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PROGRAMME ON INDUSTRIAL DEVELOPMENT FOR HEALTH
Advisory Panel Meeting for BIONUDI

XP/GLO/95/014

Technical report: Proceedings and recommendations*

Prepared by

Industrial Sectors and Environment Division

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* Mention of firm names and commercial products does not imply the endorsement of the United Nations Industrial Development Organization (UNIDO)

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ABBREVIATIONS

AMP	Association pour l'Aide à la Médicine Préventive
BCG	Bacillus Calmette Guerin
BPR	Batch Production Record
BSE	Bovine Spongiform Encephalopathy
CDMA	Canadian Drug Manufacturer's Association
CEEC	Central and Eastern European countries
CEO	Chief Executive Officer
CIP	Clean-in-Place
CJD	Creutzfeldt-Jacob disease
CVI	Children's Vaccine Initiative
DNA	Desoxyriboneuleic acid
DPT	Diphtheria, Pertussis and Tetanus
EBRD	European Bank for Restructuring and Development
EP	European Pharmacopoeia
EPI	Expanded Programme on Immunization
EVM	European Vaccine's Manufacturers
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Vaccine
HIV	Human Immunodeficiency Virus
HVAC	Heating Ventilation Air-Conditioning
IC	Institute Cantacuzino, Bucharest, Romania
ICGEB	International Centre for Genetic Engineering and Biotechnology
IPB	International production of biologicals
IPR	Intellectual Property Rights
ISO	International Standard Organization
IVI	International Vaccine Institute
MV	Measles vaccine
PAHO	Pan-American Health Organization
PHARE	Poland, Hungary Assistance for Restructuring Economy
PMAC	Pharmaceutical Manufacturer's Association of Canada
QA	Quality Assurance
QC	Quality Control
SBO	Specified bovine offal
SEAC	British Spongiform Encephalopathy Advisory Committee
SIP	Sterilization-in-Place
SOP	Standard Operating Procedure
TB	Tuberculosis
TOPV	Trivalent Oral Poliomyelitis Vaccine
TOT	Transfer of Technology
UNDP	United Nations Development Programme

UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
VAT	Value added tax
WFI	Water for injection
WHO	World Health Organization

PREAMBLE[1]

1. The Global vaccine industry is in a state of flux and uncertainty, due to:

   - Rapidly changing technology.
   - Globalization of the biologicals/vaccine industry leading to global competition, mergers, acquisitions and alliances leading to global consolidation of the industry.
   - Profound changes in the transition economies particularly in CEEC.
   - Greater efforts by traditional multilateral donor agencies to achieve greater efficiency and targeted assistance.

2. Changing vaccine markets (elimination of some diseases from the industrialized countries/greater and greater emphasis on QC/QA and more stringent regulatory environment on biologicals/universal enforcement of IPRs (elimination of import barriers in most countries) will result in international competition in vaccine industries. Small, inefficient, state-controlled vaccine producers that enjoyed protected, captive markets will no longer enjoy such protective environment.

3. Sustainable "national vaccine self-sufficiency" no longer means national production. For most small countries, it would be more cost effective to import high-quality vaccines than to produce.

4. How will the state-owned or subsidized vaccine production organisations survive in the new market? Many of these institutions perform other socially and medically essential functions in addition to vaccine production.

5. UNIDO and other public institutions should assist these institutions in examining the available options and making the current choices - sometimes including the closure of the operation.

6. While the current uncertainty clearly presents major risks, at the same time it represents a major new opportunity to introduce rational and fundamental new thinking into the vaccine industry.

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[1] The Preamble has been prepared based on the notes given by Dr. Seung-il Shin, Chief Executive Officer, The International Vaccine Institute, Seoul, Korea.

OPENING ADDRESS
(ON BEHALF OF DR. CHARLES MERIEUX CHAIRPERSON OF THE ADVISORY PANEL MEETING)

by Dr. Philippe J. Stoeckel, Director General, AMP, France

Dear Participants and Colleagues,

First, I would like to excuse the absence of Dr. Charles Merieux who cannot be here today with us in this meeting of the "Advisory Panel on Preventive Medicine". He has asked me, who was with him in 1983 and 1984 when the Panel was created, to represent him. He also has asked me to tell you how important he believes this Panel is for the progress of Preventive Medicine and Vaccinology worldwide. I am sure he would be very pleased to see today around this table, representatives from Asia, Cuba and Eastern Europe.

Recently, Dr. Merieux met with the Director General of UNIDO, Mr. Mauricio de Maria y Campos and they have signed a memorandum of understanding for the implementation of BIONUDI, an entity devoted to improving the safety and reliability of the procurement of blood derivatives in several countries where this is an issue. But, of course, his heart is in the vaccines necessary for securing safe and effective immunizations of children around the world. We will have the opportunity to hear the progress made in China, in India, in Indonesia. We will listen to our colleagues from Russia, Poland and the Czech Republic about their difficulties. We will be interested in the presentation from Cuba where research is being done continuously. We will be presented with the International Vaccine Institute being set up in Korea and certainly the two workshops that are being planned for next year with the contribution of UNIDO will be of great interest to this Panel : (1) the IVI/UNIDO workshop on quality control/quality assurance in Bandung, Indonesia and (2) the IVI/UNIDO workshop on vaccine production management in Beijing, China; it is to be noted that the vaccine industry will be actively participating in these workshops.

It is important that this Panel exist and that these participants meet together on the industrial aspects of the vaccine procurement worldwide. I hope that we will have an interesting exchange of views and animated discussions. I will certainly report these to Dr. Merieux who as ever is interested in keeping an active role in this Panel.

SUMMARY RECOMMENDATIONS FOR THE ROLE OF UNIDO IN THE VACCINE INDUSTRY

(Panel Meeting held on 12-13 October 1995 at HUMAN Ltd., Gödöllö, Hungary)

Asian Group:

Dr. Su Wan Nian
Dr. Darodjatun
Dr. Jal M. Mehta
Dr. Seung-il Shin
Rapporteur : Dr. Jal M. Mehta

1. UNIDO should participate in the global activities of Children's Vaccine Initiative (CVI) in close collaboration with the other members.

2. UNIDO should act as a catalytic agent in providing expert advice to the vaccine industry in emerging countries of Asia.

3. UNIDO in association with UNDP should form a close working partnership with the International Vaccine Institute (IVI) in developing and implementing training the technology transfer programmes for the vaccine industry.

4. UNIDO should promote and facilitate the transfer of technology developed by International Centre for Genetic Engineering and Biotechnology (ICGEB) relevant to vaccine industry.

European Group:

Dr. Mircea Musset
Mr. Walter Vandersmissen
Dr. Wolfgang Niedereder
Dr. Jiri Jansa
Dr. Tomasz Ochalek
Rapporteur : Dr. Sergey G. Drosdov

1. UNIDO should establish a strategy to harmonize production on a regional basis:
   a) a first step towards rationalization could be national feasibility studies,
   b) recommend ways to change/improve vaccine supply,
   c) monitor progress towards changes,
   d) search for partners when changes are implemented.

2. Support for National Control Authorities for all countries, both producers or importers, should be the first priority.

3. UNIDO should continue to allocate resources for the training in Good Manufacturing Practices (GMP) and other production requirements.

PROBLEMS AND OPTIONS CONCERNING THE FUTURE OF CENTRAL AND EAST EUROPEAN VACCINE MANUFACTURE

by Mr. K. Ivanov, UNIDO consultant

A. Introduction

During a recent regional meeting on "Industrial support for a pilot regional programme on biotechnological vaccines", held on 7-8 June 1995 at UNIDO in Vienna, the establishment of a professional Association of the Central and East European Manufacturers of Biologicals has been recommended.

B. Objectives

To visit the Major Manufacturing Companies in the Czech Republic, Hungary, Poland, Romania, the Russian Federation and Bulgaria and to carry out the first round of negotiations in order to identify areas and topics of common interest among these manufacturers. The topics could be in relation to privatization issues, price structure, export opportunities, research and development, national control authorities, etc. Furthermore, to discuss how to develop a dialogue with the seven western manufacturers (Pasteur Merieux Serums & Vaccins, SmithKline-Beecham, Behringwerke Hoechst, Medeva, Berna Swiss Serum Institute, Sclavo and Immuno) and how to seek eventual partnership arrangements.

C. Remarks

From the report, economic indicators and geographical or other country data, a wealth of which are available in publications of UNDP, UNIDO, the World Bank, EBRD, etc. are deliberately omitted.

The expert has also abstained from recommending obvious activities and measures to be found in management textbooks, such as:

- prepare market surveys [2] (consumer, motivation, brand awareness, etc.);
- improve capacity utilization;
- ameliorate profitability by cost reduction programmes and become more competitive;
- improve quality, striving to achieve international standards;
- prune unprofitable items;
- expand exports, etc.

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[2] Management consulting companies often charge 100-150,000 USD for feasibility studies, preparation of business plans, conducting market surveys (recent example : PE Consultants in Prague).

The report does not include comments on national vaccination programmes or production/import of biologicals, both of which will be discussed elsewhere.

Finally, due to the nature of the assignment, the mission was looking for similarities among the countries as well as mutual interests, rather than for differences, despite the fact that the group is somewhat heterogenic - for instance, some with first class manufacturing facilities and modern equipment, others - with antiquated ones, some with private interests, others - completely government-owned.

D. General Considerations

The centrally planned economies prevailing in the ex-Soviet Union and in the Central and East European countries for the last 70 or so years, are one of the main, well-understood reasons for the ensuing problems discussed in this paper, as well as for their extremely difficult and delicate solutions, especially short term.

During this period of time, a great gap in research and technology has developed with the West, leading to an almost complete isolation. This gap, widening continuously and combined with a chronic lack of financial resources, might not be compensated in a short period of time, if at all.

On this background, conflicting interests of the Western manufacturers and those of the ex-Soviet bloc ones have obviously emerged. In both cases, some of the reasons are justified.

On the one hand, western producers prefer to sell their products realizing immediate profits and would not mind closing down manufacturing facilities in the East , offering as a compromise bulk sales with local packaging only. On the other hand, the Central and East European countries are interested to remain relatively independent and continue to manufacture some biologicals.

While from a purely economic and financial point of view, some production facilities in the Central and East European countries should he shut down, acts also justified by the lack of modern technology, the low manufacturing standards, the non-compliance with GMP and QC and QA requirements, one should not forget or disregard their long experience and skills in manufacturing biologicals of acceptable quality, their patriotism and national pride [3], their customs and habits, and especially the consideration of the social stability [4] as one of the primary objectives in this transitional period. In this respect, one should also not forget to

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[3] Patriotism is to love one's country and nationalism - to hate the neighbours (Charles de Gaulle).

[4] They can neither afford to charge people for vaccinations, nor to let them do without it.

mention that for the last 45-70 years these countries succeeded somehow to produce and manage their epidemiology situation without major problems [5].

Thus, one of the main questions to be answered could then be:

- should Central and/or East European countries purchase vaccines from Western companies, or should they promote local/regional manufacture?

In other words, is it worthwhile investing in improving technologies and upgrading equipment for the production of biologicals, when the Western advance is so large and the product availability at reasonable prices insured [6]?

On both sides, the realization of relative strengths and weaknesses, as well as the adaptation to new market conditions and requirements, are important factors for a possible solution of the problem. This should be visualized without sentimental considerations and nostalgia on one side and excessive short-term profit ambitions, on the other.

Foreign companies with policies for long-term presence and acceptance in these markets should utilize local resources (capacity, techniques, skills, etc.) [7] and integrate up to a certain extent in the local economy.

Local companies should not consider foreigners as invaders, but attract them as potential partners. In this sense, local authorities should abstain from accusing that companies in their aspiration to get privatized and acquire foreign equity are selling-out national wealth to foreign interests.

Problems and mutual concerns

1. State-owned non-profitable institutions (except *HUMAN* in Gödöllö, with private Canadian interests), with relatively limited management authority, but with full operational responsibility. While the majority of the units are separate juridical persons, they have a relatively restricted autonomy, especially in acquiring or disposing of assets, entering into contractual relations with foreign partners, restructuring or reorganizing of the entities, etc. Various approvals of the government authorities are normally required.

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[5] Some of the latter occurred during this transitional period - e.g. diphtheria outbreaks, TB indecence increase, etc. In the ex-Soviet Union there were over 80 different epidemiological institutes to fight infectious diseases.

[6] For obvious reasons, greenfield development in the biologicals production should not be a priority for the Central and East European countries, at present.

[7] An example could be the poliomyelitis vaccine production in Russia.

2. Lack of understanding of all privatisation issues, especially interpretation and implementation of laws, rules and regulations, such as: mass or social privatisation programmes; cash and/or Brady bonds requirements; government and private participation; buy-in or buy-out management possibilities; privatization funds, etc.

3. Complicated hybrid structures of the manufacturing units, involving also teaching institutions (for postgraduates usually) and basic research facilities and personnel, with little government consideration for productivity, efficiency and especially profitability of the agglomerated manufacturing entities. In this respect, there is also an insufficient and unclear legislation, no real objectives, goals and plans, and decreased government subsidies. Thus, as it was said in some quarters, before there was "some discipline and defined objectives concerning the prophylactic medicine good for the vaccine manufacturers; now with a confused situation and very relaxed rules - it is not good for producers".

4. Confused relations and lack of communications of the controlling organs, acting without directives and clearly defined authority and responsibility - Ministry of Health, Academy of Medical Sciences, Ministry of Education, etc.

5. Insufficient financial resources resulting in obsolete equipment, poor maintenance, antiquated technology and obvious lack of funds to purchase modern know-how, to undertake market research, feasibility studies, purchase of imported raw materials (reagents, amino-acids, media, etc.) and packaging materials), etc. Usually, the meagre profits derived from the manufacturing units are utilized to keep alive the basic research and teaching facilities. The progressively decreasing government subsidies, originally deemed to cover these expenses are not enough for the manufacturers to sustain their normal development, i.e. technology is constantly improving, the GMP and QC/QA assurance requirements are changing. Thus, some concepts of the authorities that the gross profits of the companies and/or the government contributions should cover only the manufacturing costs, are obviously erroneous.

6. Lack of knowledge and experience in the five basic functions of management (planning, organizing, staffing, leading and controlling).

7. Excess of personnel, especially in non-productive areas, poorly remunerated and not motivated. In most cases, reducing staff becomes a major issue due to the interference of the syndicates and the government attitude for social stability.

8. Unclear relations and responsibilities of the Central Control Laboratories, often remunerated directly by the manufacturing units and sometimes even located in their premises, a fact which could negatively affect the QC/QA.

9. Superficial cooperation between various state-owned institutes such as veterinary, haematology and others.

10. Poor communication, excessive bureaucratic procedures and often strained relations with government authorities, resulting in unacceptable delays of approvals for even the slightest manufacturing modification, sometimes even more than 16 weeks.

11. High import duties and V. A. T. on equipment, machinery and raw and packaging materials, seriously affecting the cost structure and often forcing the institutions to abandon projects, or to accept difficult compromise solutions.

12. Frequent changes of responsible personnel in the Ministries are adding a feeling of insecurity and of confused policies and directives.

13. Low selling prices of vaccines, especially for children, often dictated by the authorities, which are purchasing them to execute the national compulsory vaccination programmes.

14. Misunderstanding that UNICEF prices are not based on prevailing world prices, but are sometimes much lower, depending on the situation.

15. Limited contacts with Western manufacturers [8], resulting in misunderstanding on each/others policies, conditions, problems and aspirations.

The prevailing perception was that Western manufacturers have excessive information demands, disclosing little themselves, that they prefer short-term relations with almost immediate results, that they have no interest to help the development of the Central and East European manufacturing facilities. The main fear from a potential partnership with the West is the closure of local facilities.

Recommendations

1. The consensus of opinions is that the establishment of a new professional association of the Central and East European manufacturers [9] is superfluous and unnecessary and it is certainly not the best way to solve the vaccines manufacturing problem for the following reasons:

   - there is already a functioning Western association and the Central and East European countries should strive to join the existing system under certain conditions;

   - the establishment of a new association might be counterproductive, giving the impression that of division rather than integration, of confrontation rather than cooperation;

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[8] Some of the manufacturers with private interests like HUMAN have established good relations with 16 Western companies.

[9] It was said that this recommendation was issued after the meeting in Vienna on 7-8 June 1995, where the major participants were not production people, but mainly working in government institutions.

- it is against the political and economic trends of the Central and East European countries to join the EU;

- people seem to be fed up with new associations and the resulting waste of time and resources;

- it might be construed as an additional interference of the Central and East European Governments in the international vaccine business and relations.

Finally, of the main raisons d'être of such an Association - the exchange of information on R & D, costs, marketing, clients, etc. is against the basic principle of the free market economy, where competition and secrecy are essential.

2. UNIDO should and could get deeply involved in advising and assisting to foster the privatization process of the manufacturers.

(a) the competent teams should first be very well acquainted with the existing privatization legislation rules and regulations and their interpretation in all the countries in question:
- mass or social privatization programmes;
- cash privatization and utilization of Brady bonds [10];
- MEBO (management/employee buy-out) regulations; foreign equity participation; state ownership funds;
- lists of companies offered for privatization, etc.

(b) UNIDO's expertise in this field should be used to influence and convince the respective authorities and the management of the companies about the advantages of the privatization.

(c) UNIDO should serve as a coordinator between the authorities and the companies and should be in a position to seek appropriate foreign partners, secure their understanding and cooperation in this field, to initiate dialogues and to participate in negotiations.

A joint venture with equity distribution similar to the one with HUMAN in Hungary could be envisaged, for example:
- Hungarian state property 50 % + 1 share
- Novopharm Co. Ltd. [11] (Canada) 36.21 %
- Other shareholders 13.74 %.

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[10] In some cases, for instance, 50% of the companies could be privatized with cash and the rest with Brady bonds for foreign debts

[11] Currently, Novopharm Co. Ltd. has 52.16% ownership and it has further option to increase its share.

Sometimes there is a misconception that one has to have money to participate in a joint venture, especially with foreigners. In fact, the participation in a venture could be with other assets - land, buildings, local know-how and skills in some areas, training of the foreign partners, etc.

In several cases, obsolete manufacturing facilities are located in the centres of the cities on very expensive lots of land, which could be sold and the units built elsewhere [12].

In some cases, it was suggested for obvious reasons that the bilateral contacts and negotiations be undertaken directly without intermediaries, i.e. initially not involving authorities, but presenting them the eventual agreements for approval at the end.

Finally, what was desired by all was the establishment of a long-term partnership on equitable terms with mutual respect of the parties involved. It was said that only if the partners realize these conditions, could they properly integrate in the ex-Soviet Union and in the Central and East European markets and succeed.

(d) UNIDO should closely cooperate with the EU, the WHO, the World Bank, the EBRD [13] and other international institutions, organizations and foundations to achieve this goal and to finalize the privatization process of the manufacturers, securing the necessary funds for this activity.

3. The immediate privatization not being the unique way for closer cooperation and ties with Western manufacturers, UNIDO with its endeavours to alleviate the vaccines situation, could assist, alone or with others, the progressive integration of partners in different phases:

- purchase of traditional bacterial antigen vaccines;
- purchase of viral components for contract manufacturing [14];
- marketing and selling arrangements, etc.

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[12] For example, in Prague, the price of land of the present location of SEVAC is of ca. 5,000Cr/m² with a total value of ca. USD 6 mn, whereas a piece of land owned by the company 30 km outside Prague is exactly ten times cheaper.

[13] The EBRD has issued, for instance, a privatization manual for Russia in two volumes, sold sometime ago for USD 500.-

[14] Some manufacturers have already similar agreements, like SEVAC in Prague with BIOCINE in Italy, where the first one produces under the supervision of the second which buys the entire production and sells it.

An important point, not to be omitted, in order to facilitate the issue, is the silent progressive spin-off of the manufacturing units from other activities such as the basic scientific research and the postgraduate study programmes.

4. UNIDO should organize symposia, meetings and especially training programmes for executives, with particular emphasis on modern management techniques, on various economic, financial and marketing criteria and ratios, on the preparation of business plans, etc. This is essential, especially in newly privatized companies, which are usually undercapitalized and are of urgent need of management expertise.

5. UNIDO, together with UNDP and WHO could actually seek understanding at Brussels, that more funds should he attributed to solving practical problems, and that the PHARE and/or other programmes could allocate more resources for solving practical problems, rather than to concentrate on consulting and expertise [15].

6. Payments to the Central Control Laboratories should not be done directly by the manufacturer, for obvious reasons. Normally, such expenses should be charged to the Ministries of Health and be paid from their budgets. If this is not feasible, a compromise solution could be adopted: the manufacturer pays to the Ministry and the Ministry to the Central Control Laboratory.

7. The authorities should not necessarily oblige the producers to purchase only locally available packaging materials. In the case of ampoules, for instance, the breakage and wastage of expensive lyophilized substances is very high and the purchase of imported ampoules - more than justified. A similar case, but for different reasons, is with the cartons for the sophisticated "Bosch" filling and packaging machine.

8. Since there is practically little or no money in the manufacture of vaccines, especially those destined for compulsory vaccinations of children [16], production and marketing emphasis could be put on other vaccines, basically not under Health Ministry price control, such as the influenza vaccine [17], or tetanus mono vaccine for the armed forces and the police, tetanus-diphtheria for aged people, vaccines for veterinary use, etc.

9. Wherever there are other manufactured products besides vaccines and sera in the same units, such as diagnostics and allergens, strong marketing efforts should be undertaken to promote particularly the latter [18] and improve the product mix.

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[15] The general perception in all visited countries is that the bulk of allocations are basically destined to find and remunerate jobs of West European consultants and companies.

[16] Except in cases where the economy sale enters into consideration, mostly in the West.

[17] Sold, for instance, in Romania, on the free market at competitive prices and good profit margins.

[18] The competition in diagnostics is stronger and in creasing.

10. UNIDO could assist the governments in understanding and reorganizing the manufacture of vaccines and sera for human and veterinary use, as well as blood products [19], to streamline their operations, reduce redundant personnel, ameliorate the manufacturing and product mix, control the costs, improve efficiency and profitability. If at all possible, manufacture of some selected pharmaceuticals could be also combined, like in "HUMAN" in Hungary, which might further improve the income picture.

11. UNIDO could assist the local manufacturers by serving as coordinator for their efforts to export to the republics of the ex-Soviet Union. While these markets are in practical need for everything, the manufacturers complain that they don't have the right connections and information and have difficulties in approaching and selling.

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[19] In many cases, these products are considered strategic for the country and the possibilities for involvement and reorganization might be difficult.

List of people met

Hungary

Dr. Lajos Aradi, Managing Director, *HUMAN*

Prof. Dr. Zsolt Nagy, Scientific Director, *HUMAN*

Czech Republic

Dipl. Ing. Jiri Jansa, General Director, *SEVAC*

Dr. Miroslav Reinhardt, Export & Marketing Manager, *SEVAC*

Dipl. Ing. Eva Konakova, Production and Research Director, SEVAC

Russian Federation

Prof. Dr. Sergey Drozdov, Member of the Medical Academy, Director of the Poliomyelitis Institute, Moscow

Prof. Dr. Vassily Lashkevitch, Ass. Member of the Medical Academy, Deputy Director of the Poliomyelitis Institute, Moscow

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Dr. Stanislava Popova, Head Department of Disease Prevention and Control, Ministry of Health, Sofia

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   - Institute Cantacuzino, Bucharest;
   - National Centre of Infections and Parasitic Diseases, Sofia.

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   Romania
   Czech Republic
   Poland
   Bulgaria.

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SmithKline Beecham Biologicals

by Mr. W. Vandersmissen

THE VACCINE INDUSTRY IN THE 80's

- COMMODITY PRODUCTS - OLD VACCINES
- DISAPPEARANCE OF MANY PLAYERS
- GMP/SAFETY ISSUES HAVE INCREASED
- WITHDRAWAL OF PRODUCTS FOR SAFETY
- TECHNOLOGICAL REVOLUTION
  - A FEW PLAYERS
  - HIGH R&D INVESTMENT
- VOLUMES SHIFT FROM DEVELOPED TO DEVELOPING WORLD

THE 90's AND YEAR 2000

- FULL REVOLUTION OF PRODUCTS
  - NEW VACCINES HIB/HEP.B, A
  - OLD PRODUCTS OUTDATED
    - OPV/IPV
    - DTP_W/DTP_A
    - CHOLERA
    - SALMONELLA
    - BCG ?
  - COMBINATION PRODUCTS
- VALUE OF PREVENTATIVE MEDICINE VERSUS THERAPEUTIC
- HOPE OF THERAPEUTIC VACCINES AGAINST SOME CHRONIC VIRAL DISEASES

THE VACCINE INDUSTRY - ITS SPECIFICITY

- MARKET
  - 10 MIO CHILDREN IN DEVELOPED WORLD
  - 120 MIO CHILDREN IN DEVELOPING WORLD
- R&D DOMINATED BY NEW TECHNOLOGIES
  - HIB
  - HEP.B
  - FUTURE RECOMBINANT PRODUCTS
  - DELIVERY
- R&D INVESTMENT
  - HIGH RISK
  - 100-200 MIO $/VACCINE
- POOR PERCEPTION OF VACCINATION
- COST BENEFIT - VALUE OF VACCINATION
- A FEW PLAYERS/RATIONALISATION COMPLETED

THE VACCINE INDUSTRY - OBJECTIVES

- SCIENTIFIC PROGRESS
- PROMOTE HEALTHCARE PROGRESS BY VACCINATION
- EDUCATION
- COST BENEFIT
- SUSTAIN R&D EFFORT THROUGH REASONABLE RETRIBUTION OF SHAREHOLDERS
- RESOLVE DUALITY OF PRICING
- NOT GENERATE "DOUBLE STANDARDS"
- REACH ECONOMY OF SCALE PARTICULARLY AT BULK LEVEL

THE INDUSTRY PARTNERSHIP

1. DEVELOP SAFER, MORE CONVENIENT VACCINES

2. ADDRESS IMPORTANT DISEASE PROBLEMS

   - MALARIA
   - AIDS

3. FIND SOME PARTNERSHIP FOR INTERNATIONAL, MULTICENTER STUDY WORK :
   - SERO-EPIDEMIOLOGY
   - CLINICAL EVALUATION

4. FULL SUPPORT OF MEASURES THAT CONTRIBUTE TO STATE OF THE ART REGULATORY AND QC ASSESSMENT.

5. FIND SOME PARTNERSHIP FOR SECONDARY OPERATIONS

   - IF ECONOMICAL SENSE
   - IF TECHNOLOGY UP-TO-DATE

EVM POSITION PAPER
TRANSFER OF TECHNOLOGY (TOT)
June 1993

1. *Introductory comments*

TOT must be governed by economic/industrial motives; the objective being to facilitate availability of vaccines for the world, without significantly increasing the cost to the world community. It may be acceptable to deal with a certain (marginal) increase in costs, if this incremental allows for employment and added value in a developing nation, and does not cause a drain of hard currency.

Limitation of TOT to downstream operations for liquid vaccines is probably the most readily available solution that contributes to sharing work between partners in the developed and the developing nations.

2. *Technical issues*

TOT must seek to optimise use of existing facilities to avoid the need for extensive capital investment; in the current state of affairs, this means that the manufacture of bulk vaccine must be maintained and, if needed, qualitatively improved in existing vaccine plants, and that TOT between entities in developed nations and in developing countries should pragmatically be restricted to downstream operations such as formulation, filling and packaging; these activities must be considered, for the purpose of this position paper, to be the definition of TOT. Developing nations will thus contribute relatively less for what concerns production of most viral vaccines, but should strive to produce more and better bacterial vaccines. This is of particular importance for DPT vaccine, which is now increasingly considered to be the backbone of future combined vaccines.

A fundamental rule of efficient vaccine manufacturing is utmost use of economy of scale: creation of too many and too small units, even for downstream filling and packaging units, must be discouraged. Though it is not easy to define the minimum size of a unit that will make for economic production (there are too many uncontrollable variables such as local productivity and working conditions, degree of automation, etc.), it is safe to predict that only the largest countries in the world will provide an internal market of sufficient dimensions to warrant the exercise. Indeed, if one considers the vaccine needs for a population of one million newborns and babies, receiving each four or five doses of polio, one dose of BCG, four doses of DTP, two doses of measles, or twelve doses, all vaccines confounded, and a waste factor of 100%, then 24 million doses are required yearly. Assuming all of this vaccine is filled in 20 dose vials, 1.2 million vials must be processed. At eight hours a day, with machinery capable of handling 6.000 vials per hour (a machine speed that is nothing out of the ordinary), this makes for 25 days of work.

Vaccines requiring freeze-drying are a particular problem: the equipment is costly and

requires specific a-lay-out of the production facility; productivity is not-so-evident if used without tutorship, and know-how acquired by training is not easily transferable from one type of strain to another without affecting potency and post-freeze-drying titre (and thus critical features of the product such as immunogenicity, stability and shelf life).

TOT will almost always require upgrading of local filling facilities to acceptable and reliable GMP conditions to ensure availability of suitable sterile production areas, implementation of rigorously controlled flows of materials and staff, laminar flow hoods, heat-ventilation-air-conditioning systems (HVAC), quality of water in the washing/filling area, training of staff, quality assurance, etc. It will generally be preferable to erect new, purpose built facilities, operated within an existing entity, and thus able to draw on available local expertise of qualified staff, than to try to adapt existing buildings. The constraints caused by the lay-out or structure of an existing building, or its utilities, are likely to lead to costly complications for a less than desirable result, and probably at little savings, if any. On the other hand, a "greenfield site" is not desirable either, because it will not benefit from integration in an experienced, "biologicals-minded" environment.

QC operations, who preside over controls, from raw materials to end product and batch release, must be afforded with well-trained staff and an independent management. In many a developing country, it is the same organisation that carries out production and control, and caution is heeded to avoid an "incestuous" relation between the two functions.

Training and/or scholarship requirements for local staff must be carefully addressed. Private companies in developed nations do not have unlimited resources available to handle such training. Hence, trainees must be selected in relatively small numbers; apart from indispensable western language skills, they must be sufficiently experienced to rapidly benefit from the training, and they must be the managers who will be directly responsible for the local operations, as they will have to carry on the training to the personnel of the local entity. The governing principle is to be that "Train the trainers".

3. Economic/industrial issues

To rely on export markets to justify the capital investment required, and to make up for the lack of size of the internal market, may prove to be very elusive: export markets will be fiercely competitive.

Capital investment is only part of the equation. Much thought must be given to issues that will determine the long term sustainability of the operation, and this is not a matter of hardware, but of industrial, financial and economic policy, and of training and keeping qualified staff. Brain drain is a reality. Financial upheaval causes budget cuts. Maintenance problems, inclusive of access to spare parts (that may be difficult/impossible to import without hindrances) are deleterious.

The long term economic viability of a government owned production facility that has to sell exclusively (or in vast majority) to its owner must be closely considered. Under such monophonic terms, will a reasonable profit be allowed, or will an uncompetitive but subsidised

production units result? A satisfactory answer will be required, particularly if the owner of the production unit seeks to attract other investors as joint venture partners.

Because of competitive situation of established vaccine manufacturers in the developed nations, willingness to share strains, core know-how, etc. for production is dwindling: access to such know-how is unlikely to be free of charge or free of other obligations (royalties or other charges, distribution limitations, export prohibitions, etc.).

4. Legal issues

TOT must be managed in well controlled bilateral agreements that spell out all of the rights and duties of the contracting parties; inclusive of the increasingly complex industrial property rights that frequently involve more parties than the two main contracting parties. This may be a very controversial topic in developing nations where opposition to implementation of industrial property rights is a fact of life.

Confidentiality issues must be addressed. As it is unlikely all training will be performed in only one western company, since the speciality fields of these companies may differ, trainees could potentially go from one trainingship with one company to another in the premises of a competitor. Confidentiality obligations between recipients of technology in developing countries, once they have been trained, can conflict with "solidarity" feelings between developing nations.

As most vaccine production units in developing nations are government entities, one cannot totally dismiss concern about the enforceability of contractual obligations, and the power that local governments may wield to obtain satisfaction on contentious items.

TRANSFER OF TECHNOLOGY

EVM POSITION PAPER
SUMMARY

- Governed by economic and industrial principles

- Limit to downstream operations

- Economy of scale

- No greenfield site

- Availability of independent QC

- Training requirements

- Economic sustainability in an open market

- Clear understanding of liabilities & intellectual property issues

- Fairness in legal dealings

SALE OF BULK VACCINE

EVM POSITION PAPER
SUMMARY

- Price of bulk vaccine

- To purchase bulk vaccine is to use know-how

- Understanding of liability issues
    - quality of the final product
    - control over the quality of the final product

- Understanding of legal issues
    - reputation of the parties

- Understanding of commercial rights

- Combinations not allowed

- Specifications: all components to be considered

- Bulk "ready to fill"

- Commercial policy

- QC capabilities

TRANSFER OF TECHNOLOGY

RECENT DEVELOPMENTS AT U.N. AGENCIES (WHO, UNDP, World Bank)

Countries have been classified according to GNP, population in a grid:

horizontal axis: small ⇒ large
vertical axis: poor ⇒ rich

General philosophy: moving from lower left to upper right, countries should increasingly be self sufficient for

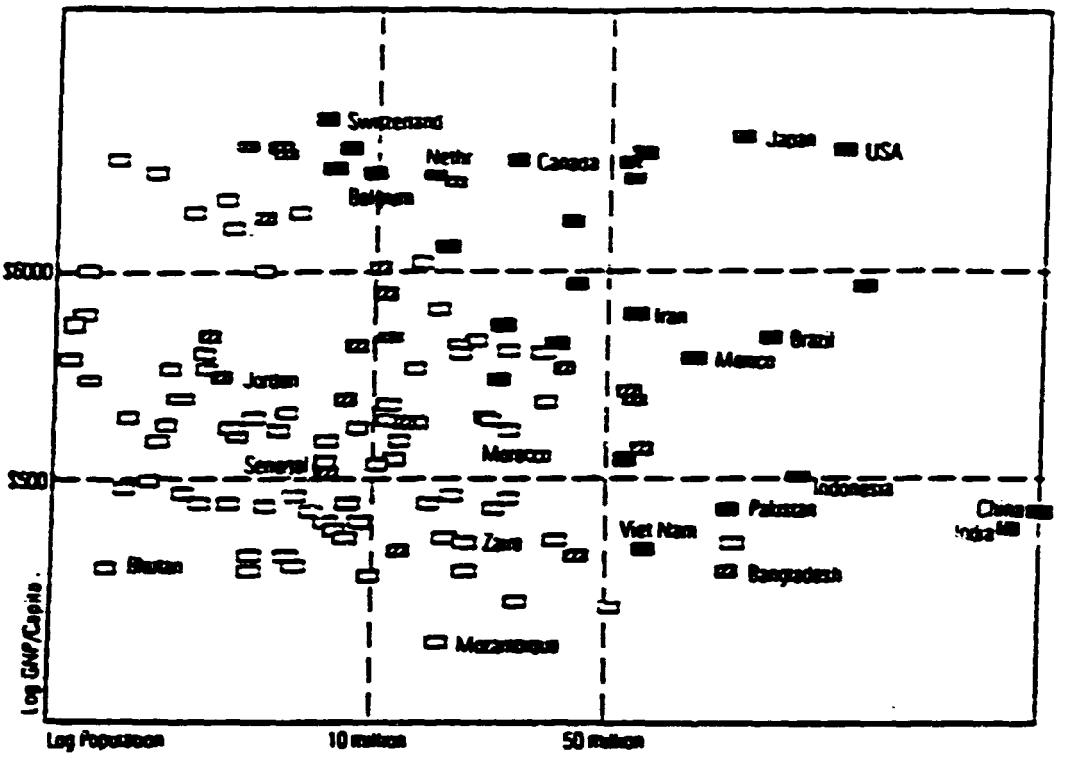
procurement

manufacture

financing of vaccines

FIGURE 1

VACCINE SUPPLY GRID



Guide to Donor Aid

Independent	Independent	Independent
Procurement Services Provide supportive services re: – Procurement – Management – Financing	**Procurement/ Production-Sharing Services** – Evaluate feasibility of production sharing – Provide supportive procurement service	**Production Services** – Strengthen/expand production as necessary – Strengthen quality assurance
Financing – Continue support – Encourage vaccine allocation in national budget	**Financing for Procurement/ Production Sharing** – Continue support – Encourage vaccine allocation in national budget	**Financing for Production** – Continue support – Evaluate feasibility of production/ production sharing – Strengthen/expand production as necessary – Strengthen quality assurance

This grid shows the positions of 130 countries (of which only a few are named), differing in wealth (per capita GNP according to the UNICEF *State of the World's Children 1991*, with cut-off points based on the World Bank GNP per capita income groups for 1991) and population size (with cut-off points based on, among other things, past experience of the market size needed to support a local vaccine industry). Countries that produce vaccines locally are shaded, either in black for those that produce viral vaccines such as polio and measles, or hatched, for those that produce bacterial vaccines such as tetanus toxoid and DTP. Those that have no vaccine manufacturing capability are blank.

