficiency particle adsorption (HEPA) filters and the maintenance of pressure differentials between adjacent areas. In situations where live organisms are handled within the manufacturing area there will also be a requirement to filter exhaust air. In small installations it is possible to achieve these requirements with simple individual "through the wall" fan/filter units. The balancing of such a system, however, can become an extremely complex problem, since the pressure drop

across, and the flow of air through, each unit may cause detrimental effects on the atmosphere of the next one.

In practice it may prove more satisfactory to use a separate fan unit to supply each related group of rooms. The same principles apply to the extraction side of the system and great care should be taken to ensure that potentially contaminated air extracted from a unit handling live organisms cannot be recirculated into clean production areas.

The detailed airflow rates and pressure differentials required depend on the particular functions and layout of the facility. In general, a minimum pressure differential of 1.5 mm water gauge between adjacent areas is normally used. Care must be taken with the layout to ensure the cumulative effect of this does not result in very large pressures on windows and doors which connect with or are related to nearby areas. This could cause problems with the sealing of windows or the opening of doors.

For general manufacturing or enclosed processing areas, an air exchange rate of seven to eight changes per hour is usually considered adequate, but for sterile areas exchange rates of at least 20 changes per hour are required if the low particle and bacterial counts specified in the European and United States guidelines are to be met. These are undoubtedly necessary to ensure that satisfactory working conditions are maintained.

It is important that inlet and outlet ducts are carefully positioned to provide a good sweeping action in workrooms. Typically, inputs are terminally filtered into the area at a high level and balanced with low-level extractors on the opposite side of the room.

STAFFING

It is essential that any manufacturing facility should be staffed with personnel who are of the right calibre and sufficiently trained to perform the tasks required of them. This will almost invariably mean that a nucleus of qualified and/or experienced senior staff will need to implement an ongoing training programme to ensure that all staff are fully conversant with the tasks required of them. To make the latter possible all personnel will benefit from an overview of the entire facility, its functions and the rationale behind the operating regimes implemented. It must be remembered that training will need to cover not only the technical methods employed but also the basis of good manufacturing procedures, safety and quality assurance in the broadest sense.

To be confident that live agents and materials, including both those used for manufacture and the adventitious agents that are inevitably present on the site, do not gain access to manufacturing areas other than those in which they originate, it is good practice, and in many situations a mandatory requirement, to restrict the free access of staff to all areas of the site. A commonly used rule of thumb restricts operations to one type of product organism, per operator, per air space, per day. The restrictions on staff, especially the time period, will depend on the particular manufacturing operation, but such restrictions should prevent the direct movement of personnel between QC facilities and manufacturing areas and between manufacturing areas handling live organisms and those in which inactivated antigens or products are handled.

These restrictions, however desirable from the manufacturing standpoint, inevitably tend to create and amplify barriers to effective communication. This places an even greater emphasis on the importance of adequate and continuing staff training and dialogue among the

various groups on site. It is essential to ensure the unit works as one and not as a series of disparate groups.

WATER

Manufacturing facilities require a reliable supply of good-quality water for general purposes and for direct use in the manufacturing process. Important factors influencing the quality of water are the microbial content and the total quantity and nature of both organic and inorganic impurities.

Traditionally, the water used in tissue culture or bacterial fermentation processes has been produced by distillation, usually following a desalting or ion-exchange purification stage. More recently, excellent results for both tissue culture and bacterial-based products have been obtained using water produced by the method of reverse osmosis instead of distillation. This is an extremely energy-efficient process and, in some situations, plants which have switched to reverse osmosis from distillation have been known to recover their capital costs in a matter of months.

Whatever the method used for the manufacture of pure water, the equipment used for its production and storage require careful management. Bacterial growth in storage tanks and purification columns, whether ion-exchange or reverse osmosis, is a constant hazard and toxins may persist even if the live contaminants are eliminated. As yet, the columns available for purification stages cannot be steam-sterilized and regular chemical disinfection must be carried out. The problem of water storage can largely be overcome by heating the storage vessel, and preferably the distribution system, to at least 65°C and maintaining that temperature until the water is required for manufacture. Careful attention needs to be paid to the layout of the distribution system itself to avoid "dead ends", poorly designed valves and other points at which water may remain stagnant.

Whatever process and procedures are adopted, the quality of both "feed" and purified water will require regular monitoring and equipment will require regular sterilization or sanitization.

LIQUID EFFLUENT

Manufacturing facilities almost inevitably produce large amounts of liquid effluent which need to be discarded in a safe and satisfactory manner. The appropriate necessary procedures depend on local regulations and the nature of the agents handled in the facility but should take into account the possible presence of live agents, their inactivation and the chemical content of the material to be discarded.

Total segregation of live from non-infective areas within the facility will minimize the volume of the more difficult materials that arise from the former areas.

Small quantities of liquid effluent can normally be rendered innocuous by autoclaving, but larger quantities require a dedicated collection and treatment facility. Heat treatment of contaminated effluent is commonly practised, either as a batch or a continuous process. Care needs to be taken to ensure that there is sufficient storage capacity for untreated material, both to balance the throughput of the sterilizer and to provide storage during equipment failures and accidents within the facility.

WASTE DISPOSAL

If the risks of environmental contamination and cross-contamination are to be avoided, solid wastes arising from areas handling live agents require decontamination prior to removal from the area in which they were generated. This can be accomplished either by fumigation (e.g. with formaldehyde) or heat-sterilization (e.g. autoclaving). This in turn requires the

provision of suitable facilities for these activities at, or close to, the perimeter of the area in which the agent is handled. With careful design one sterilization/fumigation facility can serve more than one area and, depending on the nature of the agent handled, an acceptable compromise can sometimes be found by surface decontamination of materials at the time of removal from the infected area and subsequent sterilization in an adjacent facility. It should be pointed out, however, that suitable sterilization/fumigation facilities are frequently required for the transfer of materials into manufacturing areas and, where this is so, the same facilities can serve for the removal of waste materials.

Waste materials should not be allowed to accumulate on the site or to become dispersed around the site. The identification of a single deposition point at the perimeter of the site, combined with regular collections by the appropriate waste disposal authority, should serve to minimize problems with solid waste.

MANUFACTURING MATERIALS

If a high degree of assurance is to be obtained in relation to the quality of routinely manufactured products, it is important that all materials used for manufacture are of a suitable quality. This does not necessarily require the importation of expensive high-purity components, provided a reliable source of satisfactory materials can be found locally.

Where a pharmacopoeial standard for a particular component exists, there is frequently a requirement to meet it and this can be accomplished either by purchasing ready tested material or by arranging for the appropriate tests to be carried out. Where there is no requirement to meet a pharmacopoeial standard the manufacturer needs assurance that the supplier can routinely supply material which will result in the production of a satisfactory product. Such assurance needs to take into account both the satisfactory yield and the efficacy of the final product and its safety.

In many cases it is advisable to set up routine tests on batches of raw materials prior to their use for manufacturing operations. It could also be important in the subsequent investigation of production trends and in solving the inevitable production problems, which arise from time to time in all biological manufacturing operations, that the individual batches of raw materials used for each operation can be traced. It is therefore advisable to batch-label each consignment of raw materials on arrival, to introduce some formal QC release procedure to confirm that the materials are considered acceptable for use and to record the batch identification as materials are used, thus ensuring traceability throughout the production process.

SEED PRODUCTION AND STORAGE

Under most circumstances the production of seeds, including both the live agent and, where appropriate, the substrate on which it is to be grown, will require the provision of facilities for the handling of relatively small amounts of materials under conditions in which these materials are at some stage exposed to the air in the workroom or cubicle. This will necessitate close attention to the quality of the air and the maintenance of clean conditions in the room itself.

Manufacturing operations in which live agents are handled under conditions in which sterile materials are exposed, albeit transiently, to the environment, represent one of the most difficult challenges in the design of facilities which satisfy all aspects of modern manufacturing requirements. The principles described here for seed production can be modified and extended

for other aspects of the manufacturing operation and will be cross-referenced in other sections of this chapter.

The European guidelines (Commission of the European Communities, 1992) recommend that sterile operations of the type described here are carried out in a laminar airflow cabinet (meeting the guidelines' Grade A classification) which has been installed in a "clean" room (meeting the guidelines' Grade B standard). Such a facility would require a supply of HEPA-filtered air, at a rate that provides at least 20 changes per hour to the room itself, and a similarly filtered extractor system. A full garment change facility for operators would also be required. This too, would need its own supply and extractor of HEPA-filtered air – providing the same level of air replacement as for the laboratory. A pressure differential of at least 1.5 mm water gauge should be maintained between the changing room and the laboratory. The laboratory will also need some form of transfer lock, preferably capable of fumigation, for the movement of materials into and out of the seed production facility.

With the introduction of appropriate quality assurance procedures and a suitable arrangement of pressure differentials between corridors, anterooms, changing rooms and laboratories, such a facility provides an effective barrier against the ingress of contamination from external sources (including the environment, the operators and materials brought into the unit) and an effective barrier ensuring containment of the live organisms handled within the facility. A convenient way of achieving this is to hold the workroom under negative pressure, make the changing room more strongly negative and provide an anteroom at a positive pressure. In this way the changing room acts as a plenum or "sink" and provides a barrier against air movements from either side.

Recently, totally enclosed isolation units have been developed, in which operators work through glove ports. The units are fitted with "pass-through" hatches, which can be fumigated, and sometimes even include environmental control facilities. Such units, although expensive, can be highly effective, enabling different organisms and/or operations to be handled in adjacent units without compromising either the environment or the operator.

A "master" seed bank should be established, based on an isolate of the material from which the vaccine is to be prepared and, in the case of viral vaccines, the substrate (or cell line) on which the agent is to be cultivated. The manufacturer will need to be assured that these materials are free from all adventitious agents which might cause contamination losses in the manufacturing process or untoward effects, or even disease, in animals on which the vaccine is subsequently used or on others which are in contact with such vaccinated animals.

In addition to an assurance of the purity of the material, the manufacturer also needs to be assured that the seed material will routinely produce high, and therefore economically acceptable, yields in the production system and that it produces a safe, reliable and effective end product. Examples of these requirements can be found in the series of documents issued by the European Union's European Committee for Veterinary Medicinal Products (EC, n.d.a and n.d.b).

Aliquots of suitable material need to be stored for long periods under conditions appropriate for the particular entity. Depending on the organism, storage over liquid nitrogen, storage at -70°C, freeze-drying or, occasionally, storage at cool-room temperatures may all be appropriate. The essential requirements are that the organism should not lose titre or

undergo any change in its characteristics while in storage for long periods. From this material it is customary to set up one or a number of working seed banks, which can be stored under similar conditions to the master bank and used to initiate each production cycle or series of cycles. By careful use of the seed banks in this way the original master bank becomes almost immortal and can be used to support production over long periods without the serial passaging of the organism to a level where the characteristics of the seed material itself might become modified.

MEDIA PRODUCTION

The media used for the cultivation of the agents under manufacture can be purchased ready prepared or as sterile concentrates from reliable sources. They can also be prepared on-site from component materials. In most cases considerations of cost and the volumes required dictate that media are produced on-site.

By their very nature, the components and media used for manufacture usually tend to encourage the growth of adventitious contaminants, and care needs to be taken to ensure the components themselves and the facilities in which they are prepared are as free from such contaminants as possible. It is usual to provide a dedicated media production facility, close to but separated from other manufacturing areas on the site. This unit should be well ordered, free from materials not immediately required for the process and amenable to routine and methodical cleaning. It may be considered appropriate to provide a working environment of HEPA-filtered air and it is preferable that staff working in the area should not enter other manufacturing areas on the same day.

The components used for media production should meet the general requirements outlined in the section Manufacturing materials (p. 176) and particular care should be taken over materials of biological origin which form an essential part of many culture media. In some countries there are specific regulatory requirements governing the use and testing of such materials (Medicines Control Agency, n.d.). These are intended to ensure that no disease-causing agent is introduced to the manufacturing process and, as a minimum, the manufacturer needs to be sure that the animals from which the materials, for example serum, were obtained, were healthy and from a disease-free herd and that the method of collection and processing was unlikely to have adversely affected the quality of such materials.

Depending on the nature of the manufacturing process, once prepared, the medium may be sterilized and put into storage containers – or vice versa. Alternatively, the medium may be transferred directly into the production vessel before or after the sterilization cycle. The dispensing of sterilized media into multiple storage containers may require sterile handling facilities similar to those described in the section Seed production and storage (p. 176).

ANTIGEN PRODUCTION

The facilities required for antigen production will depend on the nature of the organisms from which the vaccine is to be prepared, the manufacturing methods to be employed and the proposed scale of the operation. Manipulations in which sterile materials are effectively exposed to the operator and / or the local environment during manufacture will require facilities that are essentially similar to, but obviously may need to be larger than, those described for the production of seed materials. In cases where the utilization of facilities (and therefore volume throughput) is low, the same unit may be used for both functions,

with the provision of suitable safeguards between operations.

Where all operations are carried out within totally enclosed vessels, pumps, pipework, etc. the inside of the equipment may be considered as the manufacturing environment and a somewhat less rigorous environment is usually considered acceptable for the location of the manufacturing equipment. Nevertheless, it is important to pay attention to the design and operation of these areas in order to minimize the likelihood of adventitious contamination arising or persisting within them. Important features to consider will be: easily cleaned surface finishes, drainage, the ventilation system, the means by which materials enter and leave the area and operator access.

Where practicable it is desirable to provide enclosed processing areas with a supply of HEPA-filtered air and for antigen production (where by definition live agents are handled) it will be preferable to hold these areas at a pressure negative to the surrounding areas. As described for seed production areas, the careful planning of layouts and pressure differentials can be used to create a situation in which the work area is protected from possible external adventitious contamination, and yet there is still a containment barrier at the point of entry through the changing room.

To provide safeguards during enclosed manufacturing operations for the integrity of both the contents of the vessels and equipment and of the environment in the room, consideration should be given to the means by which samples are taken, and additions made, during processing.

Most equipment used for large-scale manufacturing operations can and should be sterilized *in situ* with steam. Equipment which cannot be steam-sterilized presents a more difficult problem, and care should be taken to ensure any procedures used for chemical sterilization are validated under the actual conditions of the operation beforehand. Assuming that facilities are available for the *in situ* steam-sterilization of major equipment, it should be a relatively simple matter to ensure that the connections used for sampling, additions and vessel-to-vessel transfers are also steam-sterilized *in situ* before and after effecting transfers.

