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INDUSTRIAL SUPPORT FOR PILOT REGIONAL PROGRAMME ON BIOTECHNOLOGICAL VACCINES

XP/RER/94/102

Technical report: Proceedings and recommendations of the regional meeting*

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).

This document has not been edited.

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CONCLUSIONS AND RECOMMENDATIONS

The sweeping political changes in Central and Eastern Europe (CEE) in the late 1980s and early 1990s followed by the drastic transformation of the economic sphere of this region shocked the world. The pharmaceutical and the allied biological industries, as the other state-owned and -controlled production and distribution sectors, underwent dramatic changes.

The raw materials required for the production were usually supplied through the state orders system, and the production was distributed by a similar state-controlled association. The products were made available to the public at state prices which hardly changed in the last couple of decades. This system of state orders for all inputs and outputs, with companion state-decision making with respect to operating costs, sourcing, pricing, product lists, and distribution was closely monitored by several levels of bureaucracies in the relevant government authorities and ministries. Even though this system was inefficient, it worked.

With regard to the biological industry and specifically to the vaccine manufacture, a significant volume of traditional vaccines were produced and distributed. In many instances the over-production was exported in the region or to the developing countries at state subsidized prices within the barter agreements characterized the trade in that time.

The national immunization schedules were also strictly controlled by the authorities of the public health care system. The well-controlled delivery system achieved very high coverages in the range of 96 - 99 % for all vaccines. The incidence of major childhood communicable diseases preventable by the original six vaccines (BCG [Bacillus Calmette-Guerin] against tuberculosis, diphtheria, pertussis, tetanus, poliomyelitis and measles) included in the Expanded Programme on Immunization (EPI) was steadily decreasing. The above mentioned high coverage with vaccines of consistent quality resulted in an unprecedented decrease of certain diseases such as whooping cough (pertussis) in the region.

The transition towards a market economy resulted in the virtual disappearance of production in a number of large-scale state enterprises. The creation of new administrative structures and legislation were lagging behind the structural transformation of the industrial sector. The emerging small-scale industries and private enterprises did not compensate for the drastic fall in the output of state-owned companies, unemployment started to increase. The trade liberalization and decrease of state subsidies triggered a significant influx of imported goods but accelerated inflation. The result was a vicious cycle of increased costs for imported raw materials and finished goods, diverting production from primary products to obtain additional resources to pay salaries and bonuses for workers to avoid layoffs. Salaries, however, could not keep pace with inflation. Short-term production could not produce sufficient amounts of pharmaceuticals and related products. In the case of vaccine production, due to the dissolution of the former U.S.S.R., the emerging nations either did not have the distribution structure or the state could not sustain the delivery system which used to provide its services through bureaucratic structures did not exist any more.

As a result major epidemics occurred in Eastern Europe. The United Nations Industrial Development Organization (UNIDO) with the Fondation Marcel Mérieux, Lyon, France and WHO initiated a pilot regional programme for biotechnological vaccines to provide advice and guidance on supply and delivery of the vaccine required to prevent and control epidemics in the region. In addition to this, specific recommendations were made for the vaccine manufacturers and the government authorities of the CEE countries. Reciprocally, the participants of the meeting gave recommendations for further actions that UNIDO should take.

In line with its mandate UNIDO is providing industrial support for this regional programme and seeking for assistance and co-operation of the industry. The regional meeting held in Vienna, Austria from 7 to 8 June 1995 on Industrial Support for Pilot Regional Programme on Biotechnological Vaccines was organized under the joint auspices and sponsorship of UNIDO, the Pasteur Mérieux Serums et Vaccins, France, the Serotherapeutisches Institut Wien GmbH, Austria and the Linde-KCA-Dresden GmbH, Germany.

The presentation of the pilot programme was focused on one, single modern biotechnology vaccine, the inactivated poliomyelitis vaccine (IPV), which has the advantage that it could be combined to the diphtheria-pertussis-tetanus (DPT) vaccine. The purity of IPV is the highest and its adverse reactions are the lowest among all of the vaccines available in the international market and therefore it is also giving an incentive for developing higher purity DPT vaccines with less adverse reactions for the new combination.

As a tradition of the meetings organized by UNIDO, the recommendations were made by consensus. Whenever a certain recommendation could not reach consensus, but its sponsors insisted to make note of it, it is mentioned in the text.

Recommendations for Vaccine Manufacturing Enterprises
(private or state-owned biological industry)
in Central and East European Countries (CEEC)

1. Each manufacturer of vaccines for human use, both private and state-owned, in CEEC should carry out a self-auditing/inspection in order to monitor the implementation and compliance with a comprehensive system of Quality Assurance incorporating Good Manufacturing Practice and Quality Control and to propose corrective measures. The aim of this exercise is to estimate what further steps should be taken to ensure compliance with the internationally accepted requirements (e.g. Requirements of WHO, European Pharmacopoeia, Code of Federal Regulations of U.S. FDA, etc.).

2. Each manufacturer of biologicals in CEEC should make an analysis of domestic and other potential markets (e.g. subregional, regional markets) based on realistic estimates of supply and demand. In addition to the market study, an evaluation of the cost structure and the actual production costs of each product should be carried out.

   The above analyses, if their results are positive, shall enable the manufacturers to:

   * Establish reasonable prices for their products resulting in net income to be made available for further development;

   * Make their prices competitive in domestic, regional and international markets;

   * Identify and determine of a product mix of biologicals which could be the basis to establish a financially sustainable production. The outputs and experience gained through such or similar exercises should make the manufacturers able to reconsider their financial situation and facilitate facing the challenges of the market.

3. State-owned producers, who are still directly financed from the government budget, should find the way to become financially autonomous, so as to be able to draw their own strategy and financial policy for development.

4. Vaccine manufacturers should be encouraged to apply for technical cooperation and other professional services of UNIDO in all relevant areas of production cycle and related business activities.

5. Producers of biologicals should facilitate and if possible provide assistance in developing and establishing of a National Control Authority and Laboratory hence this is not only one of the most important parts of international requirements but would promote their own credibility and reputation.

6. The decision to enter the production of vaccines or other biological products should be based on a reliable market survey followed by the determination of different requirements to be met in order to achieve financially viable operations The most important requirements are as

follows:

* size of capacity to be created;
* transfer of technology and know-how;
* process optimization and scaling up;
* human resource development (training);
* financing.

7. In developing new programmes or upgrading of the existing facilities, the recommendations laid out in the UNIDO paper "The Challenge of Biological Technology Transfer to Developing Countries", ID/WG.466/10 (SPEC.) should be given due consideration (see Annex 2).

8. Manufacturers of biologicals for human use in CEEC should promote the exchange and flow of information and be open to any kind of cooperation which could facilitate, based on mutual interest, developing and improving of production both in quality and quantity.

Recommendations for Government Authorities in Central and East European Countries (CEEC) on the Supply of Vaccines and Other Biological Products for Human Use

1. To continue to support the national immunization programmes, e.g. to express clearly their commitment to decrease morbidity and mortality to certain specific target values for diseases preventable by vaccination.

2. Government Authorities should elaborate national strategies how to achieve self-sufficiency in vaccines used in the national immunization programmes, either by vaccine purchase or vaccine production. In case if the latter option is applied, the existing facilities should be upgraded or new production capacities should be established. Mixed strategies achieving self-sufficiency could also be applied. The national strategies should take into consideration the domestic and international market situation, and should be based on the analysis of the internal rate of return. The Government Authorities should continue to provide vaccines included in the national immunization programmes free of charge (financed from the budget of the health authorities) or affordable and reasonable price. The provision of vaccines financed by health insurance could also be considered.

3. The Government Authorities are encouraged to conduct cost-benefit (and cost-effectiveness) analysis of local vaccine production before entering such a venture. Before making a decision on upgrading and expanding existing production capacities, the financial sustainability of local production should be assessed. In case of positive evaluation, preference and support should be given to local vaccine manufacturers, including development of new capacities.

4. National programmes on the production of biologicals (vaccines, blood products, immunomodulators, diagnostics) should be developed giving priority and support to local manufacturers to supply the domestic, and if possible regional and international, markets and providing support for modernization and development.

5. Closer co-operation among CEEC and vaccine manufacturers should be promoted in production and distribution of biologicals for utilizing, with maximal efficiency, of the production capacities in the region.

   In this view, the co-operation among vaccine manufacturers needs to be encouraged and supported. One of the participants suggested that meetings and consultations of the manufacturers in CEEC be held regularly, and eventually the establishing an Association of the Central and East European Vaccine Manufacturers should be encouraged.

6. Several participants suggested that to facilitate the co-operation of vaccine manufacturers in CEEC would require special incentives from the Government Authorities (e.g. custom duties and tax regulations).

7. One of the participants recommended that regional (domestic) production of biologicals should be supported by the following incentive measures:

* commitment to use locally manufactured vaccines, even if their production costs would be higher than the UNICEF prices;

* import duties on imported vaccines if the same vaccines are available locally;

* tax incentives fostering local production;

* developing a reasonable cost structure and pricing of locally manufactured vaccines which would cover R & D expenses.

8. Government Authorities, in those CEEC where national control institutes have not yet been established, should give priority and support to the establishment of these departments to secure the safety, quality and efficiency of all biologicals (of domestic and import origin). The Government Authorities in these countries should also give priority to cooperate with other, exinsting national control institutes in other countries.

9. The National Control Institutes should be financed from the government budget. Their services must not be paid by the vaccine manufacturers.

Recommendations for the United Nations Industrial Development Organization (UNIDO)

1. The participants of the meeting recommended that UNIDO should become a member of the Children's Vaccine Initiative (CVI) and such a way partner of WHO, UNICEF and other organizations taking care of vaccine quality and supply in developing and transition enconomy countries. The role of UNIDO in CVI should be to provide technical cooperation and services to the vaccine manufacturer in developing countries and countries of economy in transition. More specifically UNIDO should:

   * provide technical advice and guidance in all industrial aspects of vaccine manufacturing, e.g. management, quality assurance (Good Manufacturing Practice, quality control), production (production development, process improvement and optimization, scaling up, trouble shooting, etc.) and marketing;

   * provide services of consultants and experts in production of vaccines and other biologicals;
     - human resource development;
     - transfer of technology and know how;
     - advice in restructuring and privatization of biological industry.

2. UNIDO should organize in regular intervals workshops and seminars on issues related to vaccine production management and Quality Assurance (QA), Good Manufacturing Practice (GMP) and Quality Control (QC) in vaccine manufacture in CEEC.

3. UNIDO should prepare/establish guidelines for cost estimation and analysis including costs of raw materials and supplies, costs of human resources, overhead costs, etc. in vaccine production. Training in basic financial analysis and investment appraisal would also be required.

4. One of the participants recommended that UNIDO should facilitate and promote discussions on establishing a better coordination, or if possible co-operation, among the vaccine manufacturers in CEEC. This could lead to the establishment of a regional Vaccine Manufacturers Association in CEEC.