TRANSFER OF TECHNOLOGY

RECENT DEVELOPMENTS AT U.N. AGENCIES (WHO, UNDP, World Bank)

Countries selected for "increased self sufficiency"

Country	*Population (million)*	*New-borns (million)*
Bangladesh	119	4.51
Brazil	153	3.67
China	1135	24.59
Egypt	55	1.74
India	850	25.65
Indonesia	188	5.10
Iran	58	2.44
Mexico	88	2.46
Pakistan	116	5.04
Philippines	63	1.98
Russia	149	<2.00
South Africa	36	1.24
Thailand	57	1.17
Vietnam	68	2.04
Turkey	58	1.63
North Korea	22	0.53

TRANSFER OF TECHNOLOGY

Vaccine requirements per million new-borns

Type of vaccine	*number of doses*
DTP	3 - 5
BCG	1
Measles	1 - 2
Polio	3 - 5
Hepatitis B	3
Total	**11 - 16**

Taking the "high" total, and a wastage factor of 50%, some **24 million doses** are required.

These vaccines are usually taken in 10 or 20 dose vials. Assuming 50% goes in vials of 10, and 50% goes in vials of 20 doses, this means 1.2 million vials of 10 doses, and 0.6 million vials of 20 doses need to be filled, a total of **1.8 million vials.**

Working in shifts of 8 hours, with a small, relatively low speed filling line handling 6,000 vials per hour, **48,000 vials are processed per day.**

Total occupation of the filling plant thus is:

$$\frac{1{,}800{,}000}{48{,}000} = \textbf{37.5 days}$$

If running 200 days, the plant could deliver

200 x 48.0 = 9.6 vials

i. e., at the wastage rates described above, the needs of:

$$\frac{\textbf{9.6}}{\textbf{1.8}} = \textbf{5.3 million newborns.}$$

TRANSFER OF TECHNOLOGY

CONCLUSIONS

World-wide pharmaceutical industry experiences a pressing need to concentrate and rationalise, making full use of "economy of scale".

Significant pressure has been brought to bear on the vaccine industry:

- companies have left the field
- acquisitions

strategic alliances or joint ventures

Industrial vaccine production is only sustainable:

- if output is sufficient in terms of volume,
- if a sufficient part of that volume is sold a attractive terms

Caution: to create too many and too small vaccine manufacturing units is not cost-efficient.

Financial Overview of a Typical Filling Plant

Vaccines:	QTY MM Doses (1)	Price/D in $ (2)	Sales (M$) (3)=(1)+(2)	Manuf. CGS % Sales (4)	Outside Royalties % Sales (5)	Know-How % Sales (6)	Total CGS in MM$ (8)=(4)+(5)+(6)
DPT	5.0	0.10	0.50	80.0%	0.0%	0.0%	0.40
DT	1.0	0.07	0.07	80.0%	0.0%	0.0%	0.06
dT	1.0	0.10	0.10	80.0%	0.0%	0.0%	0.08
T	5.0	0.05	0.23	70.0%	0.0%	0.0%	0.16
OPV	5.0	0.08	0.42	70.0%	0.0%	0.0%	0.29
HBV	3.0	1.50	4.50	80.0%	5.0%	0.0%	3.83
MEASLES	1.0	0.16	0.16	80.0%	0.0%	0.0%	0.13
RUBELLA	0.5	0.31	0.16	80.0%	0.0%	0.0%	0.12
BCG	1.0	0.11	0.11	60.0%	0.0%	0.0%	0.07
MMR	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
			6.25				5.13
Price Surplus :			0.0%				

B. PRICE INCREASE 5.0%
CGS INCREASE 3.0%

C Operational Costs 15.0%

D. Investment in $ 28.6

Year	%	INV.
1994	33%	9.4
1995	33%	9.4
1996	34%	9.7
1997	0%	0.0
1998	0%	0.0
1999	0%	0.0
2000	0%	0.0
2001	0%	0.0
2002	0%	0.0
2003	0%	0.0
	100%	28.6

Note: 1 $ = 35 BF

FINANCIAL OVERVIEW OF A TYPICAL FILLING PLANT

(US$ MM)

	X	X+1	X+2	X+3	X+4	X+5	X+6	X+7	X+8	X+9
Net Sales	0.0	0.0	6.2	6.6	6.9	7.2	7.6	8.0	8.4	8.8
CGS	0.0	0.0	5.1	5.3	5.4	5.6	5.8	6.0	6.1	6.3
Inv. Depreciation	0.4	1.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
Gross Profit	**-0.4**	**-1.4**	**-1.5**	**-1.4**	**-1.2**	**-1.0**	**-0.8**	**-0.6**	**-0.4**	**-0.1**
			-24.2%	**-20.6%**	**-17.2%**	**-13.9%**	**-10.7%**	**-7.6%**	**-4.6%**	**-1.7%**
Operational Costs	0.0	0.0	0.9	1.0	1.0	1.1	1.1	1.2	1.3	1.3
Trading Profit	**-0.4**	**-1.4**	**-2.4**	**-2.3**	**-2.2**	**-2.1**	**-1.9**	**-1.8**	**-1.6**	**-1.5**
Investment	-9.4	-9.4	-9.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Incremental Working capital	0.8	0.0	-2.7	-0.9	-0.1	-0.1	-0.1	-0.1	-0.1	-
Cash Flow:	**-9.0**	**-10.8**	**-14.9**	**-3.3**	**-2.3**	**-2.2**	**-2.1**	**-1.9**	**-1.8**	**-1.6**
Cumulative Cash Flow:	**-9.0**	**-19.8**	**-25.7**	**-18.1**	**-5.6**	**-4.5**	**-4.3**	**-4.0**	**-3.7**	**-3.4**

I.R.R.: ERR

NPV (15%): -32.1

Financial Overview of a Typical Filling Plant

Vaccines	QTY MM Doses (1)	Price/D in $ (2)	Sales (M$) (3)=(1)+(2)	Manuf. CGS % Sales (4)	Outside Royalties % Sales (5)	Know-How % Sales (6)	Total CGS in MM$ (8)=(4)+(5)+(6)
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DT	1.0	0.07	0.07	80.0%	0.0%	0.0%	0.06
dT	1.0	0.10	0.10	80.0%	0.0%	0.0%	0.08
T	5.0	0.05	0.23	70.0%	0.0%	0.0%	0.16
OPV	5.0	0.08	0.42	70.0%	0.0%	0.0%	0.29
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RUBELLA	0.5	0.31	0.16	80.0%	0.0%	0.0%	0.12
BCG	1.0	0.11	0.11	60.0%	0.0%	0.0%	0.07
MMR	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
	0.0	0	0.00	0.0%	0.0%	0.0%	0.00
			18.74				5.13
Price Surplus			200.0%				

B. PRICE INCREASE 5.0%
CGS INCREASE 3.0%

C. Operational Costs 15.0%

D. Investment in $ 28.6

Year	%	INV.
1994	33%	9.4
1995	33%	9.4
1996	34%	9.7
1997	0%	0.0
1998	0%	0.0
1999	0%	0.0
2000	0%	0.0
2001	0%	0.0
2002	0%	0.0
2003	0%	0.0
	100%	28.6

Note: 1 $ = 35 BF

FINANCIAL OVERVIEW OF A TYPICAL FILLING PLANT
(US$ MM)

	X	X+1	X+2	X+3	X+4	X+5	X+6	X+7	X+8	X+9
Net Sales	0.0	0.0	18.7	19.7	20.7	21.7	22.8	23.9	25.1	26.4
CGS	0.0	0.0	5.1	5.3	5.4	5.6	5.8	6.0	6.1	6.3
Inv. Depreciation	0.4	1.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
Gross Profit	**-0.4**	**-1.4**	**11.0** **58.6%**	**11.8** **59.8%**	**12.6** **60.9%**	**13.5** **62.0%**	**14.4** **63.1%**	**15.3** **64.1%**	**16.4** **65.1%**	**17.4** **66.1%**
Operational Costs	0.0	0.0	2.8	3.0	3.1	3.3	3.4	3.6	3.8	4.0
Trading Profit	**-0.4**	**-1.4**	**8.2**	**8.8**	**9.5**	**10.2**	**11.0**	**11.8**	**12.6**	**13.5**
Investment	-9.4	-9.4	-9.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Incremental Working capital	0.8	0.0	-5.8	-1.1	-0.3	-0.3	-0.3	-0.3	-0.3	-0.3
Cash Flow:	**-9.0**	**-10.8**	**-7.4**	**7.7**	**9.2**	**9.9**	**10.6**	**11.4**	**12.2**	**13.1**
Cumulative Cash Flow:	**-9.0**	**-19.8**	**-18.2**	**0.4**	**16.9**	**19.1**	**20.6**	**22.1**	**23.7**	**25.4**

I.R.R.: 22.0%
NPV (15%): 6.9

REPORT ON IMMUNIZATION PROGRAMME OF THE PEOPLE'S REPUBLIC OF CHINA

by Dr. Su Wan Nian, Deputy Director
National Vaccine and Serum Institute

China is situated to the east of Asian continent and west to the Pacific. The country has a total area of 9.6 million square kms, of which 2/3 are mountains, areas plateaus or highlands.

China is administratively divided into 31 provinces, autonomous regions and municipalities (including Taiwan). These are further divided into 334 prefectures, 2,831 counties (urban districts), 58,000 townships and finally divided into 766,500 villages (residence committees).

The total population of China is 1.20 billion with 80% in rural areas. The provincial population ranges from 2 million in the sparsely populated province to over 100 million in the most densely populated one.

The annual number of births is around 21 million. The population of children under the age of 7 is 150 million or 14.2% of the national total. The birth rate is around 21/1000. Death rate is 6.65/1000 with a natural growth rate of 14.39/1000. The average life expectancy is around 71 years.

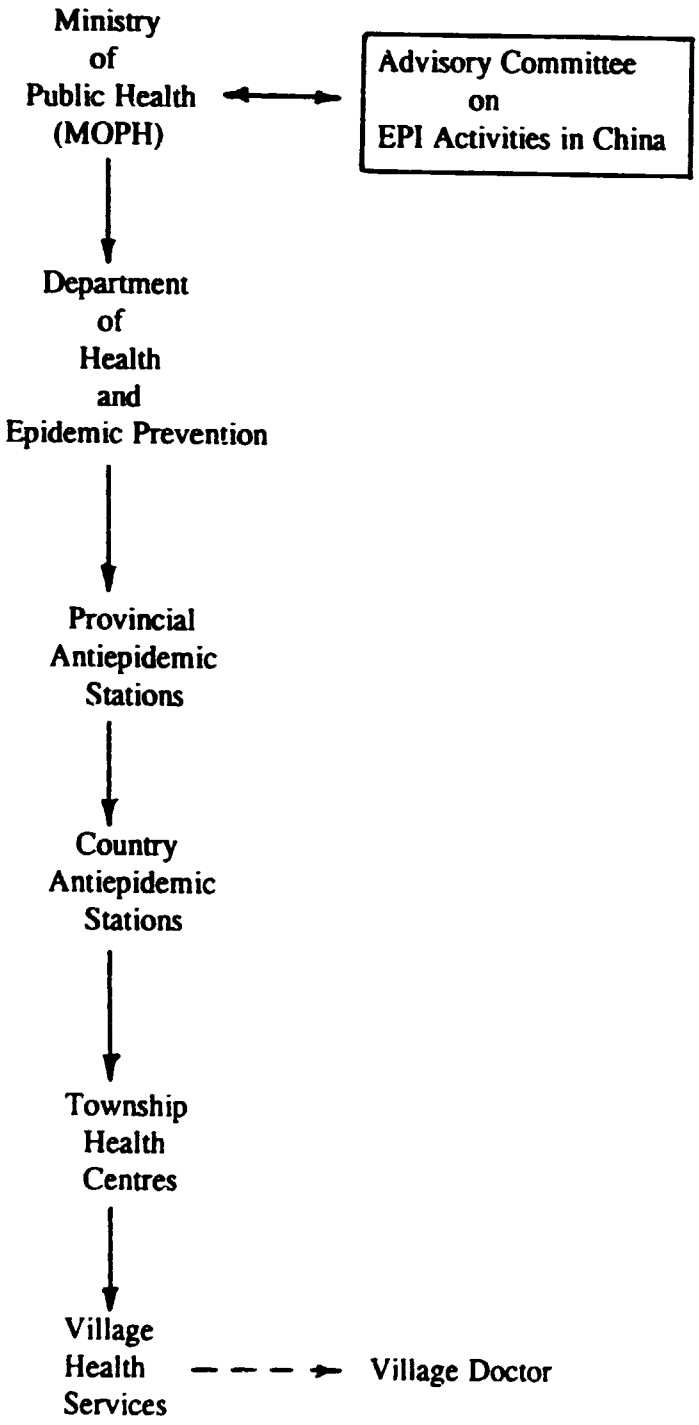
Population of China
(000's)

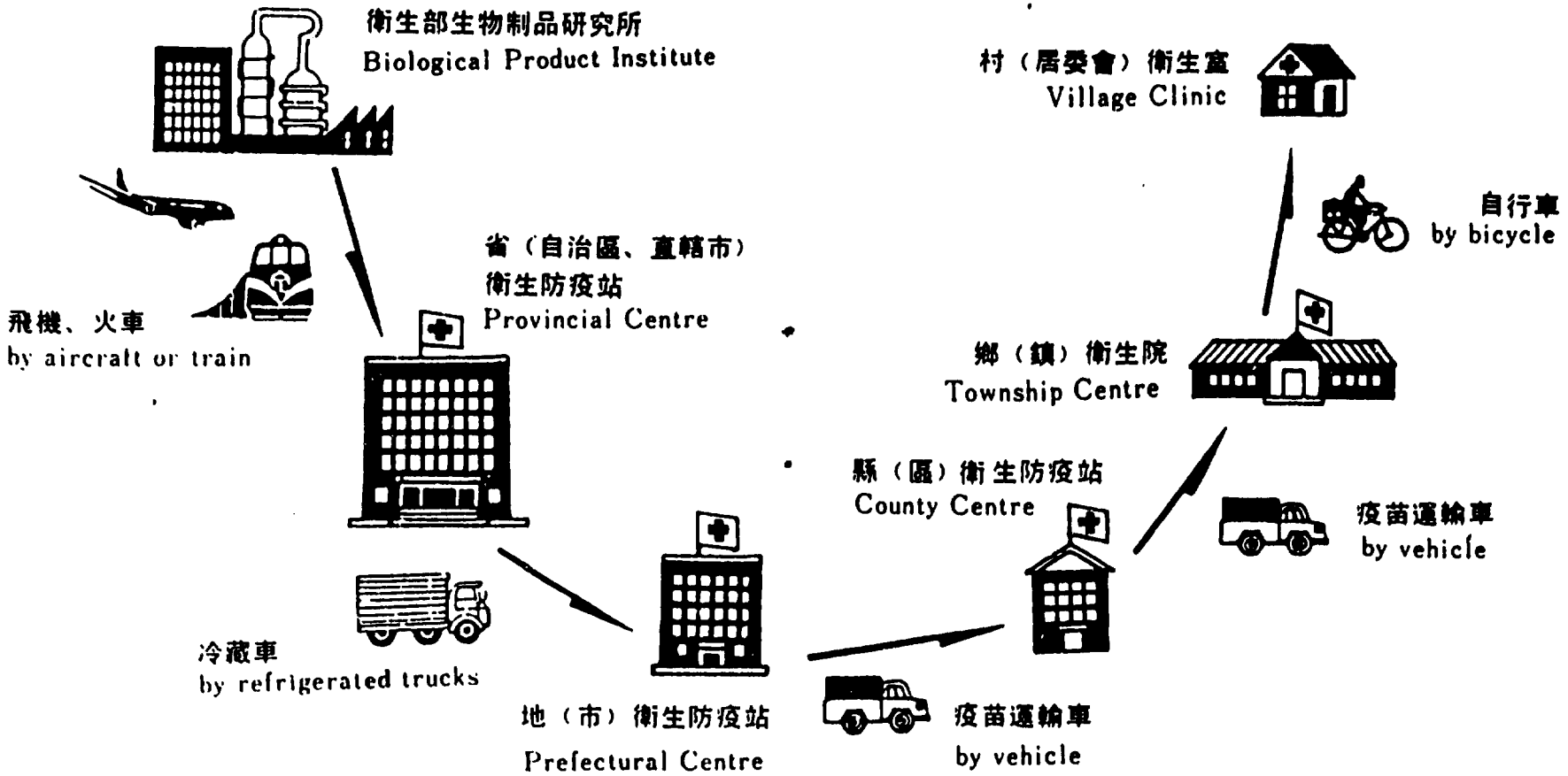
1990	1991	1992	1993	1994	1995
1,155,305	1,170,052	1,183,617	1,196,360	1,208,841	1,221,462

Number of Newborns in China
(000's)

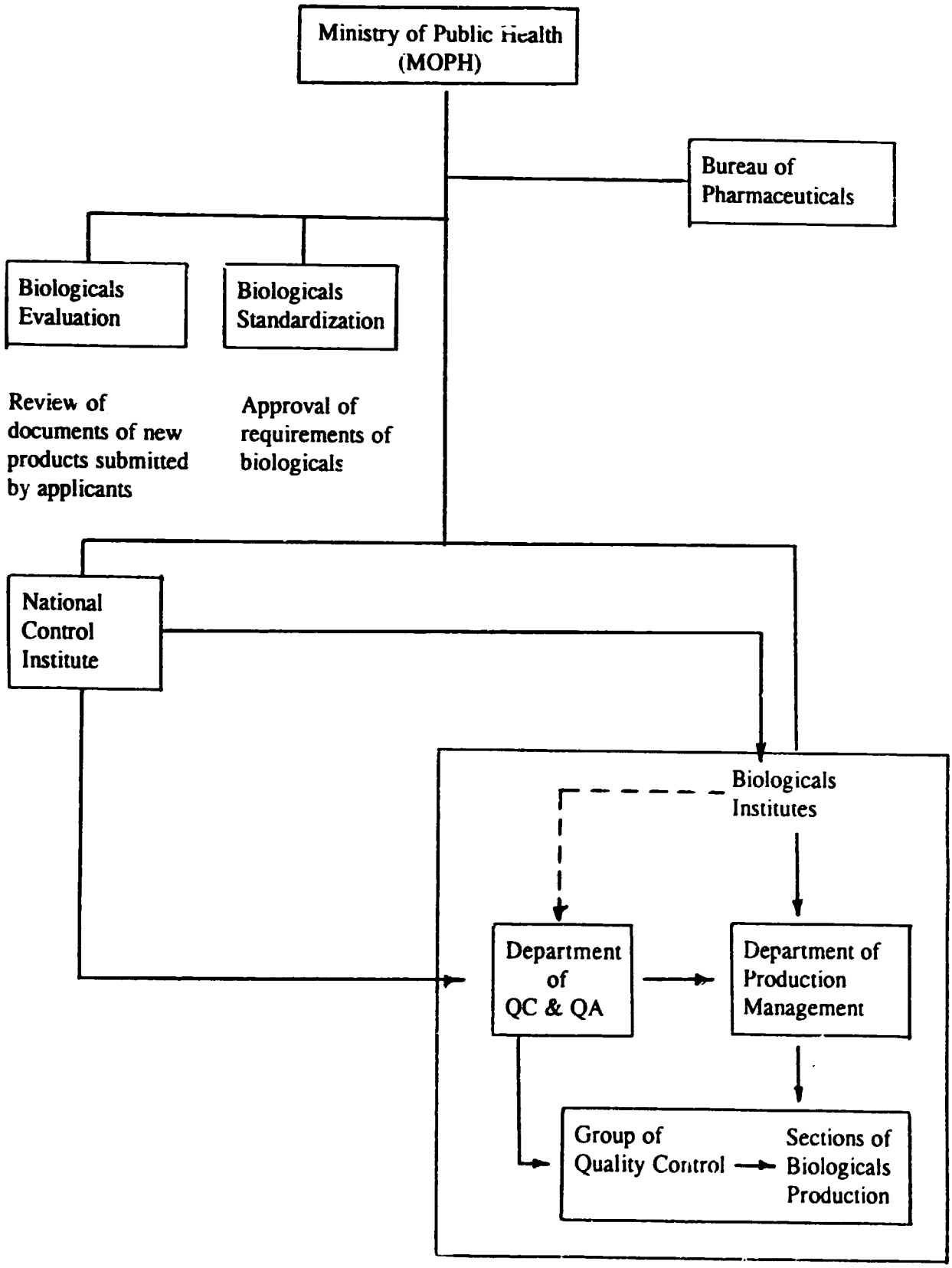
1990	1991	1992	1993	1994	1995
23,644	22,660	21,899	21,510	21,513	21,726

NETWORK OF EPI ACTIVITY




衛生部生物制品研究所
Biological Product Institute
飛機、火車
by aircraft or train
省（自治區、直轄市）
衛生防疫站
Provincial Centre
冷藏車
by refrigerated trucks
地（市）衛生防疫站
Prefectural Centre
縣（區）衛生防疫站
County Centre
疫苗運輸車
by vehicle
鄉（鎮）衛生院
Township Centre
自行車
by bicycle
村（居委會）衛生室
Village Clinic
疫苗運輸車
by vehicle

Scheme of Mechanism for Quality Control and Quality Assurance of Biologicals in China



Estimated immunization coverage with BCG, DPT, poliomyelitis, measles, Hepatitis B and tetanus vaccines based on data available as of March 1995

Country Developing countries ranked by surviving infants.	Surviving infants (millions)	Cumulative percentage of surviving infants	Immunization coverage (%)					
			Surviving infants					Pregnant women
			BCG	DPT 3	Polio 3	Measles*	HBV 3	TT 2+
1 India (94)	23.98	21	97	93	94	89	...	83
2 China (92 & 93)	20.59	39	93	95	95	94	...	2
3 Pakistan (94)	4.93	44	76	65	81	64	...	42
4 Indonesia (93)	4.41	49	94	89	93	93	14	67
5 Nigeria (93)	4.39	51	40	29	29	34	...	33
6 Brazil (7&94)	3.81	55	72	72	93	59	...	62
7 Bangladesh (93 & 94S)	3.66	58	95	74	92	71	...	73
8 Ethiopia (93)	2.23	60	46	28	28	22	...	12
9 Mexico (7&94)	2.19	62	98	91	92	90	...	42
10 Iran (94)	2.16	64	100	99	99	96	15	50
11 Viet Nam (93)	2.10	66	94	91	91	93	...	71
12 Philippines (93)	1.88	67	90	88	89	88	...	70
13 Zaire (93)	1.78	69	43	29	29	33	...	25
14 Egypt (94)	1.62	70	98	93	93	92	91	65
15 Turkey (92 & 93)	1.51	72	68	76	76	72	...	20
16 Myanmar (93S)	1.33	73	96	64	41	44	...	66
17 South Africa (93)	1.17	74	68	81	81	77	...	26
18 Tanzania (93S)	1.10	75	97	70	70	68	...	44
19 Kenya (94S)	1.09	76	95	86	86	81	...	72
20 Thailand (93S)	1.05	77	98	92	92	71	57	86
21 Sudan (93)	0.98	78	61	51	51	49	...	...
22 Uganda (93)	0.92	78	100	73	74	73	...	83
23 Colombia (9&93)	0.83	79	94	83	85	94	...	14
24 Afghanistan (93&94)	0.76	80	44	18	18	40	...	6
25 Nepal (93)	0.74	81	78	68	69	61	...	13
25 countries	91.20	81	87	81	84	79	3	47
Other developing countries	22.06	19	79	67	68	68	9	39
Total developing countries	113.26	100	85	79	81	77	4	46
Total industrialized countries	10.37		85	88	84	81	6	...
Eastern Europe	5.23		88	76	81	87	12	
Global Total	128.87		85	79	81	78	4	46

(7) 1987 reported data
(92) 1992 reported data
(93) 1993 reported data

(S) Nationwide survey data
+ Boosters included
* Up to 2 years of age
... no information available

Schedule for vaccination in China

Age	Vaccines
0	BCG
2M	TOPV1
3M	TOPV2, DPT1
4M	TOPV3, DPT2
5M	DPT3
8M	MV
1.5 - 2Y	DPT
4Y	TOPV
7Y	BCG, MV, DPT
12Y	BCG (Countryside)

Reported Annual Incidence of Diphtheria
1974 to 1994

1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984
25,859	38,246	23,968	30,721	20,084	16,921	9,767	8,481	6,502	7,227	3,418
1985	**1986**	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**	
1,423	787	427	267	343	421	231	146	124		

Reported Annual Incidence of Pertussis
1974 to 1994

1974	1975	1976	1977	1978	1979	1980
1,694,350	1,814,134	1,339,710	1,454,477	1,202,922	736,155	613,648
1981	**1982**	**1983**	**1984**	**1985**	**1986**	**1987**
510,601	422,280	331,419	215,965	147,298	83,979	59,543
1988	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**
32,937	26,985	20,015	10,679	11,182	9,190	

Reported Annual Incidence of Poliomyelitis
1974 to 1994

1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984
11,070	7,815	4,625	7,413	10,408	5,472	7,442	9,625	7,741	3,296	1,626

1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
1,537	1,844	969	667	4,623	5,065	1,926	1,191	538	158

Reported Annual Incidence of Measles
1974 to 1994

1974	1975	1976	1977	1978	1979	1980
3,276,531	2,553,084	2,558,995	2,640,161	2,377,776	1,717,031	1,122,285

1981	1982	1983	1984	1985	1986	1987
1,010,755	892,870	781,475	691,709	418,159	198,738	104,925

1988	1989	1990	1991	1992	1993	1994
96,994	85,049	85,705	123,428	140,048	117,851	

Table 1 : The Coverage Target of HBV

	Coverage %		
Area	1992	1993	1994
Newborn City (Urban)	60	85	>85
Town	40	60	>85
Rich Counties		40	>60
Ordinary Counties			>40
Poor Counties	start to use HBV		
Pre-school City	40	60	>85
Children <7 years of age			

Table 2: The Efficacy of HBV after vaccination

Name of Cities	Carrier rate before vaccination	Carrier rate after vaccination
Harbin	11.30% 1979	1.95% [a] 1989 (<3 years of age)
Xiangtan	19.30%	0.65% (<4 years of age)
Shanghai, Guangdong Hunan and Hebei Province 2 million population 30,000 Newborn immunized	18.62%	1.53% [b]
Longan (Guangxi Province)	12.40%	1.2 - 1.7%

(a) Began to immunized in 1986
(b) Began to immunized in 1986

Table 3: The Immunization Coverage of HB in Parts of Provinces and Cities in 1992

Provinces or cities	Coverage (%) in Newborns		Pre-school children
	Urban	Rural	
Beijing	95.3	95.0	81.5 - 54.9
Shanghai	95.6	85.3	64.2
Tianjin	90.8	50-54	-
Zhejiang	80-95	50-90	-
Jiangsu	62.2 - 69.2	-	-
Shandong	>80	-	-
Anhui	70-83.9	29.4	-
Jiangxi	25.5*	-	-
Jilin	91.2	86.1	71.7 - 90.1
Heilongjiang	45.7 - 75.5	-	6.4
Hebei	40.8 - 75.2	-	73.7
Neimenggu	72.0*	-	-
Shanxi	61	14.7	9.4 - 33
Hubei	15*	-	-
Hunan	91.3	-	-
Sichuan	<60	<20	-
Guangxi	45.4 - 90.5	-	22.1 - 39.1
Qinghai	39.4	-	35.7

* Average of Urban and Rural Area

Table 4: The Efficacy of HB Vaccine

Name of Cities	Carrier rate before vaccination	Carrier rate after vaccination
Harbin	11.30% 1979	1.95% * 1989 (<3 years of age)
Xiangtan	19.30%	0.65% (<4 years of age)
Shanghai, Guangdong, Hunan and Hebei Province 2 million population 30,000 Newborn immunized per year	18.62%	1.53% (<4 years of age)
Longan (Guangxi Province)	12.40%	1.2 - 1.7%

* start immunization

VACCINATION PROGRAMME IN ROMANIA

by Dr. Mircea Musset, President, Bioassistance, France

UNIDO more than ever appears as a very useful institution monitoring relationship between industrialized and developing countries.

Therefore, the involvement of UNIDO in the field of training and technology transfer for the setting up of National Control Laboratories is wished to be reinforced.

The author represented in this meeting three humanitarian Associations: "Bioassistance" from France of which he is the President and "Carol Davila" Foundation and "Bioasistenta" Association from Romania.

For the last four years with the Merieux Foundation, the Rotary International Polio Plus, the International Centre for Children in Paris or, the Centres for Disease Control in Atlanta, the author was periodically taking part in training courses in vaccinology and epidemiology organized for physicians and epidemiologists involved in the vaccination programme in Romania and Republic of Moldova.

The Budapest meeting showed difficulty to find a solution to satisfy all the participants.

* First of all one can see two categories of participants : customer countries and private producers.
* Then, 2 sizes of country: small and big ones.
* The countries can also be divided according to their level of industrial development.
* Finally, one category of countries has a long tradition in bacteriology and vaccine production, even if today they are not at the top of the modern technology.

The author thinks that the work of UNIDO to globalize the solution for all the participants is very difficult, if not impossible.

He personally believes that the recommendation to stop the national vaccine production should not be given to any country.

Vaccine production is first of all a strategic industry and also a technology which brings to the corresponding country the necessary know-how for the scientific development of the country.

The East Europe or Asian countries which remained several years isolated from other countries need to be informed of the recent scientific progress achieved in the industrialized countries.

For that, the United Nations and international organizations like WHO and UNIDO have mobilized their experts and try to find solutions.

Thus it seems to be reasonable that the international companies producing vaccines will sign agreements with large countries to produce the necessary vaccines and that the idea formulated by Dr. Charles Merieux to create a special structure in the frame of UNIDO to promote regional vaccine manufacture in developing countries could be a possible issue.

The development of such a system should be preceded by professional recycling training in prevention and modernisation of laboratories for diagnostic and controls which will at the same time serve as reference units.

UNIDO should organize training courses in production and controls of classic vaccines, developing the notions on Good Manufacturing Practices (GMP) and on Good Laboratory Practices (GLP).

In this case it is no longer the economic factor which comes first but the social and scientific factors.

Professor A. Combiescu, Director of Cantacuzino Institute in Bucharest with whom the author had a phone conversation on that matter, is sharing the same opinion.

CANTACUZINO INSTITUTE, BUCHAREST, ROMANIA

by Prof. A. Combiescu, Director

Organization: Setting-up

The Cantacuzino Institute (CI) from Bucharest, Romania, is the main scientific and technical support to the Ministry of Health for the implementation of prevention programme and control of infectious diseases. Its current status is of extra budgetary public institutions type.

Officially established in 1921 the institute took over the activities of the team headed by Prof. Ioan Cantacuzino since 1901, when he was named Professor of Medicine of the University of Bucharest and has founded the "Laboratory of Experimental Medicine". Besides its scientific activities the institute has started since 1904 the preparation of therapeutic serums, the first of a long list of biological products that the Institute was going to produce.

"The Institute of Serums and Vaccinations Dr. I. Cantacuzino" was installed in 1924 in new premises structured on the model of the Institute Pasteur of Paris.

The Institute has undertaken research in all important fields of microbiology and related sciences while developing production of vaccines, activities for public health, epidemiologic monitoring, university education in microbiology and scientific information.

Key People

People who influenced the history of the institute were:

Prof. I. Cantacuzino, founder of the institute, student of Ilya Metchnikoff, Institute of Pasteur of Paris

Prof. Ionescu Mihaesti (poliomyelite, tuberculosis)

Prof. Mihai Ciuca (malaria)

Prof. Eugenia Soru (enzymology, purification of antitoxicated serums)

Dr. Lidia Mesrobeanu

Prof. D. Combiescu

Prof. Marcela Popovici

Currently, the institute comprises 33 units, of unequal distribution and covering all the functions of the Institute: research, production, public health and education.

Personnel

It has a total of 1190 employees with 213 researchers, 82 technicians and 780 general services. 93 form part of the administrative section and 23 of the technical section. Beside the headquarter of Bucharest, the institute manages two experimental farms for the production and use of animals for laboratory tests (situated near Bucharest), and a branch (with approx. 100 workers) at Iasi.

Main Activities of Cantacuzino Institute

The main activities of the institute are in the fields of : research, production, centre of reference and action for the public health, clinical biology, university education and post graduation.

Research

The main direction in research activity are the following:

- Study of the mechanism of pathology of microbial infections: auto-immune diseases.
- Molecular epidemiology of viral and bacterial infections.
- Study on viral hepatitis and HIV infection in Romania.
- Research and development in the field of production and monitoring of biological products.
- Identification of substances of bacterial vegetal or plasmatic origin with therapeutical properties.
- Environmental monitoring of vectors, insects population and studies of biological and chemical insecticides.