Where some items of equipment must be chemically sterilized it is preferable to arrange the plant in such a way that as much of the equipment, pipework and valves as possible is steam-sterilized and reliance is placed on chemical sterilization only for the essential components that cannot be subjected to steam under pressure.

ANTIGEN INACTIVATION

Unless the vaccine undergoing manufacture is a live attenuated one, the next stage in vaccine preparation is inactivation of the antigen. The major dilemma in this procedure – from the viewpoint of facility design and operational convenience – is that the process, by definition, starts with live material and after the commencement of its inactivation every effort should be made to ensure there is no possibility of its being contaminated with other live material.

These constraints have implications for both the inactivation vessel and the workroom itself. To overcome the possible risk of droplets from within the inactivation vessel (which may not have come in contact with the inactivant) reinfecting the vessel contents, it is considered good practice to transfer the mixture of live antigen and inactivant to another sterile vessel after a period of mixing. These procedures are usually carried out in the area in which the antigen was produced and the closed vessel containing the inactivating material is either isolated within the facility or transferred to a

separate holding room while the inactivation process is completed. During this process it is often found preferable not to sample or open the vessel for any reason. Conversely, there is a good argument for monitoring the progress of each inactivation cycle, and this can only be done by sampling. The most appropriate approach in each situation may well depend on the regulatory environment or pharmacopoeial requirement for the product in question. In either case, it would be prudent to introduce some form of formal quality assurance clearance procedure before material that has completed the inactivation cycle is transferred for downstream processing or vaccine blending.

DOWNSTREAM PROCESSING

The requirements for any downstream processing depend on whether the product is live or inactivated and on the needs of the manufacturing process itself. While inactivated, innocuity tested antigens of different types may, with reasonable safeguards, be handled in the same area, a separate area will be needed for live antigens. Different live organisms can usually be handled in the same area providing it can be cleared, cleaned and fumigated between successive production cycles. If production throughput is high, however, it may be preferable to have separate areas for different products.

The most common type of downstream processing operation is probably concentration of the antigen, but other necessary procedures may include various purification or separation stages. Wherever possible it is preferable to carry out downstream processing of inactivated products after the inactivation stage has been completed in order to avoid the complication of handling the live material. Such processing should, wherever possible, be carried out in a separate area to that in which the live material was produced. Where this is not practicable, further innocuity tests should be carried out on the completion of operations and material should not be passed on for blending until satisfactory results are obtained from these tests.

As emphasized previously, the workrooms in which inactivated antigens are handled should be free from other live organisms and preferably held under a positive overpressure of HEPA-filtered air. If the manufacturing operation necessitates transient exposure of the product to the atmosphere of the room, the room should meet the standards defined for seed production but at positive pressure in relation to its surroundings. Enclosed processing operations may be carried out in a less rigorous environment, but a positive pressure of HEPA-filtered air is desirable. The same considerations relating to cleanliness, material and operator access will apply as were indicated in the section Antigen production (p. 178).

Where live attenuated vaccines are produced, the manufacturing area should be held under negative air pressure and operations may be carried out effectively in areas similar to those described for seed and antigen production.

The equipment required for downstream processing should preferably be sterilized *in situ* by steam under pressure but, where this is not possible, chemical sterilization using a fully validated process is likely to prove satisfactory. The remarks relating to chemical sterilization in the antigen production area also apply to this situation.

Whether or not separate rooms will be required for the downstream processing stages of manufacture depends on the nature and complexity of these operations in relation to other activities. In many situations, however, it will be appropriate and sufficient to perform these stages in a part of the room used for blending the vaccine.

VACCINE BLENDING

Vaccine blending is usually a mixing operation based on the combination of one or more antigens – each of which has been shown to conform to the manufacturer's quality requirements – together with the other components of the vaccine, such as adjuvant, preservative and frequently a diluent.

The mixing operation may be simple or may involve the use of specialized mixing equipment, as for example in the preparation of oil-emulsion vaccines. Antigens for blending have a high financial value resulting from the materials and labour which have been expended in their preparation and testing. It is therefore of particular importance that all the other components used, including both additional antigens and the blending materials, are of suitable quality and integrity and will result in the production of a satisfactory, sterile, safe and effective vaccine.

The blending of vaccine will usually require the same type of facilities as are required for any of the downstream processing stages and, as indicated previously, it is frequently appropriate to carry out both activities in the same area and in some cases even to use the same equipment.

VACCINE FILLING

At each successive manufacturing stage the investment in labour and materials increases and the manufacturer should introduce safeguards to ensure that only satisfactory materials are passed on for the next stage. This is certainly true for the filling operation, where the inconvenience and loss associated with discarding final filled product is considerable.

Filling operations almost inevitably expose the final product to the atmosphere at the actual dispensing point, so these operations are best carried out under a laminar curtain of HEPA-filtered air within a sterile room. Because of the large volume and number of containers involved in most filling operations, sterile rooms of considerable size are frequently required. As has been described elsewhere in this chapter, the facility will need its own sterile changing rooms, a satisfactory means of getting sterile materials (including final containers and product) into the room and a means of moving the filled containers out of the room – all without harming the filling operation itself. The basic requirements of the filling room will be similar to those described in the preceding sections for rooms in which sterile product is transiently exposed to the atmosphere. The air pressure within the room should be either positive or negative relative to the surrounding area, depending on whether the facility is for a live or inactivated product.

Final vaccine containers which can be heat-sterilized are best introduced directly into the filling room by means of a sterilization cycle through a double-ended "pass-through" sterilizer. Other types of final container, such as those sterilized by radiation, should be sterilized double-wrapped and in such a way that the outer packaging can be removed outside the filling room and the inner wrapping surface decontaminated or fumigated in a transfer lock prior to being introduced into the filling room proper.

Removal of filled containers can be done either on a batch basis at the conclusion of filling operations or continuously throughout the process. For large batches the latter tends to be preferable and this is frequently accomplished by means of a conveyor belt. The belt should not emerge directly from the sterile room and subsequently re-enter it.

In the case of live filled products, many will require a freeze-drying stage after the filling operation. It will be very convenient if the freeze-drier can be loaded directly

from the filling area. If the freeze-drier is double-ended the product may then be transferred for storage without re-entering the filling area. For single door machines, however, it will be necessary to pass the vials back into the filling facility when unloading the machine. This tends to reduce the flexibility of the filling unit which could otherwise be decontaminated and set up for processing the next batch (which could involve a different antigen).

In all cases where live products are handled it should be remembered that the filled containers may be contaminated on the outside and some form of surface decontamination will need to be considered once the final container seals have been applied.

QUALITY ASSURANCE

For the purposes of this chapter, quality assurance will be taken to encompass the elements of quality control (QC), environmental monitoring, validation and documentation leading to batch release. Each manufacturing site will require the services of a QC unit, which should preferably be located in a different building to that of the production facilities. It is highly convenient if the QC unit is situated on the manufacturing site, but specialized tests, especially those requiring sophisticated equipment, may have to be carried out by external organizations or units.

QC facilities on a manufacturing site should be operated in such a manner that the risk of agents being transmitted from the QC unit to the production facilities is minimized. This may be effected by means of the HEPA filtration of extract air from the QC unit together with restrictions on the movement of personnel and materials. Movement of samples and documentation between units may give rise to particular problems, but arrangements which permit safe and effective transfer of materials for test and the two-way transmission of appropriate documentation are not difficult to establish.

It will be important to distinguish between those test procedures that relate directly to the quality of the manufactured product (for which there should be clearly defined acceptance criteria) and those that contribute towards an overall understanding of the manufacturing process. The latter, when considered individually, would not normally be used to condemn a production batch.

Apart from both quality control and in-process tests on materials and product during the manufacturing process, the producer should also continuously monitor the manufacturing environment, in terms of both its physical and biological performances. In this way potential problems can be identified before they become critical and corrective action may be taken before production losses are experienced.

The range of environmental monitoring that might be considered is too broad to list here in detail, but it should cover at least all of the following: environmental bacterial levels in both sterile and general manufacturing areas; the quality of process fluids (particularly water); airflow pressure differentials and filter integrity; and equipment performance (particularly of sterilizers). To establish that process equipment and operating procedures are capable of performing the tasks required of them on a routine basis and under the conditions of normal use, it is necessary to have them validated. This is usually carried out as part of the initial commissioning process and, although time-consuming, thorough testing of each stage of the process at the outset can save major losses later on. Furthermore, the regular revalidation of equipment will not only increase confidence in the operation but help to identify problem areas before they become critical.

All of the above procedures should be formally documented and the documentation made available for review, so that – in considering either the factory manufacturing record or the production of an individual batch – the results of mandatory QC tests, in-process control tests, environmental and validation studies can all be taken into account. In this way, the manufacturer can have a far greater degree of confidence in the products than would otherwise be possible from the results of statutory QC tests alone and, when difficulties occur, the possible causes can more easily be identified and eliminated.

CONCLUSIONS

Careful adherence to the principles of good facility design and manufacturing practice should help to ensure that production plants function at a high level of efficiency and that losses are a rare event. Although there is undoubtedly an element of additional expenditure related to the issues raised here, much can be done without significantly increasing installation costs. Where additional expenditure is involved, the analysis should take into account the savings associated with greater production efficiency and reduced losses and also the greater confidence in the product of customers and the relevant control authorities.

In a similar way, attention should be paid to quality throughout the manufacturing operation and every effort should be made to build quality into the product, rather than relying on testing for it.

With the appropriate design of facilities, high levels of productivity can be achieved and in-process losses can be minimized. There will also be a high degree of probability that the filled vaccine will pass all required final product tests and perform in a safe and effective manner when used in the field.

BIBLIOGRAPHY

Commission of the European Communities. 1992. *The rules governing medicinal products in the European Community*, Vol. IV, *Good manufacturing practice for medicinal products*. Directorate General for International Market and Industrial Affairs.

EC. (n.d.a) *General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use*. Committee for Veterinary Medicinal Products of the European Community.

EC. (n.d.b) *General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use*. Committee for Veterinary Medicinal Products of the European Community.

Government of the United Kingdom. 1983. *Compendium of guidelines on the quality control of veterinary immunological products*. Weybridge, UK, Biological Products and Standards Department, Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food.

Medicines Control Agency. (n.d.) *Use of substances of animal origin in the manufacture of veterinary vaccines*. Document MAL 67. London.

Parenteral Drug Association. 1978. *Validation of steam sterilization cycles*. Technical Monograph No. 1, Philadelphia, Pa., USA.

Parenteral Drug Association. 1981. *Validation of dry heat processes used for sterilization and depyrogenization*. Technical Monograph No. 3, Philadelphia, Pa., USA.

Sharp, J.R. 1983. *Guide to good pharmaceutical manufacturing practice*. London, Her Majesty's Stationery Office.

Design, repair and maintenance of vaccine manufacturing establishments and equipment

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DESIGN

During the initial stage of designing a vaccine manufacturing establishment (VME) the following factors must be taken into consideration:

- national and international legal requirements;
- site location;
- general building layout;
- utilities and services;
- building construction and finishes;
- processes;
- equipment;
- maintenance and repair of premises, plant and equipment;
- maintenance records.

NATIONAL AND INTERNATIONAL LEGAL REQUIREMENTS

A VME is obliged to comply with legal requirements which may not be the same in every country. Taking the most stringent from different countries and compiling them in a theoretical international standard requirements for VMEs gives some indication of the most severe conditions which a VME would have to comply with.

The first question to be asked is whether the VME is to supply the national or international market. The costs of construction, equipment and the manufacturing process will depend on this.

SITE LOCATION

When planning and siting a VME the following points need to be considered: altitude, accessibility, terrain, neighbours, climate, security, noise, future developments, pollution and local regulations.

Altitude

Altitude affects the efficiency of, for example, internal combustion engines, standby electricity generator sets and tractors. It also affects the boiling point of water in steam boilers, etc. Engines and boilers are normally rated at sea level, therefore it is important to know what efficiency is to be expected at different altitudes and, when commissioning such plants, this factor has to be considered.

Terrain

VMEs should be sited in areas that are free from flooding and easily accessible. The ground has to be such that the foundations of the building are on a sound solid surface. It should also be in an area where such services as drainage and sewage disposal are accessible and, in cases where these have to be discharged into the ground, the ground should be such that it can accept or absorb the effluent so disposed of.

Climate

Weather conditions influence several of the requirements to be considered in the design, with regard to the construction and use of the premises. Hot and dry weather implies that the VME has to have air-conditioning and air filters will probably be required where dust is a constant

problem. With hot, wet weather, increased drying capacity will be necessary, particularly for air under pressure, and a specific type of roof and windows will have to be used.

Noise

If the VME is adjacent to such high-noise areas as major motorways, industrial sites or airports the noise level could affect the working atmosphere within the laboratory.

Pollution

The VME should be protected from the environment and the environment from the VME. It should be sited where there is no pollution from the surrounding area, but as this can never be guaranteed completely, means for water and air filtration/purification should be installed, to ensure their appropriate quality for industrial use, otherwise contamination problems may arise.

The VME itself must be designed so as to ensure that no gaseous, liquid or solid waste disposal contaminates the soil, water streams or atmosphere. A VME can cause aerial pollution by oil-fired boilers and incinerators, if these are not well maintained.

The health and safety of personnel can also be a problem unless buildings and equipment are designed to protect both the workers and the products and are well maintained to ensure that they perform to the required standards.

Local regulations

Each country has its own regulations on the construction of buildings. These requirements must conform to the published regulations pertaining to issues such as sewage and effluent discharge, the drilling of water boreholes and wells and the standard of electric installations in the establishment.

Accessibility

The site should be accessible by road and should be such that strict entry restrictions can be enforced.

Neighbours

The establishment should be located on a site where public buildings such as hospitals, farms (especially those with livestock) and factories which could cause pollution are at some distance. This is not always possible so, as noted before, the design should have provision for the installation of purification systems for air and water supplies if needed.