5. He added that based on mutual interest, UNIDO should facilitate and promote a dialogue between the Vaccine Manufacturers Association which is recommended to be established in CEEC and the European Vaccines Manufacturers. For illustration and further information the Regulations of the "European Vaccines Manufacturers" are given in Annex 3.

MARKETING OF VACCINE IN EASTERN EUROPE

by Dr. Josef Böckmann
Serotherapeutisches Institut Wien GmbH

1) INTRODUCTORY REMARKS

The simplest and most cost-efficient means to protect the general population against epidemiologically important infections and diseases is vaccination. There is no cheaper public-health measure with a comparable effect available.

However, the success of an efficient immunization programme is not only depending on the physical availability of a vaccine in a particular market, but mainly related to aspects such as: epidemiology, distribution, effective handling, communication and surveillance programmes.

The whole sequence of effects necessary to implement immunization programmes can be covered by the term **"marketing of vaccines"**.

The past, present and future of vaccine marketing in Central and Eastern Europe will be addressed in the following chapters.

2) PAST

Starting with the mid-thirties, vaccines became available on a broader scale and routine-immunization procedures were launched.

Vaccines were exclusively produced on a country-individual level and quality controlled by state-owned or state-financed institutions, which - at the same time - were in charge of distribution to mainly state-run vaccination centres. It represented a public health service rather than a business in classical terms.

Vaccines available at that time were limited to a few indications, production technology was based to a large extent on individual, experimental know-how at a laboratory bench scale.

Each country, particularly in Eastern Europe, developed its specific infrastructure for production, supply and use of vaccines. As all products originated from state institutions, driven by pure public-health concern without any commercial interest, vaccines were provided free of charge to the public. For decades, vaccines have been manufactured according to the original technology, without any major improvement in Eastern Europe, mainly due to lack of financial means for appropriate investments either in up-to-date production or in new biotechnologies.

State operated structures failed to develop and to pave the way for newly available biotechnologies by mid-sixties for mass cultivation of bacteria or viruses and/or mammalian cells. During this period, major technological improvements have been achieved in privatized biotechnology industries in the western hemisphere. Industrial property rights of western manufacturers, of course, were no more transferred to and/or shared with state-owned vaccine

institutes in Eastern Europe, which led to a complete still-stand of their development of biotech industry during the sixties.

Nevertheless, each country was more or less self-sufficient as far as the particular vaccine needs were concerned. Product registration as well as quality control related aspects were either of no concern, or controls were not properly implemented, since every vaccine not only originated from but was also controlled by the same state body.

The positive aspect of this policy was a rigorously implemented and well controlled vaccination procedure, which led to a high vaccination coverage and usually induced a dramatic decline in the epidemiology of particular diseases. A more or less compulsory vaccination scheme has been in force for decades. Failures to control certain disease areas were mainly due to batch-to-batch variability of certain vaccines.

Modern G.P. rules, the basis for product consistency such as efficacy and safety, which were implemented late sixties and early seventies by western manufacturers are until today not met by eastern vaccine producers. One particular factor applying to CIS territories concerns the geographical localization of vaccine manufacturers: all of them, with a few exceptions in Ukraine, are located in Russia, having been the supply-source to F-USSR as well as to COMECON Countries for the majority of EPI vaccines.

3) PRESENT

During the last 3 years, the political and economical liberalization process in Eastern Europe has influenced to varying degrees vaccine industry as well as vaccination policy. In order to get a comprehensive overview, the situation in Eastern Europe will be analyzed according to the following parameters:

3.1) Vaccine manufacturers
3.2) Epidemiological and medical aspects
3 3) Product registration policy
3.4) Marketing of vaccines
3.5) Position of Eastern and Western vaccine manufacturers in Eastern Europe

3.1) Vaccine manufacturers

Eastern European vaccine manufacturers are today still exclusively state-owned or controlled by state-institutions. Production programme is driven by the domestic demand by quantity and type of vaccine. Usually, vaccines in production today, have been manufactured for 50 years already with nearly no innovation in methodology, so that resulting quality is basically that of 1945.

Eastern European manufacturers are devoid of any substantial innovation which could have a significant influence on their further existence. Vaccine manufacturers till today are not operating on grounds of private economy, on the contrary, all of them are strictly government-

controlled. This refers in particular to quantities ordered and prices payed, which are fixed to compensate just partly the salary payments.

The limited types of vaccines manufactured in comparison to the number of people employed by this industry, is in a majority of cases not justifying a domestic vaccine production according to western terms. Individual evaluation of existing vaccine plants, either by supranational experts or by experts from western manufacturers, has led in no case to a recommendation as far as investment proposals have been concerned to reshape this particular industry segment.

The longer this situation is kept, the more likely the few experienced people employed in vaccine production will move to more profitable industrial segments.

3.2) Epidemiological and medical aspects

Modern epidemiology of infectious diseases is requiring rapid medical and laboratory diagnosis. It seems at present,. that Eastern European countries are still in a position to cope with these requirements, even though the Diphtheria-epidemy in F-USSR territories is causing second thoughts on the efficacy of prevention and control measurements. It is obvious, that no systematic procedures are implemented to monitor new and preventable diseases with the help of new vaccines. This limiting factor is at present reducing the chance of new vaccines or recently developed combinations to be accessible to local-public-health services.

WHO operated EPI schedules and related information sources are the only ones to which a limited number of medical doctors have access to. There is a substantial lack of vaccine related information at the level of vaccination centres. Governmental bodies dealing in vaccination have either no appropriate power or no adequate financial means to communicate routinely important parameters of vaccinology to improve efficacy and safety. As there is no private industrial sector in vaccines, these markets are devoid of this additional and major communication capacity of western countries.

3.3) Registration policy

Product registration today is defined mainly to foreign vaccines, creating a schizophrenic situation : Foreign vaccines have to conform with international standards.

The majority of Eastern European control laboratories are not in a position to repeat essential tests. However, registration procedures are getting more and more comprehensive. Local vaccine manufacturers are by no means in need to conform with these newly established requirements of national control authorities, whereby no pressure is exerted to improve vaccines of local manufacturers. None of the Eastern European vaccine producers could be in a position to get a licence granted in Western hemisphere.

In addition, Eastern European Health institutions are in the majority of countries preventing the licensure of western vaccines either on the basis of lack of epidemiological data, or by defending the domestic vaccine industry in case identical products are concerned.

Therefore the ability of foreign vaccine manufacturers to market products is limited, if not excluded, by the narrow-minded behavior of state-employees who have the feeling to protect their country. On the contrary, this splendid isolation policy is representing another draw-back for the local vaccine industry.

3.4) Marketing of vaccines in Eastern Europe

Under optimal private-market conditions, this means in terms of vaccines, that:

- appropriately designed vaccines,
- for which there is an epidemiological demand ,
- available in the necessary quantity and distributed at the right time and place under cold-chain conditions,
- and used according to the latest state of the information,
- under post-marketing surveillance conditions as far as efficacy and safety are concerned.

Before mentioned parameters of efficacious use of vaccines are mainly met by countries with liberal distribution, financing and /or reimbursement conditions. In Western countries vaccines are provided by the private industry in respective demands. Recommendations and use of vaccines are scheduled and monitored by a highly dynamic vaccine advisory board, reporting to the Ministry of Health whereby general vaccination recommendations are originating from MOH but all further procedures are managed in a decentralized manner. Major essential information on vaccines in use are originating from and spread by the private pharmaceutical sector. Vaccine meetings and symposia to train and educate specialists in vaccinology are provided and sponsored by the vaccine-industry.

Vaccination policy today is made by the vaccine-industry, MOH's are taking the benefit of it. Today, new vaccines are generated by private vaccine industry and its economic interest and used or recommended by the public health sector on the ground of cost-benefit analysis.

In Eastern Europe the above described situation is the reverse. Today, there is a clear-cut on lack of vaccines and innovation, having caused a R&D still-stand since 50 years and there is no healthy financial basis for the domestic vaccine industry. Prohibitive country legislation prevents the entry of western vaccines to the benefit of the population at risk. Therefore, no real motivation for western industry to enter into collaboration with local Eastern vaccine-manufacturers for an unknown and risky joint-venture in Eastern European is given.

3.5) Future position of Eastern and Western manufacturers

Scenario A: In case the general behavior, prevailing today with a few exceptions in more or less all the Eastern European countries, is kept for another 10 years, the Eastern European vaccine industry will not continue to exist anymore.

Scenario B: If Western vaccine manufacturers get entrance to these markets on a private economy basis, there will be a multitude of fruitful contributions to this particular

public health segment as well as to the particular vaccine-industry. Not much political room is left in between these two scenarios for Eastern Europe to define a new policy which could serve them in a positive way for the long-term.

Scenario C: The only additional way to get vaccinology improved in Eastern Europe is to invest in new or existing vaccine plants. Under today's circumstances this makes only economic sense if such a plant serves a population equal to or higher than 50 million people.

4) FUTURE

The future will greatly depend on broadening the horizon of national vaccine policy makers in order to become independent and to have access to a comparatively small amount of money which is required to finance vaccination, the most important and most cost-effective public health measurement.