Production

CI is the only producer in Romania for biological products made for prevention, treatment and diagnosis of infectious diseases for human being. Bacterial and viral vaccines and immunomodulation of bacterial origin represent more than half of the production activity (42.5%, respectively 16.9%).

Diagnosis products represent 35% of the production activity. The rest of the production is represented by therapeutical serums, antiallergic and antiinflammatory agents.

Public Health

14 centres of reference covers the fields of bacteriology, virology and medical parasitology. The main activities of these centres are in the diagnosis control, expertise, epidemiological monitoring, emergency mission, and immediate action upon request from the Ministry of Health for conceptual studies and evaluation of public health programmes in the field of prophylaxy of infectious diseases.

Education

The education activity comprises of:

- courses and laboratory training for medical doctors specialist in microbiology;
- upgrading training of short and medium term duration for doctors and biologists;
- course and practical training at university level;
- course and workshops for the training and upgrading of technicians.

At present the CI works as an International Education Centre with the assistance of the EU and the Institute Pasteur of Paris.

Priority Programmes

During the last five years, the delay accumulated over the 25 years by the Cantacuzino Institute in the field of technology, professional and scientific information which has hampered all fields of activities, has been somehow reduced with the assistance of the international community. Most of these actions has been sponsored and coordinated by Institute Pasteur, Paris, specially since CI has joined in 1991 the group of Institutes Pasteur and Associate all over the world. It consists of financial contribution and professional training for about 30 professionals in prestigious institutions in the whole world.

Among the current priorities of the CI are the following programmes:

- The setting up and the acquisition of modern equipment at the Department of Medical Microbiology and Molecular which will make possible the use of efficient methods of microbiologic diagnosis (tuberculosis, hepatitis, salmonellosis, etc.) and the utilization of modern immunologic and molecular technics in the epidemiologic study of bacterial origin and viral of interest for public health in Romania (tuberculosis, cholera, poliovirus, etc.); the professional staff of the department had already undertaken training at the Institute Pasteur, Paris and other advanced institutions.

- Modernization and application of modern technology in the production and monitoring of viral and bacterial vaccines for human being and use of norms such as GMP and GLP.

- Implementation of research contracts with foreign institutions (Institute Pasteur, Paris; Unite INSERM Nr. 354, Paris; University "Tor Vergata", Rome; Institute Pasteur-Merieux, Lyon, etc.)

CANTACUZINO INSTITUTE

PRODUCTION 1995

1. PRODUCTS:

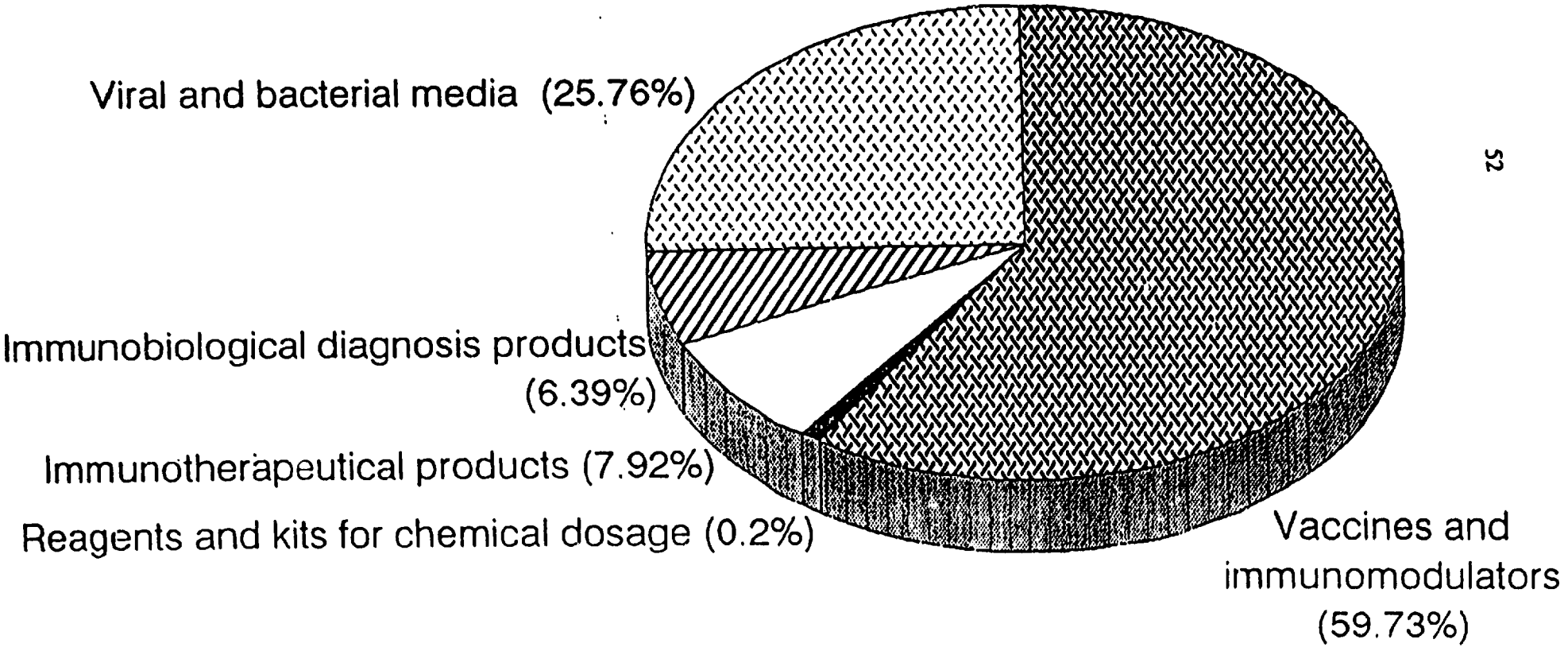
AVAILABLE:	403
ORDERED:	379
NEW:	18

2. CLIENTS:

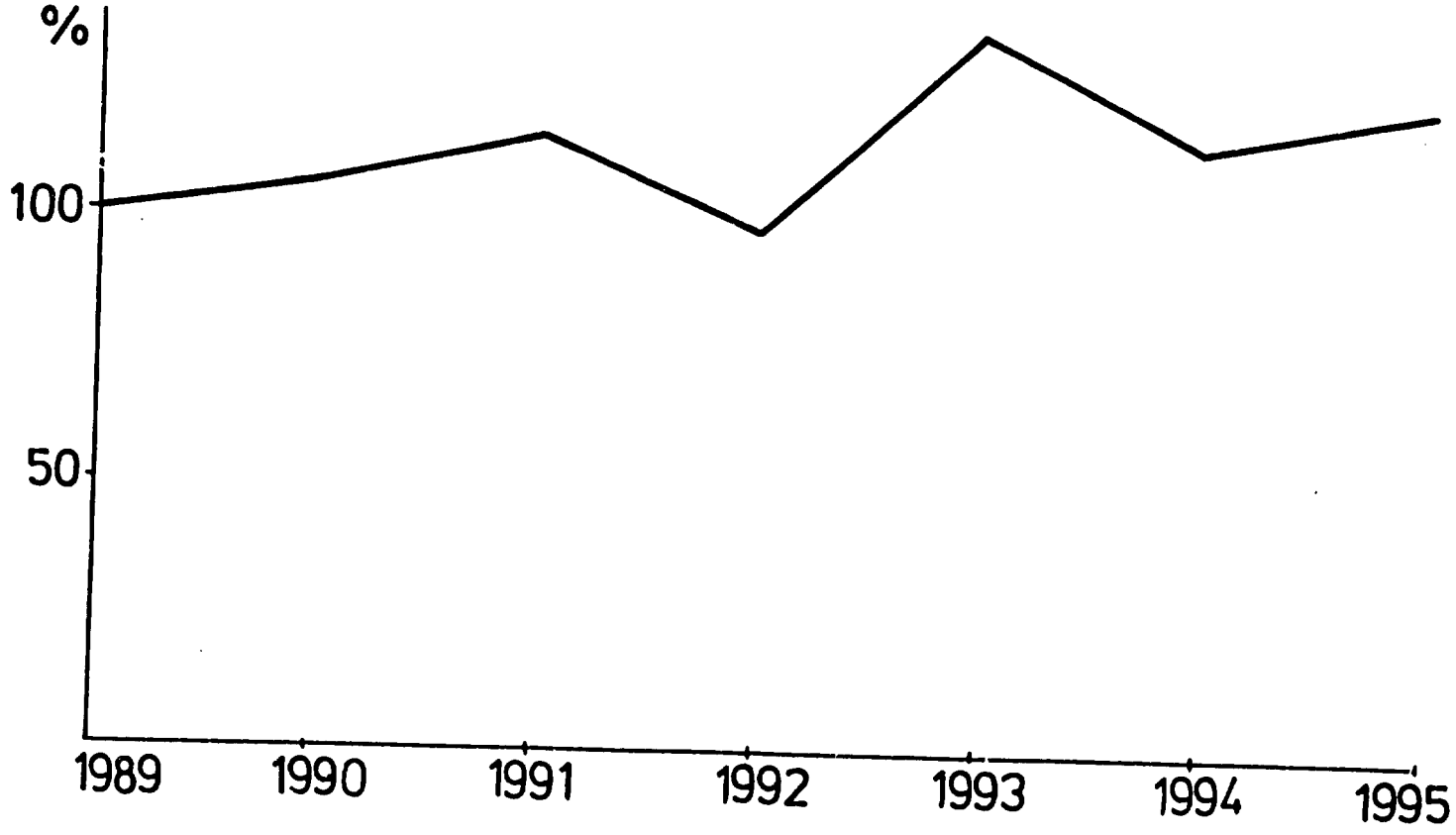
- ❑ LABORATORIES OF:
  - ◆PREVENTIVE MEDICINE CENTERS: 44
  - ◆HOSPITALS: 132
- ❑ PRIVATE AND STATE PHARMACEUTICAL UNITS: 4
- ❑ OTHERS: 29

248

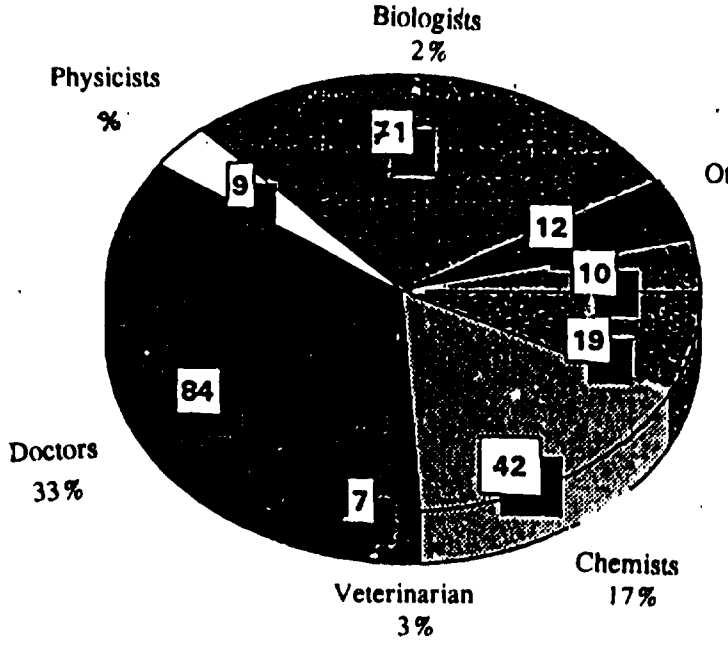
PRODUCTION : BUDGET STRUCTURE ON 1995



PRODUCTION EVOLUTION 1989-1995
(ESTIMATION IN USD)



Structure of professional staff with university background

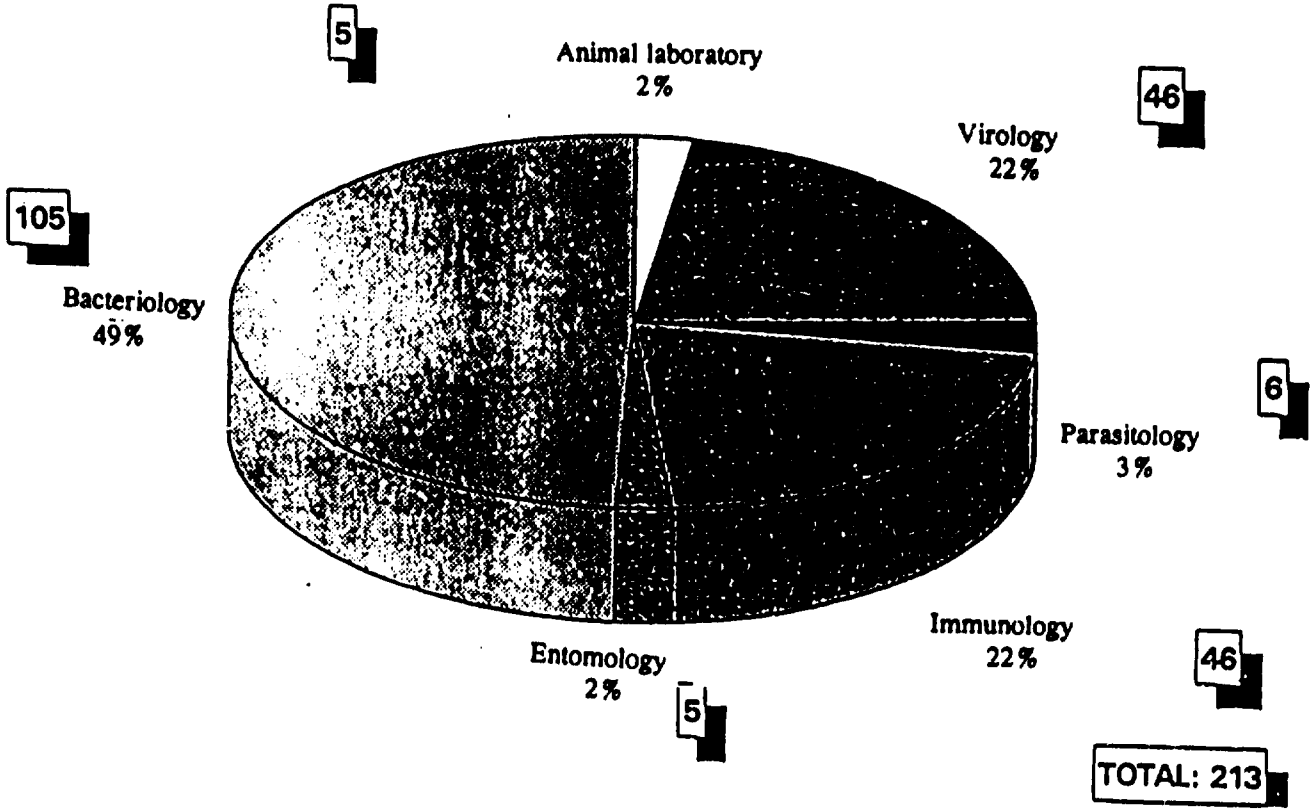


Females : 184 (72%)

Males : 70 (28%)

TOTAL : 254

Structure of professional staff with university background
(calculated in percentage of dominant profiles of the laboratory activities)



THE CANADIAN EXPERIENCE IN PHARMACEUTICAL MANUFACTURING INDUSTRY

by Dr. Dan Leslie, Chairman and CEO
Novopharm Ltd., Ontario, Canada

The Canadian Pharmaceutical market is approximately $5.8 million for 1995 and it is growing at a rate of approximately 8%. This is primarily due to the aging population and also to the advent of new branded products which are being sold at a fairly high prices.

Understandably, the government is quite concerned about the high cost of medications and for the past three years it has not accepted any price increases for pharmaceuticals despite the fact that the cost of goods and operation are constantly increasing. This poses quite a challenge for the management of our pharmaceutical companies.

Similarly, only those new products which show significant therapeutic advances are admitted into the government formulary.

The industry can be classified into two groups, namely the brand name pharmaceutical companies and the generic pharmaceutical companies. Novopharm Ltd. belongs to the Canadian Drug Manufacturers' Association (CDMA) which represents approximately 22 generic companies. The largest two companies - Novopharm and Apotex- represent approximately 80% of the total generic market sales. Most of the other companies are comparatively small and it is somewhat doubtful that they will ever grow excessively because they lack the research funding which is essential for future expansion.

In Canada, the largest number of prescriptions are filled with products manufactured by Novopharm. This means that approximately 29 million prescriptions are currently filled with Novopharm products, representing some 13% of the market.

The second company, Apotex is slightly higher in sales figures at the moment, however, the differences is not that great and the two companies virtually run neck-to-neck.

Brand name companies are the multinationals consisting of approximately 65 companies which belong to the Pharmaceutical Manufacturers' Association of Canada (PMAC) and hold different views compared to the generic pharmaceutical companies. Notwithstanding, there seem to be some merging of the two types of companies since today many of the brand name companies have interest in generic companies, predominantly in the United States of America, United Kingdom and other countries of the European Union and, to a lesser degree, in Canada. In short, brand name companies recognize that there is a generic market and they would like to be part of it. Such an undertaking is not unusual since by 2005, virtually all the patents of major products will expire and the sales of generic products are bound to increase significantly.

One might consider the changing strategy for the Canadian generic companies.

While the growth of the generic companies is predominantly in the field of producing and selling generic products, yet the two large firms - Novopharm and Apotex- entered into new field. It is recognized that sooner or later the sales of generic companies are bound to slow down and the explosive growth of 25-25% per annum cannot be maintained. Consequently, both companies decided to go global and establish operations in the United States and also in Europe. This is the very reason why Novopharm purchased Human Serum and Pharmaceutical Manufacturing Co. Ltd. and Humanpharma Ltd. and is currently seeking additional bases besides operating in the USA, Hungary and Canada.

Furthermore, Novopharm is also engaged in original research yielding novel products and formed Novopharm Biotech about 3 years ago. This company has a staff of 40 person of which 17 are Ph.D.'s. Their aim is to find a cure for cancer through the use of monoclonals antibodies which target the cancer cells like a magic bullet, bypassing the health cells without affecting them.

We are optimistic that, in the not-too-distant future, we shall find a cure for cancer and will bring untold benefit to mankind.

By the way, the staff of Novopharm worldwide is close to 3,000 persons, approximately 1,600 in Canada, 1,000 in Hungary and 400 in the USA.

I would like to consider our experience in working with Human and Humanpharma in Hungary. It is well-known that Human is engaged in the manufacture of injectable products, including vaccines, insulin, infusions, eye drops. Humanpharma manufactures solid dose products such as tablets, capsules, etc. In both cases Novopharm hold the majority interest of about 52%.

Prior to acquiring these two companies we spelled out the criteria for success.

We believe that no company can be purchased without an extremely thorough investigation of the circumstances and conditions surrounding the company which will are now spelled out below.

The first and most important criterion is outstanding management. Management is responsible for the short and long term success of any operation. Members of the management team must be highly competent, dedicated and have been of long service to the firm. If there is the least amount of doubt as to the competence of a company's management, the best thing to do is to walk away since sooner or later problems will arise for the owners.

We are glad to say that both Human and Humanpharma have excellent management staff and, as mentioned before, this was one of the reasons why we purchased the company.

The second important criterion is the reputation of the company. This is established over a period of time and it must be impeccable and outstanding. Any firm which has a questionable reputation should be bypassed.

The third criterion is the quality of the product. Without a doubt, firms do have high quality products over a period of time which are recognized by the profession. If there is any question as to the quality of the product, again, such a firm should be bypassed.

The fourth criterion is the specialization or "niche" position of the company. In the case of Human, this niche is injectable products, in the manufacture of which they are experts. Novopharm does not have injectable manufacturing capabilities, therefore, Human's contribution is essential from a short and long term viewpoint.

The fifth criterion is a satisfactory relationship with the government. Today, not only the doctors and pharmacies influence the success of a pharmaceutical company, but even more so that government which pay for the medications in most countries. It is essential that government have a high opinion of the firm and respect its competence. Some companies, for some reason, do not have a good relationship with governmental agencies and, again, such companies should be shunned.

It might be worthwhile to consider briefly how the manufacturing of vaccines fits into Novopharm's strategies. We mentioned before that we do not have an injectable department of which vaccine is a part. It is important that gradually we are represented in all different types of pharmaceutical manufacturing activities such as solid dose, ointments, liquids, biotechnology products, diagnostics, etc. including vaccines.

Besides, vaccines literally save lives and relieve the suffering of untold numbers of children.

We firmly believe that the function of a pharmaceutical company is not only to earn profits to ensure its viability but to, at the same time, render service to humanity. In short, this should be paramount, since if they do provide satisfactory service, the financial part will be successful too.

In conclusion, one should say that in order to survive the next 10-15 years, rather than being sold out or disappear through mergers, it is essential for medium and large companies to acquire working partners or enter alliances and operate globally. Those firms which recognize the changing times and respond wisely and properly will likely be in business for the next 10-20 years.

This is the intention of Novopharm and Human and this is the reason why we purchased both companies in Hungary and, hopefully, we will continue expanding as years go by.

REPORT ON INDUSTRY SUPPORT TO THE IMMUNIZATION PROGRAMME IN HUNGARY

by Dr. L. Aradi, Director, HUMAN Ltd., Budapest, Hungary

In the first meeting of the Advisory Panel on Preventive Medicine of UNIDO, held in Vienna, February 1984, it was recommended that a study should be prepared on the impact of modern technologies on vaccine production by the end of this century relevant to developing countries. The Model Programme for the Production of Vaccines in Developing Countries (UNIDO/IO.2, 1986) and its French edition (published by the Fondation Marcel Merieux in 1993) have successfully contributed to both decision making and human resource development activities.

The HUMAN Institute for Serobacteriological Production and Research, Budapest, Hungary, also as a WHO International Collaborating Centre for Research and Reference on Bacterial Vaccines was very actively involved in the Industrial Production of Biologicals (IPB) programme of UNIDO. The representative of Human Institute participated actively in the work of the Advisory Panel, but even previously, he was instrumental in preparing another UNIDO document on Prospects for Production of Vaccines and Other Immunizing Agents in Developing Countries (UNIDO/I.S. 402, 1983).

During the last Advisory Panel Meeting held in Garoua, Cameroon in January 1991, Dr. L. Aradi, Director of Human Institute offered that the next meeting would be held in Gödöllõ, Hungary. Since then Human Institute was privatized. During the course of the present meeting, the members of the Panel and the participants of the meeting could visit three plants, namely DPT vaccine production, vaccine formulation, filling and packaging as well as blood plasma fractionation (albumin, factors VIII and IX).

In the following Human Ltd. is presented.

HUMAN SERUM PRODUCTION AND MEDICINE MANUFACTURING Co. LTD.

HUMAN Serum Production and Medicine Manufacturing Company Limited by Shares started its work as Department of Biologicals for human use within the framework of today's Phylaxia Serum and Vaccine Ltd. founded in Budapest in 1912.
This Department became independent under the name Institute for Serobacterological Production and Research "HUMAN" in 1954.

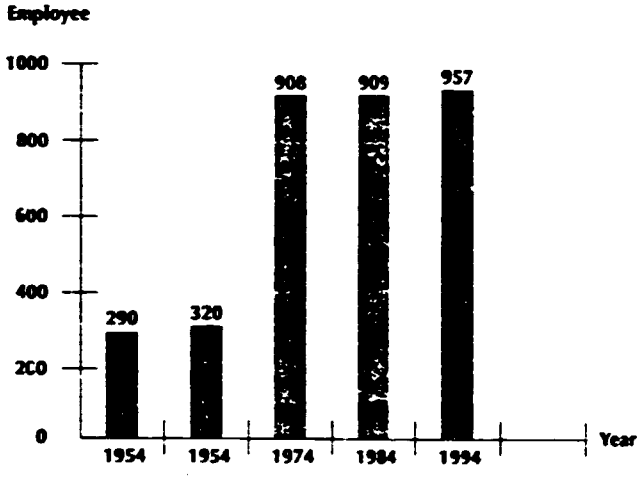
The Human Department, which later became the Human Institute for Serobacteriological Production and Research started its activity with the production of antidiphtheria and anti-tetanus horse sera to include soon afterwards the preparation of vaccines and serological diagnostics.
After Human became independent, new fields of production and research joined the traditional line of sera and vaccines.

In 1966 new production facilities and offices were built and acquired in Gödöllõ ensuring thus further possibilities for developing the Company. Gödöllõ is a town with appr. 30.000 inhabitants, 30 km from Budapest. The factory is located in the green belt of the town.
The land area is: 90 hectare.

On 1st July 1992, Human Co. was reorganized into a company limited by shares. Present owners are the Hungarian State Property Agency, and Novopharm (Canada) as well as a few thousand share holders including the staff & management. The Human shares are expected to be offered soon on the stock exchange.

Presently, HUMAN's main offices and the majority of the production facilities are located in Gödöllõ, but same laboratories and smaller production units are still at the earlier location in Budapest.

The number of employees of Human Co. Ltd. has varied between 900 and 1.000 in the last years.



The turnover was appr. 89 Million USD in 1994, from which appr. 8% was delivered to the export markets. In 1994, Human exported its products to more than 40 countries in Europe, Africa, Asia, North and South America. The following are the main fields of activity of Human:

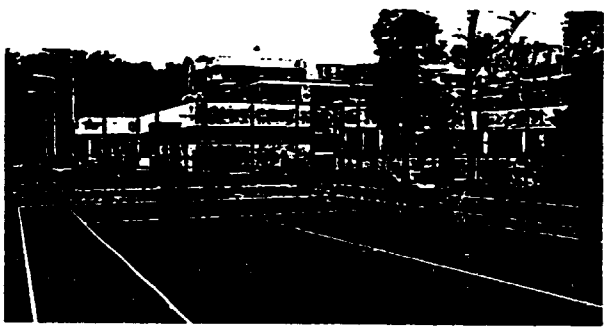
Blood derivatives
Culture media and peptones
Diagnostics and reagents
I.V. Solutions
Pharmaceutical specialities
Vaccines for active immunization

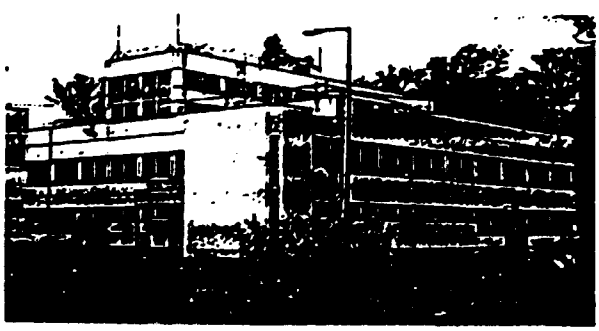
Quality assurance and innovation continue to have a decisive influence on all our operations today and for the future.

Quality in product calls for people of exceptional competence and training.

The Company provides further training for its employees in all areas of its activities as well as opportunities for getting up to date information.

HUMAN Co. Ltd. is working under the professional supervision and control of the National Institute of Pharmacy, the Johan Béla National Institute of Hygiene, and of the National Institute of Laboratories (manufacturing licensing, registration, marketing permits etc....)





Shareholder information / Present owners

Hungarian State Property Holding Ltd. (ÁV Rt.)	50,00 % + 1 share
Novopharm Co. Ltd.	36,21%
Other shareholders	13,74%

Hungarian State Property Holding Ltd.
(Hungarian State as owner in Human)

Human Co. Ltd. is to be permanently state owned pursuant to Act LIII. of 1992. and Governmental Decree No. 126/1992 (VIII. 28.) According to the Act the owner's, shareholder's rights are exercised by the Hungarian State Property Holding Ltd. (ÁV Rt.) which is a company having a single owner, all the shares embodying ownership are in the hands of the State.
The basic task of ÁV Rt. is to protect the owner's interests in state owned companies. It was a result of such activity that on July 1st, 1992, Human Institute for Serobacteriological Production and Research was transformed into Human Serum Production and Medicine Manufacturing Co. Ltd., the latter being the full legal successor of the former. The Hungarian State has 50% + 1 share in Human Co.

Novopharm Co. Ltd. (Canadian owner)

The pharmaceutical industry in Canada has changed dramatically over the last quarter-century, and Novopharm Co. Ltd. has played a key role in that change.

Novopharm's reputation is in branded generics. They expect to be adding fresh accomplishments in the years ahead.

Their technical and financial base now allows them to make an evolutionary step into original research and development of innovative pharmaceuticals.

Novopharm consist of five divisions: Novopharm Ltd. (generic manufacturing): private label products, consisting of Stanly Pharmaceuticals (Vancouver, BC) Granutec (Wilson, NC), Novopharm Biotech, Eldan Pharmaceuticals (proprietary in-licenced pharma-ceuticals), Human/Humanpharma (injectables, vaccines and solid dosage forms) in Hungary

Novopharm's commitment to quality is shown throughout the manufacturing processes.
The result is a wide range of high quality products at reasonable costs.

Novopharm Co. Ltd. has had a working partnership with Human Co. since 1991.
Novopharm is shareholder in Human Co. since 1993 with 36,21% and option up to 51%.

Other shareholders

The Company has more than 5.000 small shareholders (13,74%).
They together own shares worth 290 mill. HUF.

The shareholders, the Board of Directors, financial experts, representatives of the banks have decided - in line with their in original intentions - that Human shares should be floated on the Stock. Exchange in 1995 since Human is among those manufacturing companies having the most solid foundations.

COOPERATION

Innovation has always played a decisive role in the development of Human Co. Ltd. right from the very beginning.

In addition to the launching of new pharmaceutical and paramedicinal specialities of its own development, Human continues to be open to the manufacture and marketing of new preparations suitable for ensuring a high level of Health Care in Hungary or those intended for export. Such activity should be aimed at the utilization of Human's intellectual and free production capacity.

The validated production plants which represent a high technical standard, are under regular professional control, audit, which provides an assurance to our partners at all times. The above have made it possible for Human to enter the field of the international division of labour with good professional skills, assuring GMP conditions.

HUMAN Co. maintains scientific and technical cooperation with a number of leading pharmaceutical companies. Their products are being produced by Human Co. Ltd. at the licensor's technical level resulting in the products having the same quality as the original.

Human has the official approval to act in Hungary as distributor of medicines and paramedicines.

Human has concluded several Sole Distributor Agreements with foreign companies as well as reputed local pharmaceutical works.

Cooperation has developed in the following fields taking into account mutual benefits:

Analytical testing, QC release,
Carrying out scaling up to industrial size,
Carrying through registration applications,
Collecting human organs,
Development and manufacture of diagnostic products
Distribution,
Freeze-drying,
Manufacture of injectables, infusions, eyedrops and other solutions,
Manufacture of tablets, coated tablets, granules,
Manufacture of blood products,
Manufacture of generic products,
Manufacture of OTC products,
Manufacture of preparations with plantbased raw materials,
Production of culture media of liquid, semisolid and powder forms,
Sterile powder manufacturing for i.m.and i.v. use.,
Warehousing and marketing of pharmaceuticals

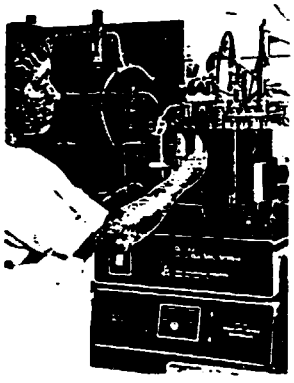
FOREIGN PARTNERS

Pharma-Serono Lab. S.A.
Baxter Diagnostics A.G.
Bayer A.G.
Behringwerke GmbH.
Biotest Pharma GmbH.
Ciba-Geigy A.G.
Du Pont Pharma GmbH.
Eli Lilly S.A.
Enzypharm GmbH.
Fisons Arzneimittel GmbH.
Fresenius A.G.
Gensia Europe Ltd.
Guerbet GmbH.
F. Hoffman La Roche Ltd.
IDA Foundation
Intervax Biologicals Ltd.
Laevosan GmbH.
Merck, Sharp and Dohme B.V.
Novo-Nordisk A/S
Novopharm Ltd.
Pharmamed Ltd.
Roussel Uclaf
Schering Plough (Essex Chemie A.G.)
M.V. Upjohn Foundation Ltd.
The Wellcome Foundation Ltd.
Ajinomoto Co. Inc.
Pasteur Merieoux Serums and Vaccines

RESEARCH AND DEVELOPMENT (R&D)

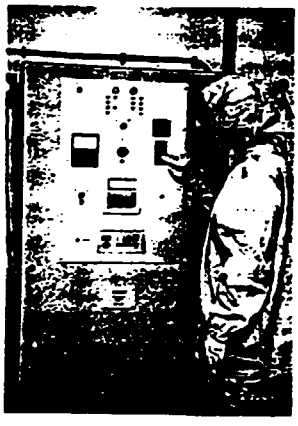
The R&D activities of Human are determined by the long term strategic goals of the company.

R&D means mainly developmental research, which means product and production technology development as well as other technical development. These development activities are carried out on the one hand in the pharmaceutical technology development laboratory, and on the other hand by the various production and quality control units.
The pharmacists, biologists, chemists and physicians who participate in development work in Human, account for some 10% of the total number of employees.

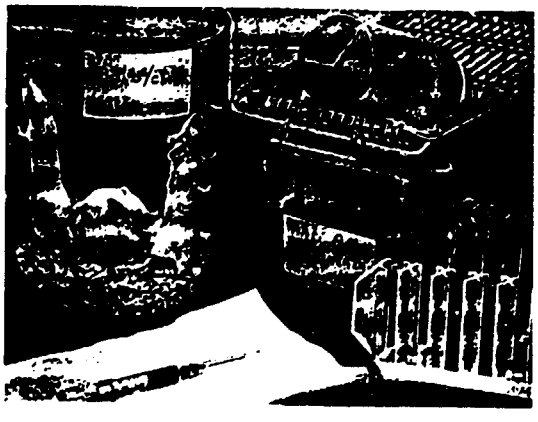


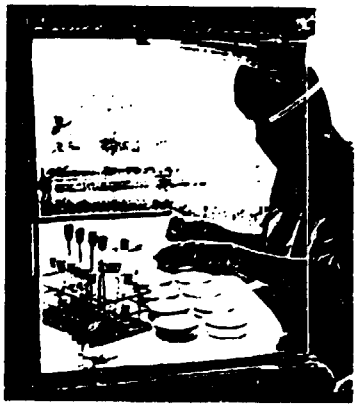
Theoretical/basic research is carried out for Human Co. by universities/research institutes on a contractual basis or in the framework of cooperation.