Security

The VME should guarantee that no disease outbreak will occur as a result of its manufacturing activities. This means the provision of adequate installations, strict adherence to good manufacturing practices (GMPs), an adequate security system for the entry and exit of personnel, staff, visitors and contractors and a good perimeter fence.

Future developments

The site should be so designed that there is room for future expansions. Buildings should be arranged so that central services such as electricity and steam generating plant and administration blocks will not be affected during future expansions.

GENERAL BUILDING LAYOUT

Consideration has first to be given to the requirements of the different areas of a VME.

General areas are those where there is no reciprocal threat between product and environment and no special requirements other than order, cleanliness (standard GMPs) and possible temperature conditioning for personnel comfort or product conservation. These are: administration offices, general stores, material washing and

preparation areas and areas for labelling, packing, storage and dispatch of the final products.

Restricted areas are those where live pathogens are handled and may impose a threat to the environment. These are: laboratories where field samples are handled, areas where seeds are prepared, areas where large-scale production takes place, areas where live vaccines are freeze-dried and areas where challenge tests take place.

In all these areas, air, liquid and solid effluents must be decontaminated and personnel leaving the area must, at least, change their clothes. Depending on the pathogen handled, showering may also be required. Access should be strictly restricted to those working in the area.

Air pressure should be negative to the ambient by air extraction through absolute, high-efficiency particle adsorption (HEPA) filters. When live pathogens are handled in open processes (e.g. freeze-drying), provisions for the supply of sterile air to the area, together with the use of safety cabinets to protect the personnel and the product are important. Liquids and solids must go through chemical and / or physical decontamination processes to avoid contamination of the environment before disposal.

Clean areas where the product must be protected from the environment include: media production, inactivated antigen process and storage, inactivated vaccine blending and inactivated vaccine filling areas. The air pressure in these areas should be positive with respect to ambient and, where sterile products are handled in open processes (e.g. sterile filling), sterile ambient conditions should be provided.

During the initial stages of designing a VME, the following are some of the many factors that should be considered:

- what vaccines are required to be produced;
- what types of laboratories are required;
- what types of animal isolation units are required;
- what equipment is required for each specific task;
- how many people are required;
- what recreational facilities are required;
- are some of the employees to be accommodated on-site;
- what services are required in the whole establishment or in specific laboratories;
- how effluents are to be treated and discharged;
- what storage facilities are required.

Once agreement on these points has been established, those concerned with the design should go through every detail and consult those who are to use the facilities, so that at this initial stage nothing is omitted.

Owing to the lack of such coordination, some establishments have had problems modifying their original plans and in many cases this has resulted in more money having to be spent.

UTILITIES AND SERVICES

Essential services are understood to be: water, furnace oils, electric power, automotive fuels, air, communications, gases, effluent treatment and steam.

Water

There should be an adequate source of water for the establishment to run smoothly. In laboratories two types of water are normally used: mains water (for cooling and heating) and purified water.

The quality of mains water is very important as this will dictate the cost of running steam boilers and water distillation plant. Where mains water is soft, say up to 23 parts per million (ppm) of hardness, scaling becomes only a minor problem and the chemicals required to

descale the boilers and water stills are not expensive. Where water is available from a borehole, it is usually hard. Treatment is expensive when a water-softening plant becomes necessary.

Adequate water storage is also very important. Ideally the VME would have an elevated water reservoir from which water will flow under gravity to all water points in the establishment. The reservoir should be accessible for regular cleaning. It should also be noted that it is important to check the quality of water and, if necessary, the water in the reservoir should be treated according to normal health requirements.

Mains water must be free of pathogens, pesticides and heavy metals since traces of any of these coming into contact with production material and equipment may lead to altered production conditions.

Cooling or heating water is used for culture vessels, process equipment or ambient temperature conditioning. It must be controlled to ensure that it will not impose a threat of chemical or biological contamination to the production process.

Purified water is obtained by demineralization followed by distillation or reverse osmosis. It should be sterilized and kept sterile or in such conditions (80°C) that will prevent the growth of contaminating organisms. It should be pyrogen free.

Electric power

In many developing countries the electric power supply is not reliable. There are permanent and serious electrical fluctuations which harm electrical equipment installed in the establishment. It is advisable to install voltage stabilizers to prevent the malfunctioning of sensitive electrical and electronic equipment, such as control panels and centrifuges, and also a power factor correction facility at the main power distribution point, as this will reduce electricity consumption and protect electrical equipment such as motors.

An electricity standby generator plant should be considered as a standard piece of equipment. To determine the size of the standby generator the following factors should be taken into consideration:

- the total electrical load installed;
- the type of fuel used in the generator engine;
- the essential electrical power demand in the VME, as this will indicate the minimum size of the generating plant;
- future load expansion.

The generating plant must be able to start up automatically under any of the following situations:

- there is no power from the main supply;
- phase failure;
- short circuit;
- low voltage.

AIR

A VME needs various ventilation systems. An adequate rate of ventilation is essential to protect the plant personnel and the product from solvents or fermentation gases and from particulate or biological contamination. Up to 20 air changes per hour may be required to maintain proper process conditions, under a positive or negative pressure differential with respect to ambient.

It may be necessary to sterilize the air supplied and/or extracted from a particular area or to heat, cool or dry this air, in which case energy will be saved by recycling it as much as possible. Specific exhaust systems may be necessary to remove dangerous gases (toxic, flammable, etc.) to prevent them from diffusing into the working space.

Gases

Generally, the gases used in vaccine manufacturing establishments include: air

under pressure, carbon dioxide, liquid nitrogen, methane, oxygen, acetylene and refrigeration gases such as R12, R22 and R502.

The availability of these gases is important because the operations of the establishment can be seriously handicapped if they are in short supply.

Air under pressure must be obtained from a clean source, should be filtered and should be dried before and after the compression process. This will prevent rust formation and the blockage or damage of prefilters and sterilizing filters by condensates or particles of rust scale. Most other gases will probably be obtained from specialized suppliers according to specifications.

It is important to note that several refrigeration gases are being phased out because of the harm they cause to the ozone layer of the earth's atmosphere. When choosing refrigeration equipment, this point should be considered and new technologies in this area should be favoured in spite of their probable initial higher costs.

Steam

In a VME, steam is used in small amounts for heating purposes in stills, temperature conditioners for ambient air and in fermenters, and in large amounts for sterilizing purposes in autoclaves, sterile lines, fermenters, process equipment and vaccine blending and filling vessels.

Generally, saturated steam is used, overpressurized at 6 to 10 kg/cm^2 in the generator and reduced to working pressure at the points of use. Steam can be produced from individual electrically heated boilers or from a central fuel-fired steam generation plant.

The availability of electricity and oil fuel varies from country to country but, in general, fuel-fired steam generators are cheaper to run than electrical ones. The steam supplied to steam receivers should be clean (free of undesirable chemicals "dragged" from the boiler) and filtered through 0.1-micron sintered 316 grade stainless steel filters. The pipework has to be of non-corrosive material, ideally 316 grade stainless steel. Safety devices should be fitted on the receivers. Condensate from steam lines should be returned to the boiler water feed tank. Steam and condensate pipelines should be lagged (insulated). If the steam is obtained from tap or industrial water, great attention must be given to impurities in the water and added softeners. "Dragging" of water from the boiler is possible on occasions of sudden high peak demand of steam but standard procedures should minimize these peak demands, as they will also condition the size of the boiler. The use of clean steam obtained from purified water is most advisable, but its high investment cost may not be compensated by the possible improvement of performance of the process.

It is also advisable to maintain steam pressure in the system for 24 hours a day. Vibrations provoked by the steam "hammering", which occurs when steam lines are warming up, impose a great stress on the integrity of sterile process lines and equipment.

Furnace oils

Where used the reliability of supply should be considered.

Automotive fuel

This commodity is nearly always available in developing countries but at high cost. Automotive fuel is normally used on electricity standby generating sets and vehicles.

Communications

Good communications are essential for the effective operation of any enterprise.

Effluent treatment

Where disease security has to be controlled, the treatment of gaseous, liquid and solid effluents must be considered. Laboratories and animal isolation units working with high-risk pathogens (e.g. foot-and-mouth disease or anthrax vaccine) should have:

- continuous air extraction through absolute filters to maintain negative pressure with respect to ambient at all times, thus preventing the escape of contaminated air from the unit through personnel or materials entry and exit pathways;
- discharge of liquid effluents chemically treated in a confined secure area, under an absolute air extraction system (the pH of the effluent is increased to 11.5 [0.25 percent free alkali] by the addition of concentrated sodium hydroxide solution, and maintained at this level for at least 24 hours before neutralization and discharge into the normal sewage treatment) or heat-treated in a pressure vessel located below ground level (so that the effluent can flow into it by gravity). The heat treatment of the effluent should be carried out under pressure, preferably by direct injection of steam or by electric heaters. The temperature has to be held at 121°C for about two hours, depending to some extent on the volume to be treated. The treated effluent may be discharged into the main city drainage/sewage system or, in areas where this is not available, into soak pits.
- all solid materials (glassware, paper, empty containers, tools, spares, the exterior of containers of inactivated antigen, etc.) decontaminated by one of the following means: autoclaving (heating up to 121°C for 30 minutes), hypochlorite, mild acid or strong alkali soaking treatment and/or formaldehyde fumigation before leaving the restricted area.

BUILDING CONSTRUCTION AND FINISHES

The building construction and finishes should ensure protection of the vaccine during manufacture from contamination and should permit efficient cleaning and avoid the accumulation of dust and dirt.

The construction design must be such as to prevent the entry or harbouring of insects, birds or rodents. Surfaces should be smooth, robust, non-porous, easy to clean and easy to maintain. They should be free from cracks, crevices and ledges.

The finishes of walls, floors, ceilings and doors should be of good quality and should not allow the accumulation of particulate matter. There should not be recesses that cannot be cleaned.

Where floors may come in contact with chemicals such as diluted acid or alkali solutions, the floor must be protected with chemical-resistant covering. This is very important since, if it is not done in time, serious damage can be caused to the floor and consequently to the foundation of the building. Expansion joints and cracks should be sealed with a suitable resilient compound.

There have been major problems with leaking roofs in many VMEs. Most flat roofs leak and in countries where rainfall is high and climatic changes are significant it is suggested that pitched roofs are used rather than roof slabs. Sometimes flat roofs are necessary where specific equipment for supply services to the establishment has to be mounted. If this is the case, proper design should be made to cover the roof as much as possible.

The ceilings in the building should be constructed and finished so that they are solid, capable of being completely sealed and easy to clean. Doors and windows should have a smooth impervious finish and should close tightly. Where the production room is under a controlled environment, the windows should be fixed and the doors should have seals. If the

building is maintained under controlled environmental conditions, say negative or positive pressure, airlocks must be provided in manufacturing areas.

The paint used on walls and ceilings should be of a quality that can be cleaned.

Where there is a lot of dust, entrances to the VME should have airlocks to minimize its entry into the building. The inlet for the supply of air to the ventilation system should be sited in a position that will minimize the amount of dust blown into the building and it should be provided with filters of a large dust-holding capacity.

Process

Work must be done according to good laboratory practices (GLPs) and good manufacturing practices (GMPs). After a thorough study of the process, the necessary equipment and procedures should be defined and validated and detailed, precise descriptions of all procedures must be written.

There is a great variety of production processes. Mammalian cells, bacterial cells (aerobic and anaerobic), mycoplasma and virus cultures all share some common requirements, but each also imposes specific conditions related to the product that has to be manufactured.

The final product may be a live or an inactivated vaccine. Inactivation can take place before or after purification steps (such as centrifugal separation, filtration, precipitation, ultrafiltration, affinity chromatography and immunoaffinity chromatography) and it is necessary to blend active components and excipients under sterile conditions, before bottling the final product.

Equipment

All the equipment used in the production process must be validated and a manual of operating procedures should be prepared. All the procedures involving the use of the process equipment have performance parameters (pressure, agitation, temperature, pH, dissolved oxygen, oxidation-reduction potential, flow control, etc.) which require monitoring/controlling equipment.

The ageing of equipment tends to increase the possibility of failure and may reduce the efficiency of the process, unless a good maintenance programme is followed.

REPAIR AND MAINTENANCE OF PREMISES, PLANT AND EQUIPMENT

Maintenance demands large resources of labour and money but it is absolutely essential if facilities such as plant, machinery, equipment and buildings are to remain in an acceptable operating condition ready for maximum utilization.

Many developing country VMEs have no maintenance facilities. This is a very important issue since, without trained maintenance personnel, the successful running of the establishment will be jeopardized. There should be a maintenance department comprising: an engineer/technician, a fitter/plumber/welder, a refrigeration mechanic, a carpenter, an electronic/electrical technician and a mason/bricklayer).

Basic tools and equipment required in a repair and maintenance workshop

The following is the recommended list of basic tools and equipment required to carry out standard repair work on process equipment, machines, buildings, etc.

Fitter/welder/plumber's tools comprising:

- various sizes of metric spanners (ring and open-ended);
- box spanners from 6 to 22 mm;
- a set of screwdrivers;
- a measuring tape;
- a brass drift;
- punches;

- a filter gauge,
- pliers;
- a ball peen hammer;
- pipe wrenches of various sizes;
- a portable electrical drill.

Refrigeration mechanic's tools comprising:
- various metric spanners (both ring and open-ended);
- a set of refrigeration spanners;
- an Avometer;
- a refrigeration charging manifold;
- a portable refrigerant cylinder;
- a set of electrical screwdrivers;
- insulated cutter pliers;
- a thermometer.

Electronic/electrical technician's tools comprising:
- a set of electrical screwdrivers;
- an Avometer;
- a diode tester;
- electronic test/check apparatus (volt-ampere meter, etc.);
- a vacuum pump.

Carpenter/mason's tools comprising:
- basic general tools.

General workshop equipment comprising:
- oxygen/acetylene welding cylinders, regulators and complete torches with hosepipes;
- a tungsten or metal inert gas arc welder;
- a pedestal drilling machine;
- a bench grinder;
- a pressure gauge testing/calibration stand;
- thread cutting tools,
- pipe vices;
- bench vices;
- a pipe bender.