CLINICAL EXPERIENCE OF THE DTP/IPV COMBINATION AND THE NEW TRENDS AND FUTURE ASPECTS OF COMBOS

by

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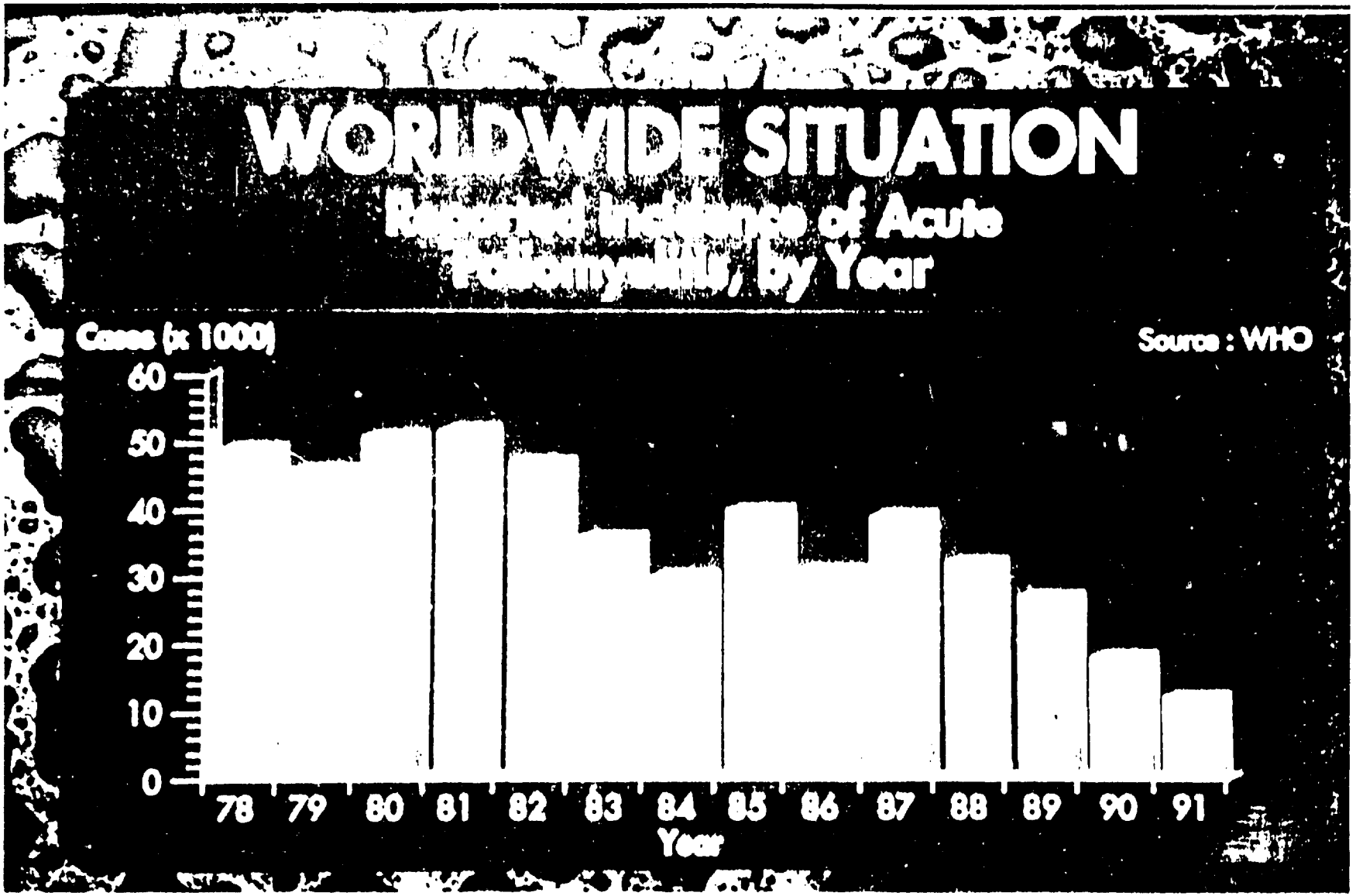
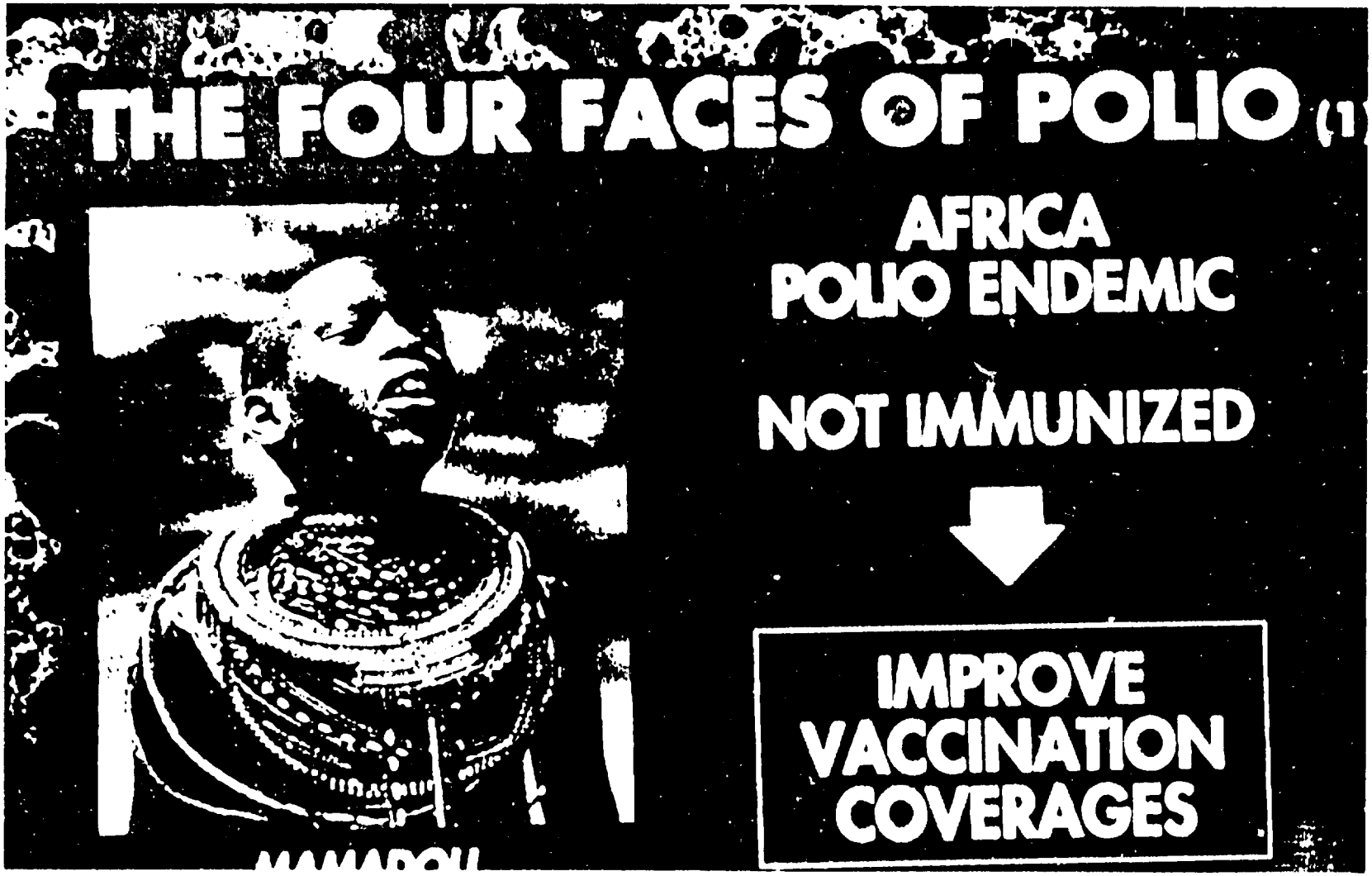
Regional Meeting on Industrial Support for Private Sector Programming
on Biotechnological Activities
7-8 June 1995 - UNIDO, Vienna


WORLDWIDE SITUATION
Reported Incidence of Acute
Poliomyelitis, by Year
Cases (x 1000)
Source : WHO
60
50
40
30
20
10
0
78
79
80
81
82
83
84
85
86
87
88
89
90
91
Year