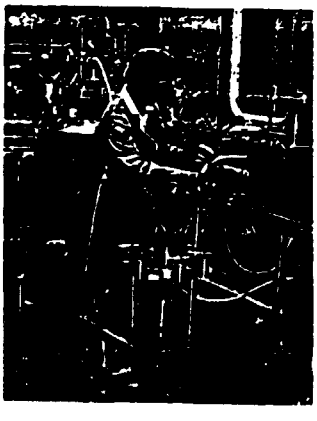
The result of R&D: expansion of the product range through the appearance of new products, preparations, such as:



- Blood products
- Diagnostics
- Infusions and dialysis preparations
- New drugs, generics
- Preparations containing natural active substances
- Vaccines

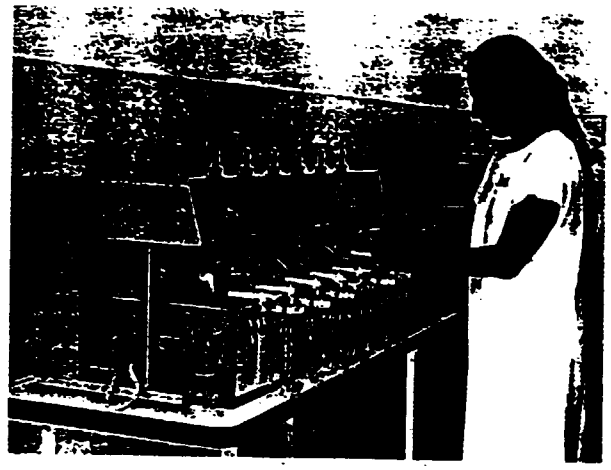






QUALITY ASSURANCE AND QUALITY CONTROL SYSTEM

The traditions of Human and the dynamic development of the last decades have resulted in the company having a very colourful range of products. Most of the products belong to the LVP and SVP groups, which require high standard production technology, careful, conscientious and skilled work done under aseptic conditions both in production and quality control.

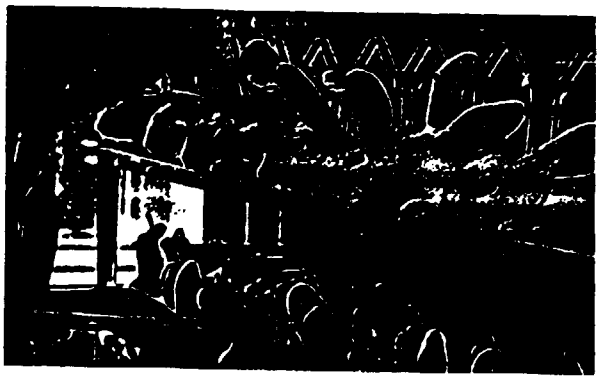


Due to the ever tightening Hungarian and international GMP requirements, Human has changed its traditional quality control organization into a well functioning Quality Assurance System (Q.A). The Quality Assurance Department supervises, organizes and performs all duties that pertain to quality assurance and are necessary for guaranteeing top quality products.

New laboratories and organizational units have been established within the Quality Control Division to supplement the work done by the traditional laboratories. New instrumental testing methods have been introduced.

The **Strain Bank** maintains and regularly controls on the basis of international methods the bacterial strains used for vaccine production, and carries out furthermore, the maintenance of the bacterium and fungus strains and supplies its customers "strain conserves". It identifies the microorganisms isolated in the course of environmental hygienic tests and handles them in a "validation" control collection.

Validation work is of special importance, and this is carried out by a separate validation group.



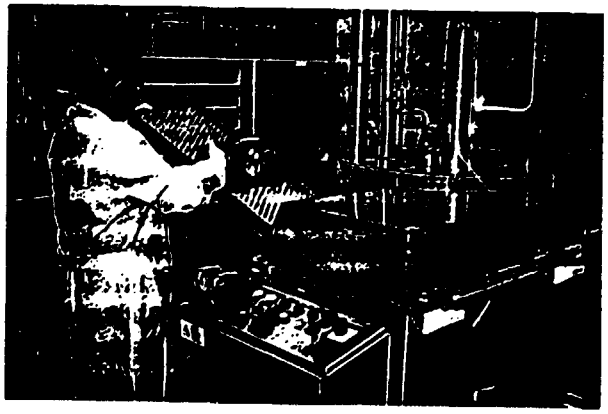
INJECTABLE AND EYEDROP PLANTS

In order to comply with ever tightening requirements and to accelerate development work, manufacture of licence products started in the Injectable Plant in the middle of the 1980's. Meeting the quality requirements of Western European and American pharmaceutical companies of international renown, thus providing life-saving drugs for Hungarian patients.

The insulin group of products, and within that the production of human monocomponent insulin preparations manufactured by using genetic engineering, was given top priority.
Local production of these followed that of PIF insulins and MC (monocomponent) insulins of pork and beef origin.

Modern antibiotic treatment by the Hungarian Health Service was helped through local production and marketing of powder injectables, notably second and third generation cephalosporins. The quality control of these products is carried out parallel by the multinational licensors, thus the quality of these products is guaranteed to be identical to that of the corresponding preparations manufactured by the licensors.

Production conditions in the new plant for eye drops built in 1992 meet international requirements in every respect.
Preparations containing antibiotics, injectables and eyedrops are manufactured in separate parts of the plant with independent air supply.

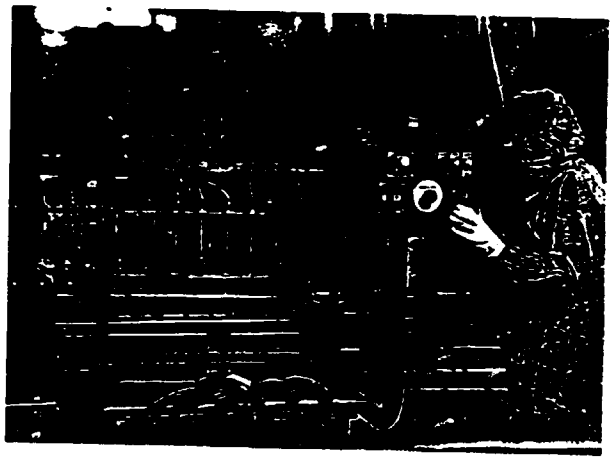


INFUSION PLANT

Human Co. is the only Hungarian pharmaceutical manufacturing company, which produces i.v. fluids and peritoneal dialysis solutions using industrial scale technology. Human Co. has a 70% market share of the infusions used by Hungarian hospitals.
Human's current product range in this field encompasses practically all fields of infusion therapy.

Both professional and technical preconditions are given for meeting the ever increasing market demand and for increasing the range of products.

It is the intention of Human to continuously expand its range of products and to increase its total output, while ensuring appropriate quality at all times.



The expansion of the production of dialysing solutions is among the goals set for the coming years.

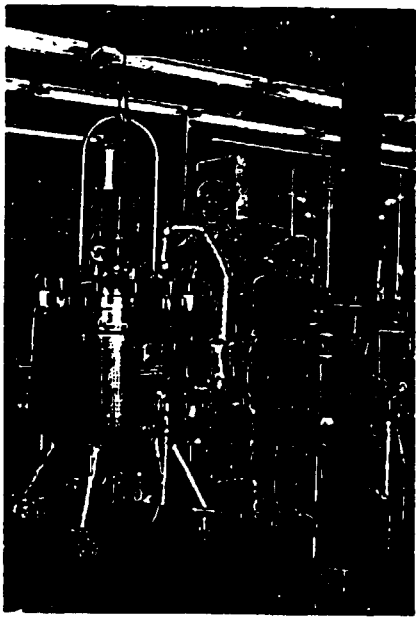
As part of expanding the range of products, manufacture of the volume substitution infusions has also started.

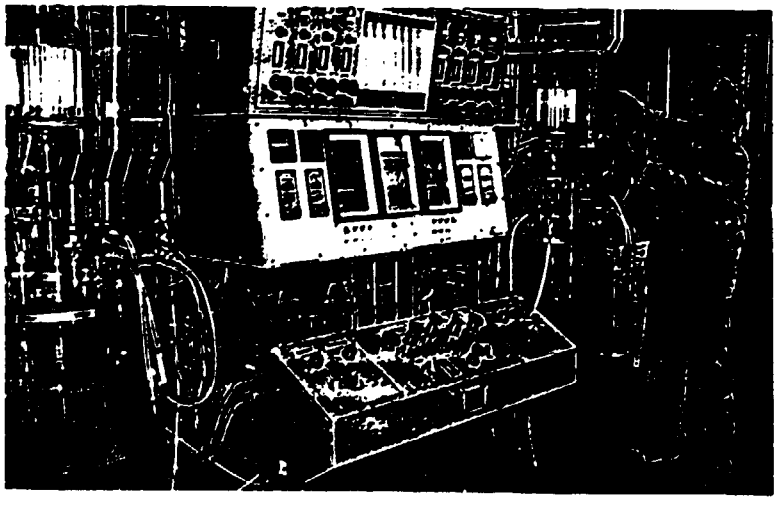
Out of the other pharmaceuticals of liquid form Naksol/Irix is worth mentioning.

VACCINE PRODUCTION PLANT

The activities of Human are closely bound to the production and marketing of vaccines, which Human was already doing as a laboratory in the first decades of this century.
In addition to meeting the vaccine requirements of the Hungarian Health Care, active participation in the immunization programme of WHO-UNICEF - Health for all by the year 2000 - (EPI) is a fundamental goal.
A new production facility has recently been built, which meets every international requirement, in order to ensure GMP conditions and compliance with WHO requirements.

The **Pepton Plant** works as a submit of the Vaccine Plant. It produces culture media in liquid, semi-solid and power forms, as well as peptons for both other departments of Human and outside customers, in custom-made composition.

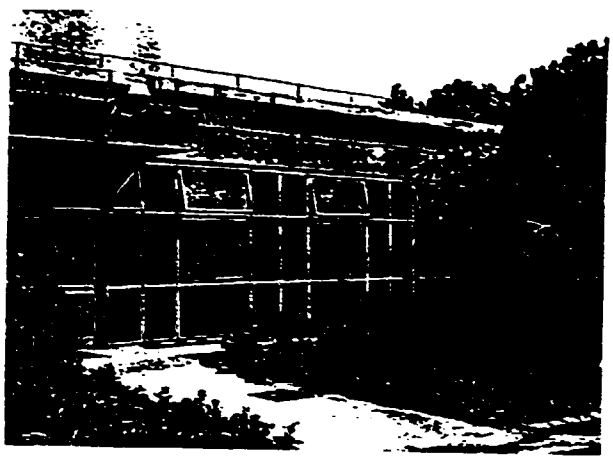


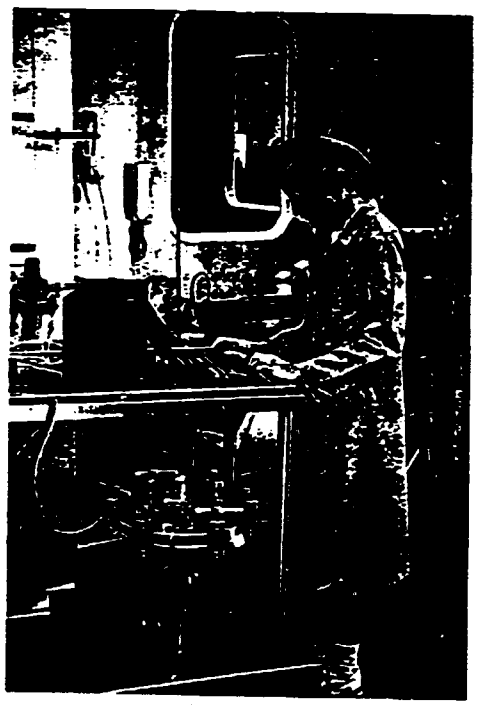


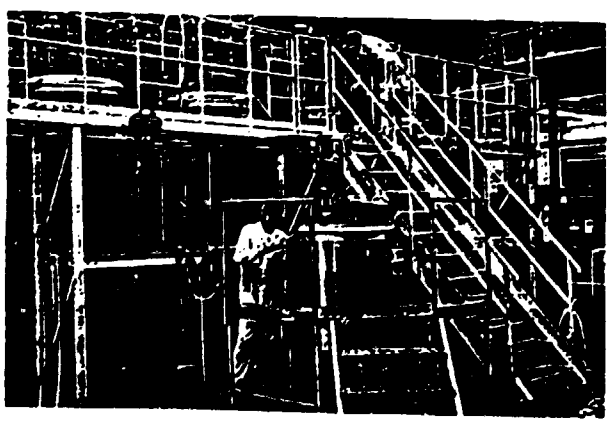
BIOCHEMICAL PLANT.

Plasma derivatives are produced in the Biochemical Plant. Albumin infusions of various concentrations and gamma-globulin preparations are manufactured from outdated plasma and fresh frozen plasma (FFP) derived from voluntary blood donations collected in Hungary.

Production of Factor VIII. and Factor IX. products will also start on the basis of a know-how transfer agreement concluded with Behringwerke AG.







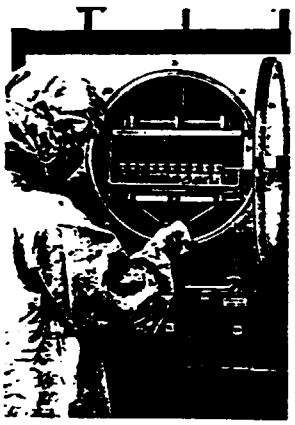
PRODUCTION OF DIAGNOSTICS

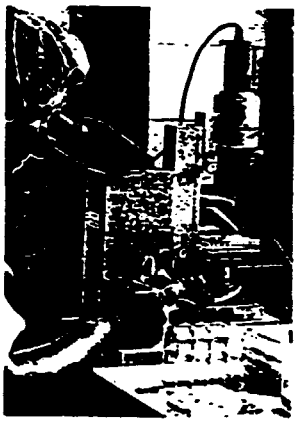
The **Immune Chemical Laboratory** produces the following products and provides an immune chemical background for the production units and laboratories:

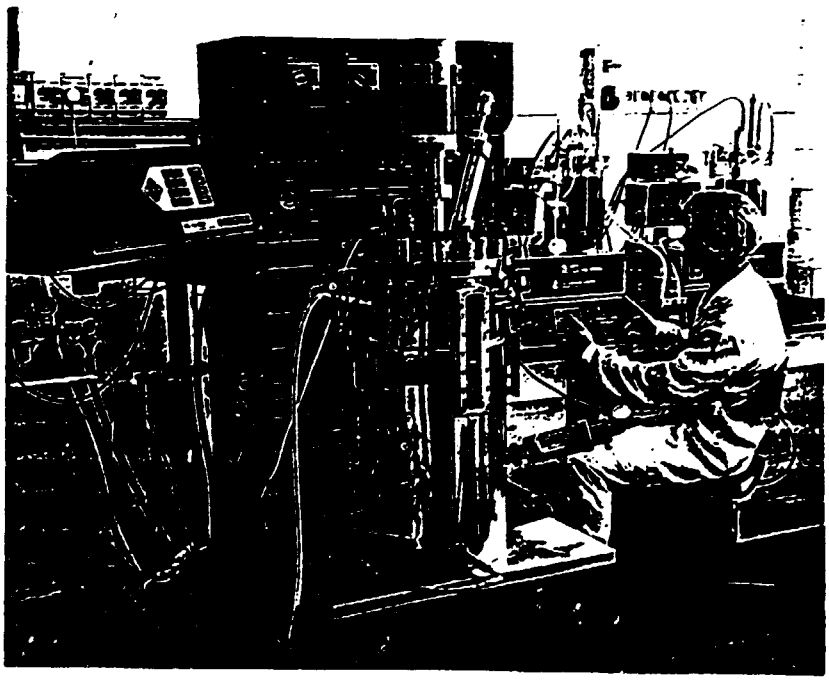
- immune chemical reagents, and immunological diagnostics. polyclonal antibodies, laboratory standards,
- clinical-chemical antisera and standards,
- immune chemical adjuvants.

The **Blood Serological and Diagnostic Laboratory,** produces in compliance with the standardization and quality recommendations of WHO the following products using biotechnological methods:

- monoclonal and polyclonal reagents for the determination of blood groups,
- resistest discs,
- bacterial laboratory diagnostics.





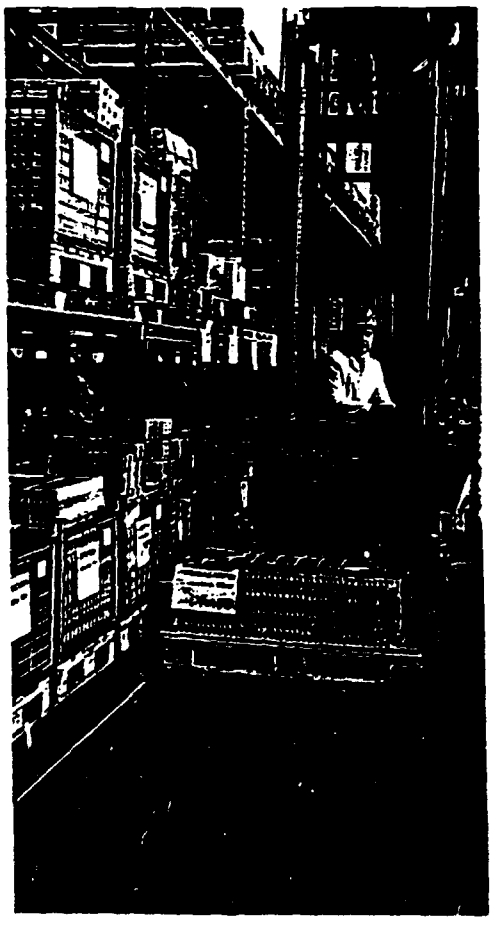


COMMERCIAL ACTIVITIES

Growing competition in recent years in the area of drug distribution has helped professional development a continuously increasing level of service in the market. Therefore, Human not only provides its multinational partners technical-scientific ground support, but helps the marketing and storage of its own products and those of its international partners through its distribution organisation and foreign trading activities. It summarizes customer experiences for its partners, Human medical representatives promote both products manufactured and those imported by Human in the finished form, by drawing attention to their scientific and economic advantages.

Human Co. Ltd. is a direct supplier of every Hungarian hospital, 60% of the distributors and 95% of the private pharmacies.

Human distributes some 700 preparations manufactured by itself and in addition some 300 other Hungarian and imported products. Hospital sales account for 60% of Human's total sales.



The remaining 40% of Human's Hungarian sales are made through direct sales to pharmacies, pharmaceutical distributors and pharmacy centers.

Almost 100 deliveries are made daily. Human's distribution organisation has established its image through the strengthening of the work of its sales managers/representatives.

We provide for our international partners the possibility of consignment stock keeping.

Human carries out its own export-import activities.

Human Co. intends in the coming years to increase the number of new products and their turnover.

HUMANPHARMA Pharmaceutical Manufacturing Co. Ltd.

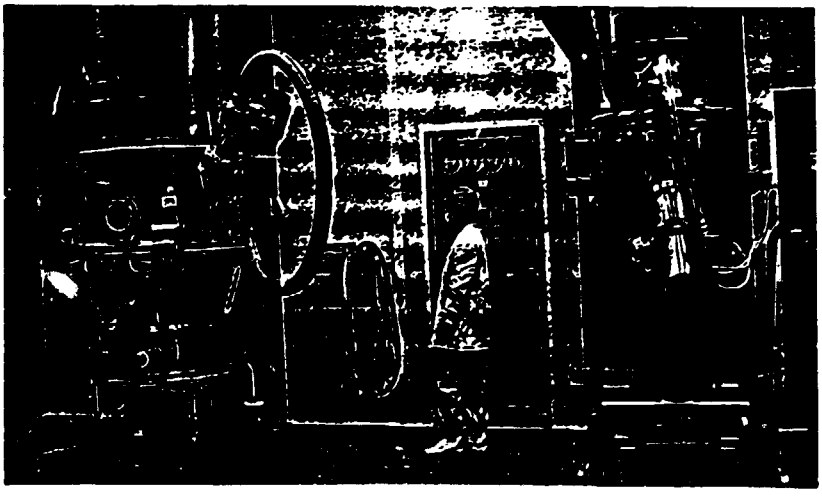
Humanpharma Co. Ltd. was established in 1991 as a joint venture of Human Serum and Medicine Manufacturing Co. Ltd. and Stanley Pharmaceuticals Ltd. for the manufacture of solid dosage forms (tablets, capsules, coated tablets).
Human Co. has in this way created the possibility for the manufacture of solid dosage forms, too, through Humanpharma Ltd.

Stanley Ltd. is one of the largest Canadian pharmaceutical manufacturing companies, one of the leading suppliers of house-branded products (pharmaceutical preparations, OTC products, vitamins, hospital products, paramedicines, veterinary products) to the most important drug store chains in Canada, a member of the Novopharm Group, which was looking for and also found in this way an European manufacturing base and market for its products.

The shares of Stanley were taken over by Novopharm Ltd. in 1994.

The most important partner of Humanpharma is Novopharm Ltd., which - through the licensing and registration of its generic products to Humanpharma - makes a contribution to the development of the product range of Humanpharma. Through this arrangement, generic products of excellent quality are being made available on the Hungarian and European market at affordable prices.

Some of the best known international pharmaceutical companies can also be found among the partners of Humanpharma Ltd., such as F.Hoffmann-La Roche Ltd., Roussel Uclaf., Ciba-Geigy A.G.



Humanpharma products are distributed by Human.

MEDCO LTD.

It is a joint venture established in 1994 50% owned by **Human RT.**, 50% owned by **Eli Lilly.**

Eli Lilly and Company, Indianapolis (USA) is one of the leading pharmaceutical companies of the world.

As a result of co-operation between Human RT. and Lilly which started in 1983 the Hungarian health care has been supplied with medicines of high quality and efficacy like ***Ceclor, Mandokef, Vancocin, Dobutrex, Brietal.***

The objective of **MEDCO** is to continue and build upon the already existing co-operation in the manufacturing and to provide Hungarian health care with a range of proven, high quality products.

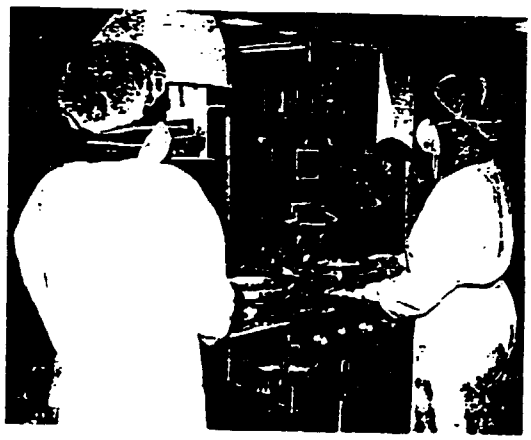
Human RT. brings manufacturing expertise, facilities and highly trained staff to **MEDCO.** Lilly contributes to the operation of **MEDCO** with its pharmaceutical developments, marketing expertise and training possibilities.

The founders of **MEDCO** are sure that the company can contribute to the further improvement of medication supply of Hungary through its high quality and reasonably priced products.

MEDCO LTD.

Hungary 2100 Gödöllő,
Táncsics M. str. 82.
Phone: 36-28-320 723
Fax: 36-28-320 724

medco



General information on the firm

Name: Human Serum Production and Medicine Manufacturing Co. Ltd.

Date of foundation: 1954

Form of economic association: Company Ltd. by shares

Capital: 2,130 million HUF (21,3 mill. USD 1993)

Number of employees: ≈1000

Bank:

Hungarian Credit Bank Ltd
International division
H-1133 Budapest Pozsonyi u. 77-79
Account No: 20103143

Credit Lyonnais Bank Hungary
H-1051 Budapest József Nádor tér 7
Account No: 1000261020-00-0-36

City Bank Budapest
H-1052 Budapest Váci u. 19-21
Account No: 000 25 20001

Location:

Headquarters: Gödöllõ H-2100 Táncsics Mihály str. 82.

(Plant I.) Hungary H-2101 Gödöllõ P.O. Box. 402.

Telefon number: (36) - 28 - 320-733

Fax number: (36) - 28 - 320-177

Telex number: 224010

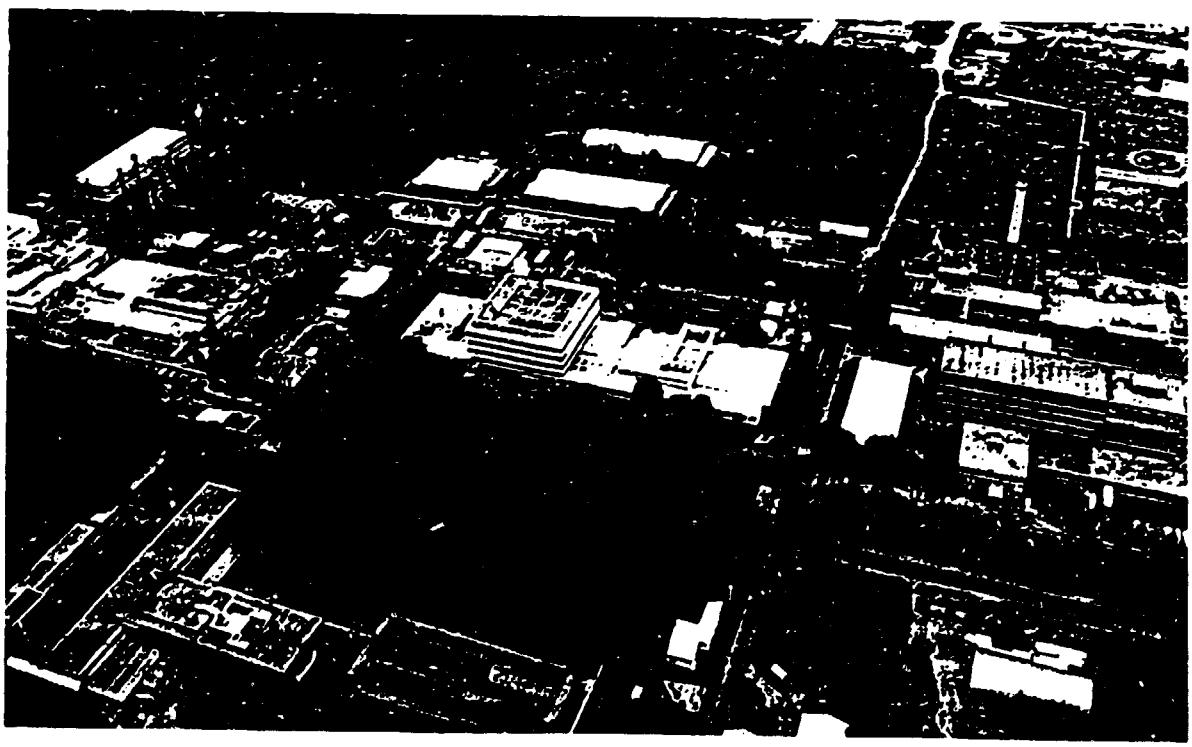
(Plant II.) Budapest H-1107 Szállás str. 5-7. Hungary

Telefon number: (36) - 1-262-9323

Fax number: (36) - 1-262-3416

Warehouses: Gödöllõ H-2100 Repülõtéri str. 2.

Telefon number: (36) - 28 - 320-370



HUMAN SERUM PRODUCTION
AND MEDICINE
MANUFACTURING CO. LTD.
2100 HUNGARY Gödöllő,
Táncsics M. u.82.

NOVOPHARM LIMITED
30 Nably Court, Scarborough
Ontario, Canada M1B2K9

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) AND QUALITY OF RAW MATERIALS USED IN VACCINE PRODUCTION

by Z. Csizer, M.D. Ph.D., UNIDO

Close to the end of the preparation of this proceedings, the issue of possible link between BSE and Creutzfeldt-Jacob Disease has emerged. UK government ministers announced on 25 March 1996 new beef safety measures following the report by an independent expert advisory committee of a possible link between bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jacob disease (CJD).

The British Spongiform Encephalopathy Advisory Committee (SEAC) considered 10 recently identified cases of CJD that have occurred in people under 42 and concluded that, "the most likely explanation at present is that these cases are linked to exposure to BSE before the introduction of the specified bovine offal (SBO) ban 1989". The government stressed that there is still no proof of a definite link but accepted that the new evidence was cause for concern.

Due to the actuality of the issue, the Secretariat of UNIDO decided to publish a paper on the subject prepared earlier for the request of Johann Wolfgang Goethe-University, Frankfurt am Main, Germany.

"BSE - The Ultimate Challenge in Pharmaceutical Quality Assurance"

Dr. Z. Csizer

United Nations Industrial Development Organization

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* The lecture was delivered as part of the Pharmaceutical Seminar of Johann Wolfgang Goethe-University, Frankfurt am Main. on 4th January 1995.

BLOOD AND SERUM-DERIVED RAW MATERIAL ISSUES

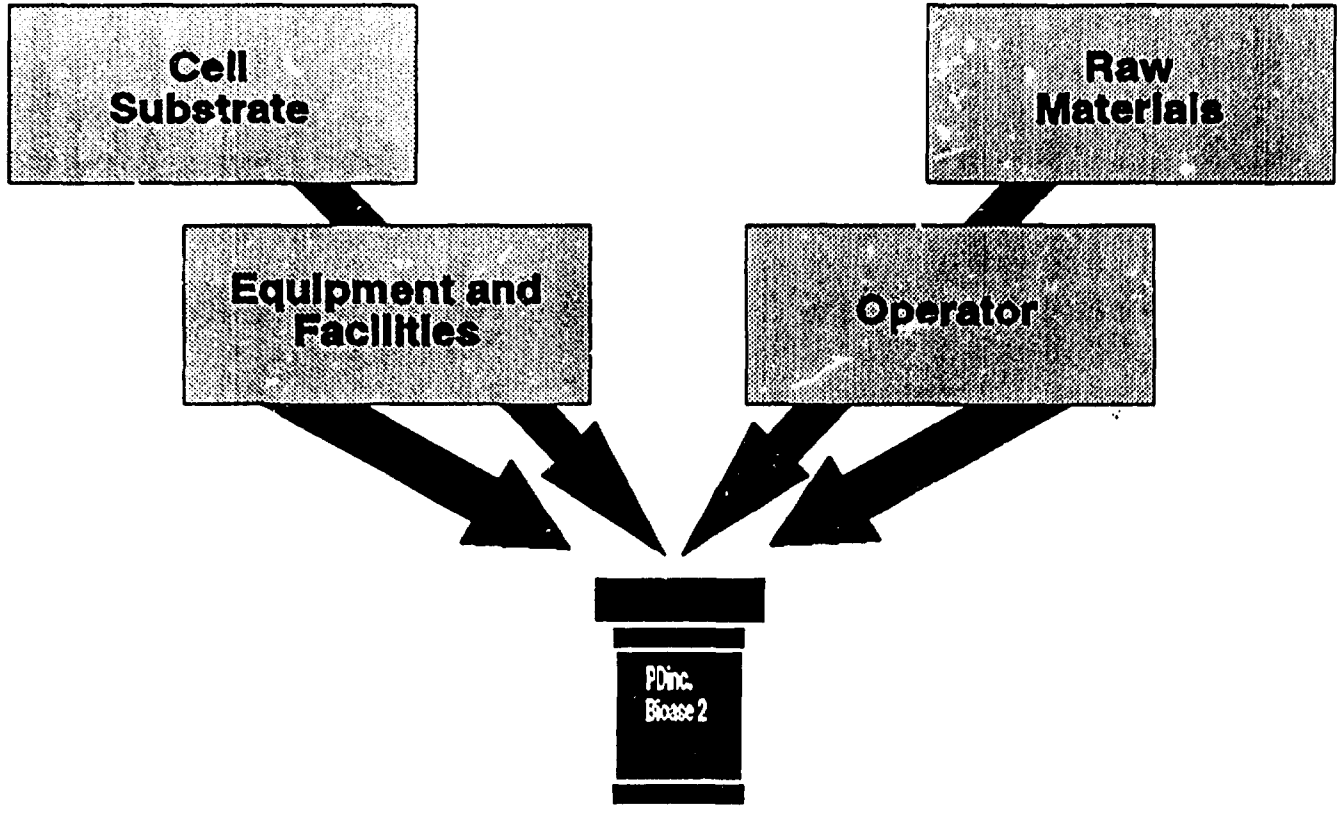
OBJECTIVES

1. Review Common Blood/Serum-Derived Raw Materials as Portals of Entry for Contaminants.

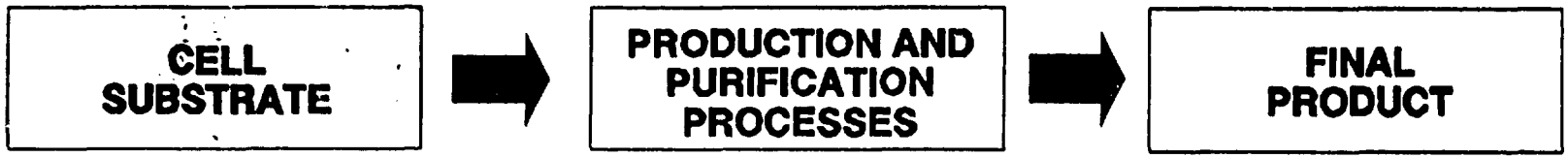
2. Review Viral and Microbial Contaminants and Standard Methods for Their Detection.

3. Review the Threat Posed by These Contaminants to Biologics.

PORTALS OF ENTRY FOR CONTAMINANTS



PRODUCTION OF A BIOPHARMACEUTICAL PRODUCT



- Cell Line Characterization
- Process Validation
- Product Analysis
- Lot Release Testing
- Cell Stability

COMPONENTS FOR CELL GROWTH IN VITRO

Proteins:

Albumin	Fetuin
Transferrin	Fibronectin

Hormones:

Glucocorticoids - Hydrocortisone, Dexamethasone
Steroids - Estradiol, Testosterone, Progesterone
Thyroids - Triiodothyronine (T3), (T4)

Polypeptides and Growth Factors:

Insulin	Epidermal Growth Factor
Insuline-Like Growth Factor	Fibroblastic Growth Factor
Somatomedin A and C	Endothelial Growth Factor
Platelet-Derived Growth Factor	

Peptides:

Glutathione

Lipids:

Essential Fatty Acids
Prostaglandins
Cholesterol

Minerals:

Inorganic Trace Elements - Se, Fe, Cu, Zn, Co, Mn, Mo, etc.

ALTERNATIVES

- Serum Free Media
- Protein Free Media (Defined Media)
- Recombinant Growth Factors
  Insulin
- Human Transferrin
  (Heat Inactivation 62°C, 10 Hours)
- Human Serum Albumin
- Filtration
- Organic Solvents
- Low pH Steps

CHANGING PATTERNS OF ANIMAL PRODUCTION

Intensive Animal Production

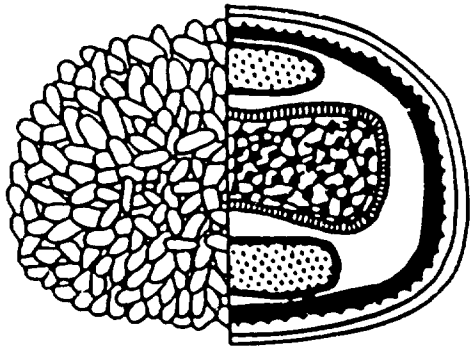
- Large Numbers of One Species of Animal, Diverse Background, Limited Space, High Density.
- Asynchronous Turnoff and Introduction of New Animals.
- Elaborate Housing, Complex Ventilation, Feeding, Waste-Disposal and Cleaning Systems.
- Animal Care By Few, (Inadequately) Trained Staff.
- Manipulation of Biological Rhythm.
- Large Batches of Easily Digestible Foodstuffs.
- Improved Hygienic Conditions, Isolation of Animal Populations.