When selecting equipment or machines it is important to consider their complexity of maintenance, the availability of spares and the knowledge and expertise of maintenance staff. There have been cases where a VME has acquired equipment that was so sophisticated that nobody was able either to operate or maintain it. When an establishment acquires an expensive machine or piece of equipment, it should be ensured that whoever is to take care of the machine is properly trained by the supplier or manufacturer in its operation and maintenance. Planned preventive maintenance is the best method to adopt but it requires that spares be available at all times, and this is a major problem for many VMEs in developing countries.

Preventive maintenance is carried out on plant equipment or machines to prevent breakdowns. It is done on a scheduled basis and also when required, especially if machine performance is seen to be deteriorating.

To determine when a machine should undergo preventive maintenance it is necessary to know the machine's breakdown characteristics and also to adhere to the manufacturer's recommended schedules.

The stocking of spare parts is difficult in developing countries owing to a lack of finances and spares not being available locally when required. It is advisable, therefore, that when a machine or piece of equipment is bought a reasonable number of the spares recommended by the manufacturer should be kept in stock and supplied regularly under contract, for at least three or more years, to ensure the proper operation of the equipment.

INSPECTION

Each step of the production process should have a written inspection procedure to be followed and recorded. Equipment inspections can be carried out by different individuals as long as they are all specialists for the objects of the inspection. Easy access and correct illumination are important for inspection procedures, as

poor working conditions lead to careless, inefficient work.

The following tests should be performed on process or controlling equipment for validation, when the equipment is to be used for the first time, after a modification or for verification within a maintenance routine, when applicable.

Leak tests

Leak tests should be performed on culture vessels, process and blending vessels, associated pipelines and, in general, on all pressurizable equipment. Such equipment should be filled with liquid (usually water alone or with detergent to promote penetration) in order to check the integrity of the system. These tests should be carried out under both positive and negative pressure (vacuum) as leaks may show up under only one situation.

Temperature mapping

It is necessary to ensure that the sterilizing or working temperatures are achieved at all required points of the equipment and associated pipelines. Multipoint recording equipment fitted with thermocouples will facilitate this test.

The following equipment should have temperature maps to confirm that it works correctly and that the procedures achieve the results expected:

- liquid nitrogen containers for seeds or product storage (-190°C);
- deep freezes and freezers for seeds and product storage (-120°C, -80°C, -30°C, -20°C);
- refrigeration cabinet or cold rooms (4°C);
- autoclaves and ovens with different sterilizing temperatures and workload conditions;
- culture vessels, intermediate process vessels and associated pipelines for sterilizing, working and storage conditions.

Depending on the size of the equipment and process conditions, between six and 30 recorded points will provide sufficient information to assess or confirm whether the equipment is working correctly and whether the procedures followed are achieving the expected results.

Sterilization

Sterilization parameters are established according to temperature mapping and reaction times. There is a tendency to increase sterilization time to ensure that it has been effective. This is misguided; a correct procedure should sterilize for the minimum length of time required, thus prolonging the working life of sensors and equipment. If steam traps are being used, they must be periodically tested during sterilization with an external contact thermometer.

Washing

Dirt, particularly protein, must be eliminated from the process equipment and associated lines, before the next process takes place. Careless washing leads to protein coat build-up, increased contamination rates, earlier instrument and equipment deterioration and, in general, poorer process conditions. This becomes particularly critical in centrifugal separation equipment.

Membrane integrity testing

Sterilizing (HEPA) air filters for ventilation and laminar flow units (LFUs) and sterilizing air filters for process equipment should have their integrity tested regularly by means of: specific particle-size oil aerosol penetration tests (applicable to all filters); or other tests, such as the water intrusion test applicable to hydrophobic air filters, which are generally used in small filtration units installed in process equipment.

Aerosol penetration detection equipment

is expensive and a contract service with a specialized company may be the best solution to having filters tested regularly.

Process equipment

Culture vessels and associated pipelines. Usually, standard culture vessels are bought from a specialized firm, but sometimes they are built to match the required purpose. The culture vessel should be insulated (lagged) and the stirring system should be magnetically driven whenever possible – this is the most reliable, long-term, leak-proof system.

The slope (gradient) of the associated pipelines is of great importance for the proper cleaning and sterilization of the system. The system must be equipped with vent or drain valves to prevent air or condensate accumulation in piping during steam-sterilization. Special care must be given to welded joins as these may cause failure by developing minor cracks. Contact with steam or chilled water is particularly critical for welded joins. Welds may also suffer great tensile stress owing to great and sudden changes in temperature.

All drain lines should be connected to an enclosed drain system to prevent aerosol formation and increased contamination risks.

Air filters. The glass fibre "depth" type of sterilizing air filter can deal with gases at high rates of humidity, but is unable to sterilize filtered gas when it is wet and it is therefore essential to prevent the "dragging" of condensates into this type of filter which is gradually being replaced by the hydrophobic membrane type. These new filters are very reliable and resistant to sterilization. Their integrity can be tested easily by means of water intrusion tests. Hydrophobic membranes may suddenly become clogged with humidity caused by microcondensation in the vicinity of the membrane, but they do not lose their sterilizing capacity when this occurs. The working procedures must be such that the moisture saturation point is not reached, in order to have a reliable gas filtration process.

Laminar flow units. These are required whenever sterile work has to be assured in an open process. Standard LFUs may have either horizontal (100 percent of the filtered air is run to waste) or vertical airflow (100 percent of the filtered air is recycled) and are designed to protect the product. Safety or security LFUs are designed for work with pathogens and protect both the worker from the product and the product from contamination. They are fitted with a second fan for the extraction of part of the recycled air (30 to 70 percent) through HEPA filters to prevent the escape of contaminated particles from the secure environment of the LFU. The ambient air, driven by suction into the LFU, is kept away from the sterile product by the design of the cabinet and there is therefore no risk of contamination if GMP procedures are observed.

Liquid filters. These are used for coarse or fine clarification as a specific process or for prefiltration in a final sterilization process. Liquid filters must comply with the legal requirements for pharmaceuticals production. It is usually cheaper to use depth filters for prefiltration, but the sterilizing filters should be of the membrane type. The whole system should be provided with facilities for purified water washing, *in-situ* steam-sterilization, liquid displacement by sterile air or nitrogen under pressure, draining, sterile sampling ports and the means of integrity testing of the final sterilizing filters.

Valves. Diaphragm valves are the most reliable, although care must be given to

the diaphragm, as its working life is reduced by overtightening of the valve. Solids such as glass fragments from a broken electrode or metal particles released from the equipment can perforate the diaphragm. If only the first layer is perforated, a dirt pocket will be created, so valves must be dismantled routinely and inspected for cuts or holes. Valves situated on horizontal pipelines should be placed at a 45° angle from the horizontal to prevent the accumulation of condensate during steam-sterilization.

Monitoring and controlling equipment

Connections for electronic equipment. Usually monitoring and controlling equipment is installed in panels located at some distance from where the sensors are installed. The sensor transmits an electric signal which is translated in terms of the required parameter (pH, redox, dissolved oxygen, temperature, pressure, etc.) in the receiving monitor/controller. Electronic connections may be welded or of the tight plug type. They must be moisture-proof. All connecting cables should be protected from external electromagnetic interference and checks should be made to ensure that no distorted signals are received by the monitor/controller.

Manometers. Manometers installed in process lines or equipment should be regularly calibrated against a standard certified manometer.

Thermometers and thermostats. Thermometers should be calibrated against a certified thermometer in a water or oil bath. If the equipment is a controller it should have a second alarm limit set at not more than 1°C above and below the standard working limits.

pH - pOR - D.O. - meters/controllers. It is very important to check the wire connections regularly and to ensure that they are in good condition. It is also essential to check the condition of the wire mesh (shield). External induction parasitic signals gain in power relatively as the specific signal weakens, owing to poor connections or a poor shield. Probes, particularly those for dissolved oxygen, should not be kept out of solution longer than is strictly necessary, as this causes rapid ageing. Electrolytic solutions must be replaced regularly.

It is important to have electronic calibration simulators to ensure that the monitor/controller is working well, but the final calibration should be made by placing the sensors in standard solutions freshly prepared for the purpose. Specialized advice should be sought from equipment suppliers, as all the particular situations that could arise cannot be covered in this chapter.

Flow meters. Flow meters for liquids and gases must be calibrated under different working conditions against certified ones. The testing process must be conducted in such a manner as to prevent breakages and operators must be protected against such accidents, particularly when working with flow meters that measure gases under pressure.

Calibration can also be done by comparing the theoretical volume that should be obtained at a fixed flow rate and time against the volume actually obtained. This has to be done at different flow rates.

Dosing equipment. If dosing is carried out with a peristaltic pump, it is important to use high-quality flexible tubing to avoid unexpected breakages.

Solution containers must not be allowed to run empty or dry out, since this will promote the formation of crystals which will cause the dosing system to wear out prematurely.

Recorders. These have to be calibrated to register precisely the figures that the monitors/controllers show. These in turn should be in strict agreement with the real figures of the process. In critical processes, inspection and manual recording of parameters must be performed at least once a day and the results noted on worksheets or on the recording chart itself where this is necessary.

Timers. These are useful pieces of equipment where reaction times are long or where it is necessary to control a lengthy process. Computer- or PLC-controlled processes have timers incorporated as standard devices.

Maintenance records. It is important to have a register of all the process equipment and machines that are looked after by the maintenance department. For each piece of equipment or machine the register should comprise:

- identification (model/make/serial number);
- modifications or repairs carried out so far;
- the location of the equipment or plant;
- the total cost of the maintenance and repairs carried out so far.

This information will assist in assessing each individual piece of equipment and in deciding whether it is worth spending more money on it or whether a replacement is required.

Each piece of equipment should have its own logbook to record every inspection, calibration, repair job or changes of defective parts. This information will be very useful in estimating the working life of the different components and will permit the implementation of a maintenance prevention routine, which will reduce production losses caused by unexpected failures of equipment.

BIBLIOGRAPHY

Barrer, P.J. 1983. Crucial factors for design of a pilot plant. *Biotechnology*, October 1983: 661-666.

Commission of the European Communities. 1992. *The rules governing medicinal products in the European Community*, Vol. IV. *Good manufacturing practice for medicinal products*. Directorate General for International Market and Industrial Affairs.

EC. (n.d.) *General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use.* Committee for Veterinary Medicinal Products of the European Community.

EC. (n.d.) *General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use.* Committee for Veterinary Medicinal Products of the European Community.

Everett, K. 1984. Planning for a new laboratory. *Manuf. Chem.*, April 1984: 30-33.

Glacen, M.W., Fleischaker, R.J. & Sinskey, A.J. 1983. Mammalian cell culture: engineering principles and scale-up. *Trends in Biotechnol.*, 1(4): 102-108.

Ríos, S. & Chaib, M. 1993. Sistemas integrados de salas blancas o limpias para la industria farmaceutica. *Ind. Farm.*, November-December 1993: 27-42.

Sharp, J.R. 1983. *Guide to good pharmaceutical manufacturing practice.* London, Her Majesty's Stationery Office.

Aspects of financial management of veterinary vaccine manufacturing operations in developing countries

P. de Greve

Veterinary vaccine manufacturing, like any other manufacturing process, can be referred to as a product transformation process, that is a process in which a finite number of inputs (production factors) are converted into a finite number of different outputs (products) (Naylor and Vernon, 1969). An assessment of such a process of product transformation is usually based on the neoclassical production function model whereby output is considered to be a function of fixed and variable factors in the firm's production process (Naylor and Vernon, 1969). This model basically serves as a framework for the globally applied contemporary practices of cost accounting and financial management.

Veterinary vaccine manufacturers in developing countries often face a number of specific problems including: macro-economic reforms, distorted markets, government interference and a poor financial investment basis.

In addition, in many developing countries the production of veterinary vaccines takes place in laboratories that are either owned and run by government services or at least have strong controlling links with government departments. In these government-controlled veterinary laboratories, production, research and animal health control functions are intermixed. In some rare cases, separate subunits may be in charge of specific functions, for example vaccine production units are separate from serological services or research. In most cases, however, veterinary laboratories lack the necessary transparency in managerial (i.e. functional, commercial, financial and institutional) performance to allow a detailed financial analysis of specific operations and/or functions. In other words, only seldom will a veterinary laboratory in a developing country be able to indicate the unit cost of, say, producing a specific type of animal vaccine or carrying out a specific serological service.

In an era of structural adjustments in which government services are increasingly driven by the forces of market demand and supply, the management of such services requires transparent production processes that yield products that can be valued against apparent demand in the market.

This chapter aims at highlighting some of the important managerial and, more specifically, financial aspects of the veterinary vaccine manufacturing process with special emphasis on locally based, government-controlled production units in developing countries. The following discussion will be of less relevance to the production and trading of vaccines by private companies.

Obviously, it is impossible to consider in great detail the issue of financial management within the limits set for this manual. The professional literature on the topic of financial management and cost accounting is extensive but publications

that discuss this topic in relation to the production of veterinary vaccines in developing countries are all but non-existent. Field experience is limited and little has been published in this regard. The reflections found in this chapter are based on a limited number of field experiences in East, southern and West Africa in combination with the overall principles of applied economics and accounting.

FINANCIAL MANAGEMENT

The management of a firm is a process of planning, controlling, organizing, communicating and motivating with the ultimate goal of attaining the organization's objectives in the most effective manner.

Financial management – which is part of the overall management task – serves three main purposes: i) stock valuation for profit measurement; ii) decision-making (including planning); and iii) control (accountability).

In the discussion of financial management, some authors distinguish between management accounting and cost accounting (Drury, 1988):

- *Cost accounting* relates to the process of calculating actual (unit) production cost for the purposes of stock valuation and profit measurement (objective i) above).
- *Management accounting* relates to the provision of information to help management make proper investment decisions (objectives ii) and, partly, iii) above).

Cost accounting makes use of historical data that are collected and categorized on a regular basis (accountancy) with the ultimate purpose of assessing the performance of a firm and ensuring that it is profitable and thus viable.

Management accounting relates to future costs (and benefits) with the aim of planning future activities and investments. Strictly speaking, historical costs are irrelevant to the decision-maker but they are used as the best available basis (although not the only one) for predicting future costs.

Business plans and financial control

Financial statements are needed to project and/or analyse the functioning of a production unit and to allow an assessment of the efficiency, creditworthiness and liquidity of the unit. For a veterinary vaccine production unit (under public-sector control) three financial statements should be made: the balance sheet, the profit and loss account and the sources and uses of funds statement, which may also be called the cash flow.