LATION
Source: WHO
April 92
No report
0 - 9 cases
10 - 100 cases
Over 100 cases

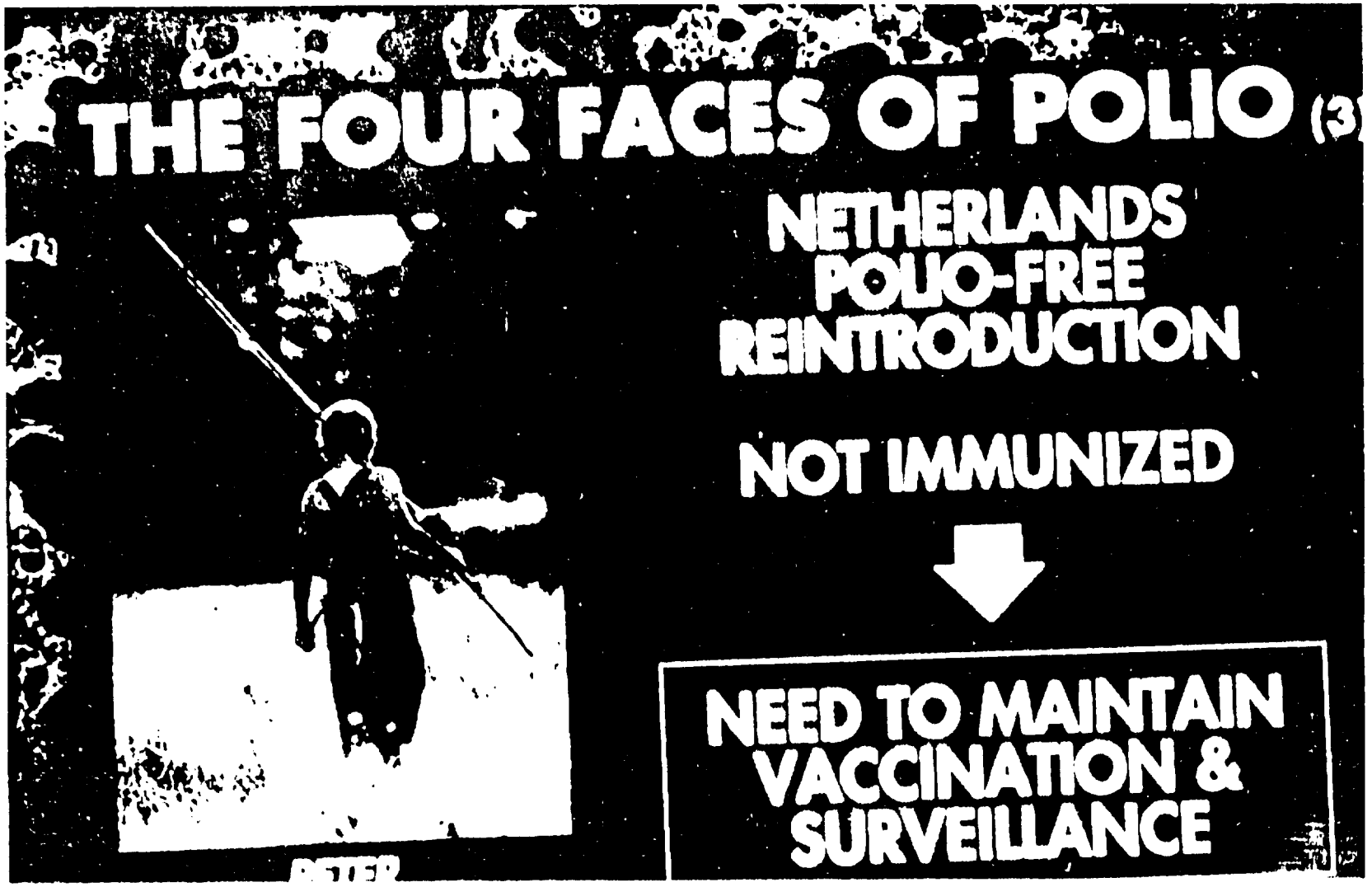

THE FOUR FACES OF POLIO (1)
AFRICA
POLIO ENDEMIC
NOT IMMUNIZED
IMPROVE
VACCINATION
COVERAGES

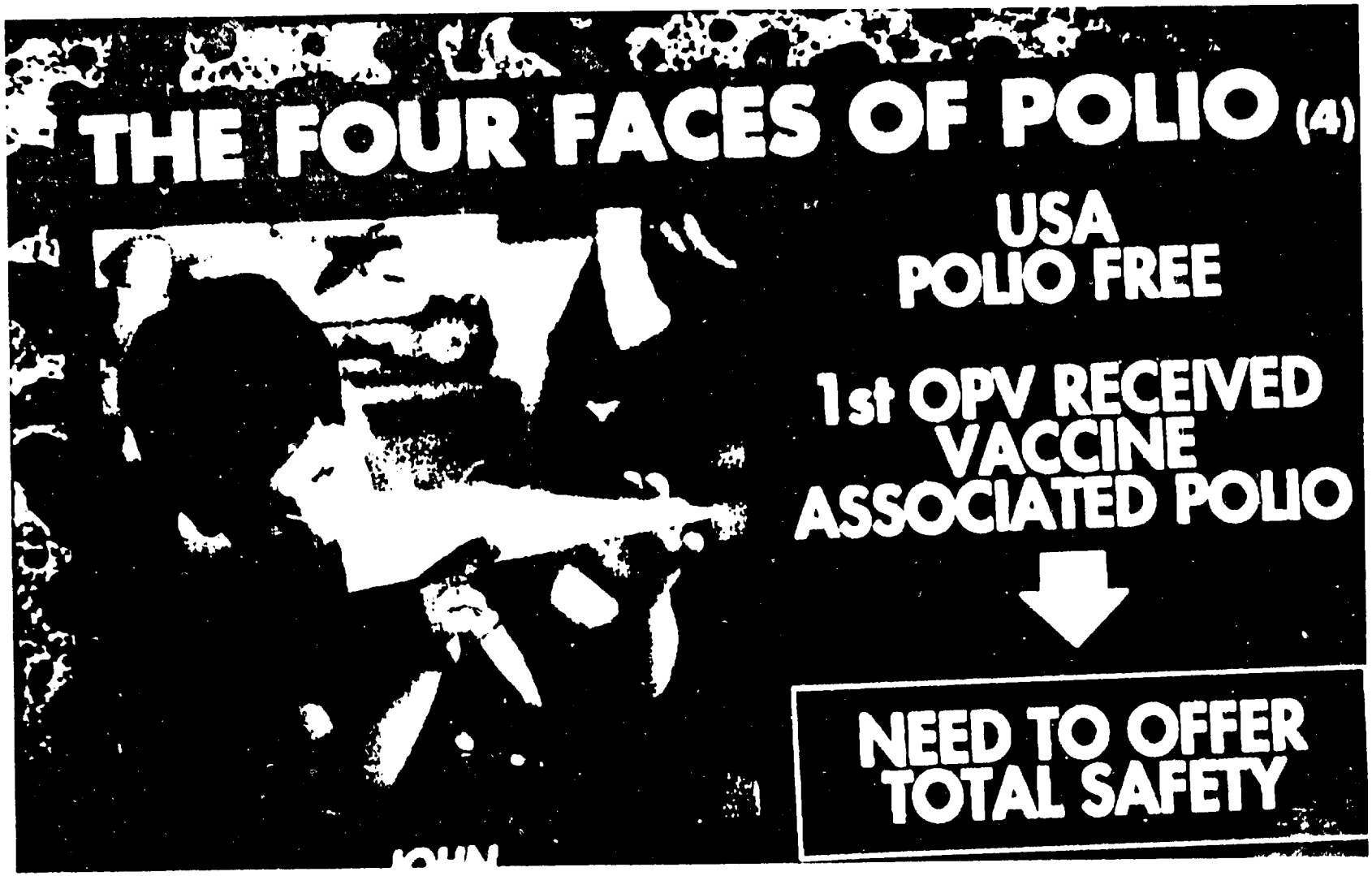
THE FOUR FACES OF POLIO (2)