CONSEQUENCES OF INTENSIVE LIVESTOCK PRODUCTION

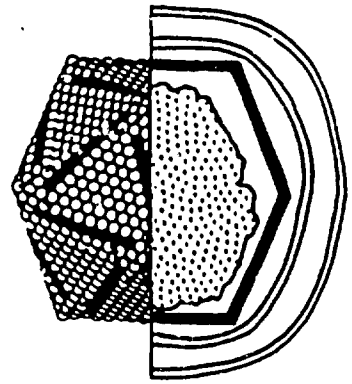
- Favor Emergence and Spread of Enzootic Infectious Disease and Opportunistic Infection.
- Populations Are At Great Risk from Non-Enzootic Viruses (Barriers by Design).
- Conditions Favor Multiple Infections Working Synergistically, Further Complicates Diagnostic, Preventative and Therapeutic Measures.

SHAPES AND SIZES OF ANIMAL VIRUSES

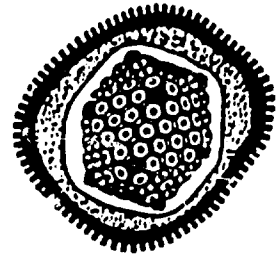
DNA Viruses



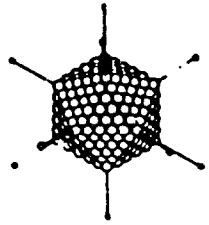
Poxviridae



African swine fever virus



Herpesviridae



Adenoviridae

Papovaviridae

Hepadnaviridae

Parvoviridae

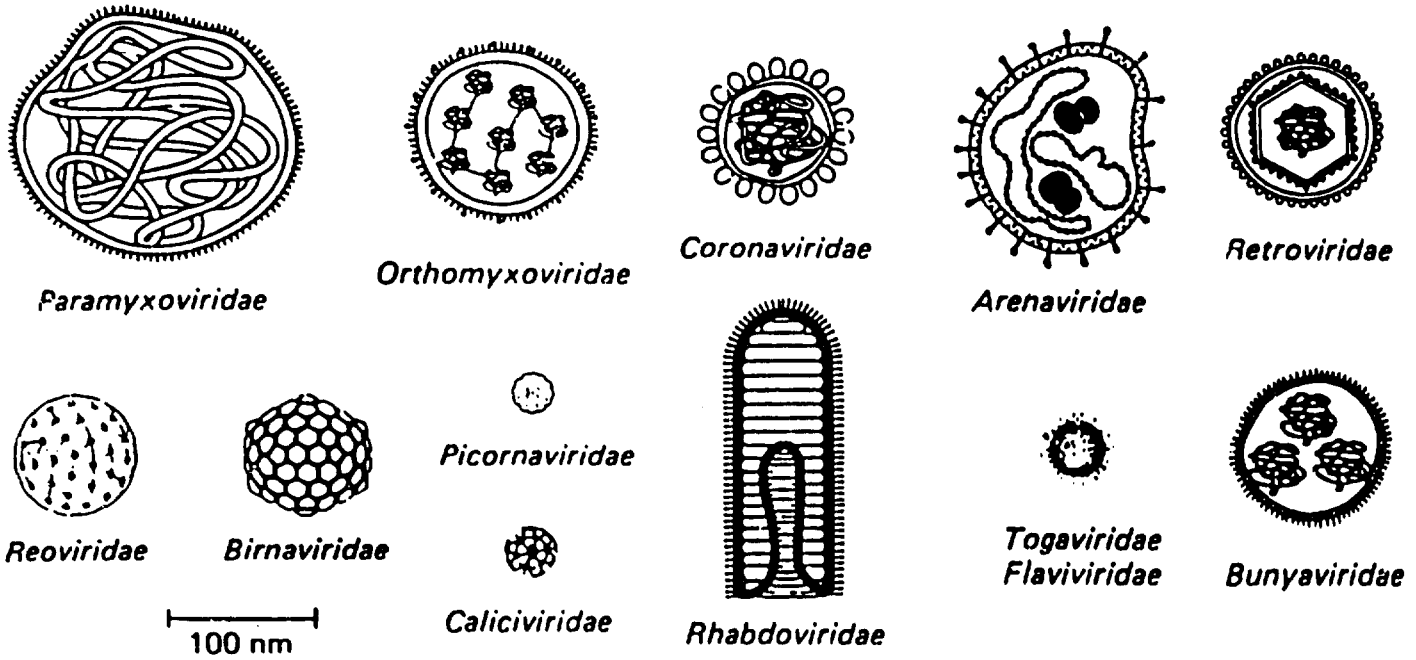
(From Veterinary Viroiogy, Fenner et. al., Academic Press, 1987)

QUALITY ASSESSMENT OF FETAL BOVINE SERUM

- Traceability - Establish Geographic Origin
  - Imported Serum - Vendor Policy
  - Abattoir → Broker → Vendor
- Validated Filtration System
- Viral Screening
- Microbial Screening

SHAPES AND SIZES OF ANIMAL VIRUSES

RNA Viruses



(From Veterinary Virology, Fenner et. al., Academic Press, 1987)

SUMMARY OF REPORTED VIRAL INFECTIONS OF THE BOVINE FETUS AND PLACENTA

DNA Viruses

Virus	Family	Geographical Distribution	Persistence
Pseudorabies	Herpesviridae	Worldwide	+
Infectious Bovine Rhinotracheitis	Herpesviridae	Worldwide	+
Malignant Catarrhal Fever	Herpesviridae	Worldwide	+
Bovine Adenovirus	Adenoviridae	Worldwide	+
Bovine Parvovirus	Parvoviridae	Worldwide	+

SUMMARY OF REPORTED VIRAL INFECTIONS OF THE BOVINE FETUS AND PLACENTA

RNA Viruses

Virus	Family	Geographical Distribution	Persistence
Bovine Rhinovirus (FMD)	Picornaviridae	Eradicated: NA, CA, Aust., Japan; controlled: Europe Common Elsewhere	+
Bluetongue	Reoviridae	Tropics and Subtropics Temperate Areas of NA	±
Rotavirus	Reoviridae	Wolrdwide	-
Parainfluenza 3	Paramyxoviridae	Worldwide	-
Bovine RSV	Paramyxoviridae	Worldwide	-
Rinderpest	Paramyxoviridae	Eradicated Except Africa, Asia	-
Wesselsbron	Togaviridae	Africa	-
Rift Valley Fever	Bunyaviridae	Africa	-
Bovine Viral Diarrhea	Togaviridae	Worldwide	+
Bovine Leukemia	Retroviridae	Worldwide, Control/Eradication Program: Europe	+

BOVINE VIRAL DIARRHEA VIRUS (BVDV)

Chief Viral Serum Contaminant

- 65 nm, Enveloped-RNA Virus
- Lowest Contamination Rate Observed:
  33% In Sera Certified as Free of BVDV
- Gamma-Irradiation at 2.5 to 3.5 mRad Yields
  6.3 log 10 $TCID_{50}$ Inactivation
- Cell Growth Properties

(Erickson et. al. Developments In Biological Standardization (1989) Vol. 70, 59-66)

BOVINE POLYOMAVIRUS (BPyV)

- Initial Isolation - Stump-Tailed Macaca Cells (STMV)
- Later Isolated from Calf Kidney Cell Cultures
- Antibody Commonly Found in Serum
- Intra-Uterine Infection - Rather Frequent
- Antibody Positives:

  Cattle: 1 Mo. - 40%

  1 Yr. - 11%

  Beyond 1 Yr. - 80%

  Humans: 70% of 90 Veterinarians Seropositive for BPyV Antibody
- Small 40-50 nm, Relatively Resistant to Inactivation
- BPyV DNA - Serum Substitutes with Bovine Components

(Schuurman, et. al., Biologicals (1991) 19, 265-270)

BOVINE/PORCINE

Bovine Viruses

- Infectious Bovine Rhinotracheltis (IBR)
- Bovine Viral Diarrhea (BVD)
- Parainfluenza Virus Type 3
- Bovine Adenovirus
- Bovine Parvovirus

9 CFR Testing Includes:

Reovirus Type 3

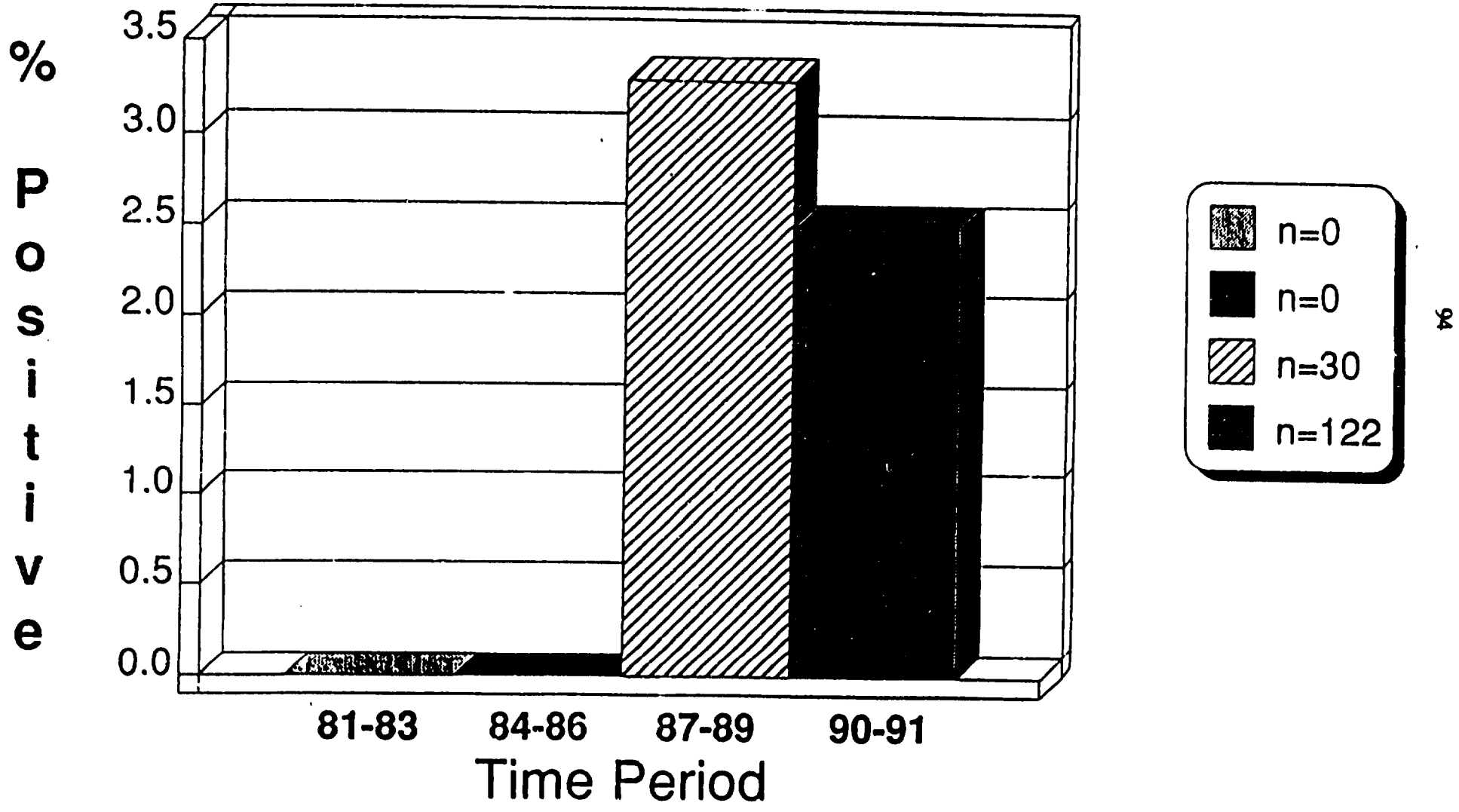
Rabies

Porcine Viruses

- Porcine Parvovirus

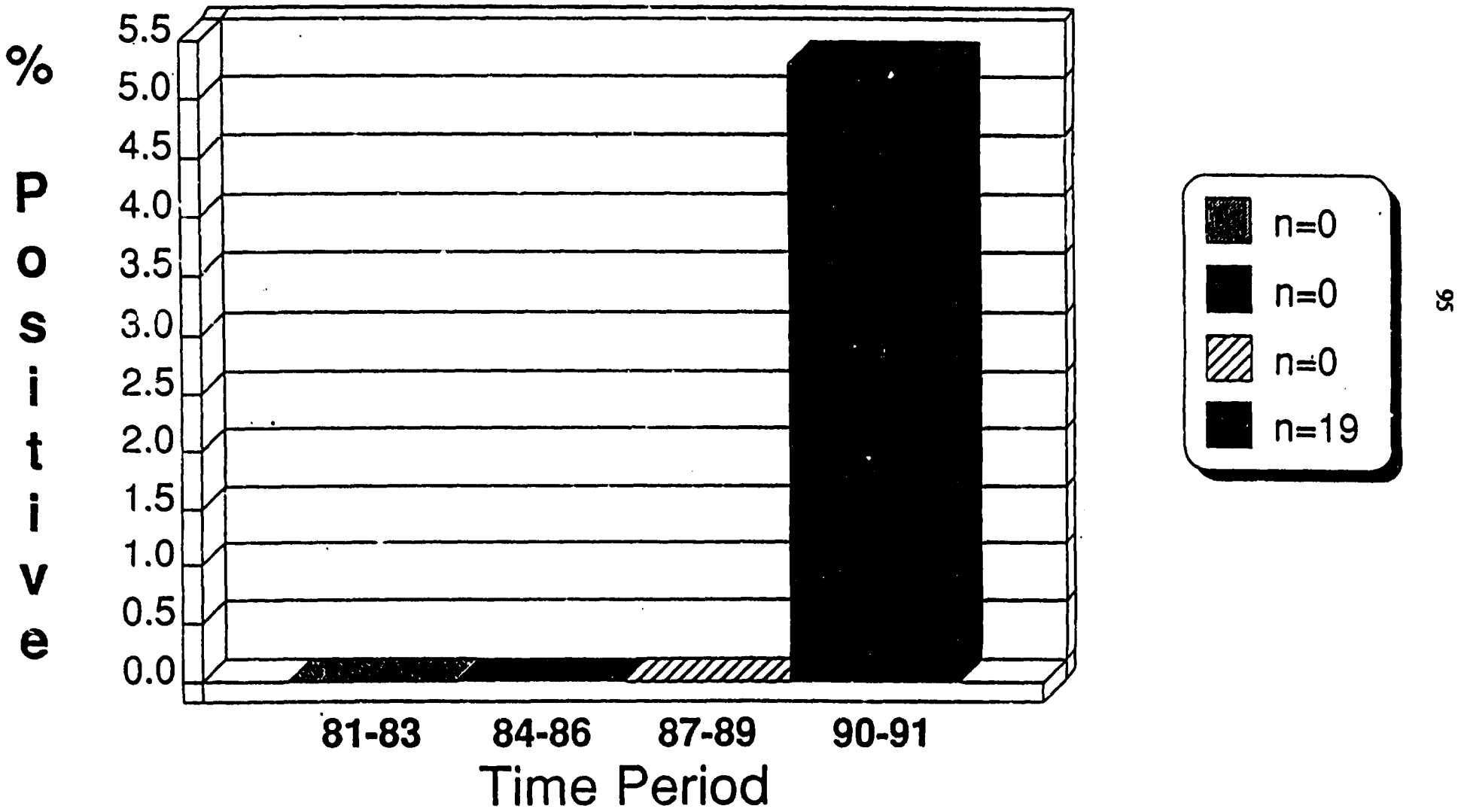
Results of Adventitious Agent Testing

Bovine Viral Screen



Results of Adventitious Agent Testing

Porcine Parvovirus Assay



MYCOPLASMA

Continuous Cell Cultures - Frequently Contaminated

- 15% (>3,000) Contaminated of >20,000 Cell Cultures Tested
- 1,262 (45%) of 2,800 Isolated Were Bovine Species
  - Mycoplasma Arginini - 26%
  - Acholeplasma Laidlawii - 8.5%
  - M. Pirum - 7%
- 929 (33%) of 2,800 Isolated Were Human Species
  - Mycoplasma orale - 29.5%
- 591 (21%) of 2,800 Isolated Were of Porcine Species
  - Mycoplasma Hyorhinis

Michael F. Barile and Shlomo Rottem (Submitted for Publication - Plenum Press)

MYCOPLASMA

Bovine Sera Contamination

- 104 Bottles Final Processed Serum (395 Separate Lots) from 5 Commercial Suppliers Were Contaminated
  - Frequently One to Ten Viable Mycoplasmas/ml
- 159 Lots of "Raw" FBS Contaminated of 438 Lots from 8 Different Abattoirs
- "Test Bovine Serum and Other Reagents Before Use"

Michael F. Barile and Shlomo Rottem (Submitted for Publication - Plenum Press)

MYCOPLASMA TEST METHODS

Three Phase Assay

Semi-Solid Broth Cultures Incubated 14 Days:

- Volume Dependent On Test Type
- Aerobic and Anaerobic Cultures
- Three Subcultures Onto Agar, Incubated 14 Days
- Provides the Amplification Mechanism

Direct Inoculation Onto Agar

- Two Types of Agar, Glucose and Glucose/Arginine
- Aerobic and Anaerobic Cultures Incubated 14 Days
- Allows Visualization of Specific Colonies

Vero Cell Culture With DNA Staining

- Detection of Strains Hard to Grow on Agar

MYCOPLASMA POSITIVE CONTROLS

- Support Test For Each Lot of Broth and Agar Medium Using A Number of Mycoplasma Species

- Specific Species of Mycoplasma Used As Concurrent Controls For Each Assay
  - Live, Concurrent Controls Required
  - FDA Requires:
    - *M. Pneumoniae* (Strain PI-1428)
    - *M. Orale* (Strain 1596 or Eq.)
    - *M. Hyorhinis*

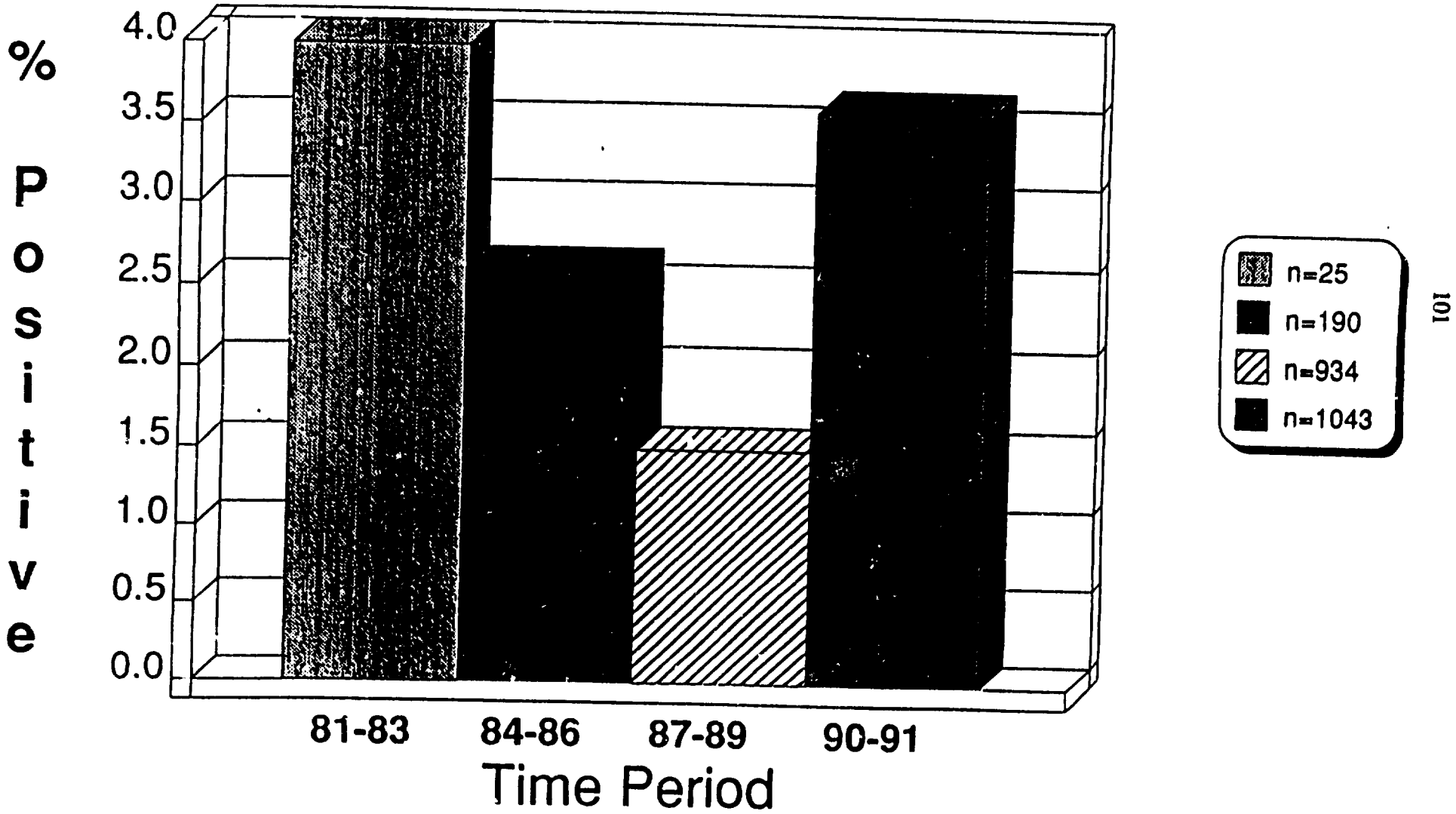
- European Pharmacopoeia:
  - *M. Gallisepticum*
  - *M. Synoviae*

MYCOPLASMA CONTAMINATION

Sample	# Tested	# Positive	% Positive
Research Assay			
Cells	2340	341	15%
Compliant Assays (CFR/P to C)			
Cells Product	691 1935	30 12	4.3% 0.6

Results of Adventitious Agent Testing

Mycoplasma Tests

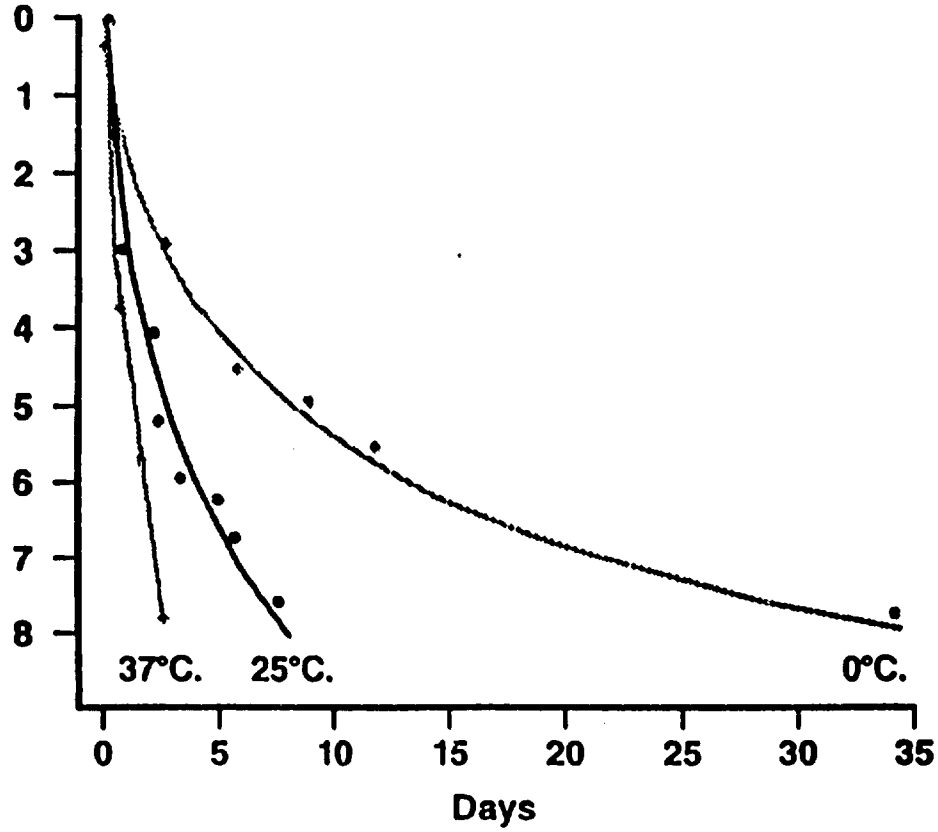


PROCESS VALIDATION
VIRAL INACTIVATION STRATEGIES

- Chemical - pH, Detergent, Solvent/Detergent, Reactive Inactivants

- Physical - Thermal, UV, Ionizing Radiation, Pressure, Sonic

PROCESS VALIDATION
FORMALIN INACTIVATION OF POLIOVIRUS



Salk, J.E. & Gori, J.B. Ann. N.Y. Acad. Sci. 83 626 (1960)

PROCESS VALIDATION/ VIRAL CLEARANCE STUDIES

Design

- Design Scaled-Down Version of the Process
- Choose Appropriate Spiking Viruses
- Select Appropriate Spiking and Sampling Points
- Growth, Titration, and Storage of High Concentration Viral Stocks
- Preliminary Buffer Cytotoxicity and Buffer Inactivation Studies
- Spiking Experiments and Viral Detection Assays
- Determine Clearance Factors

PROCESS VALIDATION
VIRAL CLEARANCE STUDIES

Virus Selection - Human and
Human x Murine Cell Substrates

• **DNA Viruses**	**Enveloped**	**Herpes Simplex 1**
	Non-Enveloped	**SV40**
• **RNA Viruses**	**Enveloped**	**Murine Leukemia Virus**
	Non-Enveloped	**Poliovirus 1 - Sabin**

PROTEIN SEPARATION TECHNIQUES
VIRAL LOG REDUCTION

Size Exclusion	1-5
HIC	2-6
Ion Exchange	2-6
Filtration	3-9
Affinity	2-6

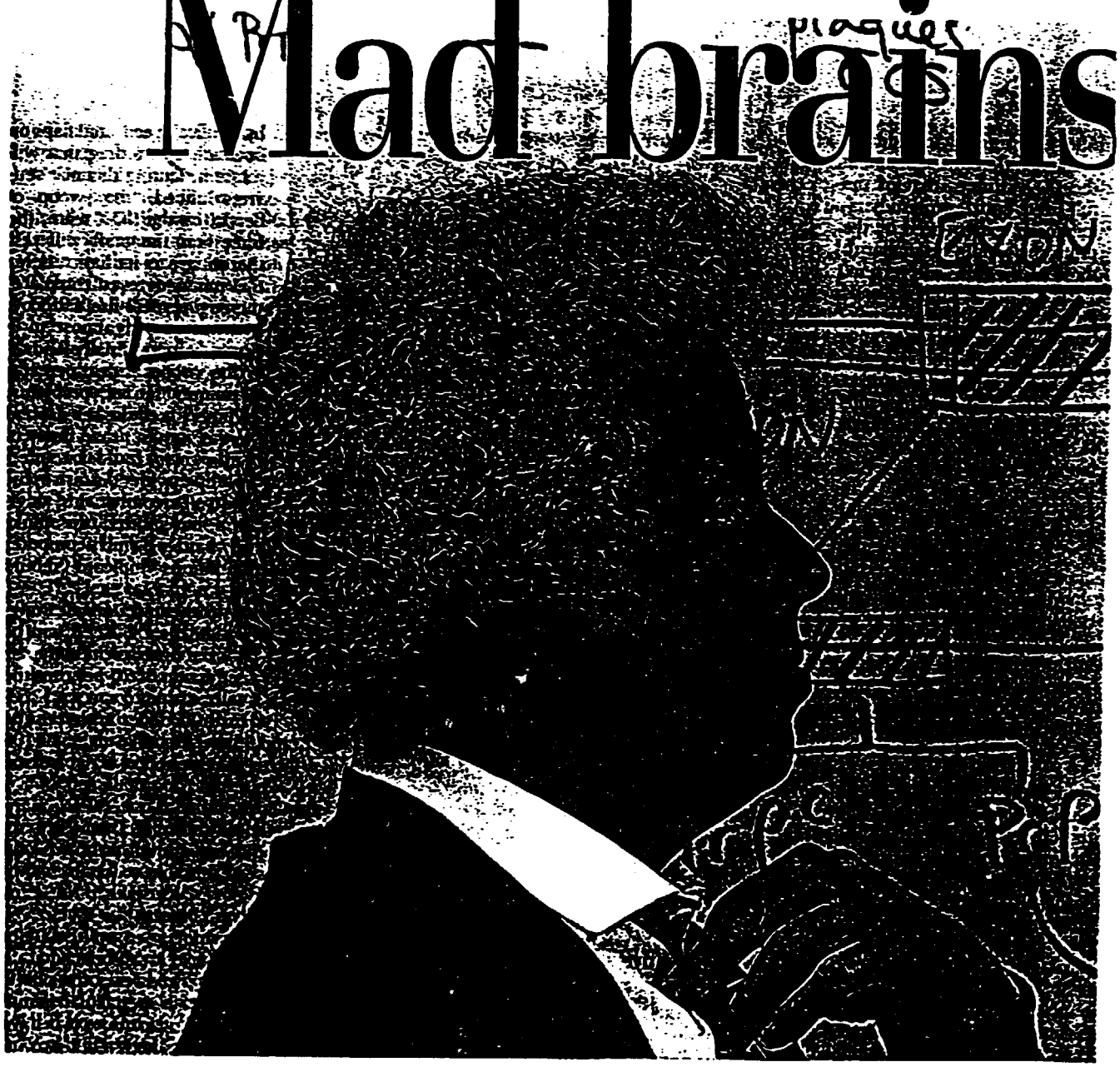
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSE)

Animals

- Scrapie - Sheep, Goats
- Similar TSEs - Mule Deer, Elk
  - Exotic Deer (Nyala, Gemsbox, Kudu, Impala)
- Transmissible Mink Encephalopathy (TME)
- Bovine Spongiform Encephalopathy (BSE)
- Domestic Cats
- Pigs?

Disease	Species	Source of Infection	Natural Spread
Bovine spongiform encephalopathy	Cattle	Scrapie infected food	?
Mink encephalopathy	Mink	Scrapie infected food	No
Scrapie	Sheep Goats	Natural	Yes
Wasting disease of deer	Mule deer, Elk	Natural	Yes
Expt. disease in laboratory animals	Mice, Hamsters	Injection of infected material from man, or ruminants or experimental animals	No No No
	Monkeys		No
Kuru	Man	Man	Yes
Creutzfeldt-Jakob disease	Man	?	No

Mad brains and the prion heresy



Enrico Ferorelli

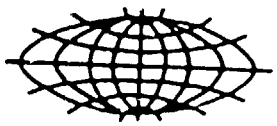
The idea that a simple protein could act as an infectious agent was too much for most biochemists. Georgina Ferry reports on what happened when one man dared to go out on a limb

FIDIA
RESEARCH
FOUNDATION

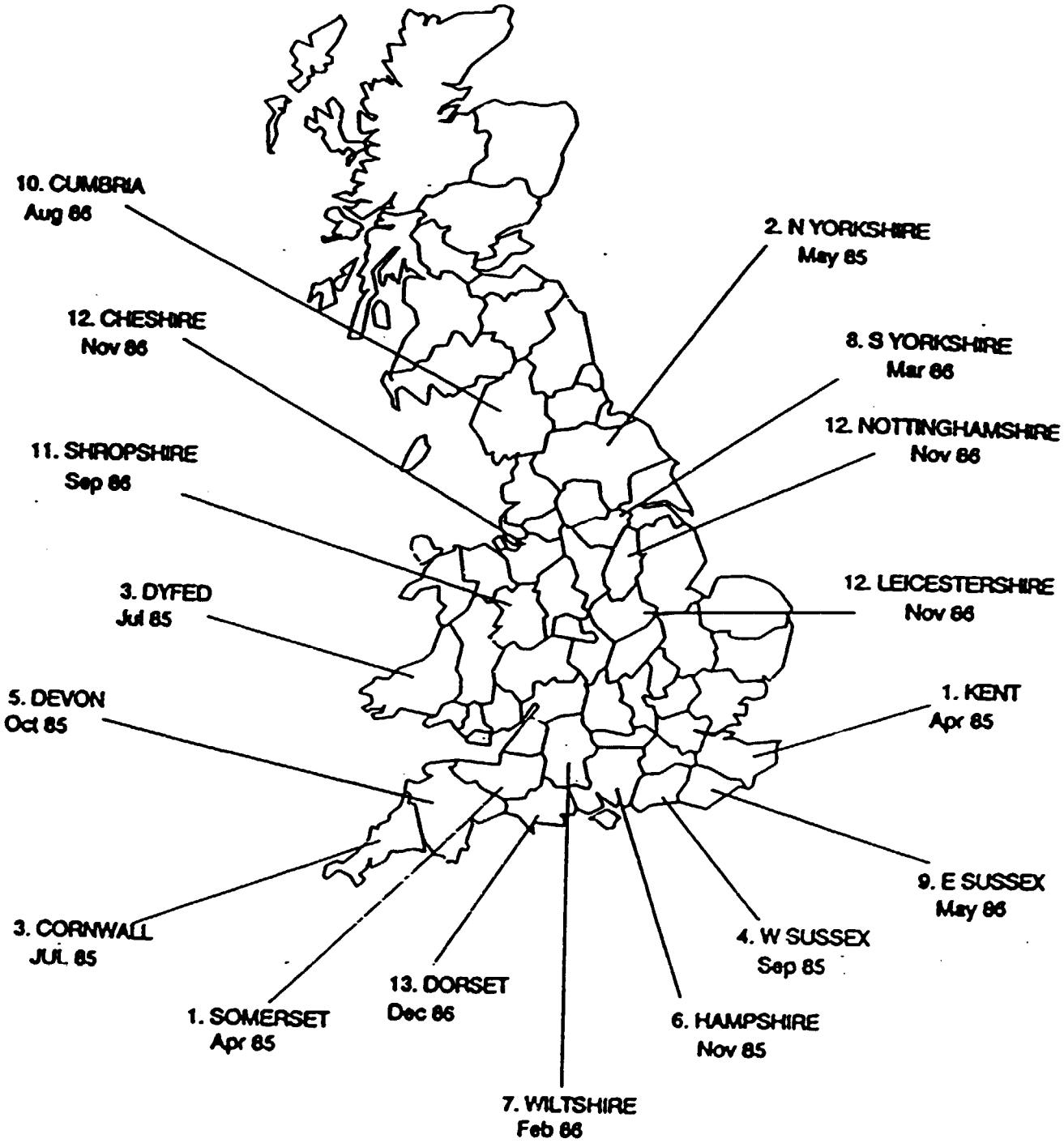
ARES
SERONO
SYMPOSIA

International Meeting on TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES Impact on Animal and Human Health

The Kongresshaus
Stadthalle, Heidelberg
Germany
June 23-24, 1992



INTERNATIONAL ASSOCIATION
OF BIOLOGICAL STANDARDIZATION

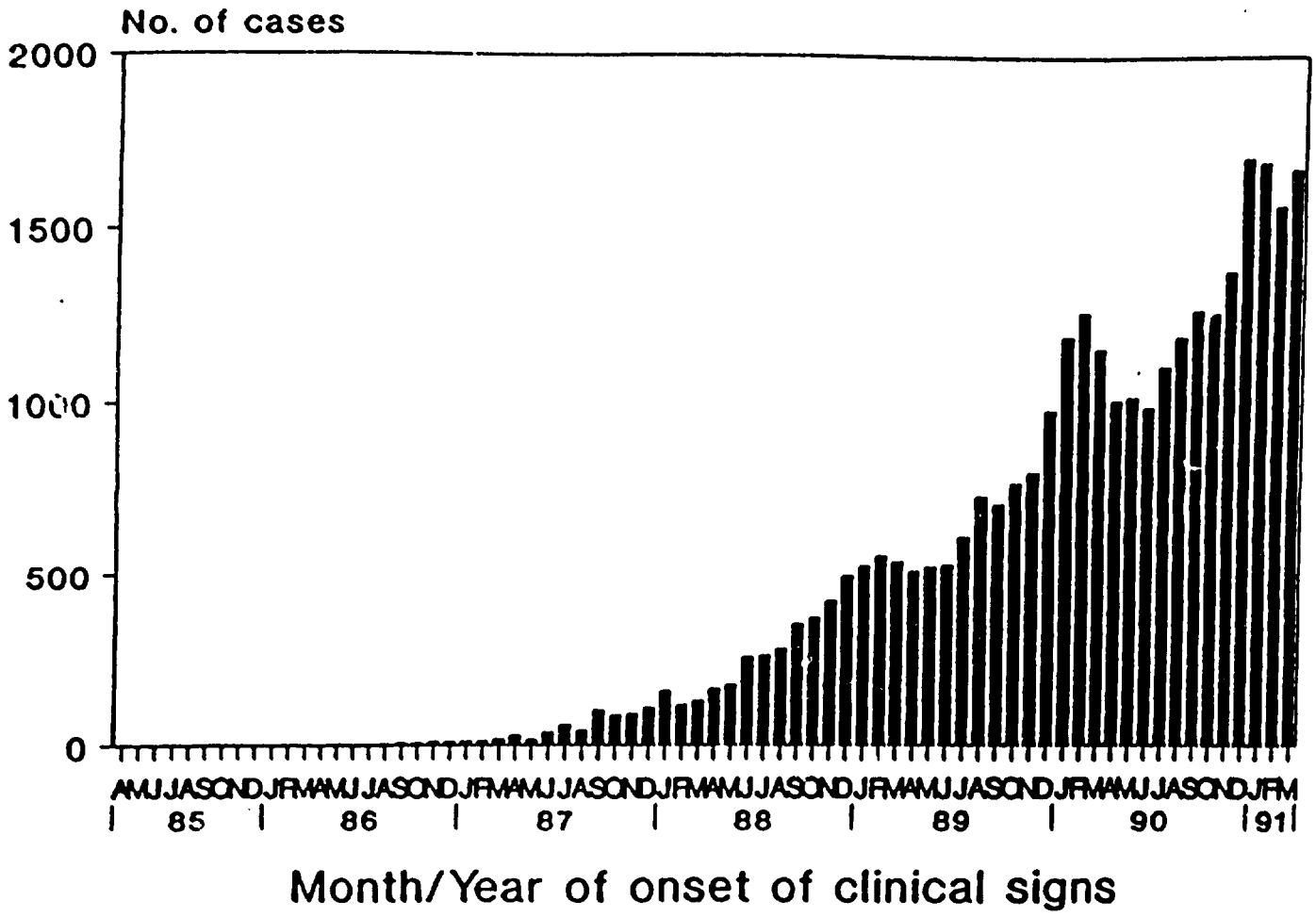


Geographical distribution and date of the first suspected cases of BSE, April 1985-December 1986.