Balance sheet. Balance sheets give a view of the assets and liabilities of the processing enterprise at the end of each accounting period, which is usually 12 months (Gittinger, 1982). The balance sheet is a kind of static picture of the financial state of the enterprise at a given moment.

The format in which balance sheets are presented may vary from country to country, but the contents are always the same. Example 1 is an example of a balance sheet (United Kingdom model) of an imaginary vaccine production plant under joint project/government control, presented with equity and liabilities in the upper section and with assets given below. The figures are based on real data from an existing plant.

In the case of Example 1, it was possible to work out a balance sheet because the vaccine production unit was set up independently from other government departments. Often, however, manufacturing units are integrated in government departments that carry out various functions, some of which belong to the public-sector mandate while others may be more related to the private sector, for

EXAMPLE 1

Balance sheet for a vaccine production plant (United Kingdom model)

	31/12/1996 *(US$)*
Equity	
Share capital	-
Vested capital	7 000 000
Retained earnings	(800 000)
Liabilities	
Current	
short-term loans	50 000
suppliers' credit	50 000
taxes payable	
Long-term	
long-term loans	400 000
	8 300 000
Assets	
Fixed	
buildings and equipment at cost	5 600 000
less accumulated depreciation	(1 100 000)
construction in progress	
Current	
cash and bank balance	200 000
inventories (stocks)	3 300 000
debtors (accounts receivable)	300 000
less overdraft	-
	8 300 000

example viability testing for other manufacturers.

It follows that in those cases where governments are involved in vaccine production, certain constraints and peculiarities may affect the management of the manufacturing plant. Looking at the data above, a number of observations can be made.

Vaccine production units are often government-owned, i.e. capital is vested with the public sector and not in the hands of private-sector shareholders (whether individuals or holding companies). This is reflected in the balance sheet in Example 1 by the somewhat unusual addition of vested capital in the equity listing. Obviously, combinations of public- and private-sector ownership are possible as well. In fact, under structural adjustment or similar macroeconomic reform programmes, many developing countries try to turn their public-owned services and/or manufacturing organizations into commercially oriented companies, at least partly owned by private-sector agents or holdings.

The balance sheet in Example 1 is a "still photograph" and does not indicate exactly how capitalization of the production unit has been realized. The inclusion of long-term loans in this particular example points at a financing construction in which outside sources (development agencies in this case) have provided part of the capital base of the unit. The other part of the capitalization presumably originates from public finance sources. Various scenarios are possible whereby the financing of new investments is done from public finance sources, private investors (through the issue of new shares) or long-term financing through funding agents (such as development organizations or the banking system).

Retained earnings are a fourth important source of capital creation in a company. In the past, government-controlled vaccine production was based on policy guidelines set out by the government and often stipulating exactly what had to be produced and in what quantities – without any linkages to market forces. This kind of uninspired management practice is slowly disappearing, even in government-controlled manufacturing units. However, it may be difficult for the management of such units to convince the owners of the company (in this case, the government) of the need to retain profits (if there are any) for reinvestment in the firm.

Valuation of stocks is a crucial factor in financial management. This issue is discussed in more detail in the section Price setting and stock valuation (p. 203).

Suppliers' credit on the equity side and debtors on the liabilities side of the balance

sheet refer to temporary capital creation and culmination, respectively, because of the time lags between delivery and the payment of invoices. A common concern of financial managers will be how to avoid tying up too many funds in short-term assets such as accounts receivable or inventories. Accounts receivable are often a bottleneck, notably when government services are a main customer of the firm in question. In fact, governments are often notoriously bad in paying their arrears, especially to companies or institutes which they control and own themselves. This often leads to the cash needs of such companies being seen as part of the annual operation plan approved by government and, eventually, its designated bank and not as a business-determined factor. The problem of accounts receivable from official or semi-official sources may well be the single worst bottleneck for many semi-governmental firms involved in manufacturing for service sectors such as veterinary departments. In addition, whereas private customers can be blacklisted as bad debtors, this is often impossible with governmental customers. This problem is even more acute in cases where the product concerns essential services to society – such as for vaccinations against serious contagious diseases. In the case of outbreaks of such a disease, the delivery of vaccines is expected to be immediate and frequently in relatively large volumes. Payment is often delayed because substantial amounts of money are involved, for which no allocation was made in the government's recurrent budgets.

Cash and bank balances could be negative if – as happens far too often in government-controlled organizations – operations must be financed through bank overdrafts because the government is late in channelling the necessary (and budgeted) funds to the production firm it owns and controls. Manufacturing units must therefore try to create a sufficient recurrent capital base to finance regular operations. As indicated above, there may also be the problem that too much funding is tied up in short-term assets, such as accounts receivable or inventories. If this is the case, the manager of the manufacturing plant should try to reduce the tied capital base.

Profit and loss account. The profit and loss account is the most widely used financial statement. It is also the one which is easiest to understand since it refers to the common principle of profit analysis by comparing revenue with cost. A fairly straightforward model of profit and loss accounts is shown in Example 2.

The profit and loss account is a financial report that summarizes the revenues and expenditure of an enterprise over an accounting period (usually one year)

EXAMPLE 2

Profit and loss account

	Profit and loss account 1996 *(US$)*
Revenue	
Vaccine sales	1 450 000
Antigen sales	150 000
Cattle sales	600 000
Serology services	100 000
Donor support	500 000
Miscellaneous	–
Total revenue	2 800 000
Expenditure	
Salaries	900 000
Production cost vaccines	650 000
Production antigen	50 000
Maintenance and repairs	200 000
Office, communications and utilities	100 000
Transport/travel	80 000
Depreciation	100 000
Loan repayment and interest	110 000
Interest on overdraft	–
Bank charges	10 000
Total expenditure	2 200 000
Net profit (loss)	600 000

EXAMPLE 3

Profit and loss account (revised format)

	Profit and loss account 1996 *(US$)*
Gross revenue	2 800 000
- Cash operating expenses	-1 880 000
= Gross income	920 000
- Selling and administrative costs	-100 000
= Operating income before depreciation	820 000
- Non-cash operating expenses (depreciaton)	-100 000
= Operating income (profit)	720 000
- Non-operating income and expenses (interest, taxes other than on profit, subsidies, etc.)	-120 000
= Net income (profit) before income taxes	600 000
- Income taxes	-
= Net income (profit) after taxes	600 000

(Gittinger, 1982). It shows the results of the operations of the enterprise during that period. The format shown in Example 2 is a very simple one which perfectly suits the needs of smaller manufacturing units run under government control. A more standardized model might look as in Example 3.

Revenue can come from various sources but basically relates to the sales of goods and/or services. In the case of veterinary laboratories, sales of vaccine could be a major source of revenue as shown in Example 2, but others might exist as well, for example payment for serological services, antigen slides sales, veterinary advice against payment and sales of animals. Cash operating expenditures would include all cash expenditure incurred to produce the output. Important costs in this category are labour and material inputs. Selling and administrative costs concern the so-called overheads, which also include training, ongoing research and development and training.

The non-cash operating expenses item has one major element – depreciation. Depreciation refers to the process of allocating a portion of the original cost of an asset to each accounting period so that the value is gradually used up, or written off, during the course of the useful life of the asset (Gittinger, 1982). Depreciation may allow for a "rest value" which is treated as revenue at the time of write-off of the capital item. For example, a CO_2 incubator costing US$40 000 may have an expected useful lifetime of ten years and a rest value at the end of this lifetime of US$4 000. The annual depreciation would thus be:

$$\frac{(40\,000 - 4\,000)}{10} = 3\,600$$

This amount would appear as a non-manufacturing or period cost in the financial statement and, consequently, it would be used in deriving the unit production cost in the cost accounting exercise. The US$4 000 rest value would be treated as revenue at the end of year ten.

The profit and loss account is an extremely important source of management information. Obviously, building up the database of summarized profit and loss accounts requires a breakdown of total revenue and expenditure into its constituent parts, each of which may require various subtables with their own sets of assumptions and inputs. The following annual (or possibly quarterly) statements are usually needed:

- production and sales figures including opening and closing stocks for factor inputs and product outputs with expected losses and rejections;
- total revenues based on the production,

sales and stock figures and price information;
- a detailed costing for specific (technical) cost centres, such as different production departments, research department and advisory and research department;
- a detailed costing for support centres such as farm, rabbitry, breeding units, sales and distribution, administration, garage and workshop;
- input data for depreciation – i.e. original cost, useful life and rest value;
- financial costs and bank charges;
- the capital expenditure budget (investment planning).

It is impossible to cover these input tables in any detail in the context of this brief overview so, because the key to successful financial management lies in the development of correct and proper financial statements, reference is made to handbooks on financial management and cost accounting for further information.

It should be indicated that the profit and loss account also serves to bridge the gap between subsequent balance sheets. The net income (profit) from the profit and loss account, after the payment of dividend to shareholders (if there are any) is transferred to the balance sheet as retained earning and, if positive, will thereby increase the owners' equity.

Financial indicators. The combination of profit and loss account and balance sheet allows the manager of a production unit to assess the financial viability of the plant. For this purpose, a number of financial indicators can be used. An outline of the common financial efficiency indicators follows. For further information refer to Gittinger (1982, p. 203-209).

Inventory turnover can be calculated by dividing the cost of goods sold by the value of the inventory at year end. It measures the number of times that an enterprise turns over its stocks each year and indicates the proportion of the inventory required to support regular sales levels throughout the year. This ratio also indicates the average length of time a firm keeps its products in stock. A low inventory turnover may mean difficulties in selling the product and/or poor stock control practices. Low inventory turnover also means that a relatively large amount of capital is tied up in inventories. For veterinary vaccine producers there is a specific problem of safety stocks and non-continuous production processes.

As an example, a firm that sold US$2.8 million worth of goods and was left with $3.3 million inventory at year end would have an inventory turnover of 2 800 000/3 300 000 = 0.85, pointing to a low turnover rate of on average around ten months before a vaccine or service is sold.

Operating ratio is calculated by dividing the operating expenses by the revenue. It is an indicator of the management's ability to control operating costs, including administrative expenses. This ratio is especially useful in a comparative framework, i.e. when comparing one company's performance over several years or the performances of different companies. A ratio that increases over time is a sign of imbalance between costs and revenues, i.e. of disproportionately rising costs or decreasing sales prices. In vaccine production, sales prices can reasonably be controlled and the operating ratio will in the first place be useful to give an indication of the relative cost of production. In addition, if a firm has made a large investment, it will need a high cash flow in order to enable repayments. This requires a low operating ratio.

In the example above the operating ratio would be:

$$\frac{(1\,880\,000 + 100\,000 + 100\,000)}{2\,800\,000} = 0.74$$

Income ratios. The viability of a firm depends greatly on its ability to generate funds to repay investments, reinvest and compensate owners for their capital contribution.

Some useful income ratios which reflect the financial viability of a firm are: the return on sales, the return on equity and the return on assets. The return on sales shows how large an operating margin the firm has on its sales. Return on sales is calculated as net income (revenue minus costs) divided by revenue. The lower the margin (and thus the return on sales) the more the firm will have to sell in order to reach an acceptable return on investment. Return on equity is the ratio of net income (after taxes) to equity and is the main guidance to owners of the firm in their investment decisions. This applies equally well where the government is the owner of the firm. Return on assets is a more theoretical income indicator reflecting the overall return of the company on all the resources it engages. This ratio is the nearest to the internal rate of return and discounted measures of project worth (Gittinger, 1982, p. 206-207).

Financial ratios. Apart from efficiency and income ratios, there is a third important class of financial indicators that reflects a manufacturing company's financial strength, i.e. the creditworthiness ratios. These ratios concern the degree of financial risk inherent in the enterprise (Gittinger, 1982). Creditworthiness indicators are the current ratio (current assets divided by current liabilities), the debt-equity ratio (long-term liabilities divided by long-term liabilities plus equity) and the debt service coverage ratio (net income plus depreciation plus interest paid, divided by interest paid plus repayment of long-term loans).

Sources and uses of funds statement. The fourth financial statement that is used to assess the operations of manufacturing units is the sources and uses of funds statement, or the cash flow table. As the latter name indicates, the cash flow table provides an overview of the total flow of financial resources into and out of an enterprise during an accounting period and is useful for determining the likely flow of financial resources in future. Reference is made to textbooks on financial management for more information.

PRICE SETTING AND STOCK VALUATION

Price setting by (government-controlled) vaccine manufacturers is a difficult issue. In theory, the market should dictate price levels but in practice it does not. Markets for veterinary vaccines are far more imperfect than those for, say, consumables or inputs such as fodder. Quantitative knowledge of "willingness to pay" by potential customers (e.g. farmers) is often scarce and unreliable, if available at all. Moreover, in a number of cases, society is willing to cover at least part of the cost price of a vaccine because of the potential disease threat to humans. In such cases, willingness to pay cannot be assessed as customers are more or less forced to accept the product and market demand cannot truly be established.

Nevertheless, the issue of price setting is closely linked to cost accounting, in that an estimation of unit output cost is a guideline in determining break-even sales price levels. In more general terms, price setting is a less central issue than is the evaluation of stocks, being the input and output factors of the product transformation process, and financial management is concerned with the determination of the cost of all single resources used in the transformation process, including non-physical resources, and the consequent value of single outputs of the process. Once these unit values are known, management can determine proper pricing policies.

Period costs and product cost

In the process of cost accounting, individual cost items that constitute the cost "chain" – from basic inputs to final product – must be identified, quantified, valued and summarized in order to arrive at a unit product cost. In this process, a distinction is made between period costs and product cost as illustrated in Figure 3.

Product costs are directly related to the manufacturing process. Their treatment in the financial statements, however, depends on whether the output produced is actually sold or not. Non-manufacturing costs are period-related costs and thus always appear in the profit and loss account as expenses. Some of the direct manufacturing costs, on the other hand, may not appear as an expense unless the product is sold. The terms product cost and period cost are thus interchangeable with direct and indirect costs.