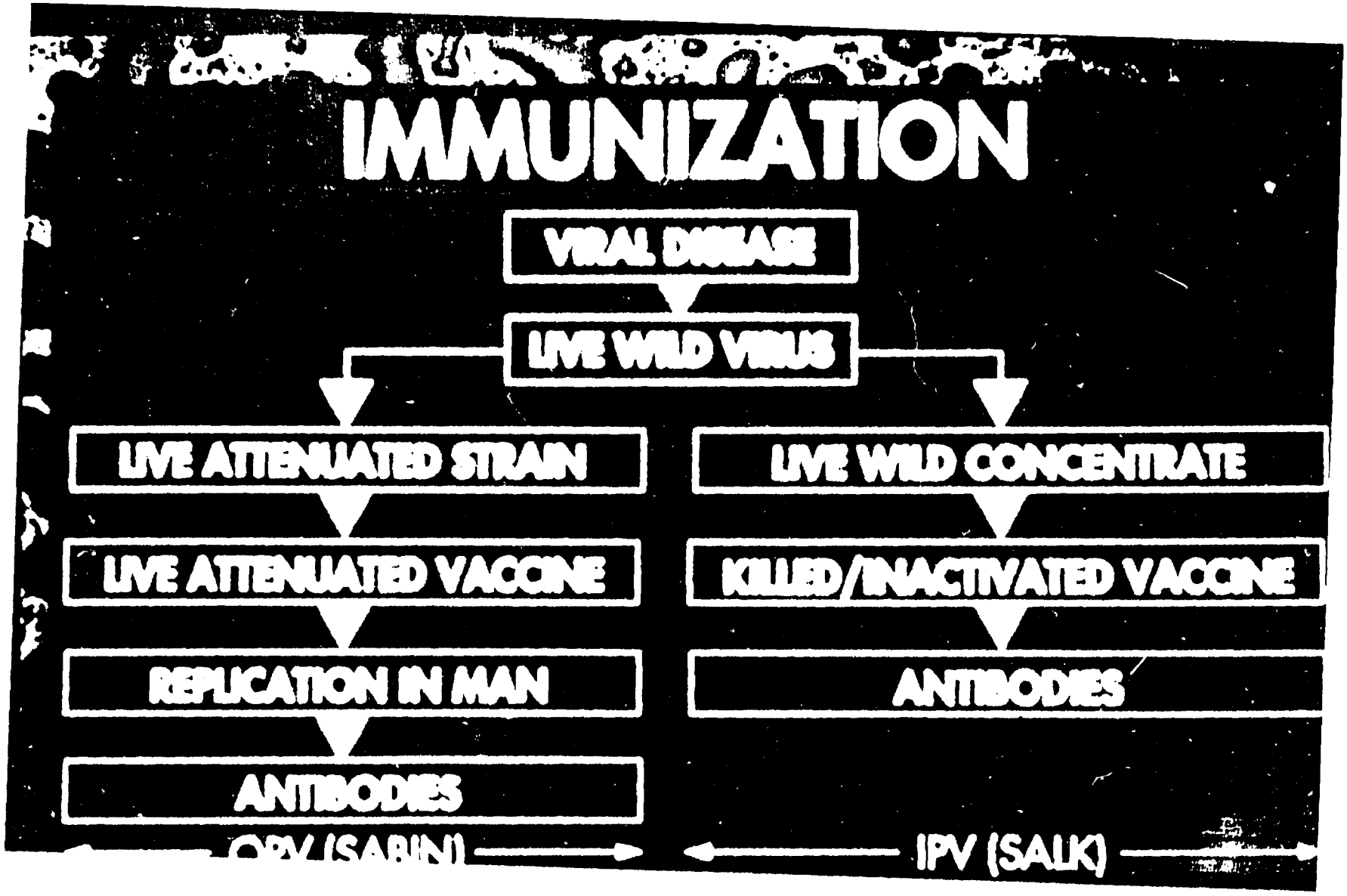
INDIA
POLIO EPIDEMIC

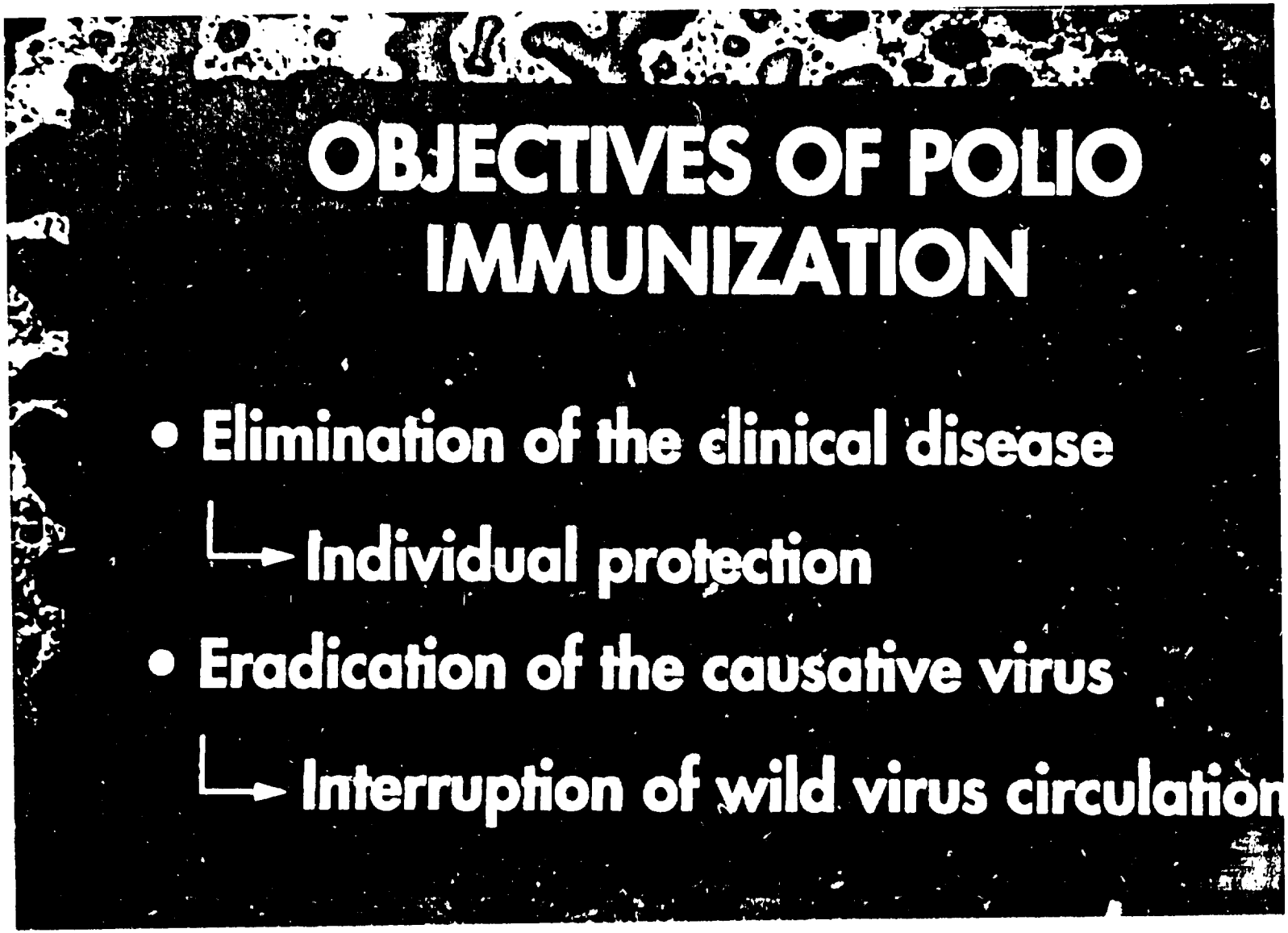
3 OPV RECEIVED

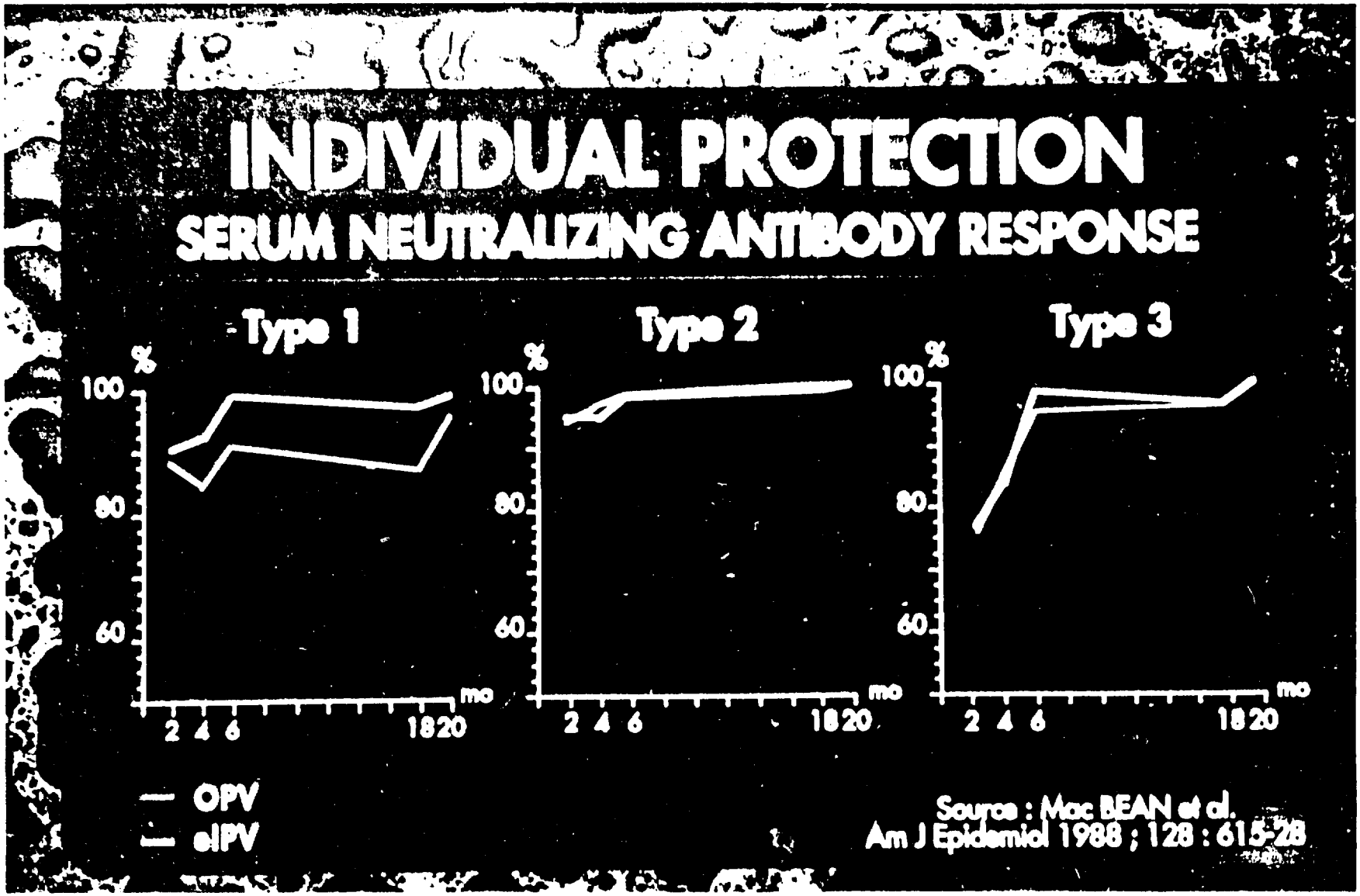
IMPROVE
INDIVIDUAL
PROTECTION


THE FOUR FACES OF POLIO (3)
NETHERLANDS
POLIO-FREE
REINTRODUCTION
NOT IMMUNIZED
NEED TO MAINTAIN
VACCINATION &
SURVEILLANCE


THE FOUR FACES OF POLIO (4)
USA
POLIO FREE
1st OPV RECEIVED
VACCINE
ASSOCIATED POLIO
NEED TO OFFER
TOTAL SAFETY


IMMUNIZATION
VIRAL DISEASE
LIVE WILD VIRUS
LIVE ATTENUATED STRAIN
LIVE WILD CONCENTRATE
LIVE ATTENUATED VACCINE
KILLED/INACTIVATED VACCINE
REPLICATION IN MAN
ANTIBODIES
ANTIBODIES
OPV (SABIN)
IPV (SALK)


OBJECTIVES OF POLIO IMMUNIZATION
• Elimination of the clinical disease
└→ Individual protection
• Eradication of the causative virus
└→ Interruption of wild virus circulation


INDIVIDUAL PROTECTION
SERUM NEUTRALIZING ANTIBODY RESPONSE
Type 1
Type 2
Type 3
%
100
80
60
mo
2 4 6 18 20
OPV
eIPV
Source : Mac BEAN et al.
Am J Epidemiol 1988 ; 128 : 615-28

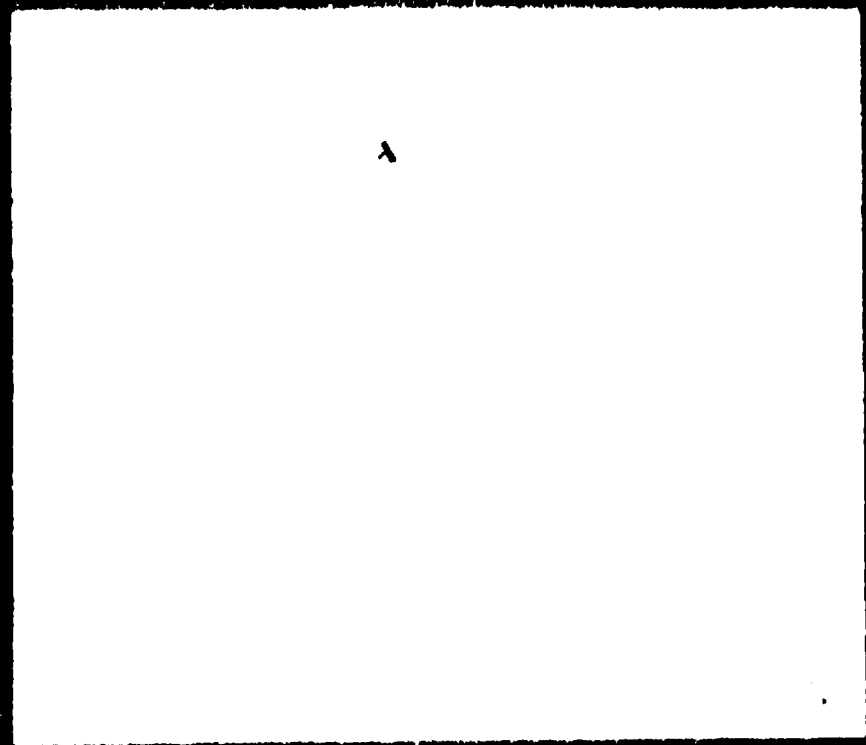
EPIDEMIC POLIOMYELITIS

POLIO IMMUNIZATION STATUS OF REPORTED CASES OF PARALYTIC POLIOMYELITIS

Country (V.C.)	Year	Reported cases	Percentage of patients who received			
			0 OPV	1 OPV	2 OPV	3+ OPV
Oman (88%)	1988/ 1989	119	14%	15 %	16 %	55 %
Brazil (89%)	1986	612	17%	20 %	16 %	47 %

Source : Summary of poliomyelitis outbreaks 1978 - 1988 WHO Document

POLIO FREE COUNTRIES
UNITED STATES (1951-1990)



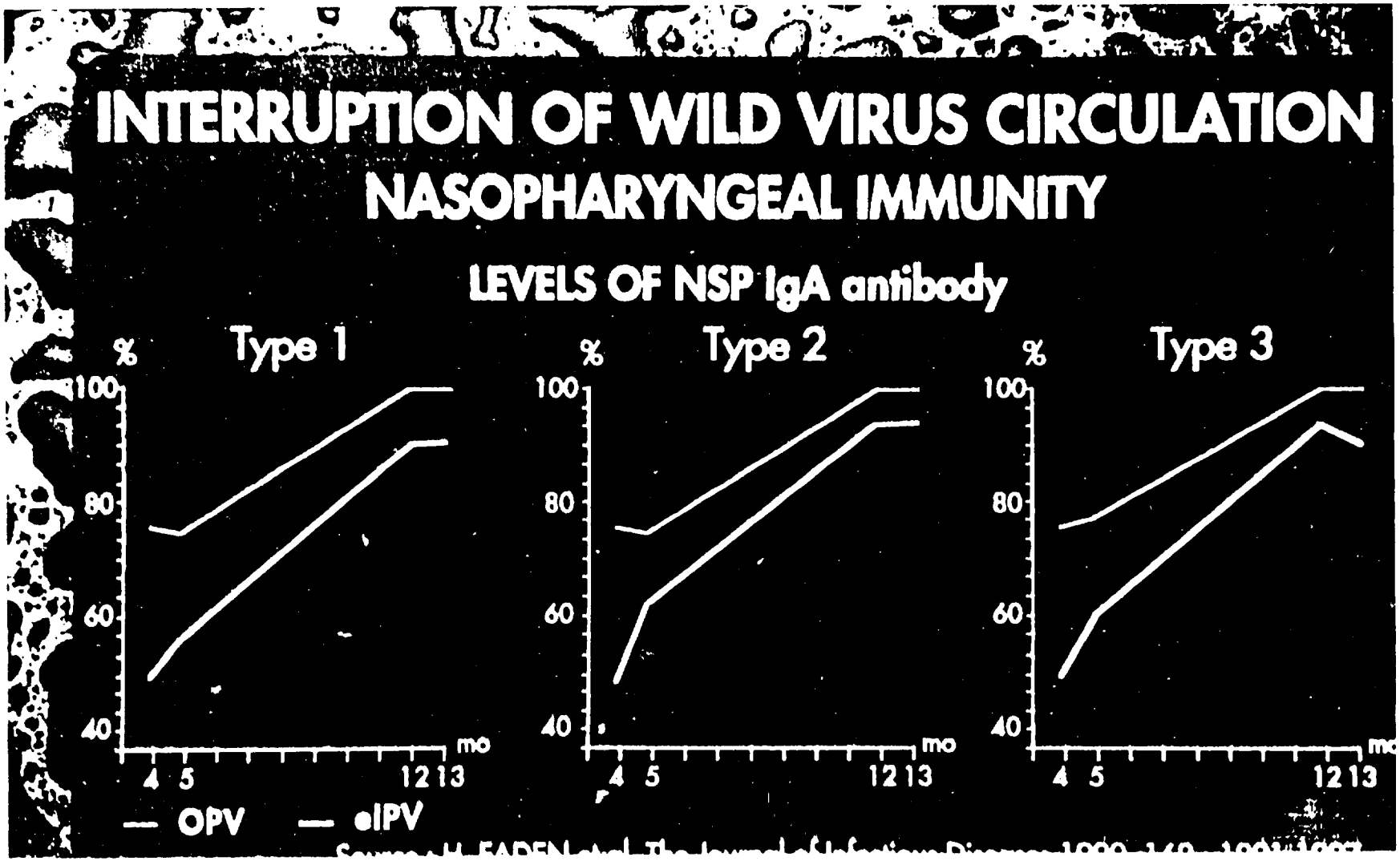
Comparison of the annual number of cases of PARALYTIC POLIOMYELITIS due to wild poliovirus and live virus vaccine (C.D.C.)