Cumulative proportion of herds with BSE in homebred cattle by herd size and herd type

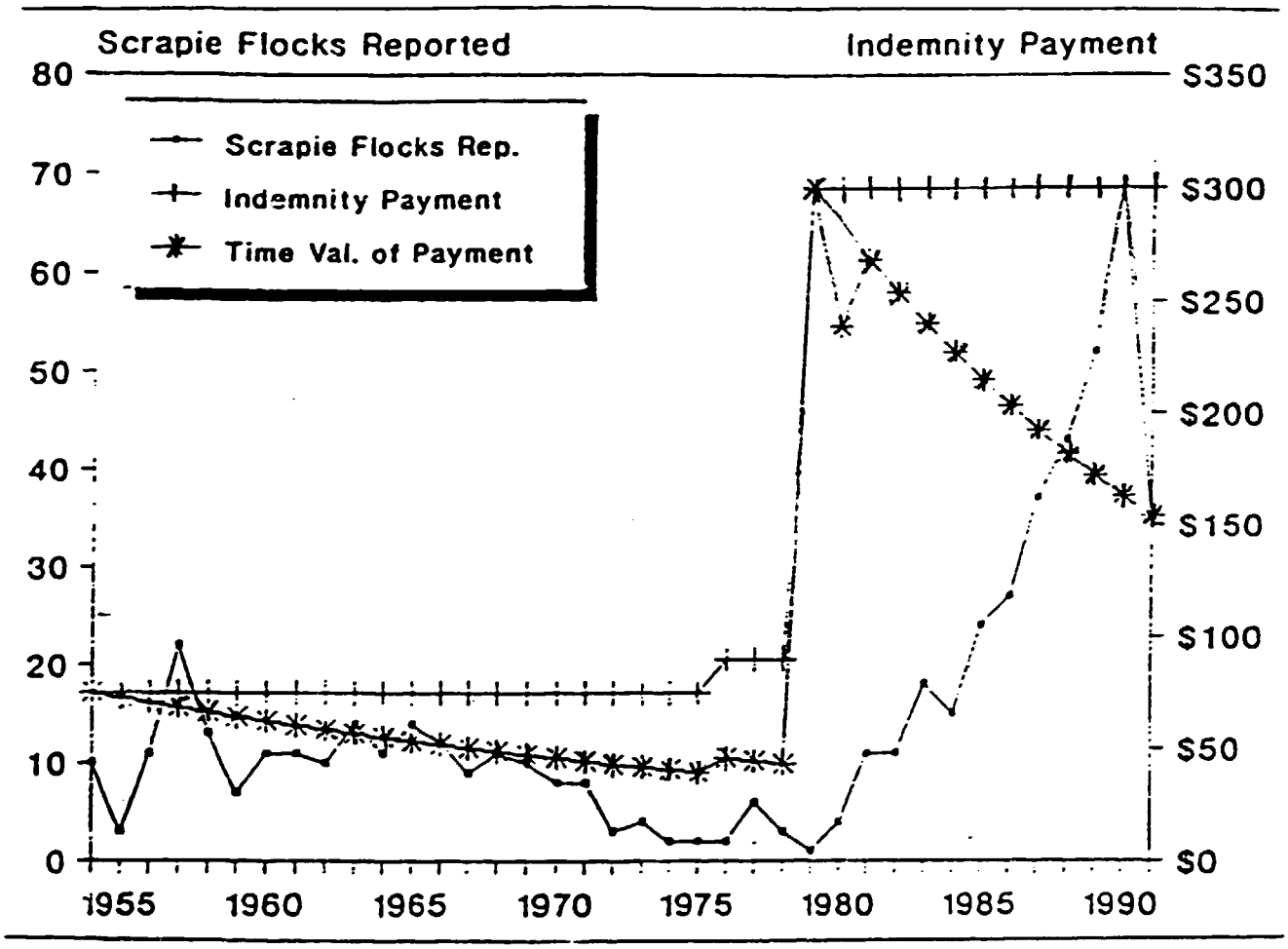
	Adult herd size			
	<50	50-99	100+	Total*
Dairy & mixed herds:				
No. herds affected	995	2778	3493	7266
No. herds at risk	18809	14632	7416	40857
% herds affected	5.29	18.96	47.10	17.78
Beef suckler herds:				
No. herds affected	112	50	30	201
No. herds at risk	49281	5179	1847	56307
% herds affected	0.23	1.14	1.62	0.36

* Total includes 65 dairy herds and one beef suckler herd with unknown herd size

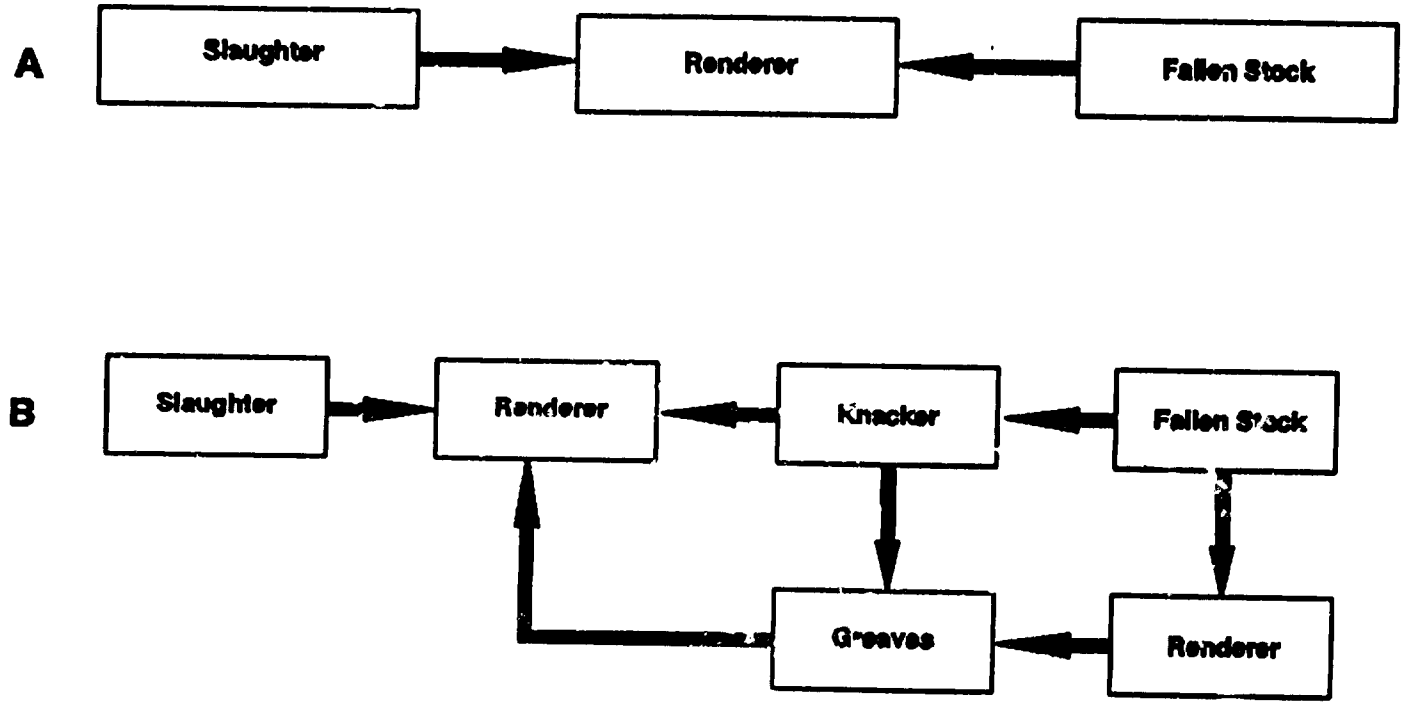


Epidemic curve of cases of BSE in Great Britain, April 1985-March 1991.

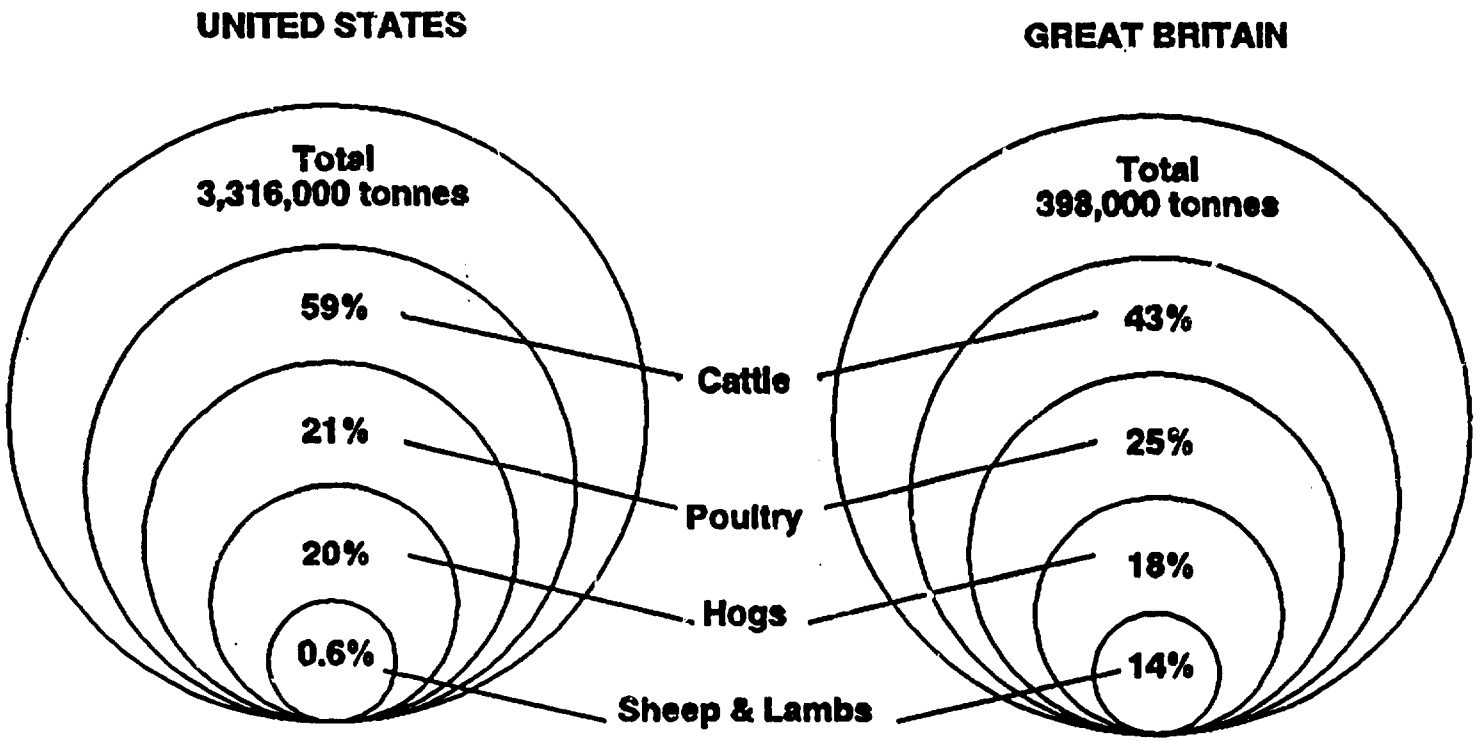
United States scrapie reporting and indemnity payments. Source: USDA-APHIS, 1955-1990.

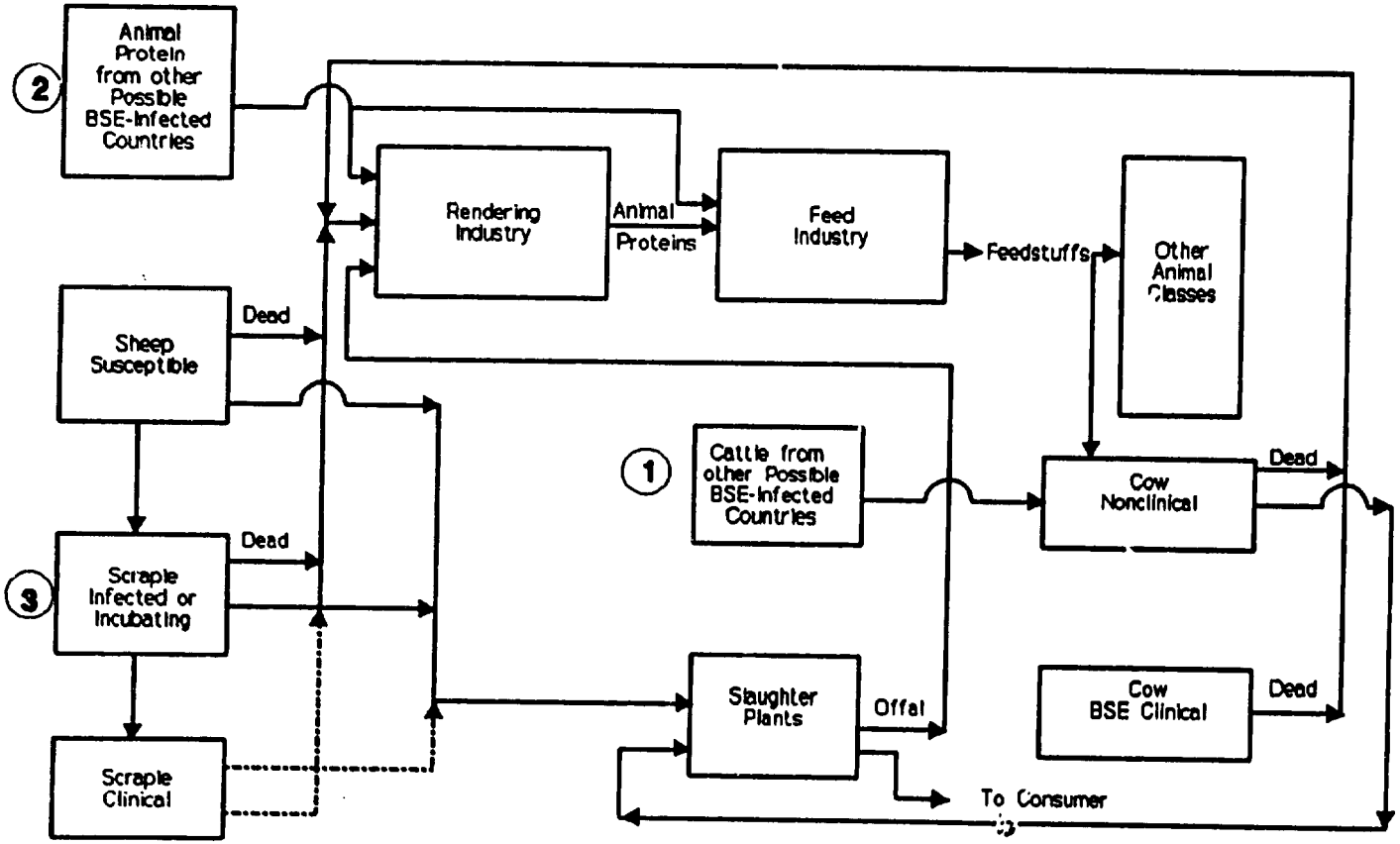


UNITED STATES (A) AND GREAT BRITAIN (B) RENDERING INDUSTRY STRUCTURE



UNITED STATES AND GREAT BRITAIN RENDERED ANIMAL PROTEIN ESTIMATED SPECIES COMPOSITION IN 1989.

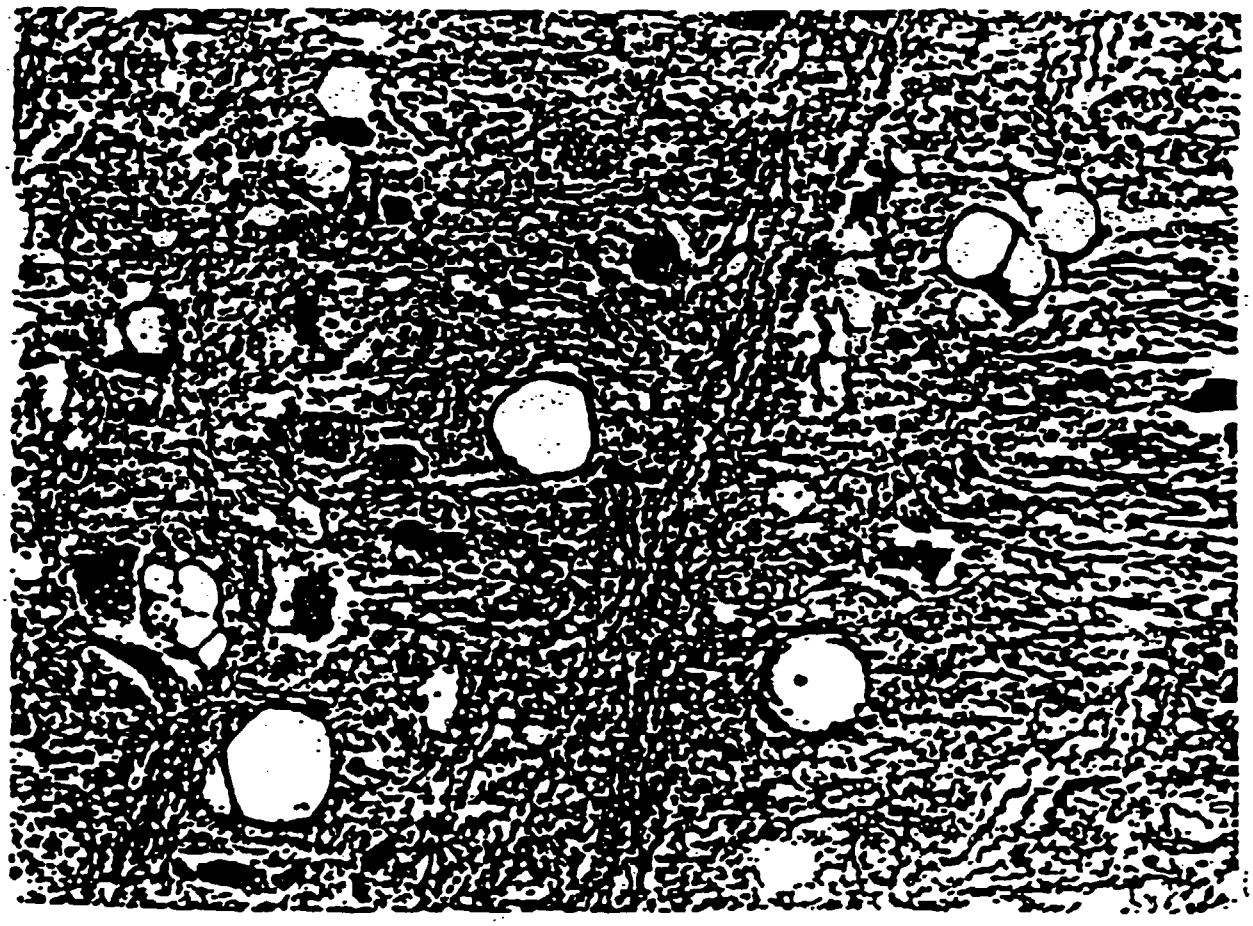




Systems model of hypothesized bovine spongiform encephalopathy epidemiology. Potential routes of transmission in the United States. Source: USDA-APHIS Veterinary Services.

BSE CHARACTERISTICS

- Spongiform Vacuolation of Brain
- Long Incubation Period - No Prior Clinical Indications
- Fatal
- No Immune Response
  - No Antibodies
  - No Inflammation
  - No Immune Suppression
  - No Interferon Response
  - No IL-1 Increase
- Scrapie Associated Fibrils (EM)
- Accumulation of a Modified Host Protein in Brain - Amyloid Plaques



The pathology of the spongiform encephalopathies is characterized by the presence of vacuolated neurones.

Properties of Cellular and Scrapie PrP Isoforms

	PrP^C	PrP^{Sc}
Normal cells	~1–5 μg/g	–
Scrapie-infected cells	~1–5 μg/g	~10–20 μg/g
Purified prions	–	+*
Protease resistance	–	+†
Amyloid rods	–	+‡
Subcellular localization	Cell surface	Primarily intracellular
PIPLC release from membranes	+	–
Synthesis ($t_{1/2}$)	≪2 h	~15 h
Turnover ($t_{1/2}$)	~5 h	≫24 h

* Copurification of PrP^{Sc} and prion infectivity by two protocols: (1) detergent extraction, sedimentation protease digestion; and (2) PrP 27-30 monoclonal antibody affinity chromatography.

† Limited protinease K digestion of hamster PrP^{Sc} produces PrP 27-30.

‡ After limited proteolysis of PrP^{Sc} to produce PrP 27-30 and detergent extraction, amyloid rods form; except for length, the rods are indistinguishable from amyloid filaments forming plaques.

Convergence of experimental results arguing that PrP^{Sc} (or PrP 27-30) is a major and necessary component of the prion

A. Biochemistry

1. Enriching brain fractions for scrapie infectivity using limited proteolysis, detergent extraction, differential centrifugation and sedimentation through discontinuous sucrose gradients led to the discovery of PrP 27-30.

2. Prion titers were found to be proportional to the PrP 27-30 concentration

3. Denaturation, hydrolysis or selective modification of PrP 27-30 also diminished prion titer.

4. Scrapie infectivity and PrP 27-30 copartition into multiple forms - membranes, rods, spheres, DLPCs and liposomes.

B. Immunology

1. Immunoaffinity purification of scrapie infectivity was accomplished using PrP monoclonal antibodies.

2. Rabbit antiserum raised against SDS-PAGE- purified PrP 27-30 neutralized scrapie infectivity in DLPCs.

C. Genetics

1. Genetic linkage of the PrP gene to loci controlling the scrapie incubation time (*Prn-i and Sinc*). Mice (*Prn-p*^{b})of long incubation times exhibit amino acid substitutions of codons 108 and 189 of their PrP gene.

2. Genetic linkage of an amino acid substitution at codon 102 of the human PrP gene with development of GSS.

3. Tg mice expressing hamster PrP exhibit incubation times, amyloid plaques, hamster PrP^{Sc} and scrapie characteristics of hamsters after inoculation with hamster prions.

D. Neuropathology

1. PrP amyloid plaques are specific to prion diseases in animals and humans.

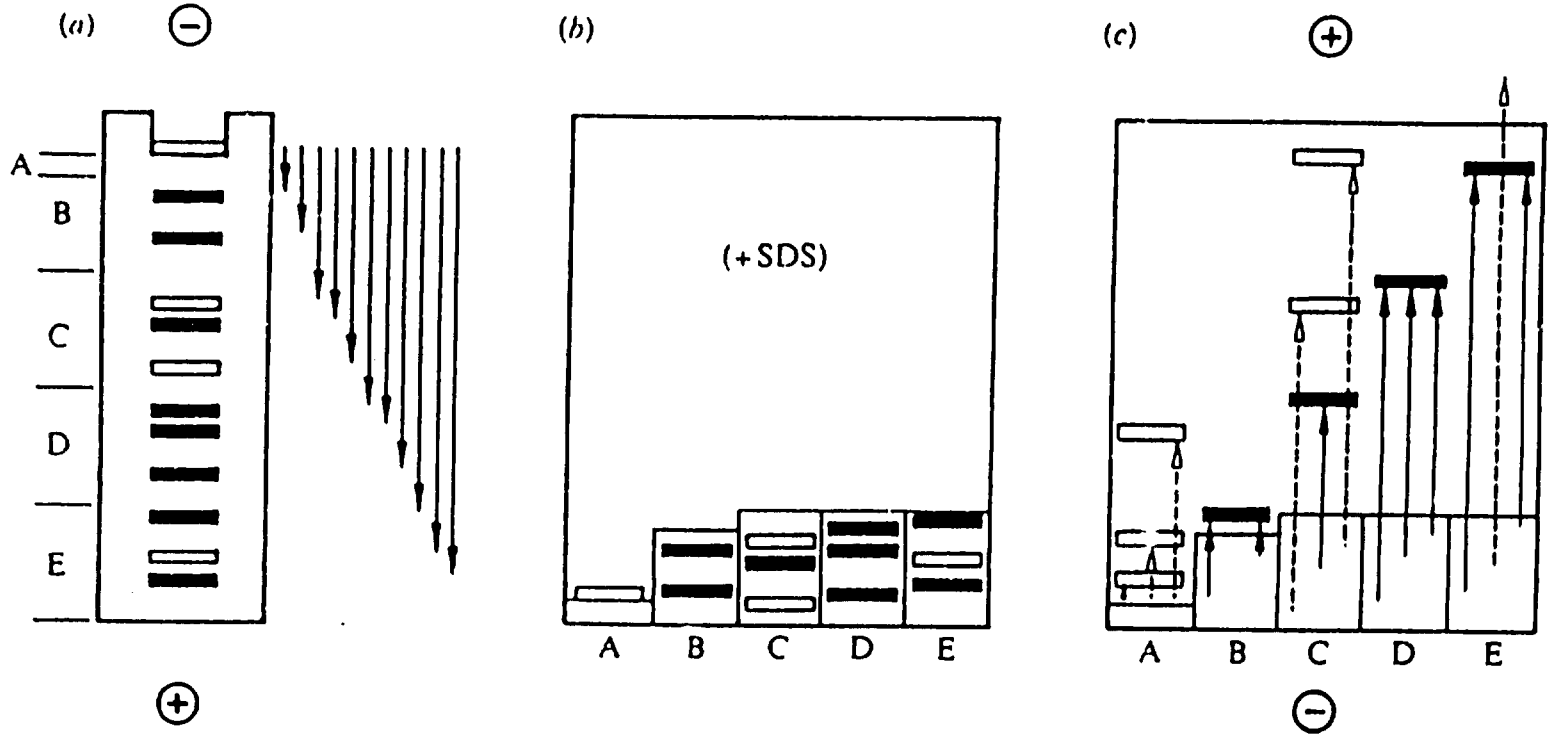
2. Hamster prions inoculated into Tg mice expressing hamster PrP induce cerebral amyloid plaques that are composed of hamster PrP and distributed in patterns similar to those seen in hamsters with scrapie.

3. Using a sensitive dot-blot assay for PrP^{Sc} (or PrP^{CJD}), there is an excellent correlation between prion diseases confirmed neuropathologically and that presence of protease-resistant PrP.

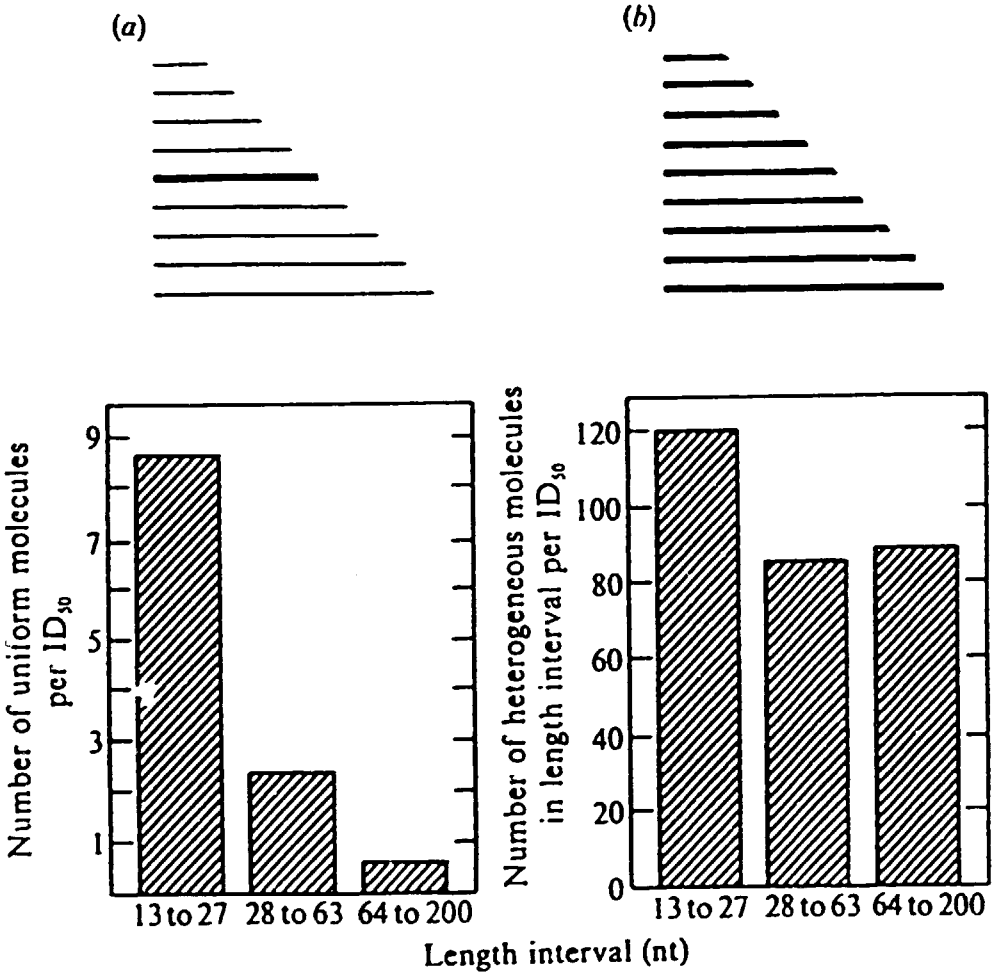
E. Cell biology

1. Cultured cells infected with scrapie prions produce PrP^{Sc}.

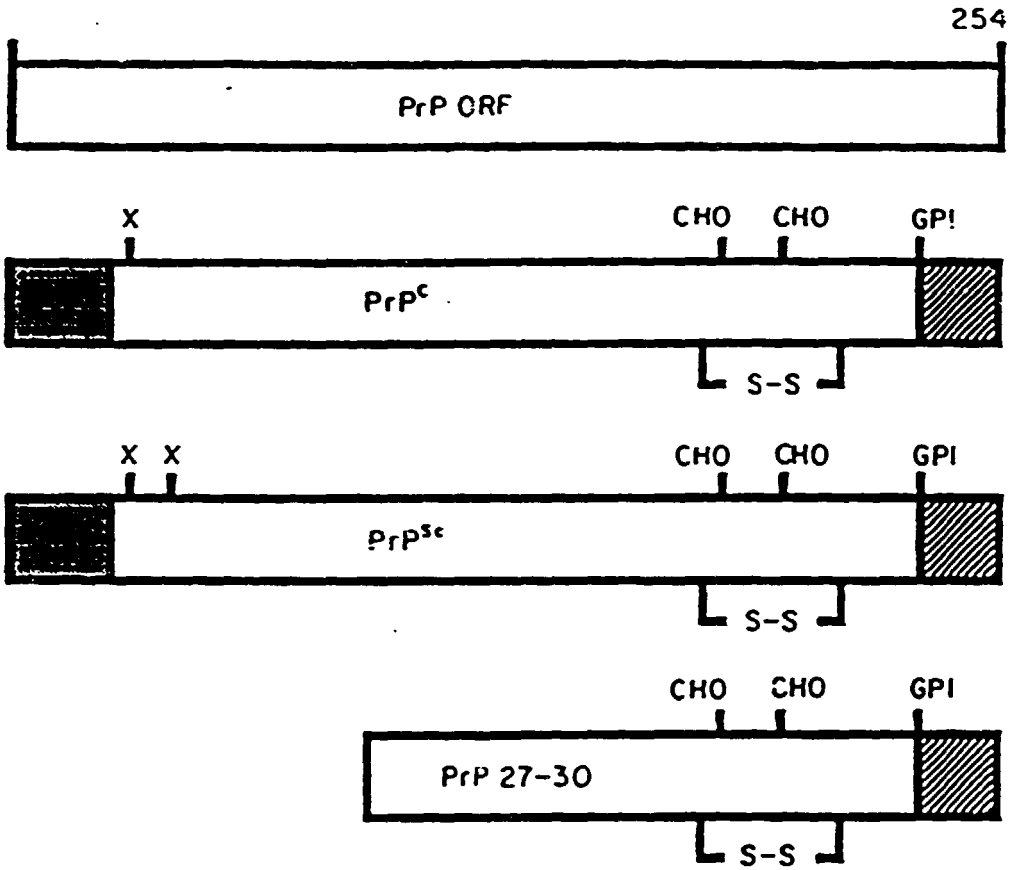
2. PrP^{Sc} is produced more slowly than PrP^{C}; furthermore, PrP^{Sc} accumulates primarily inside cells while most of the PrP^{C} is transported to the external cell surface.