An example (based on an example by Drury, 1988) may clarify this issue:

A vaccine manufacturing laboratory produces 50 000 units of vaccine A during year 1. The costs for year 1 were (in United States dollars):

Manufacturing costs	
Labour costs	50 000
Materials	20 000
Manufacturing overheads	30 000
Total	100 000
Non-manufacturing costs	40 000

During year 1 the laboratory sold 20 000 units for US$90 000. The remaining 30 000 units remained in stock at the end of year 1. The profit and loss account for year 1 would then look as follows:

Gross revenue (sales)	90 000
Manufacturing costs	
Labour costs	50 000
Materials	20 000
Manufacturing overheads	30 000
Total	100 000
Less closing stock	
60 percent of total	60 000
Cost of goods sold	40 000
Gross profit	50 000
Less non-manufacturing cost	40 000
Net profit	10 000

Because only 40 percent of the produced vaccine was sold in the same accounting period, only 40 percent of the total product costs appear in the profit and loss account as an expense. The remaining 60 percent is included in the value of the closing stock which appears in the balance sheet but not in the profit and loss account. So these costs are not expenses but will become expenses in the next accounting period (assuming that the remaining 30 000 doses of vaccine will then be sold). On the other hand, all period costs (non-manufacturing) will appear as expenses in the profit and loss account because they were incurred in this period. The cost of goods sold is derived only from (part of) the product costs and not from period costs.

Another notable effect is that, because of this allocation to different periods, the unit cost of a vaccine may differ from period to period if period costs are included. For example, from the first data it appears that in order to produce 50 000 vaccines, total expenses are (in United States dollars):

Manufacturing	100 000
Non-manufacturing	40 000
Total	140 000
Number	50 000
Unit cost	2.80

But if related to year 1 the unit cost appears to be different:

Manufacturing	40 000
Non-manufacturing	40 000
Total	80 000
Number	20 000
Unit cost	4.00

It is clear that only the second version

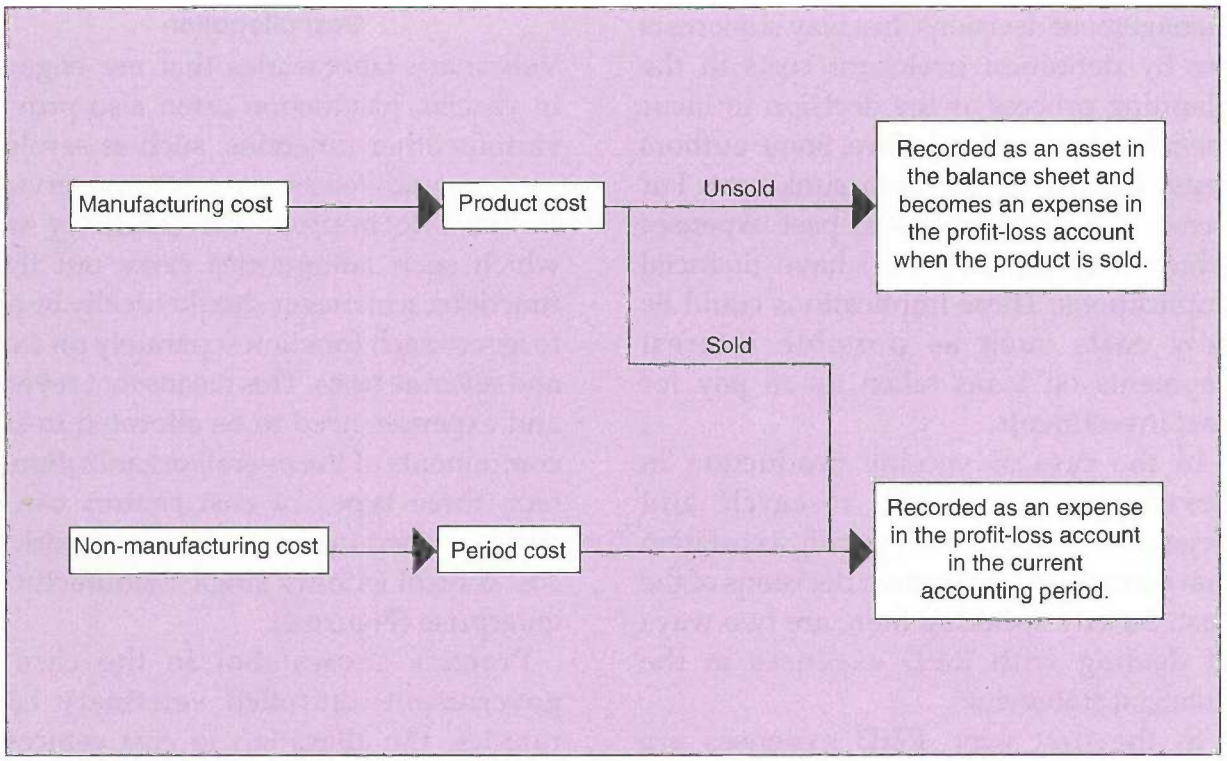

FIGURE 3
Comparison of manufacturing and non-manufacturing costs

Source: C. Drury, 1988.

(unit cost 4.00) is the correct one – if, as assumed, only 20 000 vaccines are sold in year 1. It should also be clear that the unit cost in year 2 could be different from year 1 depending on the total number of vaccines (of this particular batch) sold and the exact period costs for year 2.

Sunk costs

Sunk costs are the costs of resources that have already been acquired and that will not be affected by present and future management decisions. In a way sunk costs are by definition irrelevant costs in the planning process as the decision to incur them has been taken before. Some authors resist the use of the term sunk cost. For them, it simply applies to past expenses which may (or may not) have financial implications. These implications could be new costs such as possible interest payments on loans taken up to pay for past investments.

In the case of vaccine production in developing countries, research and development (R&D) is typically a cost item that concerns management decisions of the past. Strictly speaking there are two ways of dealing with R&D expenses in the financial statements.

In the first way, R&D expenses are considered to be investment costs and are therefore depreciated over the useful lifetime of the investment. As a result, the profit and loss account will contain an item for annual depreciation of R&D costs for the various products put on the market. In practice, however, there may be difficulties in assigning R&D costs to specific end products in a unit cost assessment.

Alternatively, R&D can be considered as period costs before the actual revenue started accruing. In this case, these costs should have appeared in the profit and loss accounts of those years in which they were incurred. This should still be reflected in the balance sheet as R&D in early years probably led to substantial negative retained earnings being carried over from the profit and loss account to the balance sheet.

In practice, however, development costs are often regarded as sunk costs and are thus not recovered through sales of final products. Often they are even disregarded in the profit and loss accounts and the balance sheet, unless they concern material assets.

Cost allocation

Veterinary laboratories that are engaged in vaccine production often also provide various other functions, such as serology services and veterinary advisory services. In order to improve the efficiency with which such laboratories carry out these functions, a manager should ideally be able to assess each function separately on a cost and revenue basis. This means that revenue and expenses need to be allocated to sub-components of the overall organization. In fact, three types of cost centres can be distinguished in a possible framework for cost control within a single manufacturing enterprise (Figure 4).

Practice shows that in the case of government-controlled veterinary laboratories, the allocation to cost centres is more of an exception than the rule even though there are tremendous differences in the kind of services offered by such laboratories, some of which belong to the public domain while others may well be commercially oriented. The establishment of cost, profit or investment centres can also be considered at the level of vaccine production when different vaccines are produced.

However, there are constraints which make the establishment of such centres more complicated in the case of animal vaccine production in developing countries.

One such constraint is the fact that the

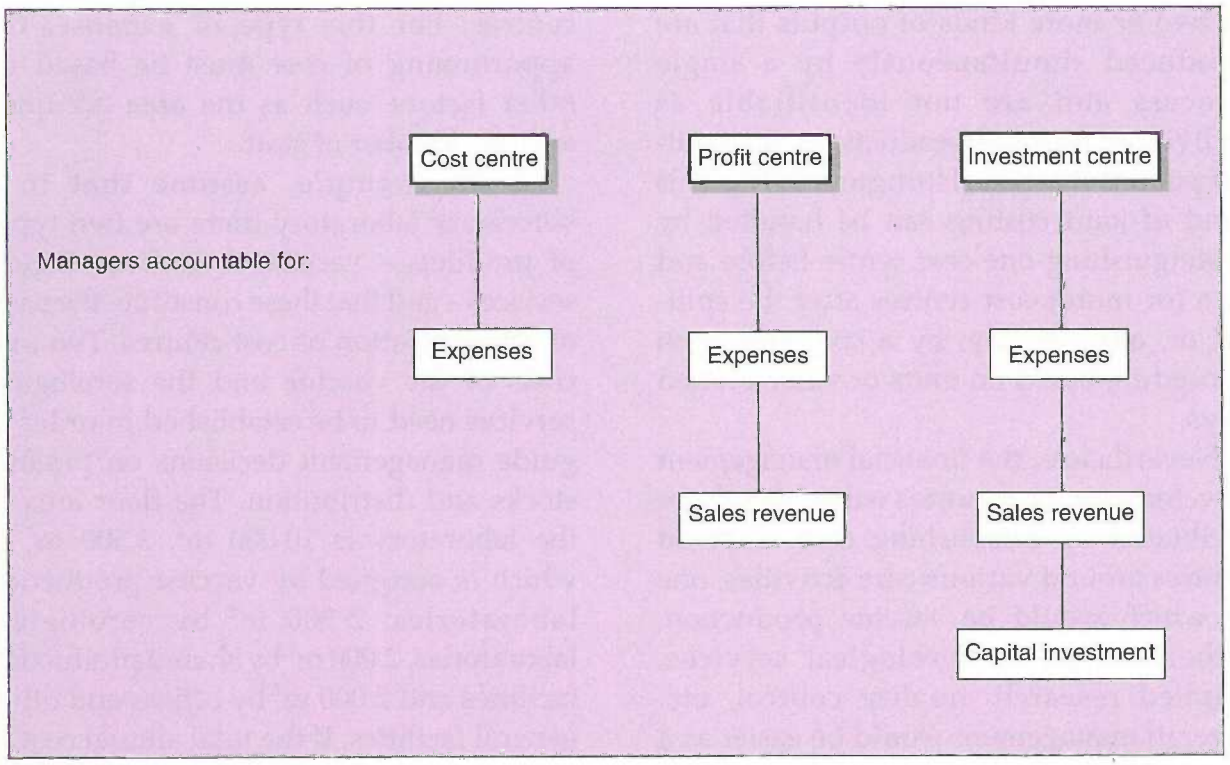

FIGURE 4
Cost control framework for single manufacturing enterprise

production of vaccines is done in batches and not continuously as for most industrial products. Nevertheless, the production process is repetitive and thus open to unit costing or cost accounting. The greater number of inputs and processing steps are very strictly defined, which in a way makes the process of unit costing easier.

Another potential constraint is that joint product costing (Drury, 1988) may complicate the financial control of the manufacturing process. Joint costs are costs of two or more kinds of outputs that are produced simultaneously by a single process and are not identifiable as individual types of products until a split-off point is reached (Horngren, 1977). This kind of joint costing can be handled by distinguishing one cost centre before and two (or more) cost centres after the split-off or, alternatively, by a cost allocation procedure based on units or value related keys.

Nevertheless, the financial management of veterinary laboratories would clearly be facilitated by establishing cost or profit centres around various core activities, one of which would be vaccine production. Others might be serological services, applied research, quality control, etc. Overall management would be easier as a number of tasks and functions could be delegated to the appropriate centre. This type of business framework is quite common in the commercial world but, unfortunately, still rare in parastatal or government institutes in developing countries.

Overhead costs

In practical terms, developing unit costings in a set-up with cost or profit centres requires the allocation of overhead costs to these centres. When, for the sake of estimating unit production cost, a veterinary laboratory differentiates expenditure according to cost centre, there are usually a number of overhead costs which can fairly easily be allocated to specific centres.

Time recording can be of help in assessing the labour inputs of employees not directly linked to a specific cost centre, for example the distribution of indirect materials such as stationery can be recorded for each cost centre. On the other hand, expenditure on general maintenance of the building, rent, heating, lighting, etc. cannot be allocated directly to specific cost centres. For this type of expense, the apportioning of cost must be based on other factors, such as the area occupied and the number of staff.

As an example, assume that in a veterinary laboratory there are two types of products – vaccine A and serological services – and that these constitute the basis of differentiation of cost centres. The unit costs of the vaccine and the serological services need to be established in order to guide management decisions on pricing, stocks and distribution. The floor area of the laboratory is 10 000 m^2, 3 500 m^2 of which is occupied by vaccine production laboratories, 2 500 m^2 by serological laboratories, 2 000 m^2 by shared production facilities and 2 000 m^2 by offices and other general facilities. If the total annual cost of rent, lighting, heating, etc. is US$50 000 then the apportioning could be done as follows: for vaccine production 35 percent of its own area plus 10 percent of the shared laboratory (50 percent of the total) plus 10 percent of the allocation for offices (50 percent of the total) which comes to 55 percent of total costs, or US$27 500. The remaining 45 percent, or US$22 500, would be the apportioned overhead cost for serological services.

Note that this method includes a second level apportioning for the expenses that are not directly linkable and that expenditure for offices could even be allocated on the basis of a specific

apportioning method, for example one based on the total turnover of each cost centre.

It must be noted that there is no standard method for apportioning overhead costs; in each case a method should be found that has a causal ground for allocating costs to specific centres, such as the floor area used in relation to building-related expenses as shown above.

Similarly, labour inputs that cannot be directly allocated have to be apportioned on the basis of a key determinant, for example technicians who maintain and/or repair equipment in different departments can easily record time expenditure on job sheets for the individual cost centres. Even management staff can to some extent record time expenditure by cost centre. It is clear, however, that this cannot be done for the entire labour input of service departments or management, since part of their input is of a general nature and cannot be allocated to specific departments.

Other service departments that work for the laboratory as a whole include libraries, the stores department, accountancy and security guards. Their expenditure has to be allocated on the basis of the perceived benefits that each cost centre receives, for example the stores department's expenditure could be allocated on the basis of the number of material requisitions from each centre or on the more difficult to assess basis of the value of materials dispatched to each centre.

In advanced cost accounting systems, overhead allocation does not stop at the level of cost or profit centre, but relates to the specific tasks that pass these centres. In the context of vaccine production, this leads to cost accounting being brought down to the level of individual batches and not just to the vaccine production unit. Desirable as this may be, in government-controlled veterinary laboratories this kind of breakdown is often far too ambitious and cost allocation at the level of cost centres is usually quite adequate.