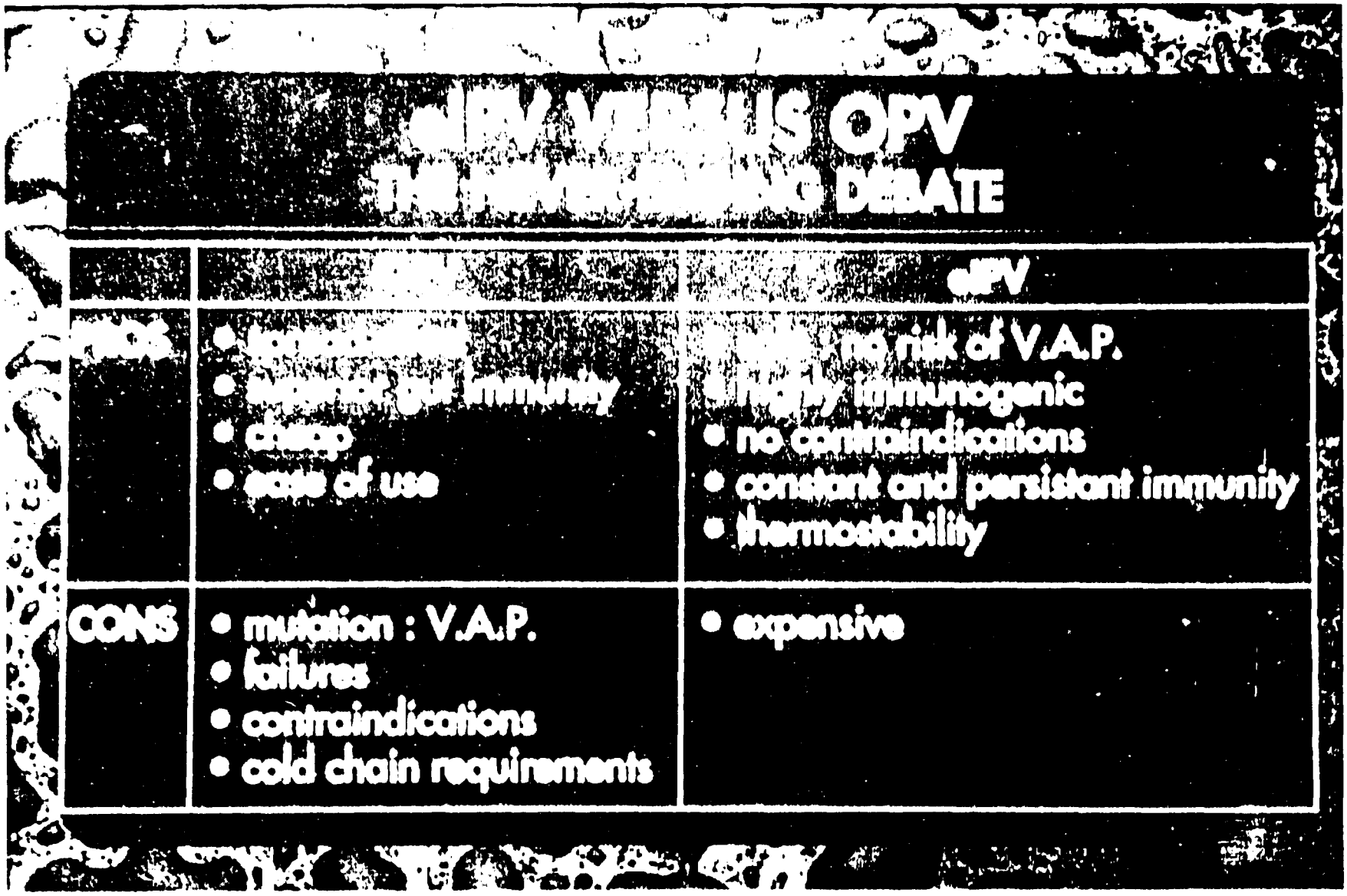
INDIVIDUAL PROTECTION
VACCINE-ASSOCIATED POLIOMYELITIS

n = 80 cases — Review of the US situation (80-89)

Groups at risk	Recipients	Contacts	Immunocompromised
% Cases	38 %	45 %	17 % (Recipients : 64 % / Contacts : 36 %)
% Cases associated to the first or second dose of OPV	93 %	78 %	57 %
Median interval from vaccination to first symptoms	21 days (4-34)	31 days (5-68)	42 days (9 days-6 months)

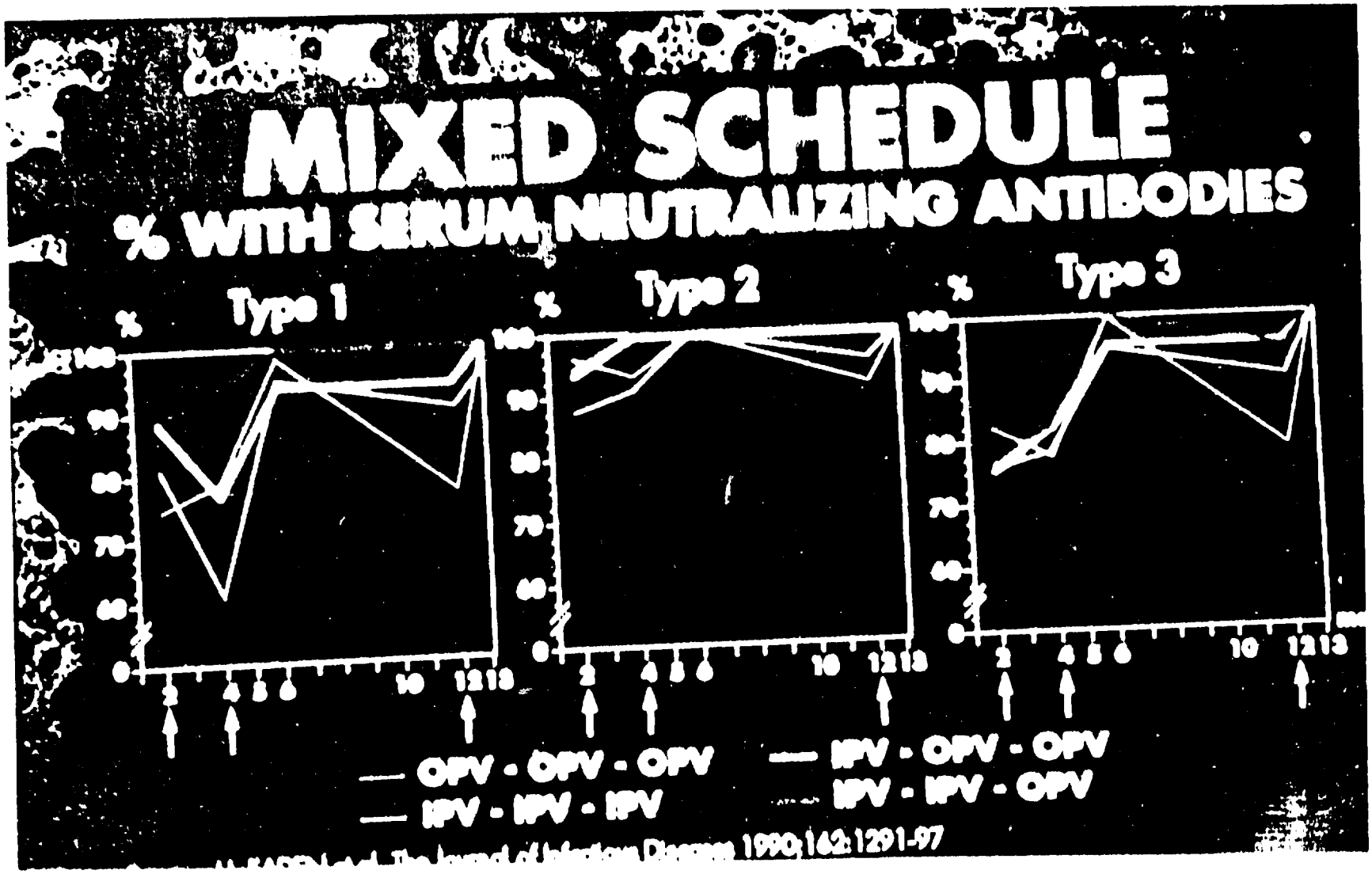
Source : P. M. STREBEL et al. Clinical Infectious Diseases 1992 ; 14 : 568-79