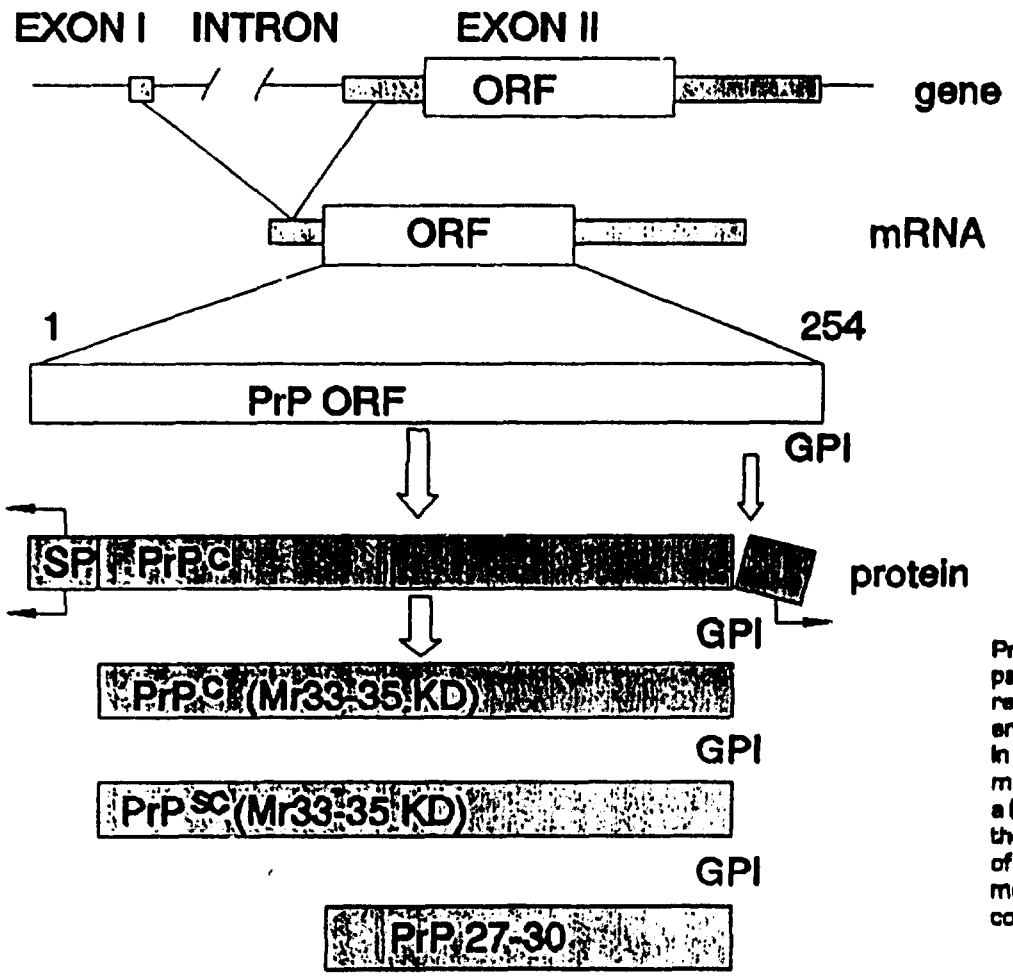
RRGE procedure. (*a*) The first electrophoresis is a conventional PAGE carried out in the absence of SDS. It is not possible to distinguish between protein and nucleic acids by silver staining. (*b*) The gel lane is cut into the segments A to E. The gel segments are polymerized at the bottom of a new gel matrix containing SDS. (*c*) A second electrophoresis in the reverse direction is carried out in the presence of SDS. The nucleic acids ▬ migrate back the same distance as they did in the first run (filled arrows with continuous lines) refocusing into one band. Owing to the presence of SDS, proteins ▭ do not move the same distance as in the first electrophoresis (open arrows with dashed lines) and are not refocused. To avoid slot artefacts, a small extra piece of gel was cut from the top area of the gel lane in segment A.



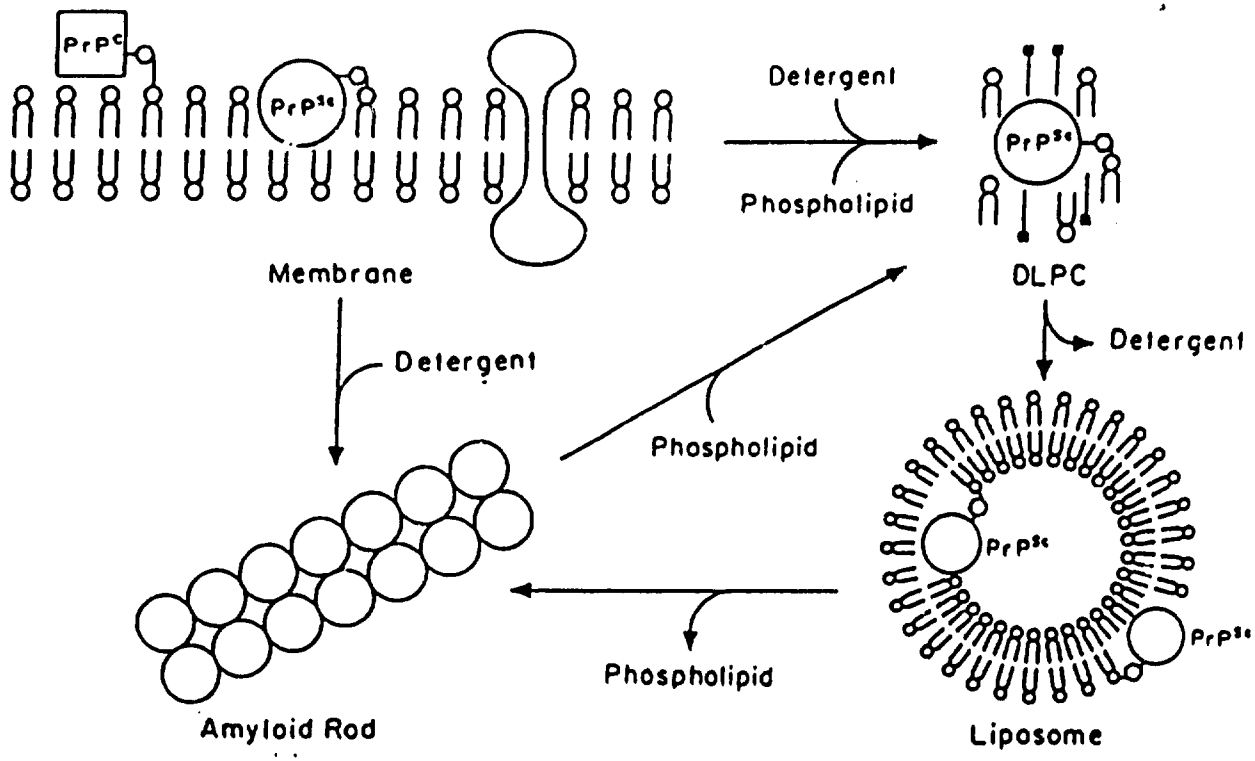
Two possible models for hypothetical scrapie-specific nucleic acid molecules. The results shown in Fig. 6(*b*) and (*c*) for prions after DLPC formation and treatment with nucleases (procedure II) were averaged for these estimates. The number of polymeric nucleotides was estimated for each gel segment separately and was correlated with the corresponding size range. The number of putative scrapie-specific nucleic acid molecules per infectious unit was based on alternative assumptions. (*a*) A putative scrapie-specific nucleic acid molecule of uniform length (heavy line) is hidden amongst an ensemble of background nucleic acids. (*b*) All nucleic acid molecules detected are putative scrapie-specific nucleic acids, although of different size (all heavy lines).



Prion protein structure. Hamster PrP gene encodes a protein of 254 amino acids. The N-terminal signal peptide of 22 amino acids (stippled pattern) is cleaved during maturation of PrP^{C} and PrP^{Sc}. Modified Arg residues (X) at codons 25 and 37 have been identified as well as Asn-linked oligosaccharides (CHO) attached to codons 181 and 197 within a loop formed by a disulfide bond which joins Cys at codons 179 and 214. Upon removal of a C-terminal hydrophobic peptide of ~20 amino acids (diagonal line pattern), a glycosyl phosphatidylinositol (GPI) anchor is added. Reproduced, with permission, from the Annual Review of Microbiology, Vol. 43. Copyright 1989 by Annual Reviews Inc.



PrP gene organization and prion protein structure. Upper part: The open reading frame (ORF) or protein coding region is indicated by the open box. Lower part: The gene encodes a protein of approximately 250 amino acids (aa). In this example the hamster PrP (254aa) is used. During maturation a signal peptide (SP) of 22 aa is cleaved off and a (GPI) anchor is added upon removal of a 23 aa peptide at the C-terminal. The resulting product is the PrP^{C}, with a Mr of 33 to 35 kDa, the precursor of PrP^{Sc} with identical molecular weight. PrP 27-30 is the protease-resistant core of PrP^{Sc} (after Prusiner, 1991b).



Interconversion of multiple prion forms. PrP^{Sc} is a membrane-bound protein which upon limited proteolysis produces PrP 27-30. Detergent extraction of membrane-bound PrP 27-30 produces amyloid rods which can be dispersed into DLPCs by addition of phospholipids. DLPCs can be formed directly from membranes by addition of detergent and phospholipid. Removal of detergents from DLPCs produces closed liposomes. Removal of phospholipid from liposomes by organic solvent extraction ($CHCl_3$:methonal) regenerated the rods. All of the prion forms shown here possess high levels of scrapie infectivity. Reproduced, with permission, from the Annual Review of Microbiology, Vol. 43. Copyright 1989 by Annual Reviews Inc.

SCRAPIE

- Route of Infection
  Lymphoreticular System to CNS
- Efficiency of Transmission
  (Studies With Hamster/Mice)

Route	LD_{50}
IC	1
IO, IV	10
IP	500 - 4000
SC	25,000
Oral	> 40,000

Relative scrapie infectivity titres in tissues and body fluids from naturally infected Suffolk sheep and goats with clinical scrapie

Category I High infectivity
- BRAIN, SPINAL CORD

Category II Medium infectivity
- SPLEEN, TONSIL, LYMPH NODES
- ILEUM, PROXIMAL COLON

Category III

a) Some infectivity
- SCIATIC NERVE, PITUITARY, ADRENAL
- DISTAL COLON, NASAL MUCOSA

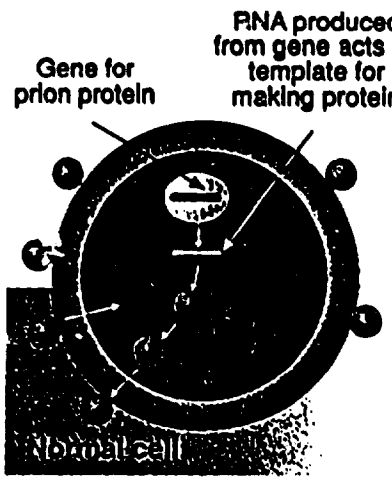
b) Minimal infectivity
- CEREBROSPINAL FLUID, THYMUS, BONE MARROW
- LIVER, LUNG, PANCREAS

Category IV No detectable infectivity
- SKELETAL MUSCLE, HEART
- MAMMARY GLAND, COLOSTRUM, MILK
- BLOOD CLOT, SERUM, FAECES
- KIDNEY, THYROID, SALIVARY GLAND, SALIVA
- OVARY, UTERUS, TESTIS, SEMINAL VESICLE

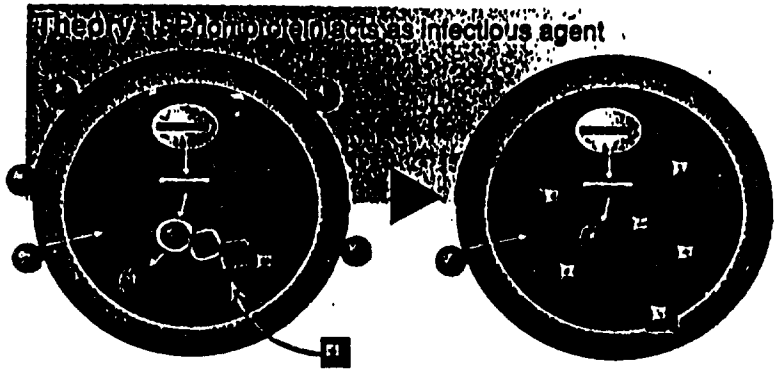
SCRAPIE INFECTED TISSUES

Tissue	*Titre*
Brain Spinal Cord	7
Spleen	6
Peripheral Lymph Nodes Thymus Intestine	5
Lung Femoral Bone Marrow	4
Submaxillary Salivary Gland	3
Uterus Liver Kidney	> 3
Testis Blood Clot Serum	ND

How scrapie infects brain cells

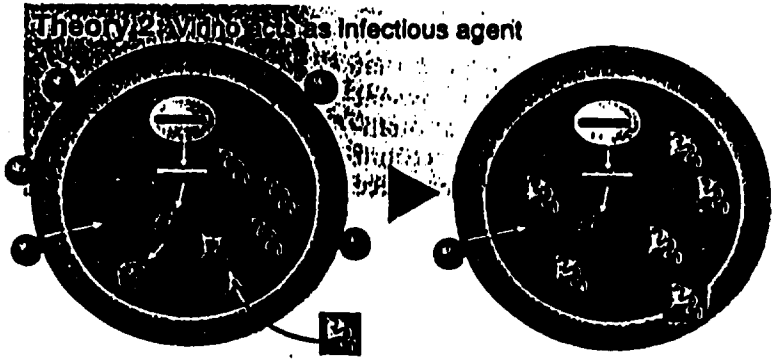


Normal prion protein is transported to cell surface and then back into cell



Abnormal prion protein enters cell and corrupts normal protein

Abnormal protein builds up in cell, eventually causing cell death

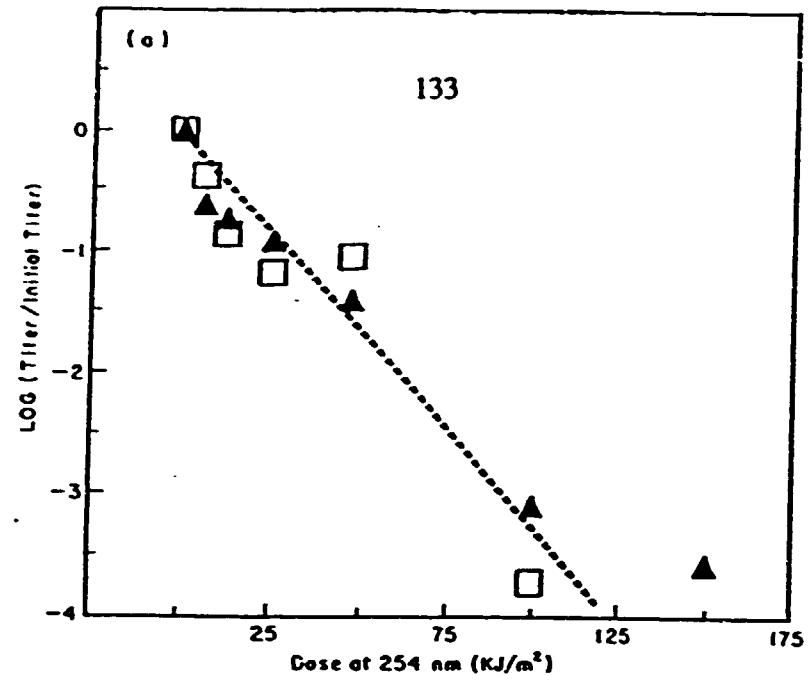


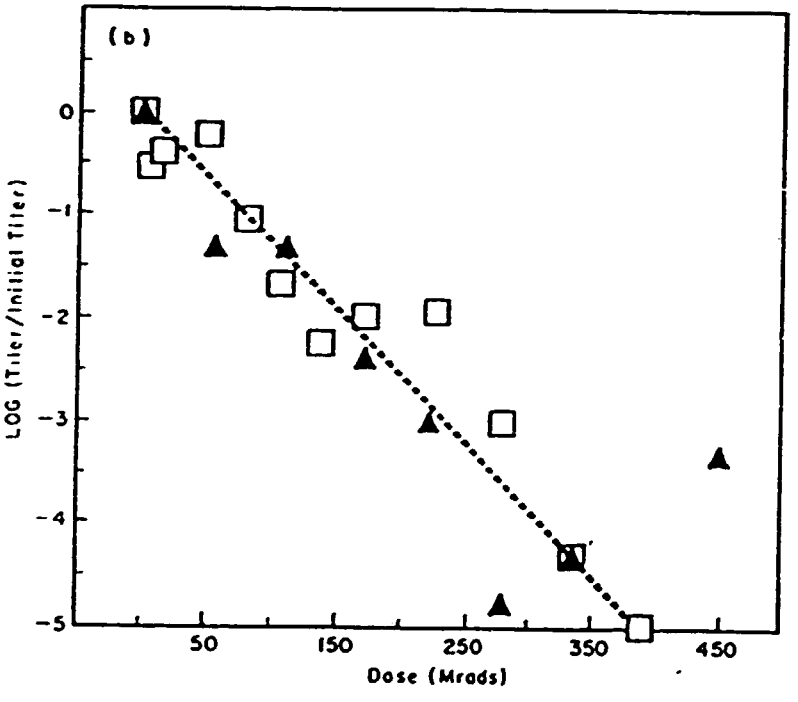
Virino (abnormal prion protein plus nucleic acid) enters cell. Nucleic acid replicates inside cell

Nucleic acid corrupts normal prion protein, causing more virinos to form inside cell

PROCESS VALIDATION
BSE REMOVAL/INACTIVATION

- BSE - Not Cloned, Long Incubation Period in Rodents
- Model Agents
  - Hamster 263K Clone
    - High Titre (10^{11}/G)
    - 90 Day Incubation
    - Short Life of Hamsters
  - Mouse Strains (ME7, 22A)
    - Incubation Period 150-160 Days
    - Longer Lifespan of Mice
- Use Clarified Brain Homogenate For Spiking
  - Solubilization in Sarkosyl
- Titration By Intra-Cranial Injection
- Numbers of Animals For Statistical Significance

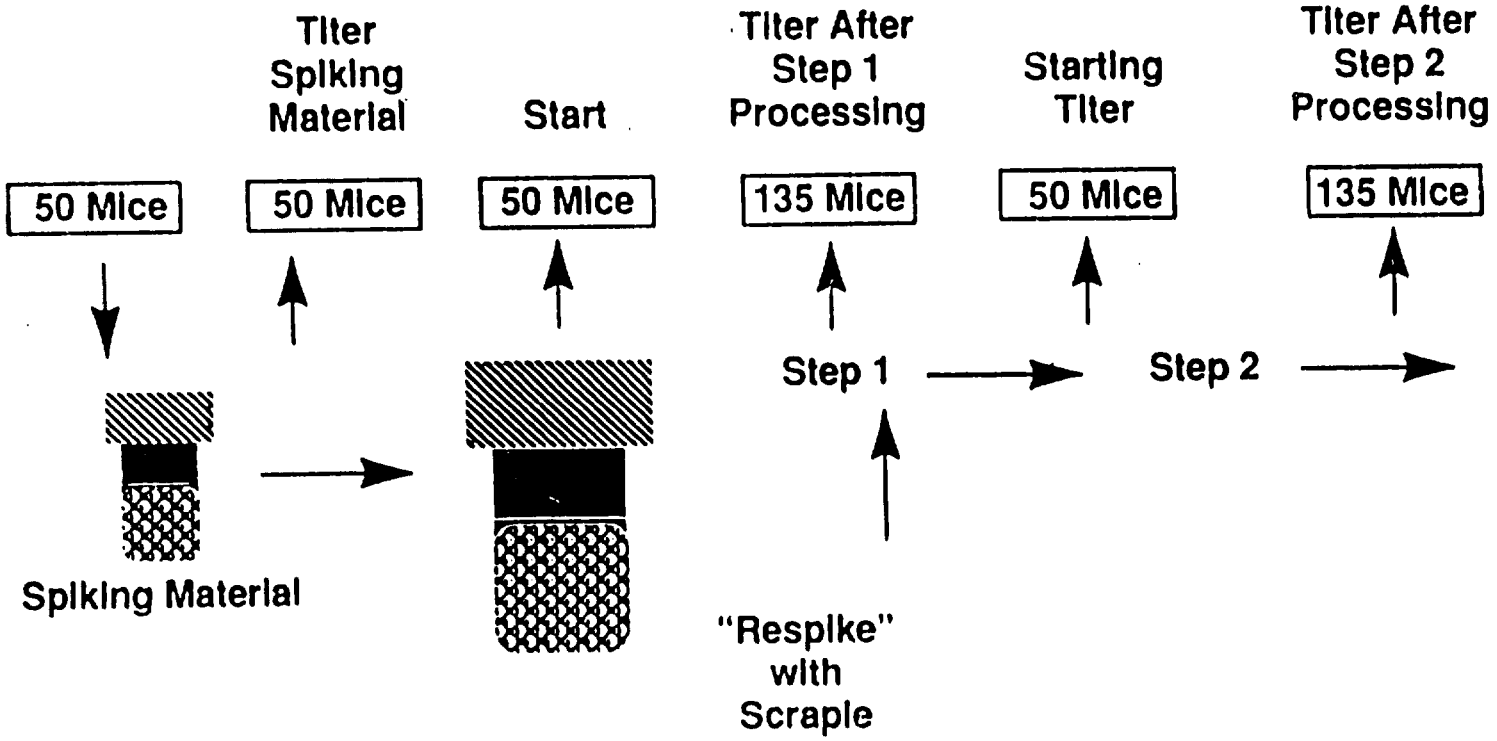




Inactivation of scrapie prion rods and liposomes by irridation. (□), Amyloid rods containing ~30 μg/ml of PrP 27-30; (▲) dispersed PrP 27-30 in 20 mg/ml PC as DLPCs were prepared as previously described. After irradiation studies, samples were inoculated intracerebrally into Syrian hamsters for scrapie bioassay. Log (titer of irradiated samples/titer of unirradiated samples) were plotted as a function of the irradiation dose. Curves were visually fitted. (a) Ultraviolet irradiation of prions. Fractions were irradiated with ultraviolet light with a 5 GE germicidal lamp for increasing periods of time. (b) Ionizing radiation of prions. All samples were frozen in ethanol dry ice baths prior to storage at −70°C. The samples were irradiated with 13 MV electrons at 135°C. Controls receiving no irradition were subjected to the same protocol. Reproduced, with permission, from Biochemical Journal, Vol. 266, pages 1–14, 1990.

SCRAPIE PROCESS VALIDATION

Animal Requirements



CANADA CONFRONTS THE POORLY UNDERSTOOD, FATAL CATTLE DISORDER THAT HAS WREAKED HAVOC ON THE BRITISH BEEF INDUSTRY

ERIC NELSON

Agriculture and Agri-food Canada

News Release

For immediate release

Single Case of BSE Reported in a Cow from the U.K.

OTTAWA, Dec. 8, 1993 – Agriculture and Agri-Food Canada today announced an imported beef cow, which died recently on a central Alberta farm, was infected with Bovine Spongiform Encephalopathy (BSE).

The animal was imported in 1987 from the United Kingdom as part of a very small shipment. The farm has been quarantined by federal veterinarians while an on-site investigation is being conducted. The cow was one of a group of imports under surveillance since 1990.

BSE is a slowly progressing, fatal nervous disorder of adult cattle. The disease has been a serious problem in cattle herds in the U.K. since the first case was diagnosed in 1986. Researchers believe the disease was spread in the U.K. when rendered material from infected ruminants was fed to cattle. The circumstances which led to the U.K. outbreak do not exist in Canada.

Agriculture and Agri-Food Canada has monitored the U.K. situation closely and in 1990 implemented a ban on the importation of live ruminants from there.

Both Canada and the United States have active surveillance systems in place. No previous case of BSE has been reported in North America.

Scientists in Europe and North America say there is no evidence that BSE is transmissible to humans.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

JAN 13 1994

May 3, 1991

Dear Biologic Product Manufacturer:

The Center for Biologics Evaluation and Research (CBER) is seeking clarification of the procedures and precautions used in controlling materials of bovine or ovine origin in the manufacturing of biologic products intended for administration to humans. This will assist CBER in evaluating the impact of evolving information regarding infectious agents potentially present in materials from bovine or ovine sources (e.g., spongiform encephalopathies).

We are therfore requesting, pursuant to 21 CFR 207.31, that manufacturers of biologic products provide information regarding the source(s) and control of any bovine- or ovine-derived material(s) used in preparing products to be administered to humans for prophylaxis, therapy, or diagnosis. This is directly incorporated into the product, but also for information on any materials used in manufacturing (e.g., enzymes, cell culture components, chromatographic media, etc.).

Some specific examples of materials that are, or may be, of bovine or ovine origin include bovine fetal serum, bovine serum albumin, fetuin, proteolytic enzymes (e.g., protease, trypsin, chymotrypsin, etc.), deoxyribonucleases (this is not intended to be a complete listing). If you are unsure of the origin of a component used in the preparation of your products, please obtain this information from the supplier.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

JAN 13 1994

December 17, 1993

TO: Manufacturers of FDA-regulated Products

The Food and Drug Administration (FDA, the Agency) is issuing this letter to request that bovine-derived materials from cattle which have resided in or originated from countries where Bovine Spongiform Encephalopathy (BSE) has been diagnosed not be used in the manufacture of FDA-regulated products intended for administration to humans. We are advising you of our current recommendations pertaining to the use of such bovine-derived products.

The Agency notes that regulated products intended for administration to humans and manufactured with bovine-derived materials derived from cattle that have at any time been in BSE-countries may be adulterated under Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), for drugs and biological drug products; or Section 501(h) of the Act, for medical devices and biological device products. The Agency is considering rulemaking to restrict the use of bovine-derived materials from BSE-countries. At this time, FDA recommends that bovine-derived materials from BSE-countries not be used in the manufacture of FDA-regulated products.

a. identify bovine-derived materials used in the regulated product and identify all countries where the animals used for the material have lived. This information may be provided to the regulated-product manufacturer by the supplier of the bovine product. The supplier may also provide the manufacturer with appropriate veterinary regulatory inspection certification of slaughter, as required by the country of origin of live animals.

b. maintain traceable records for each lot of bovine material and each lot of FDA-regulated product using these materials. These records should be part of the batch records, and available for FDA inspection.

c. document the country of origin of the live animal source of any bovine-derived materials used in the manufacture of the regulated product. Documentation should be maintained for any new or in-process lots of licensed, cleared, or approved products; products pending clearance or approval; and investigational products intended to be administered to humans. Such documentation should be a part of the traceable records maintained in conjunction with batch production records, and such information should be available for review during FDA inspections.

d. maintain copies of the records identified above for FDA-regulated products that are manufactured with bovine-derived materials at foreign sites, or by the foreign manufacturers. The U.S. firms responsible for marketing these products should be responsible for these records. Manufacturers of products subject to licensure should maintain records at the site of manufacture.

Regulated-product manufacturers are referred to the USDA for current information and countries on the "BSE-list". Additional information and regulations concerning bovine spongiform encephalopathy (BSE) and affected animals may be obtained from the open veterinary literature and the United States Department of Agriculture (see 9 CFR 94.18).

COMMISSION OF THE EUROPEAN COMMUNITIES
DIRECTORATE-GENERAL III
INDUSTRY
Industrial affairs III: Consumer goods industries
Pharmaceuticals

Brussels, 16 March 1994

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Background Document on medicinal products derived from human blood or plasma

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded.

In order to fully inform both doctors and patients, the Committee recommends that the summary of product characteristics and the user package leaflet of all medicinal products derived from blood or plasma should include the following warning:

"When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This applies also to pathogens of hitherto unknown origin.

THE STATUS OF MODERN VACCINE MANUFACTURING: A POSITION PAPER (Draft)

by Z. Csizer, M.D. Ph.D., UNIDO

A. Introduction

This paper describes modern industrial vaccine manufacturing from a number of perspectives. The focus is to illustrate current and future trends, and areas where manufacturers face uncertainty or change.

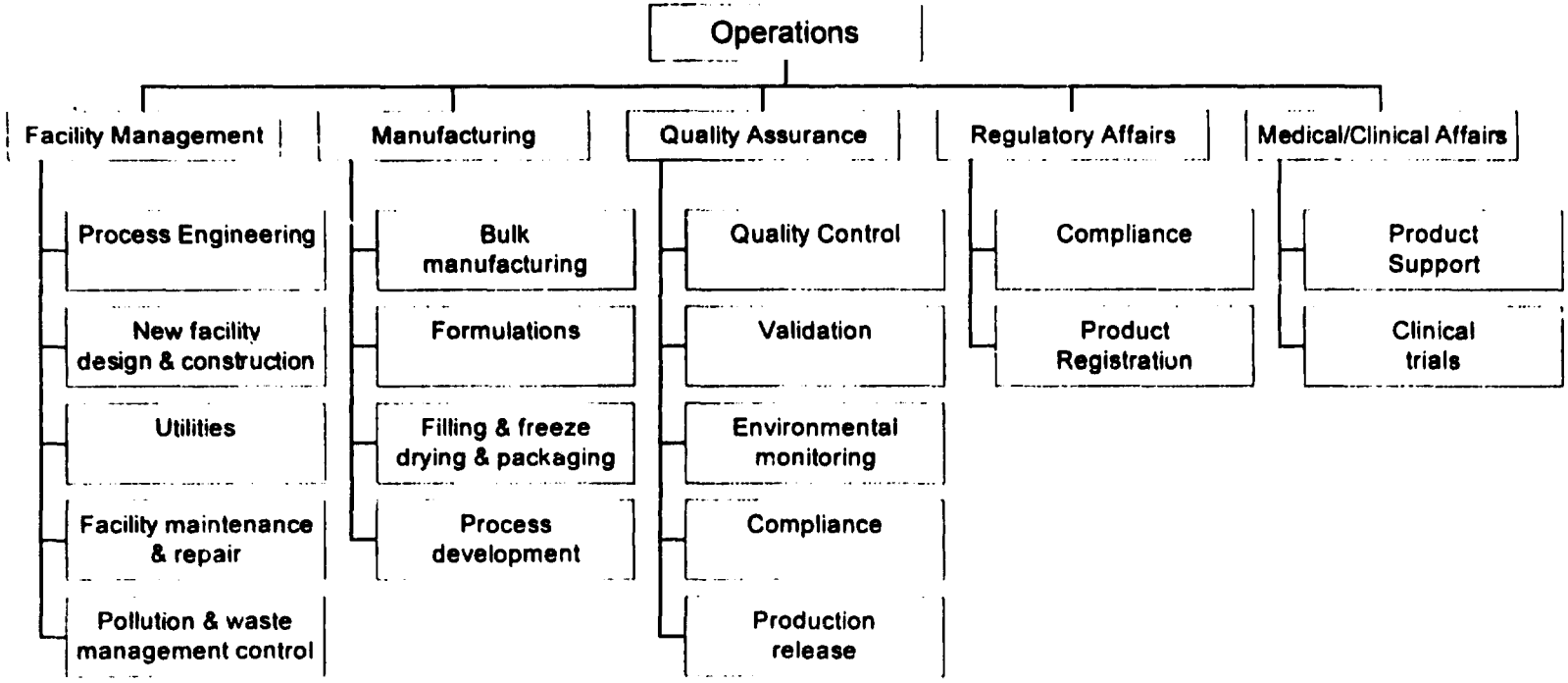
B. Modern Manufacturing Issues

Vaccines production can be considered as one of the earliest examples of industrial scale biological pharmaceutical production. In some cases, the scientific nature of the processes for making traditional vaccines has changed little in the past 30 years. However, today's manufacturing practices for pharmaceuticals result in some of the most closely controlled processes in the industrial world. In modern production terms, vaccines are considered no differently from other similar biological therapeutic products. For modern purified or subunit vaccines, the processes are often as complex as for making a therapeutic protein (for example, Factor VIII produced from a genetically engineered mammalian cell or Insulin produced from genetically engineered yeast or E.coli). It follows that, in today's industrial setting all vaccine manufacture is required to meet the same standards as are applied to the other new products of biotechnology and the rest of the parenteral drug industry.

Some issues for modern vaccine manufacture are described briefly in the following section. Many issues stem from the high quality specifications and control as required by most Regulatory Authorities e.g. European Pharmacopoeia (EP), Food and Drug Administration (FDA) - Code of Federal Regulations, International Standards Organisation (ISO) and many other government Regulatory Authorities. These requirements specify for facilities, utilities, raw materials, good laboratory practices (GLP), good manufacturing practices (GMP), quality assurance, quality control, control and trail of all documentations, filling and packaging and release of the vaccine. Technological innovations, for example in equipment design, and automation and control systems, are becoming consistently applied to improve production and maintain competitiveness, but often create issues in their application and implementation. But when these innovations are used correctly, they can increase the control and consistency of manufacturing.

In any modern vaccine manufacturing plant, manufacturing is one of the team player amongst a large team that make vaccines happen. The role of these other team players are briefly described to give the reader the appreciation of the scope and complexity of the vaccine business. The following chart demonstrates a typical vaccine manufacturing organization:

Vaccine Manufacturing Organizational Chart



Facility Management

Facility management has become very sophisticated since the last 30 years, as then, most of the innovation came through manufacturing and the process evolved. However, with today's high standard requirements from the Regulatory Authorities and the demands of modern manufacturing, the facility management has evolved into at least five distinct functions.