STOCK OR INVENTORY CONTROL

Inventories can be a major source of cash drain for any kind of company. This is especially so in firms that have little working capital. As vaccine producing laboratories often depend on government support for establishing a capital basis, it is clear that they very often struggle with financial constraints because of a lack of working capital. Good stock control, of both inputs and outputs, is thus an important element in the financial management of such (semicommercial) manufacturers.

Inventories must be maintained so that the customer can be served on request (Horngren, 1977). In addition, in the case of veterinary vaccines it may be necessary to maintain a certain stock of specific vaccines in case an outbreak of a specific disease requires immediate and medium- to large-scale intervention.

Inventories are cushions to absorb planning errors and unforeseen fluctuations in supply or demand and to facilitate smooth production and marketing operations. Inventories can also minimize the interdependence of different parts of the organization, so that each can work effectively (Horngren, 1977). Another reason for companies to hold stocks is for speculation whereby a firm buys in more or fewer inputs than are required from a strict managerial point of view in order to take advantage of anticipated price fluctuations. Unlike the other reasons for stockholding, this latter motive cannot be generalized in guidelines for stock control as the speculation motive is by definition a matter of uncertainty. Disregarding the speculative aspect, the problem that management faces regarding stock control is to find a good balance between the need

for inventories of inputs and outputs and the desire not to tie up too much of the firm's capital in idle stocks. As far as stock control is concerned, manufacturing companies in developing countries find that the shortage of raw materials is often more of a problem than controlling excess inventories.

The question of stock valuation is important in the sense that management must decide on a policy for attaching specific values (costs or prices) to individual inputs or outputs that are released from storage for use in either manufacturing or sales. The inventory valuation methods used are usually one of the following three:

- First-in first-out (FIFO): the earliest acquired stock is assumed to be used first, so that the impact of present price effects is delayed, as the prices used reflect historical acquisition prices or unit costs.
- Last-in first-out (LIFO): the latest acquired or produced units are supposed to be used or sold first. With this method, the value of stock items released is a reflection of present (or at least recent) costings. LIFO usually leads to somewhat higher values as price levels over time generally show rather a rising tendency than a falling one.
- The obvious compromise is the use of some kind of average inventory method, which could be a moving average whereby each new addition to the stocks is lumped with the previous ones and average unit prices have to be adjusted with each change in stocks.

None of the above methods is entirely satisfactory and each has it own advantages and drawbacks.

Security stocks

The financial burden of keeping stocks of vaccines ready at hand for emergencies should, in theory, not be borne by the producing firm. In practice, however, this is usually what happens. As a result, the complex administrative channels through which reimbursement has to be channelled in case of emergency delivery constitute an additional financial bottleneck for vaccine supplying companies.

The question is whether the cost of holding such emergency stocks should and can be included in the firm's manufacturing cost and consequently be covered by the sales price of the vaccine. The answer to this question is primarily a policy issue which is related to the more general problem of differentiating between the health-related aspects of veterinary services, which are beyond the control of individual livestock owners, and those services that primarily relate to the productive activities of the livestock sector and are under the control of individual farmers.

As a general rule, cash generated from sales or the collection of receivables is an idle asset unless it is put to use internally (reinvested) or externally (invested in short-term securities). If, however, the economic situation in a country is characterized by high inflation rates, investment in short-term securities can only make sense if the real interest rate is positive, i.e. higher than inflation. If not, investments are a waste of resources. The problem in many developing countries, however, is the lack of efficiently functioning and fully developed money and capital markets (Sun, Gao and Soenen, 1993). This may mean that capital markets are not tuned to the characteristics of the economy but are centrally controlled by government.

On the other hand, manufacturing companies that are controlled and/or owned by governments may also benefit from this situation. The firm's equity is often provided by government authorities

without having an explicit cost attached to it, for example enterprises have been financed in the past by state equity capital that was free of charge (Sun, Goa and Soenen, 1993). This situation came about because veterinary vaccine production was thought to belong to the government's essential tasks and was therefore monopolized under government control. The lack of competition gave companies no incentive to aim at efficiency gains and governments considered it appropriate to support these firms through the provision of equity capital, independent of the conditions in the capital markets. In recent years discussions have increasingly centred around the question of what exactly is included in the government's essential tasks. There is a tendency among donor agencies and international banking institutes to consider the support of vaccine production as non-essential for a government. Vaccinations, on the other hand, will in many cases continue to be considered as an essential task of the government and explicit government interference may therefore be deemed feasible and acceptable.

CONCLUDING REMARKS

On the basis of historical costs and with a proper accounting system it should be possible for veterinary vaccine producers to keep track of both direct and indirect costs and overheads. The principal problems that remain will be the proper allocation of overheads and the clarification of the goal of manufacturing versus other social or commercial functions. In the context of this manual it is impossible to cover the details of cost control in the different cost centres of a manufacturing firm. Nor is it possible to deal with the accounting principles behind such a cost control system in any detail. Apart from indicating some fields of special interest, reference will have to be made to the professional literature in this field.

The main purpose of this chapter has been to point out a number of problems that may arise, especially in animal vaccine manufacturing institutes or enterprises in developing countries. The role of the government, often as owner and/or controller of veterinary laboratories, is crucial in this respect. Mostly because of external pressures, this role is changing rapidly and the process of manufacturing is increasingly being left to the private and semi-private market. Whenever this is happening, businesslike approaches to the management of such manufacturing processes become increasingly important. Donor agencies may play an important role in this respect in supporting and/or organizing management training for scientific staff of such veterinary institutes.

Such actions would encourage a real incentive for improved economic performance and this in turn would lead to a better and more efficient use of scarce resources for the benefit of the community. This is the major goal of economics.

BIBILIOGRAPHY

Drury, C. 1988. *Management and cost accounting*. London, Chapman & Hall. 857 pp.

Fama, E.F. & Miller, M.H. 1972. *The theory of finance*. Hinsdale, Ill., USA, Dryden. 344 pp.

FAO. 1992. *A coordinated multi-donor programme for tick and tick-borne disease control in Eastern, Central and Southern Africa*. Report of the Formulation Mission, Rome.

Gittinger, J.P. 1982. *Economic analysis of agricultural projects*. Baltimore, USA and London, Johns Hopkins University Press. 505 pp.

Horngren, C.H. 1977. *Cost accounting – a*

managerial emphasis. London, Prentice-Hall International. 934 pp.

Naylor, T.H. & Vernon, J.M. 1969. *Microeconomics and decision models of the firm*. New York, Harcourt, Brace and World. 482 pp.

Sun, B., Gao, G. & Soenen, L. 1993. *Financial management practices in Chinese state enterprises*. RVB Research Papers, p. 1-5.

Thompson Jr., A.A. 1977. *Economics of the firm – theory and practice*. N.J., USA, Prentice-Hall. 638 pp.

van Hemert, P. 1972. *Vaccine production as a unit process*. Delft, the Netherlands, Technische Hogeschool. 175 pp.

The logistics of vaccine manufacture in developing countries

P. Hunter

Producers of veterinary vaccines in developing countries are faced with constraints not encountered by manufacturers in industrialized countries; many vaccine production centres are government-funded with limited resources, often with facilities not specifically designed for the purpose. The implementation of good manufacturing practices (GMPs) (Sharp, 1983) is difficult under these conditions. Financial constraints limit flexibility in the modification of existing plants and producers usually obtain little support from fiscal authorities owing to a general lack of insight into the requirements of vaccine manufacture.

A producer may be forced to make a particular biological product as a result of political or administrative policy, despite a lack of appropriate technology or funding. Faced with the responsibility of producing a safe and effective product under suboptimal conditions, the decision as to whether to produce or import an equivalent product must be assessed. The relatively high price of imported products needs to be weighed against the capital outlay needed to manufacture products of equivalent quality and safety. Since the role of vaccine producers is ultimately the benefit of agriculture, no advantage can be gained from insisting on producing substandard or excessively expensive vaccines locally.

While vaccine manufacturing plants should comply with certain minimal standards, the structural shortcomings of buildings should not be used as an excuse for failing to implement operational GMPs such as correct work flow procedures, hygiene and documentation. With ingenuity and dedication a safe and effective product can usually be obtained.

FORWARD PLANNING

In many developing countries animal immunization is conducted on a campaign basis and planning of vaccine production must make provision for producing large quantities of vaccines in a short period of time.

Vaccines for important diseases such as rinderpest and foot-and-mouth disease can be stored as strategic reserves; the Plowright rinderpest vaccine is stable for approximately four years in the freeze-dried state at 4°C (Doel, 1993) while foot-and-mouth disease vaccine can be stored as a frozen concentrate in liquid nitrogen indefinitely and formulated on demand. Freeze-dried lumpy skin disease vaccine stored at 4°C or -20°C will retain its original titres for two to four years (Doel, 1993).

In countries where important arthropod-transmitted diseases are endemic, there is usually a seasonal demand for vaccine in spring and early summer. Failure on the part of farmers to immunize their livestock on a sustained basis can result in massive logistical problems for producers; for example the vaccination of sheep against Rift Valley fever in southern Africa should be carried out to provide animals with adequate herd immunity during the long

intra-epidemic periods which characterize the disease. Live Rift Valley fever vaccine is easily produced in large quantities and confers lifelong immunity, but at the onset of an epizootic of Rift Valley fever, farmers cannot make use of the live vaccine in pregnant animals. There is therefore a massive demand for the inactivated vaccine which requires a larger antigenic mass per dose and a longer lead time for production.

The clostridial toxoid vaccines are generally very stable and lend themselves to storage as concentrates at 4°C.

A campaign approach to production, whereby only one product is produced for a short period of time, allows the manufacture of a large amount of vaccine to supply seasonal or other demand if production capacity is restricted and prevents cross-contamination if containment facilities are suboptimal. This is also a practical approach with a vaccine such as anthrax which has a disastrous potential for the contamination of production and bottling plants.

The production of vaccines which have a very short shelf-life, such as the blood vaccines for rickettsial and protozoal diseases in Africa, need special attention with regard to planning. The procurement of susceptible animals, infection, bleeding, collection and bottling of vaccines must be carefully planned to avoid the wastage of resources. Producers may have to supply clients according to a schedule, for example weekly in the summer months but only monthly in winter.

Ordering materials

As in any production plant, ordering materials for vaccine production must be done in a timely manner, so that there is sufficient time for checking and quality control (QC). In developing countries, there is the additional problem of raw materials frequently being imported and time must be allowed for importation and release from customs. Further problems such as receiving the wrong product in a consignment of raw materials can delay production. Stockpiling crucial raw materials is advisable if sufficient storage space is available and as long as the product is stable on storage (Lambert and Birch, 1985). However, stockpiling ties up capital and adds to the unit cost of the product compared with those produced in developed countries where manufacturers can rely on a *just-in-time* approach.

Since many raw materials for vaccine production are analytical grade chemicals, most conform with the specifications of the manufacturer. Using cheap culture substrates which are available locally to reduce costs (e.g. using meat broth or corn steep for clostridial vaccines) causes complications because these substances may vary in composition from batch to batch. Additional QC tests such as protein or nitrogen content (on meat broth) and total solids (on corn steep) are necessary to eliminate poor substrates. In addition, careful growth tests must be done to ensure their suitability for use.

Since few laboratories can afford to import complete cell culture media, powdered media or individual components are usually purchased. Although buying from reputable companies may cost more it does reduce the risks of unscrupulous companies dumping poor-quality products in developing countries.

THE PRODUCTION PROCESS

Media preparation

Cell culture medium. Cell culture medium must be formulated with double-distilled water or water produced by reverse osmosis and filtered sterilely into stainless steel tanks or into bottles. If sterile room facilities are unavailable for sterile filling, small laminar flow units can be used. Careful sterility checks at 37°C and room

temperature are essential if conditions are not optimal.

Bacterial culture media. Bacterial culture media are usually sterilized by heat in tanks or glass flasks – a process which is generally associated with fewer problems than sterile filling. However, the function of autoclaves and the quality of the steam used for sterilization may affect the heat-sterilization process and sterility tests must be carried out.

The preparation of agar plates or slopes should be done in laminar flow cabinets or under laminar flow units if no sterile rooms are available.

Virus vaccines

Cell lines. Cells for virus production can be obtained from culture collections or reputable laboratories, where the identity, chromosomal characteristics and freedom from extraneous agents have been established. If in-house testing is not possible intermittent checks can be done by other local laboratories that are able to check cell identity and freedom from mycoplasmal and viral contamination.

It is essential to check cell lines for extraneous viruses. As in-house facilities are seldom available for this, help should be enlisted from universities or other laboratories with experience in detecting the viruses that may affect the cells used for production. With this in mind, it is more convenient if viral vaccines produced from cell lines are manufactured on a campaign basis to eliminate the need for continual testing for extraneous viruses.

Media. The importation of complete formulated media for vaccine production is impractical owing to freight costs, despite the advantages of QC and growth checks thereby becoming unnecessary. It is more economical to buy powdered media, but cell growth checks must be done, as the quality of water used for formulation can affect the product.

Storing cell and virus seed. Erratic power supplies make it essential that cell and virus stocks should be duplicated and stored at various institutes as back-up supplies.

Viral master seed stocks. The identity, purity, passage history and titres must be carefully noted. Recording the passage level of live attenuated virus vaccine strains is of major importance and failure to control this can lead to serious problems in the field.

Production

The production of live vaccines on cell culture requires less antigen and can therefore be performed in roller bottles or in Roux flasks. Inactivated virus vaccines require a large amount of antigen, which may necessitate the production of vaccine virus in suspension culture. This has been done successfully with BHK cells for rabies and foot-and-mouth disease vaccine production.

However, in developing countries it may be more practical to use a labour-intensive, scale-up monolayer system as has been used for foot-and-mouth disease vaccine production (Ubertini *et al.*, 1963) and for IBR, Aujesky's disease and PI3 vaccines (Panina, 1985).

Bacterial vaccines. The production methods of many bacterial vaccines are uncomplicated and appropriate for use in most developing countries. However, the production of vaccines for *Brucella abortus* and *B. melitensis* should not be attempted without adequate containment and biosafety facilities.