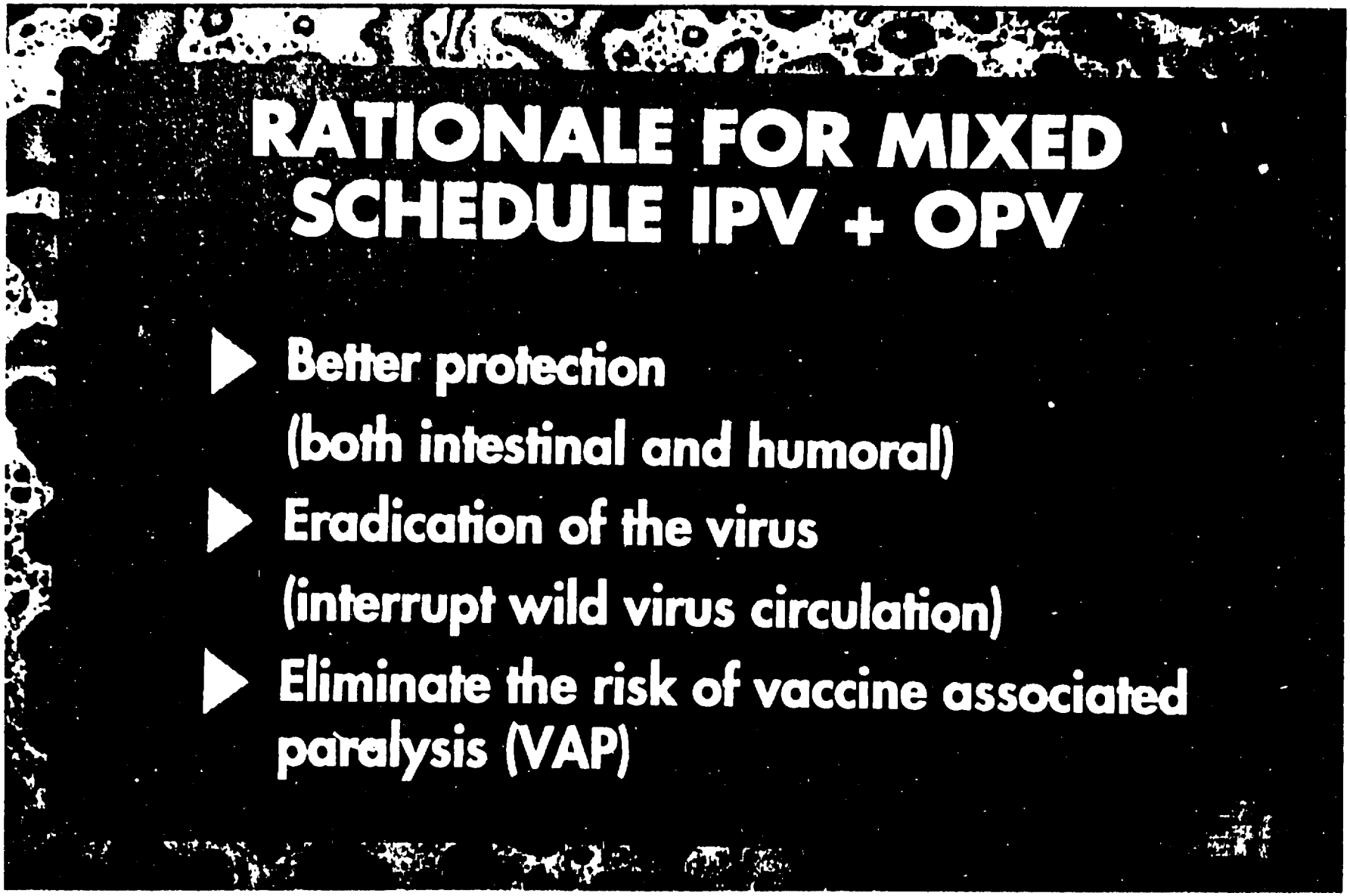

INTERRUPTION OF WILD VIRUS CIRCULATION
NASOPHARYNGEAL IMMUNITY
LEVELS OF NSP IgA antibody
Type 1
Type 2
Type 3
%
100
80
60
40
mo
4 5
12 13
— OPV
— eIPV


OPV
DEBATE
dPV
• no risk of V.A.P.
• no contraindications
• constant and persistant immunity
• thermostability
• expensive
CONS
• mutation : V.A.P.
• failures
• contraindications
• cold chain requirements

AVAILABLE TOOLS & STRATEGIES

	INDIVIDUAL PROTECTION	ERADICATION
IPV	+ + + Predictable - Safe	+ + Not proven in Developing Countries
OPV	± Failures Vaccine Associated Poliomyelitis	+ + + Mass campaigns in Developing Countries
MIXED SCHEDULE	+ + + Primo Immunization DTP-IPV - Routine	+ + + National Immunization Days - with OPV


MIXED SCHEDULE
% WITH SERUM NEUTRALIZING ANTIBODIES
Type 1
Type 2
Type 3
%
100
90
80
70
60
0
2
4
5
6
10
12
13
— OPV - OPV - OPV
— IPV - IPV - IPV
— IPV - OPV - OPV
— IPV - IPV - OPV
1990;162:1291-97


RATIONALE FOR MIXED SCHEDULE IPV + OPV
Better protection
(both intestinal and humoral)
Eradication of the virus
(interrupt wild virus circulation)
Eliminate the risk of vaccine associated paralysis (VAP)

EXPERIENCES WITH COMBINED USE OF IPV/OPV IN HUNGARY

by Dr. I. Dömök, Deputy Director General
"B. Johan" National Institute of Public Health, Budapest

In Hungary a new schedule has been introduced in 1992 for vaccination against poliomyelitis: the sequential use of eIPV and OPV. In order to understand the main reasons for this decision, I have to give an account on the history of vaccinations against poliomyelitis in this country.

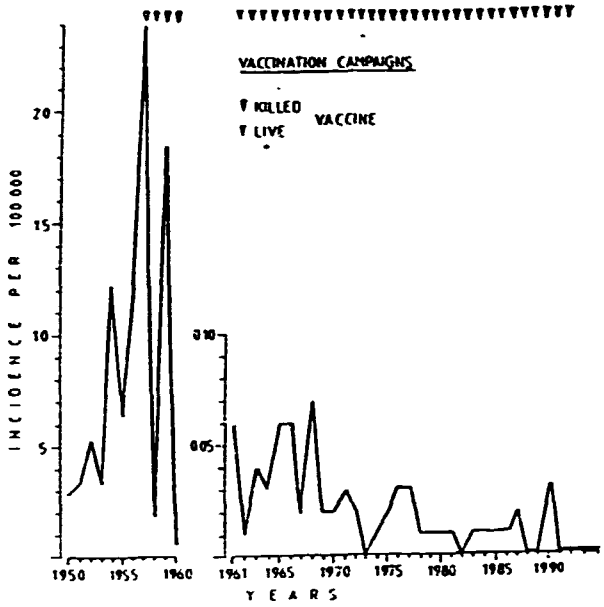
Hungary was among the first countries which have introduced the live Sabin vaccine for prevention of poliomyelitis. This was because in the second half of 50s there was a very serious poliomyelitis situation in Hungary with repeatedly occurring epidemics which could not be influenced with the contemporary Salk vaccine. Thus vaccinations with the Sabin vaccine were started in the whole country already in December 1959.

From 1959 to 1991 vaccinations were carried out with the OPV in nation-wide campaigns repeated annually in the winter months until 1977 and after that in the autumn between September and December.

Monovalent vaccines (MOPV) were used in 1,3,2 sequence of types, each administered within a week all over the country at intervals of five to eight weeks, except for the 2nd campaign in 1960, when trivalent vaccine was fed twice; and the 3rd campaign in 1961, when a balanced schedule (1, 1+3, 1+2+3) was applied. In the lst and 2nd campaigns children up to the age of 14 years, whilst in the 3rd campaign those up to the age of 9 years were vaccinated. Since 1962 year by year children between 2 and 38 months of age have been vaccinated, thus since that year children received one primary and two repeated courses of monovalent vaccines by the time they reached 38 months of age. Vaccinations have been compulsory and the coverage rates attained at least 97% in every campaign.

Besides virological control examinations (seroconversion rates, seroepidemiological investigations) the epidemiological efficacy of vaccinations proved highly satisfactory (see Fig.1). A spectacular decrease in incidence of poliomyelitis could be observed and thus the effectiveness was proven already in 1960, when as few as 38 cases were reported. From 1961 to 1991. i.e. during a period of 31 years a total of 66 cases were registered. The mean annual incidence of poliomyelitis decreased to 0,04 per 100,000 between 1961 and 1970, to 0,02 per 100,000 between 1971 and 1980 and to 0,01 per 100,000 between 1981 and 1990 from a level of 12 per 100,000 observed in a five year period just before the use of live poliovirus vaccine.

Figure 1



Of the 66 cases registered since 1961 56 (85%) were temporarily associated with the vaccinations (see Table 1). Of these 56 cases 47 (84%) were confirmed virologically, 39 being associated with administration of type 3, 5 with type 2 and 3 with type 1 vaccine. Majority of type 3 vaccine associated cases (35) occurred in recipients.

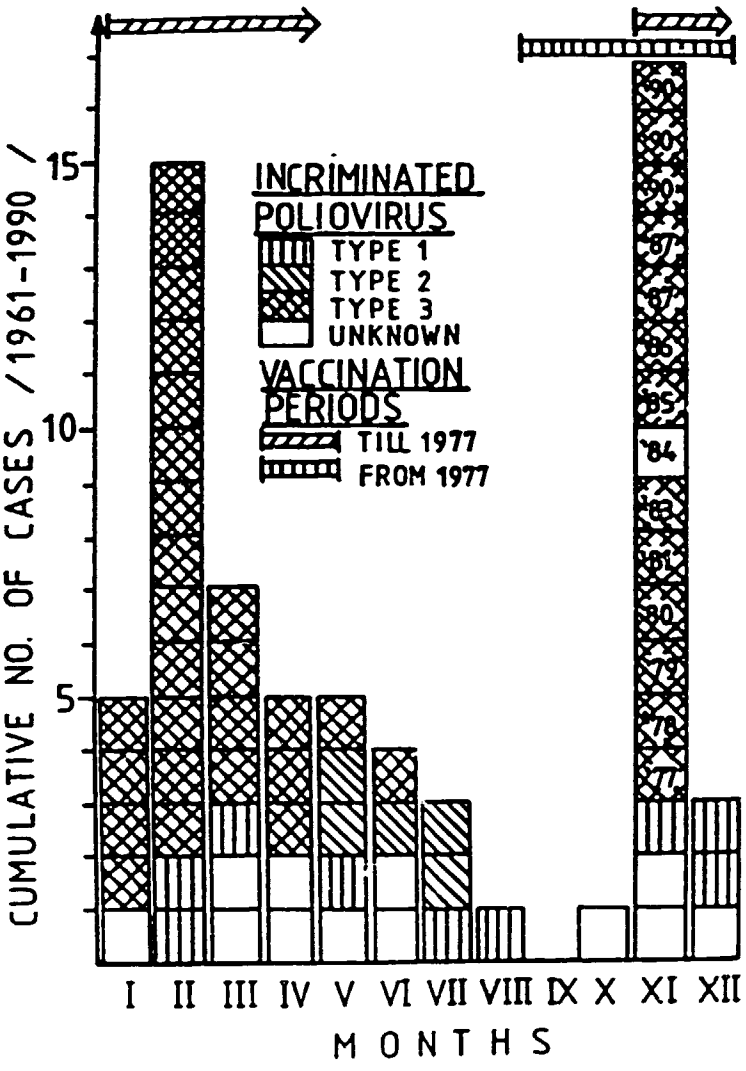
Nine of the 10 cases temporarily not associated with vaccinations were classified as indigenous and one as an imported case from the Middle East. The last indigenous case elicited by a type 1 poliovirus occurred in 1969.