Process Engineering: professionals with chemical, process and biotechnology engineering qualifications evaluate new product or existing processes for scale up or to redesign the process and flow and finally to equip the plant. Automation, process controllers, remote controls, process flow, use of computers, selection and specification of equipment, are all under this department. Skilled professionals are an integral part to succeed.

New facility design and construction: staffed with draftsman, mechanical and electrical engineers oversee the requirement for space, specifications for vaccine manufacture and finally tender the project for construction. The success of the manufacturing plant is highly dependent on this critical stage as poor design can severely hamper smooth operations or may infringe regulations that specify proper flows for raw materials, intermediate and final products, air and garbage.

Utilities is the blood line of any manufacturing plant and is highly regulated. The demands on consistent quality and quantity of electricity is crucial as most processes today are computer or process controller driven. High voltage surges can damage systems, no power can cripple processes. Back-up electrical systems (e.g. diesel generators) is an essential safety measure.

* Potable water, water for injection, process steam, purified steam are essentials for manufacturing. Each of the above utilities has its own specifications which at times are difficult to maintain due to the complexities of the systems. These systems have and need diligent maintenance and are operationally expensive to maintain as daily/weekly and monthly chemical, bioburden, particulate and purity tests have to be performed to ensure compliance and the integrity of the systems. Some of the equipment used for the water and steam systems are : water softeners, carbon beds to remove organics from potable water, desalination systems where the salt content of water is high, large scale distillation system for distilled water and redistillation to produce water for injection. Plant or process steam require large steam generators which in turn feed into pure steam generators to produce pure steam. These systems are high energy users and a reliable source of electricity, gas or oil is essential. These systems must be managed by staff who are Stationary Engineers and qualified to operate high pressure systems.

* The quality of air supplied to manufacturing areas varies with the operations. This in itself is a complex function as different classes of air have to be monitored and regularly tested for compliance. The monitoring includes changes of air per hour, quality of air (i.e. particle number and sizes, temperature, humidity and microbial containments). Air handling systems are complex and require constant monitoring and validation to ensure all the different types of filters/dampers, air velocity, air ducts and

diffusers are functioning optimally. Mechanical Engineers and Technical staff trained in monitoring the systems oversee these installations and maintenance.

* Compressed air, medical gases, liquid nitrogen, etc. must also be monitored for chemical purity, biobirden and safety requirements. Many manufacturers have these utilities permanently installed for ease of manufacturing.

* Pollution and waste management control is being highly regulated and in vaccine manufacturing there is no exception. The use of solvents, chemicals, biological waste, sewage, bio-containment, production of gases, etc. have all to be addressed to meet the environmental requirements of the region. This requires on-going monitoring, installations of systems to scrub gases, neutralize high acidic or basic wastes, appropriate decontamination of pathogenic waste. This department has grown significantly in the last 10 years as environmental group pressures have forced these issues. Chemists and Environmental Engineer professionals are normally monitoring this department.

* Facility maintenance and repair houses, all the skilled trade professionals who look after the plumbing, electrical, mechanical, steam, etc. and whose responsibility is to ensure all systems are regularly serviced and maintained for optimum compliance. Regulations require complete documentation of all services and repairs and also the trending of these repairs as a tool to predict problems.

The modern vaccine manufacturing facility

Manufacturing can be broadly divided into four areas : Bulk concentrate manufacturing which includes fermentation, purification and manufacture of the bulk concentrate vaccine, formulations where vaccine monovalent antigens are pooled and blended into. Bulk vaccines of multivalent antigens and adjuvanted; filling and packaging and storage and finally the process development that supports all the manufacturing in optimization, trouble shooting and new procedures.

* The Bulk manufacturing plant is designed to meet all the requirements for raw material flow, intermediate product flow, bulk concentrate flow, waste flow, personnel flow, air flows, storage of raw materials and intermediates, bio-containment, air classification. Appropriate layout for the essential operations for washing and sterilization rooms where equipment and glassware is washed, depyrogenated and sterilized. Media and diluent preparation rooms where sterile media and diluents are prepared for need in production. Fermentation suites which could be multiple suites for aerobic and anaerobic fermentation, each in turn controlled separately with its own air handling, entry and egress, and containment. Downstream processing suites - after all pathogens are removed. Detoxification suites - to inactivate the toxins. And finally the bulk concentrating suites - where the final bulk concentrate is manufactured.

  Current air handling systems, validation, decontamination and entry and egress procedures permit multiple pathogen manufacture in one facility simultaneously

provided it is in separate fermentation suites. Otherwise different products can be campaigned in the same suite but after vigorous decontainment and validation.

However, there is reluctance to campaign sporulating anaerobic bacteria with aerobic pathogens and regulations in the case of Cl. tetani specify a separate dedicated facility for its manufacture. Most manufacturers successfully campaign diphtheriae B. pertussis, S. typhoid, V. cholerae, N. meningititis, Haemophilus influenced in the same plant and in one suite.

The fermentation suites have become very sophisticated in the modern plant. Large scale usually batch processed, fermenters with pure steam sterilization capability, fully controlled for temperature, CO_2, PO_2, pH, stirring, etc. are standard equipment. Skilled persons with knowledge and experience are a must for these operations as errors can cost significant losses in raw materials. This is especially true where the size of fermenters is reaching the 3000 - 5000l range. In the case of polio manufacture, the value of the raw materials can easily reach half a million dollars per batch. Process flow, piping, all electronic controllers and computers must be serviced, maintained and validated regularly to ensure consistency and the integrity of the systems. The control of these processes is often a problem for new vaccine manufacturers who frequently do not have a strong engineering background to run and maintain these systems.

Most of the tanks and process piping is nowadays stainless steel 316L and highly polished to resist corrosion and for ease of cleaning. Most of the welding in these systems are X-rayed or dyed tested for welding imperfections. Nowadays, most of the good welding is plasma gel welding that affords excellent results.

The WFI systems supporting these suites are circulating in a loop at 80°C to contain bioburden and to meet the compliance requirement for WFI storage. The distilled and WFI systems are expensive to purchase and maintain as it has to meet the WFI chemical and bioburden requirements.

Other equipment that is usually associated with the fermentation suites are hermetically sealed centrifuges for pathogenic organisms or toxins. These are medium speed centrifuges which separate the cells from the fermented broth and depending on the case either the cells are harvested (as in B. pertussis) or the supernatant (as in tetanus and diphtheria toxins). These centrifuges are expensive and require good quality maintenance and repair programmes for best operations. Manufacturers of these centrifuges are Alfa Laval and Westphalia.

Classical downstream processing using precipitation and centrifuges are being replaced by membrane filtration and chromatography and different suppliers of purification systems often have similar products, however, they vary in support they can provide to vaccine manufacturers. Validation of these reusable membranes is possible but a challenge and depending on the vendors the support can be helpful.

Other considerations in downstream processing are the personnel. Microbiologists, biochemists, biotechnologists, chemists, laboratory technicians are the skilled discipline

required to run these operations. Constant training in new techniques, processes, GMP and Regulatory requirements is an essential factor for the success.

Formulation is blending and compounding multiple antigen vaccines in a highly controlled areas. Air classifications and complete gowning is essential as this is the last step before filling. Any contamination here can be very expensive as the cost of multiple antigen and adjuvants can be significant.

Large formulation stainless steel tanks are "in-situ" sterilized with pure steam and can also be maintained cold by circulating cooled glycol. The size of the tank can vary from 100L to 3000L. During formulations, the environment personnel and the room surfaces are monitored for particles and bioburden as required by Regulations.

Filling and freeze drying and packaging facilities are getting sophisticated and highly automated. As people are one of the biggest bioburden carriers, vendors of these systems have moved more towards automation where fewer people are required to wash, depyrogenate/sterilize vials, fill the vaccine on high speed machines, load freeze dryers, unload and cap or seal. These systems are available, however with these sophistication, one must have full time mechanics to trouble shoot the complex machines, and have a good compliment of staff to run the systems. Validation is a major undertaking and a challenge at best.

The tunnel washer and sterilizer, filling machines, freeze dryers have high demands on electricity, WFI and pure steam and these must be readily available in consistent supply.

Freeze dryers come with Sterilization-in-Place (SIP), Clean-in-Place (CIP) and available optionally with redundant back-up systems. These are emergency backups for any system that fails except for power which must be connected to an auxiliary power system. These systems have complicated hardware and software for the operation of the systems and a full time qualified engineer is a requirement especially during the validation and operation of the systems.

With high speed washing/sterilization/filling and freeze drying systems, efficient use of time allows these systems to be used for many different types of filling schedules and also to be campaigned with live bacterial (BCG) or viral products. However, it should be stressed that it is not favoured by Regulatory Authorities but with the appropriate design, controls and validation, this concept may get a favourable review from authorities.

Filling equipment are nowadays purchased with complete barrier technologies, which encloses the filling line in a proven sterile environment. Barrier-type systems increase the cost of the process equipment to which they are applied, but they reduce the cost of the facility required to house them, and are cheaper to operate than the traditional clean room. Overall manufacturing costs can be reduced by 10-20% by barrier technologies.

Automation in final container inspections include black and white background inspections, vial or ampoule seal tests, label correctness check and packaging. However, these systems are expensive and can be justified when high volume is demonstrated. As with any automation and high speeds proper trained staff are important.

It is cheaper to fill and package multidose presentations, however with the increase of hepatitis and HIV infections, manufacturers are moving towards single dose refilled syringes or the bubble inject concepts. These systems again are expensive and costly to run and maintain but they are the solutions to a single dose delivery systems. Single dose refilled systems are currently available. However, to house these pieces of equipment and to maintain them is costly. Cost of drug per dose also increased significantly.

Depending on the size and sophistication employed building costs can vary from $2,500 to $5000 per square metre. The cost of process equipment can cost up to $7000 per sq. metre of manufacturing space. Typical operating costs for a vaccine manufacturing facility range from $140 to 220 per sq. metre per year. These are rough estimates, the actual cost will vary on individual circumstance and the total of automation and speed chosen.

Quality Assurance (QA) is an integral part of manufacturing. QA in many organizations is divided into five generic departments : compliance, validation, QC, product release and complaints and environment monitoring

* Compliance which ensures that all products are made to regulations and evaluate deviations for appropriate actions, training of GMP and GLP and control of all standard operating procedures (SOP), Batch Production Records (BPR) and all documentation for tests and final summary for product release. This is a large paper bureaucracy and computer & software have eased many of the day to day operation chores.

* Validation is the fastest growing industry in pharmaceutical manufacturing. With strict regulations on validation and documentation for every strep during facility commissioning to final product release. It has a very high operating budget, but the advantages are obvious when all systems perform with assurance.

Validation oversees the Installation Qualifications (IQ), the Operational Qualifications (OQ), and the Performance Qualifications (PQ) for every equipment, process and facility systems. An estimated 10-15% of the total budget for equipment and facility is dedicated to validation costs. Mechanical, process, computer hardware and software, systems engineers all support this task on on-going basis. All systems have to be validated on minimum yearly basis or in other instances more frequently. Equipment required for validation can vary from low to very high technology and can cost between $ 200K to 500K.

Validation of all parts of manufacturing is becoming the norm

Cleaning validation has become focus of much effort in the USA for all processes involved in vaccine manufacture, from primary medias to filling and packaging operations. Quantification of all residuals requires examination of all process equipment, cleaning processes and materials, with an emphasis on the toxicological impact of contaminants.

Purification processes must be validated for viral inactivation and/or removal. Standard clearance factors (eg. a 12 log reduction for viruses) must be consistently demonstrated by spiking studies with viruses and potentially contaminating macromolecules such as DNA.

* Quality control whose functions are to monitor the quality of incoming raw materials, in process material and final testing of products is also responsible for test development. The sophistication that is required for the newer generation tests also requires more complex and sophisticated equipment.

  High pressure liquid and gas chromatography, capillary electrophoresis, page electrophoresis, isoelectric focusing, thin layer chromatography, NMR, micro Kjeldahl are some of the equipment that many of the QC departments use for purity and identity tests. Coulter counters, microscopes, moisture analysers, spectrophotometers (UV, infra red), osmometers, pH metres, balances, scanning microscopes, electron microscopes, Elisa readers, are some other tools that QC laboratories need to test and analyse the products.

  Invivo testing requires live rabbits, mice, guinea pigs, monkeys and other species which are either purchased from reputable vendors or are bred in-house. These facilities are specially designed for optimum care of animals. Operating costs are high and unless sufficient volume of products are tested it is not easy to justify in-house animal breeding, it is best to buy from reputable breeders. Testing can be contracted out to reputable, validated laboratories as any alternative.

  Operating costs of QC is high, professional and skill levels required are also high. Pharmacologists, Immunologists, veterinarians, chemists, microbiologists are some of the professionals required for QC department.

* Environment monitoring is essential during manufacturing especially during filling. The strict requirements of class 100 air in filling suites can be easily breached due to terminal filter failures or procedural failures. This is closely monitored by QA to ensure total integrity of the process. Environmental monitoring requires air particulate number and size, bioburden volumetric samples, settling plate bioburden and touch plates to check operators for procedural and shedding of particles and bioburden. These are strictly controlled by regulatory requirements and must be met for release of products.

  The cost of equipment in a modern QC facility could easily run into half a million dollars, but this could vary with the sophistication and automation employed.

High cost of building and operating modern facilities

The **capital cost** of modern manufacturing facilities is typically in the range of $2500-5000/m^2. This includes the manufacturing, support and mechanical service areas. Facilities are designed such that the manufacturing areas are clean-rooms, with sophisticated control of the environment, especially the quality of the air supplied to the rooms.

Typical **costs for operating** vaccine manufacturing facilities are in the range $140-220/m^2/year. Up to half of this cost is due to the cost of the utility systems, and from maintenance and repair. The cost of routine environmental monitoring is high. Also, the cost of maintaining manufacturing clean-rooms at temperatures removed from ambient (ie. warm or cold rooms) is considerable because of the difficulty of controlling humidity and air quality in these areas.

Raw materials

All raw materials must be controlled to rigorous acceptance criteria. Special attention must be given to biological materials, including the cell lines used in production. The supply of any animal products has to be very carefully scrutinised given the rising concerns over bovine spongiform encephalophaty (BSE) or more generally transmissible spongiform encephalophaty (TSE) contamination. Blood products and derivatives are prone to viral contamination. Competition for the limited supplies of high grade sera and albumin is already very fierce, and will likely become more so as the demand from the growing number of biotechnology products being manufactured increases. Discovery of new viral agents will continue to make all animal derived substrates undesirable. Manufacturers must employ new procedures, pretreatment and assays to qualify raw materials for vaccine manufacture (for example, the use of gamma-irradiation to pre-treat sera). The high standards for raw materials extend to include process components such as chromatographic resins and filters. Appropriate methods for testing such components are often not clearly defined.

Vendor certification

Vaccine manufacturers are becoming even more integrated with their raw material and equipment suppliers to assure quality. Manufacturers seek vendors with a proven quality program, such as ISO 9000 certification or ISO14000 for environmental management. Vendors are seeking manufacturers who will collaborate extremely closely in development and production, especially in the areas of new culture and media equipment. Manufacturers must become open to these collaborations, Some filter suppliers offer extensive support services to qualify their products in a given product application. There is a danger of overreliance on such services, without enough thought applied by the end-user to the applicability of the science behind the testing provided.

Staff Training

Updated equipment and procedures must be accompanied by training of manufacturing staff. Education must cover technical, regulatory and quality assurance areas. In practice, training becomes a continuous updating process. In some areas, such as fermentation, a combination of mechanical and biological skills are needed which are rarely achieved by normal schooling. Dealing with the concepts of scale-up from laboratory procedures to manufacturing equipment is a challenge even for well-educated staff. A recognition that the staff are as vital to the product quality as the facility or equipment is essential.

C. Safety/Regulatory/Issues

The regulations applied to vaccine manufacture have become progressively more thorough. The effect of some new biotechnology products and novel technologies passing through a licensing process has sometimes been to alert the health authorities to issues for other biologies such as vaccines. As a result, high standards for purity, including a detailed identification of contaminants, and the need to control rigorously processes such as cleaning, have become the norm even for traditional vaccines.

Regulatory and compliance climate

The industry is becoming more closely regulated. New products, and their method of production, are setting new standards, which are then often applied to traditional vaccines.

Guidance on how to approach new processes is limited. "Points to Consider" and "Notes for Guidance" are the norm. [20] Strict adherence to these documents imposes a rigidity never intended by the regulators.

An intimate dialogue with regulatory agencies is always necessary. Out-dated regulations require changes only achievable after careful lobbying. The change process may take 10 - 20 years, if it is successful at all.

Harmonisation of regulations in the major markets of North America, Japan and Europe

Whilst goal of harmonization is to streamline the steps necessary to develop and manufacture pharmaceuticals, at this point, the recommendations can only be considered as "hopeful gestures". Global registration still requires considerable customising of testing and stability programmes.

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[20] see under G. Reference

Increased standards of stability and purity

The improvement of some traditional vaccines has prompted a need to improve others with which they are associated in combination vaccines. The purity of new acellular pertussis vaccines requires a similar high purity for diphtheria and tetanus components for use in DPT combinations.

The inclusion in vaccines of anti-microbials as preservatives is a hot topic for regulatory authorities worldwide. There is concern that preservatives may disguise less than adequate production (especially filling) standards. A difficulty faced by manufacturers who seek improved preservatives is that different markets have different requirements for validating the antimicrobial efficacy of a preservative.

Increased standards for shipping

Customers are requiring validated control of temperature during shipping. (In the future, humidity control may be demanded as well.) This requires investment in validatable temperature monitors, and very close control of the cold chain during shipping. Manufacturers are being asked to provide stability data to justify any deviations from temperature during shipping.

Increased standards of inspections

Inspections to check compliance are becoming more intensive and sophisticated. Inspectors are using computer aided techniques that have been developed to detect patterns and trends in data influenced by multiple variables.

D. New Vaccines - Recombinant Products

The majority of new vaccines being developed are products of recombinant DNA technology. A manufacturing process using a recombinant system is faced with a number of issues related to the safety of product, the manufacturing staff and the environment.

High standards of purity

Recombinant products are required to have a very high standard of purity. Special attention is paid to contaminants from the host cell and expression system.

It is common to express new bacterial vaccine products in heterologous host systems. Cells expressing the product are normally selected by the presence of an antibiotic resistance, and antibiotics are frequently added to maintain expression during the culture process. The regulators are requesting to see no detectable levels of antibiotic in the products from such

expression systems. This requires very effective purification processes and analytical detection systems. Contaminants that must be reduced tc very low or non-detectable levels include host cell proteins, host cell nucleic acid, endotoxins, and other biologically active macromolecules that may be introduced from the host cell or media.

The product antigen itself must be analysed by multiple analytical techniques to differentiate contaminating proteins, degradation products, and deaminated protein forms. All must be characterised. Limits must be set, and purification processes designed and validated to meet those limits.

Containment of recombinant products

Containment regulations are imposed on manufacturing operation as part of an establishment license. In general, recombinant hosts containing genes from pathogenic organisms must then themselves be considered as pathogenic. The environment must be protected from the release of recombinant organisms and pathogens, a hazard which is considered greater as the scale of operation increases. Larger scale facilities require more engineering, and more validated systems to ensure containment. Spills and emergencies must be planned for, systems must be monitored and alarmed, and staff must be trained. Standards/regulations now exist to allow minimum environmental safety precautions in the use of recombinant products even at the large scale if the strains/hosts are carefully chosen The first companies in the field have had to demonstrate data to show the environmental fate of recombinant DNA from their systems in the event of an accidental release. This issue of persistence in the environment remains for new live recombinant vaccine products.

Occupational health - safety of staff working with recombinant products

Include : growth media and cellular by-products; genotoxins; intentionally modified biological systems; pathogens; allergens; ionising radiation.

Infections of workers handling recombinant products by the organisms themselves have generally not been observed, although this may be because, to date, industry has used organisms of low infectious potential. Studies of several population of workers involved in recombinant product manufacturing have suggested no effects unique to this technology.

E. New Directions for Vaccine Manufacture

A very large number of private companies and public institutions are involved in developing new vaccines. Even the near future is difficult to predict because of the breadth of technologies being investigated. Some of the following technologies may become more generally applicable, and have particular relevance to vaccine manufacture.

Combination vaccines

The opportunities for making increasingly complex combination vaccines appear quite good. The recently proposed uniform childhood vaccination schedule in the USA covers nine diseases, 19 vaccine doses, with up to 12 doses before the age of two years. Interference between components appears often to be relatively low especially when the components are purified vaccines. The ability to create successful combinations requires careful formulation. and understanding of the stability properties of the components. The complexity of testing existing products in combinations is made difficult because of subtle differences in features such as adjuvant type, formulation and preservative.

DNA vaccines

Naked DNA vaccines may allowing an entirely uniform process for manufacturing.

Different vaccines will be created by different DNA sequences, however the process for expressing and purifying every product will essentially be the same.

The products being tested are being developed as plasmids produced in bacteria, most commonly E.coli. In general, the processes for purifying the plasmids are similar to those used for other macromolecules. Large scale handling of macromolecular DNA requires special designs to avoid denaturing shear.

Vaccine production in plants

The successful engineering of vaccine antigens in some plant species suggests a viable technology for producing very large quantities of new and existing vaccine. Manufacturing the raw vaccine material in this way will require new approaches to production control. However there are some parallels with use of transgenic animals for the production of therapeutic proteins.

New presentations and routes of administration

The fact that most vaccines are currently administered as injections is a significant disincentive against vaccination, even in well educated, wealthy populations. In some cases, infection may be more effectively prevented by alternative routes of administration, eg. to induce mucosal immunity. New formulations and devices are needed to allow development of new routes of vaccination that are generally applicable.

New stabiliser technologies

Novel stabilisers such as deuterium oxide to improve heat stability or improved freeze drying excipients such as trehalose may have general applicability. A better understanding of

the chemistry of biological stability will allow a better prediction of vaccine behaviour during manufacture and storage.

New adjuvants

Eg. liposomes; iscoms; glycolipids, biodegradable microspheres.

More complex adjuvants may require chemical reaction and formulation processes more typical of drug manufacture than vaccine production.

F. Business Issues

Vaccine manufacture started predominantly as a non-profit activity, but over the last twenty years has become steadily more commercial. Vaccine manufacturers are mostly now either part of large commercial pharmaceutical companies, or are attempting to survive and grow as independent profit-making ventures. Several issues and trends can be seen which will probably influence the development of the vaccine business.

Vaccines yield relatively low margins compared to drugs

Profit margins for vaccines have been estimated overall to be 20 - 30%, whilst drugs achieve 60 - 80%. The legacy of the non-profit days of vaccine supply live on in the expectation even in wealthy markets that vaccine prices should be low. The fact that several traditional vaccines have been around for very many years adds to the impression that they should be cheap. This is in comparison to many new drugs, which have typical life cycles of about five years. The low prices obtained by UNICEF and PAHO are often at or below the cost of production for most commercial companies. Vaccines are supplied in many countries though health authorities (ie. governments), and the public market environment promotes low pricing through high volume low bid tenders. Psychologically it remains much more difficult to market prevention than cure, especially to the adult market. The relatively low price of vaccines makes it difficult to recover the increased costs of production and of R&D.

More competition in most markets

Almost all developed world markets are highly competitive. This trend will likely continue as vaccine producers become more commercially orientated.

Mergers and collaborations

Allow faster development of new products, sharing of technology, products and facilities. In the short term these collaborations will be particularly important with respect to

the development of new combination vaccines. No one major producer makes in-house all the vaccines required for some of the most desirable combinations.

Intellectual property

Companies are becoming much more organised to patent all inventions and novelty. This includes patenting of new vaccine formulations and combinations. Most of the best currently available good bacterial expression systems are patent protected.

Technology transfer

Successful technology transfer requires large investments of time and money. It is important that the collaborating organisations have similar cultures and approaches to solving problems. Different standards, facilities, and equipment all conspire to make transfer problematic. Even when conditions are favourable, an exacting rigour is needed, especially by the originators, in applying the process in new hands. Good technology transfer is recognised as a major skill by those involved in collaborative work.

Separation of bulk production from fill and pack operations

The advantages seen in the drug industry of separating bulk production from packaging are also true, though as yet less exploited, for vaccines. Separated facilities can allow access to protected markets which prefer a made-at-home product, They also allow cost saving in manufacturing and shipping. Depending on the proposed location there are issues as to whether an off-shore facility should be "high-technology" (eg. including freeze-drying, syringe filling) or "low technology" (ampoule and vial filling lines).

To conclude, it is evident that to enter the vaccines business from scratch is a giant task. If the manufactured products are to be licenced in other countries, the task becomes even tougher depending on the regulations. It is advisable to collaborate with a large manufacturer or organization such as WHO or UNIDO to assist in this endeavour. Where facilities are being modernized, be cautious and ensure you have the expertise in-house or else collaborate with an experienced manufacturer or consultants. Vaccine manufacturing is complex, highly regulated, costly unless large volumes are produced for sufficient enough markets. Alternatively, purchases through the WHO or other sources may be an easier solution then building a facility or planning through small steps of filling and packaging gaining experience and moving to the next step of formulations. Followed by manufacture of the drug from scratch, it must be stressed that professional help must be utilized as this is a complex business and poor planning will definitely lead to failure.

G. References

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ANNEXES

ANNEX 1

UNIDO ONUDI

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

AIDE-MEMOIRE

Advisory Panel Meeting for BIONUDI - Programme on Industrial Development for Health

(XP/GLO/95/014)

Organized under the auspices of the
United Nations Industrial Development Organization

to be held at
Human Ltd., Gödöllö, Hungary
12-13 October 1995

AIDE-MEMOIRE

1. Background

One of the most pressing problems of health care delivery in developing countries (and transition economy countries as well) is the fact that they cannot afford the prices of high quality traditional and modern biotechnology vaccines. Moreover, these products are mostly protected by patents and their technological know-hows are restricted therefore entering domestic manufacture would not be a feasible option for most of these countries.

At present, the need for vaccines of many of these countries is covered through donations and subsidized importations, e.g. through UNICEF. However, UNICEF can only meet a fraction of the total demand of the developing countries, which would amount to more than US$ 1 billion per annum. As a result of this shortage of supply the largest developing countries, e.g. Brazil, China, India, Indonesia take, at least partly, care of their own production.

As the production of the needed vaccines at a national level would not be, in most cases, a viable option, the alternative for developing countries would lie in the establishment of regional manufacturing facilities for the production of a selected number of high quality "traditional" vaccines. A very similar conclusion has been reached by the Children's Vaccine Initiative (CVI), an international group financed by the UNICEF, World Bank, UNDP, WHO, Rockefeller Foundation, etc. and it is ready to consider support for activities in this field.

A recent idea from Dr. Charles Merieux, Chairman of the Fondation Marcel Merieux, was to create a new foundation to coordinate those international efforts aimed at promoting regional vaccine manufacture in developing (and transition economy) countries. He coined in French the word **BIONUDI** as an appropriate name for such a foundation. It stands for LIFE (BIO), UNITED NATIONS (NU) and INDUSTRIAL DEVELOPMENT (DI). He envisaged that under BIONUDI - as a new foundation - WHO, UNICEF, UNESCO, FAO and UNIDO would work together with Fondation Marcel Merieux and other NGOs (particularly in transition economy countries) to cover the four most important elements of human life namely health, education, food and industry. Dr. Merieux has earmarked FF 5 millions for the establishment of this new foundation provided a joint programme of mutual interest be agreed. In view of this, it should be noted that the subject project has at this very early stage started to fulfil its seed money function.

This programme offers UNIDO a unique opportunity to become actively involved together with some of the major vaccine manufacturers in the world (the Pasteur Merieux Connaught group is one of the major vaccine manufacturers both in EU and in North America) in these on-going programmes for the promotion and development of the biotechnological industry in general and vaccine manufacture in particular in developing and transition economy countries. Moreover, it is believed that another major UNIDO project, the ICGEB in New Delhi, India and Trieste, Italy could play a significant role in this programme too.

2. Objective of the meeting

To establish an Advisory Panel on Industrial Biotechnology with the task of supplementing and finalizing the draft technical programme on issues related to the manufacture and distribution of vaccines into a plan of action.

3. Programme of the meeting

The programme of the meeting will be as follows:

Day 1:

Opening	Opening address by Dr. Charles Merieux, Chairperson of UNIDO Advisory Panel on preventive medicine[21]
	Welcome address by Dr. Lajos Aradi, Director of Human Ltd.[22]
	Welcome address by Dr. Z. Csizer, UNIDO
Theme 1	Discussions on the Regional meeting on industrial support for pilot regional programme on biotechnological vaccines in Central and Eastern Europe with specific reference to the recommendations on establishing of a Central and Eastern Europe Vaccine Manufacturers' Association.
Theme 2	Co-operation between the European Vaccine Manufacturers and the vaccine production institutes/enterprises in Central and Eastern Europe
Theme 3	How to meet the vaccine demand in the Russian Federation
Theme 4	Vaccine production and supply in China. Business opportunities and risks.
	Discussions on the above themes.

Day 2:

Visit some selected facilities of Human Ltd.
Discussions continued
Conclusions and recommendations

Closing

[21] On behalf of Dr. Charles Merieux, Dr. Philippe Stoeckel took the chair.

[22] The welcome address was made by Dr. L. Dan, Chairman of the Board of Directors, Human Ltd.

4. Expected outcome of the meeting

A meeting report including specific recommendations for UNIDO how to develop a programme for vaccine production and supply in the Russian Federation and in the largest countries of Asia e.g. China, India and Indonesia. The programme should aim at sustainability and therefore a long term support and advice would be needed from the leading vaccine manufacturers of the world. The programme if developed shall be part of the Children's Vaccine Initiative (CVI) and will be also offered to be implemented as a joint programme with WHO. Finally, the meeting should give recommendations for UNIDO how to develop further co-operation with the International Vaccine Institute (IVI), Korea.

5. Date and Venue

The meeting will be take place at HUMAN Ltd., Táncsics Mihály út 82, Gödöllö H-2100, Hungary, fax: (3628) 320177, tel: (3628) 320733 or (361) 1330564 from 12-13 October 1995.

6. Participants

The Governments of China, Russian Federation, Indonesia and India as well as high level participation of industry (e.g. Pasteur Merieux, Novopharm Ltd., MSD, Human, Heber Biotec, SmithKline Beecham, etc.) will be invited to present their countries at the Advisory Panel Meeting.

Participants should be selected from the highest management and decision making level of vaccine production and marketing authorities.

Participants are expected to contribute to the discussions of each theme freely and to the preparation of conclusions and recommendations.

The representatives of local/regional office of WHO and UNICEF will be invited as observers. Representatives of financial institutions (World Bank) will also be invited. [23]

7. Language Requirements

Since the programme and the discussions of the panel meeting will be conducted in English, it is a prerequisite that the participants must have a good working knowledge of the English language.

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[23] Representatives of UNICEF and the World Bank did not attend.

8. Financial and Administrative arrangements for the meeting

Financial and administrative arrangements for the participants will be made in accordance with UNIDO Rules and Regulations.

UNIDO will provide the following:

The most direct route and reasonable way of transportation e.g. round-trip economy class (or excursion) air transportation, second-class train tickets or mileage between home country and Budapest, Hungary. Transport from airport to Gödöllö, Hungary will be provided by HUMAN Ltd.

Daily subsistence allowance for three (3) days will be paid. No additional claims can be considered.

Hotel reservations in Budapest, Hungary will be made for 3 nights.

The participant's Government or his/her employer will be required to bear the following expenses:

All expenses in the home country incidental to the travel abroad, including expenditure for passport, visa and other such miscellaneous items as well as internal travel to and from the airport or station of departure in the participant's home country.

Salary and other benefits for the participant during the period of the meeting.

UNIDO will not assume responsibility for the following expenditures in connection with the participant's attendance at the Advisory Panel Meeting:

Costs incurred by the participants with respect to any insurance, medical bills and/or hospitalization fees.

Compensation in the event of death, disability or illness of the participant.

Purchase or loss of personal belongings or compensation for damage caused to them by climatic or other conditions.

9. Visa/passport

Before leaving the home country, participants should complete all formalities regarding entry and transit visas which they may require for the journey to Hungary and back.

Before leaving their home countries, they are urged to contact the nearest Hungarian diplomatic or consular office to obtain visa and information on customs regulations.

10. Time of arrival

Participants are requested to leave their home countries in time to arrive in Hungary not later than Wednesday, 11 October 1995, and to depart on Saturday, 14 October 1995 or as close to that date as airline schedule permit. UNIDO can not assume financial responsibilities for earlier arrivals/later departures for personal reasons.

Flight reservations for the homeward journey should be made before departing from the home country. UNIDO will not pay additional costs, such as daily subsistence, due to failure to make such reservations.

11. Hotel Accommodation

Hotel reservations for the participants will be arranged by Human Ltd.

12. Enquiries and Correspondence

All enquiries and correspondence should be addressed to:

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ANNEX 2

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

AGENDA OF THE ADVISORY PANEL MEETING
12-13 OCTOBER 1995, GÖDÖLLÖ, HUNGARY

Wednesday, 11 October		Arrival of participants
Thursday, 12 October	9:00	Participants will be picked up at the Hotel
	9:30	Opening of the meeting
		Opening address on behalf of **Dr. Charles Merieux**, President, Fondation Marcel Merieux and Chairperson of UNIDO Advisory Panel on Preventive Medicine by Dr. Philippe Stoeckel, Director General of AMP
		Welcome address by **Dr. Lajos Aradi**, Director of HUMAN Ltd.
	10:00-10:30	Theme 1: Discussions on the regional meeting on industrial support for pilot regional programme on biotechnological vaccines in Central and Eastern Europe with specific reference to the recommendations on establishing of a Central and Eastern Europe Vaccine Manufacturers' Association
		Theme 2: Co-operation between the European Vaccine Manufacturers and the vaccine production institutes/enterprises in Central and Eastern Europe
	13:00	Lunch offered by HUMAN Ltd.
	14:00-19:00	Theme 3: How to meet the vaccine demand in the Russian Federation

		Theme 4: Vaccine production and supply in China. Business opportunities and risks.
	19:00	Reception offered by **Mr. Leslie L. Dan,** President of HUMAN Ltd.
Friday, 13 October	9:00	Participants will be picked up at the Hotel
	9:30-12:00	Visit to some selected facilities of HUMAN Ltd.
	12:00	Lunch provided by HUMAN Ltd.
	13:00	Discussions continue Conclusions and recommendations
	17:00	Closing Departure of participants

ANNEX 3

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

ADVISORY PANEL MEETING
12-13 OCTOBER 1995, GÖDÖLLÖ, HUNGARY

List of participants

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