Undemanding anaerobes such as the clostridia can be produced without difficulty but strict anaerobes such as

Bacteroides nodosus require totally oxygen-free gases which are not readily available in developing countries.

Although most modern bacterial vaccines are produced in fermentation vessels, labour-intensive methods of producing vaccines on agar layers in Roux flasks are suited to the conditions in some developing countries. Clostridial toxoid vaccines such as those against botulism and tetanus are easily produced by the dialysis bag method (Sterne and Wentzel, 1950) if fermentation technology is unavailable.

Protozoal vaccines. Since the production of redwater (*Babesia* spp.) and anaplasmosis (*Anaplasma centrale*) vaccines for cattle may require the use of splenectomized cattle, the appropriate facilities must be available or the services of universities or private clinics must be elicited. Animals need to be maintained under tick-free conditions, by means of water-trenches around stables and the provision of sterilized feed.

Tick stabilate vaccines such as those prepared for *Theileria* sp. and heartwater, where the vaccine consists primarily of infected ticks ground into a suspension, must be prepared with caution because of the prevalence of tick-borne diseases which can affect humans such as tick-bite fever (*Rickettsia conori*) and the viruses which cause haemorrhagic fevers.

Serum for culture media. Foetal calf serum is rarely available in developing countries and has to be imported. Although expensive, the advantage of this is that a sterile product which has passed appropriate growth tests is received.

Normal bovine or other sera are usually more easy to obtain from abattoirs but the quality can be a problem. Collection is rarely from animals bled by trochar and inevitably the blood collected at exsanguination has high microbial contamination and resultant high endotoxin levels. However, the serum collected in this manner is cheap and, providing the laboratory has a separator for defibrination and facilities for sterile filtration, a usable product is usually obtained although the suitability of each batch for cell culture needs to be checked and stringent sterility checks are essential. Because of the risk of adventitious viruses which may be present in serum, for example BVD virus (Kriazeff, Wopschall and Hopps, 1975), bovine sera for use in live vaccines should be irradiated or heated.

The problem of the presence of antibodies in serum, which may react with the virus to be cultured, can be overcome by precipitation with polyethylene glycol (Abaracon and Giacometti, 1976; Barteling, 1974).

Downstream processing

Whether it be the removal of bacterial cells for the processing of toxoids or the concentration of virus harvests, the major concern for a vaccine producer in developing countries is the selection of methods which combine low capital outlay with low-cost maintenance. Of the variety of processes available, only ultrafiltration is suitable for large-scale processing; the equipment is simple and of relatively low cost but it has the disadvantage that purification cannot be achieved to any great extent.

Adjuvants

Adjuvants. Alum (potassium aluminium sulphate) and aluminium phosphate are relatively cheap and easy adjuvants to formulate. They are commonly used for adjuvanting toxoid vaccines. The in-house production of aluminium hydroxide gel (alhydrogel), which is the most widely used adjuvant for veterinary vaccines, is more demanding. The aluminium content,

pH and conductivity need monitoring and the poor heat conduction of the gel requires careful control of sterilization. With this in mind, the cost-effectiveness of buying a commercial product which conforms to safety and efficacy requirements must be weighed against that of in-house production of the product.

Oil adjuvants. Mineral oils used for single or multiple oil formulations in veterinary vaccines are usually imported into developing countries and, because of the propensity of oil formulations for causing local reactions, attention must be paid to the quality and purity of the oils. Vaccine producers must insist on certificates of analysis and must check the containers in which the oils are delivered to ensure the absence of contamination with other products. The oils should be stored under nitrogen to prevent oxidation during storage.

Saponin. This adjuvant usually has to be imported and the producer should be aware that the quality varies with supplier. While some brands which are not highly purified have good adjuvant activities and can be used with success, for example in the anthrax spore vaccine, they can affect certain antigens such as foot-and-mouth disease virus on storage. Some initial research should therefore be undertaken to determine an appropriate supplier. Purified saponins are less likely to destroy the antigen, but are extremely expensive and some have poor adjuvant activity.

Filling and freeze-drying

The vaccine filling and freeze-drying plant is the bottleneck area in most production facilities. In developing countries the additional problem exists that equipment is imported and service back-up from the supplier becomes very important. Ampoules used for freeze-drying can be manufactured locally to keep the unit price low, but these are often not produced to specification, leading to breakages by capping machines. This is a serious problem not only because of wastage, but because it becomes a safety problem when bottling freeze-dried products such as *Brucella* sp. and live attenuated mouse-brain adapted strains of African horse sickness virus (Erasmus, personal communication).

Producers are often forced to use a filling line for both live and killed products; if this is unavoidable, live products must be bottled at the end of a week, after killed products, and the facility must then be disinfected with an appropriate disinfectant, or fumigated with formaldehyde, and allowed to stand over a weekend.

The malfunctioning of freeze-drying machines can cause a high moisture content in the product which results in poor stability of the vaccine, which is important in tropical and subtropical countries.

QUALITY CONTROL

As the number of QC tests performed increases, so does the cost of the final product, and often only essential tests are selected.

Physical and chemical tests

The manufacturer should not underestimate the value of visual inspection of the product. Numerous problems can be detected merely by looking at a formulation: the colour, consistency, presence of foreign bodies, proportion of alhydrogel and appearance of freeze-dried pellet can indicate a problem in the final product. Basic tests such as pH determination are simple to perform and give valuable information about the reagents used and in monitoring each stage of the vaccine production process. QC tests must be

validated by including standards and, if necessary, by requesting other laboratories to duplicate tests.

Raw materials. The extensive QC tests performed on raw materials in developed countries are seldom performed in developing countries because of the cost. Less affluent producers must nevertheless ensure that analytical grade chemicals are used and growth tests are performed on formulated media.

In-process tests. The monitoring of inactivation is essential in order to obviate using vaccines containing non-inactivated organisms. When aziridines are used as inactivants, the inactivation process can be controlled by monitoring the pH changes during the process of cyclization of the reagent and by sampling and titration of the antigen (Bahnemann, 1990).

Moisture content of freeze dried vaccines. Since a high moisture content will affect the stability of vaccines Karl Fischer moisture determination should be performed, if possible, by the producer or an analytical laboratory. An accelerated stability test can pre-empt the issuing of vaccine with high moisture content if moisture determination tests cannot be performed.

Biological tests

Innocuity/safety testing. Abnormal toxicity testing is done on two guinea pigs (2 ml intraperitoneally or subcutaneously) and on five mice (0.5 ml). This test is important if the analysis of raw materials and in-process controls cannot be done.

Specific safety tests, as for the abnormal toxicity test, are essential and become all the more important if the quality of raw materials and other reagents cannot be controlled. These tests are essential for live attenuated vaccines. Susceptible target animal species are inoculated with at least one dose of the specific vaccine.

Potency testing. As with potency testing in developed countries, titrations of live organisms or serology are performed in place of challenge tests on large or small animals, where this is possible. Performing serological tests may be difficult in some countries, owing to the problem of finding seronegative animals to ensure immunological responsiveness to specific antigens. In South Africa, sheep have to be purchased from an area in the country where bluetongue does not occur and have to be maintained in insect-free stables while they are tested for their serological response to the bluetongue vaccine.

The lack of containment facilities may prevent developing countries from performing challenge tests for vaccines such as rinderpest and contagious bovine pleuropneumonia and only serology will be carried out.

PROTOZOAL AND RICKETTSIAL VACCINES

The cattle used for the production of blood vaccines, such as those for babesiosis and anaplasmosis, should be tested for infectious agents which could contaminate the blood vaccine (OIE, 1992) and sheep used for heartwater vaccine production should be free of *Anaplasma ovis*, *Erlichia ovis* and *Trypanosoma ovis* (Oberem and Bezuidenhout, 1987).

STORAGE

Sufficient storage capacity in cold rooms, freezers or liquid nitrogen tanks is essential for storing vaccine or antigen. A minimum requirement is a recording system for validating constant temperature control, since a loss of refrigeration or freezing in cold rooms can affect the antigen or the finished product. If temperature monitoring cannot be done electronically, manual hourly checking can be done by production

staff and after hours by security staff. Ideally, alarm systems should be utilized to alert production managers to such eventualities.

DISPATCH AND DISTRIBUTION

Dispatch and distribution should preferably be undertaken by distributors with facilities for handling and dispatching the finished product. Consigning vaccines to the mercies of rail or road transport in developing countries can lead to serious losses. Vaccines are often offloaded at small railway sidings or bus depots over weekends and the recipient is only informed of the arrival of the consignment the following Monday.

Maintaining a cold chain during the dispatch of biological products is commonly believed to be an obstacle to using vaccines in developing countries. Yilma (1989) mentions a particular problem in Ethiopia with regard to hot arid conditions. Other authors (Belsham *et al.*, 1989) have stated that cold chains are often available for medical supplies and human vaccines and these can be utilized for veterinary biologicals. Effective cold packages can be devised using polystyrene containers into which frozen cool-bricks can be packed to keep vaccine within the optimum temperature range for 24 hours, provided the package is well sealed.

Cold chain monitors are available commercially. These indicate by a colour change on an indicator card whether the product has been exposed to high temperatures for any length of time. Maximum/minimum thermometers can be included in packages to monitor their ability to maintain the required temperature. In some countries, such as Lesotho, where temperatures drop below freezing in winter and vaccine is sometimes carried on horseback, inactivated vaccines such as rabies must be transported in insulated packages to prevent freezing.

POULTRY VACCINES FOR DEVELOPING COUNTRIES

Producing vaccines for intensive poultry raising systems in developing countries is uneconomic owing to the very low unit cost at which these vaccines can be supplied by large international companies. The latter also produce a wide variety of vaccines and can therefore provide the poultry producer with a complete range of products. In addition, intensive poultry farming calls for vaccines with a high safety and efficacy index. Any reactions caused by virulence of an attenuated strain, adjuvant reactions or infection with adventitious agents causing death, failure to protect, failure to gain weight or a drop in egg production will occur on a scale which affects the profit margins of the producer. *De novo* development of poultry vaccines, therefore, requires extensive efficacy and safety testing which few developing countries are able to undertake. The production of vaccines in embryonated eggs requires a source of specific pathogen-free (SPF) eggs and SPF birds are required for many of the QC tests performed for poultry vaccines.

COMPANION ANIMAL VACCINES

Developing countries vary in their demand for companion animal vaccines, other than rabies which is usually the concern of government authorities. In general, the greater the affluence of the country the more the attention given to the vaccination of pet animals. As in the case of the poultry industry, the demand for safety and efficacy of vaccines is high and, unless a producer can do sufficient research and development and safety testing, producing these vaccines is not economically viable. Producing a single component vaccine such as live attenuated distemper may be feasible, but more sophisticated consumers will demand combination vaccines which contain multiple antigens.

LICENSING OF BIOLOGICAL PRODUCTS

The situation with regard to the licensing of biologicals in developing countries varies considerably; in some South American countries government authorities have the facilities for testing vaccines and have personnel who are well informed on vaccine production facilities and processes. Other countries may have only a small government department with a few officials encumbered with the licensing of local and imported biologicals. These officials may not be well informed about vaccines and vaccine production; often minimal data on safety and efficacy is required to license a product. In the southern African region, for example, each country has its own small group of technical advisers. It may be advantageous for countries in this situation to pool resources and devise a harmonized registration and regulatory system, which will prevent duplication of registration offices and costs.

BIBLIOGRAPHY

Abaracon, D. & Giacometti, H. 1976. Vaccines against foot-and-mouth disease and virus produced in cell cultures with bovine serum treated with polyethylene glycol. *Bol. Cent. Panam. Fiebre Aftosa,* 21-22: 49-53.

Bahnemann, H.G. 1990. Inactivation of viral antigens for vaccine preparation with particular reference to the application of binary ethylenimine. *Vaccine,* 8: 299-303.

Barteling, S.J. 1974. Use of polyethylene glycol treated serum for the production of foot-and-mouth disease virus in growing BHK suspended cell cultures. *Bull. Off. int. Epiz.,* 81(11-12): 1243-1254.

Belsham, G.J., Anderson, E.C., Murray, P.K., Anderson J. & Barrett, T. 1989. Immune response and protection generated by a vaccinia virus recombinant expressing the F protein of rinderpest virus. *Vet. Rec.,* 124: 655-658.

Doel, T.R. 1993. *In* A.R. Peters, ed. *Vaccines for veterinary application.* London, Butterworth-Heinemann.

Kriazeff, A.J., Wopschall, L.J. & Hopps, H.E. 1975. Detection of bovine viruses in bovine serum used in cell culture. *In Vitro,* 11: 400-403.

Lambert, K.J. & Birch, J.R. 1985. Cell growth media. *In* R.E. Spier & J.B. Griffiths, eds. *Animal cell biotechnology,* Vol. 1, p.111. London, Academic.

Oberem, P.T. & Bezuidenhout, J.D. 1987. The production of heartwater vaccine. *Onder. J. Vet. Res.,* 54: 485-488.

OIE. 1992. *Manual of Standards for Diagnostic Tests and Vaccines for List A and B Diseases of Mammals, Birds and Bees,* 2nd edition. Paris, Office International des Epizooties.

Panina, G.F. 1985. Monolayer growth systems: multiple processes. *In* R.E. Spier & J.B. Griffiths, eds. *Animal cell biotechnology,* Vol 1. London, Academic.

Rogers, R.J., Dimmock, C.K. & de Vos, A.J. 1988. Bovine leucosis virus contamination of a vaccine produced *in vivo* against bovine babesiosis and anaplasmosis. *Austr. Vet. J.,* 65: 285-287.

Sharp, J.R. 1983. *Guide to good pharmaceutical manufacturing practice.* London, Her Majesty's Stationery Office.

Sterne, M. & Wentzel, L.M. 1950. A new method for the large-scale production of high-titre botulinum formol-toxoid types C and D. *J. Immunol.,* 65: 175-183.

Ubertini, B., Nardelli, L., Dal Prato, A., Panina, G.F. & Santero, G. 1963. Large-scale cultivation of foot-and-mouth disease virus on calf-kidney cell monolayers in rolling bottles. *Zentralbl. Veteriner. Med., (B),* 10: 93-101.

Yilma, T.D. 1989. Prospects for the total eradication of rinderpest. *Vaccine,* 7: 484-485.