Table 1
Distribution of poliomyelitis cases registered between 1961 and 1991
by their relationship to vaccinations

Temporal Relation to	Category of Cases	Poliovirus etiology			
		Confirmed with type 1 2 3	Could not be tested	Excluded	Total
MOPV-1	Recipient	3 - -	-	-	3
MOPV-2	Recipient	- - -	2	-	2
	Contact	- 5 -	-	-	5
MOPV-3	Recipient	- - 31	4	-	35
	Contact	- - 8	1	-	9
BOPV, TOPV	Recipient	- - -	2	-	2
Subtotal	Recipient	3 5 39	9	-	56
None	Imported	1 - -	-	-	1
None	Indigenous	5* - -	-	4	9
Total		9 5 39	9	4	65

* Last case in 1969

Figure 2



As Figure 2 demonstrates, after the vaccination campaigns have been transferred from the winter period to the autumn in 1977, all the 14 cases occurred in November of the respective years, i.e. in the period after administration of type 3 live vaccine. During this period there were 4 years when no cases were observed (1982, 1988, 1989, 1991), 9 years when one case, one year when 2 cases and one year when 3 cases were detected. Among the 14 cases registered since 1977, 12 were primary vaccinees between 6 and 13 months of age and 2 were contacts of vaccinees both with an age of 4 months. During this period total number of primary vaccinees with type 3 vaccine was 1 784 885. Thus the complication rate of type 3 vaccine proved to be 1:150 000 for primary recipients (and 12:5 ,641,000 or 1:470, 000 for all the vaccinees).

This complication rate is higher than generally published by others, but it has to be taken into consideration that this is calculated for the susceptible recipients which was possible only because of the special administration of vaccine in yearly repeated campaigns always for the same determined age groups.

Table 2

Vaccination schedule against poliomyelitis in Hungary since 1992

Vaccines Administered	Age of eligible children	Application
DPT I/a + eIPV*	3 months	continuous
DPT I/b + TOPV^	4 months	continuous
DPT I/c + TOPV	5 months	continuous
MMR + TOPV	15 months	continuous
DPT II + TOPV	3 years	continuous
DPT III + TOPV	6-7 years	Campaign at school entry

* Tetracoq. D antigen contents : P1 40 U; P2 8U; P3 32 U
^ Balanced vaccine with $TCID_{50}$: P1 10^6; P2 10^5; P3 $10^{5.8}$

In 1992 a new vaccination schedule has been introduced which is shown in Table 2. Vaccination campaigns have been replaced by continuous vaccinations. Children at 3 months of age receive "Tetracoq" vaccine containing besides diphtheria-pertussis-tetanus components also poliovirus D antigen according to the so called enhanced inactivated polio vaccine formulation.

Children at 4, 5, 15 months, 3 and 6-7 years of age - i.e. five times - receive trivalent oral polio vaccine together with diphtheria-pertussis-tetanus, or with measles-mumps-rubella vaccine. The administered polio vaccine is a balanced vaccine containing 10^6TCID_{50} of type 1, 10^5TCID_{50} of type 2 and $10^{5.8}TCID_{50}$ of type 3 vaccine strain.

Main reasons for introduction of this schedule were as follows (See Table 3).

Table 3
REASONS FOR CHANGING THE VACCINATION SCHEDULE AGAINST POLIOMYELITIS

1.	Increased international movements created a hazardous situation for susceptible newly born children accumulating in a year period between vaccination campaigns.
2.	Vaccination campaigns caused difficulties in administration of other vaccines in due time.
3.	To make an attempt for prevention of cases associated with OPV by introductory administration of eIPV and to ensure a strong immunity by repeated feeding of TOPV.

Due to the East- and Middle-European political, social, and economic developments the population movements dramatically increased in Hungary. Total annual number of visitors, tourists, transit passengers, refugees, legal and illegal immigrants has been 3 to 4 times higher than the whole population of Hungary. The same time Hungarians also have got unrestricted opportunities to travel abroad. It is certain that under these conditions massive importation of wild polioviruses became an every-day event. This created a real epidemiological danger, since in the 8-10 months' periods between vaccination campaigns high number of susceptibles accumulated composed of newly born children and of those who for any reason remained out from vaccination in the previous campaign.

The second reason was that vaccination campaigns caused difficulties in administration of other vaccines in due time owing to recommended intervals between live polio and other live vaccines for which children were eligible when they reached the appropriate age.

When the conclusion was drawn that vaccination campaigns should be replaced by continuous vaccinations owing to the formerly mentioned reasons the next question for consideration was: What kind of vaccine or vaccines should be used for continuous vaccinations?

The basic point was that the change in polio immunization scheme should result in at least the same level of protection as had been ensured with the former schedule. Monovalent oral polio vaccine given in campaigns certainly induced high level of immunity in the population - as it was indicated by the seroepidemiological investigations - owing to the fact that during the campaigns the vaccine virus was spreading intensively from vaccinees to unimmunized children or to those whose protection became incomplete. This resulted in additional and reinforced immunizations. For continuous vaccinations however, the monovalent vaccines are unsuitable for organizational reasons.

Thus instead of monovalent, the balanced trivalent oral vaccine was chosen and in order to attain surely a high level of protection it was decided to administer it five-times to children at those ages when other vaccines are also administered.

A further point was that if we change the schedule we have to try to chose one which may result in reduction or even in elimination of risk of vaccine associated polio cases.

In this respect especially the experiences obtained in Denmark published by von Magnus and Petersen (1) and those in Gaza and West Bank published by Lasch et al (2) by Tulchinsky et al (3) were taken into account as well as theoretical and practical considerations published among others by Melnick (4,5), by McBean and Modlin (6) as well as by Sutter et al (7).

Ten-years, experience in West Bank and ~Gaza and since 1989 in Israel clearly indicated that combined use of eIPV and OPV results in successful elimination of poliomyelitis even in developing areas (3). On the other hand the Danish experiences showed that since 1968, i.e. since introduction of initial vaccination with IPV followed by vaccination with TOPV practically no vaccine associated cases have been detected in contrast to the vaccination campaign in 1966 when 2.7 million individuals below 40 years of age were vaccinated with type 3 Sabin vaccine and 5 vaccine associated paralytic cases had been reported (1).

So it seemed justified to accept the statement of McBean and Modlin (6) that "there are many reasons to believe that polio immunization schedule that incorporates sequential doses of

inactivated ... and live attenuated poliovirus vaccine would provide both humoral and intestinal immunity to the fully immunized person ... Furthermore, most of the cases of OPV associated paralytic poliomyelitis could be prevented".

In spite of the fact that neither Sabin (7) nor Salk (8) agreed with this opinion we thought that it is worthy to make an attempt to reduce the risk of vaccine associated cases by polio vaccine combined with DPT.

Department of Virus Vaccine Control of our Institute made investigations on seroconversation rates after primary vaccination with one dose of Tetracoq. Among 91 triple negative children measurable neutralizing antibodies to poliovirus types 1,2 and 3 were found 30 days after vaccination in 41%, 66% and 58% respectively.

When the effect of eIPV and two doses of TOPV were investigated among primary vaccinees it was found that 30 days after the 2nd dose of TOPV children had antibodies in 100 per cent against types 1 and 2, and 98% against type 3 of poliovirus. Geometric mean titres were high against all three types.

About 3 and a half years have elapsed since the introduction of combined vaccination schedule and already more than 4 years without a single poliomyelitis case. Thus neither vaccine associated nor wild virus elicited poliomyelitis was observed in Hungary which indicates that a single introductory dose of eIPV may be enough for prevention of OPV associated poliomyelitis cases and that the combined schedule can give adequate protection against wild polioviruses.

To our opinion, the sequential schedule is the method of choice for vaccination against poliomyelitis in countries where vaccine associated poliomyelitis has become a major concern and the same time threat of importation of wild polioviruses exists.

References

1. von Magnus, H., Petersen, I.: Vaccination with inactivated poliovirus vaccine and oral poliovirus vaccine in Denmark. Rev. Infect. Dis. 6, S471-S474, 1984.

2. Lasch, E.E. et al: Successful results of a program combining live and inactivated poliovirus vaccines to control poliomyelitis in Gaza. Rev. Infect. Dis. 6, S467-S470, 1984.

3. Tulchinsky, T.H. et al: A ten-year experience in control of poliomyelitis through a combination of live and killed vaccines in two developing areas. Amer. J. Publ. Hlth 79, 1648-1654, 1989.

4. Melnick, J.L.: Combined use of live and killed vaccines to control poliomyelitis in tropical areas. Development in Biol. Strandard. 47, 265-273, 1981.

5. Melnick, J.L.: Poliomyelitis: eradication in sight. Epid. and inf. 108, 1-18, 1992.

6. McBean, A.M., Modlin, J.F.: Rationale for the sequential use of inactivated poliovirus vaccine and live attenuated poliovirus vaccine for routine poliomyelitis immunization in the United States. Pediatr. Infect. Dis. J. 6, 881-887, 1987.

7. Sutter, R.W. et al.: Current poliomyelitis immunization policy in the United States. Pediatr. Ann. 19, 702-706, 1990.

8. Sabin, A.B.: Commentary: Is there a need for a change in poliomyelitis immunization policy? Pediatr. Infect. Dis. J. 6, 887-889, 1987.

9. Salk.J.: Commentary: Poliomyelitis vaccination -choosing a wise policy. Pediatr. Infect. Dis. J. 6, 889-893, 1987.

PRESENTATION ON

* IPV/OPV - AN EXAMPLE OF AN INDUSTRIAL ACHIEVEMENT

* CHOICE FROM PRIMARY MONKEY TO VERO CELL TECHNOLOGY

* REGISTRATION STATUS OF IPV

* STATE OF THE ART QUALITY CONTROL OF VACCINES

by

Dr. B. Montagnon
Pasteur Merieux Serums & Vaccins, France

PASTEUR MÉRIEUX
Sérums & Vaccins

POLIOVACCINE OPV

- **Purification : 2 different stages**
  - Ion exchange chromatography
  - Zonal centrifugation (sucrose)
- **Monovalent concentrated OPV**
- **Trivalent bulk OPV vaccine**
- **Finished OPV Vaccine**
  - 10 Doses
  - 20 doses

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POLIOVACCINE IPV / OPV

CHOICE FROM PRIMARY MONKEY TO VERO CELL TECHNOLOGY

- **Problems with supply of monkeys**

  Adventitious agents
  - **B Virus (Herpes simiae)**
  - **SV-40 (Vacuolating agent)**
  - **SIV (Simian Immunodeficiency Virus)**
  - **Ebola (Marburg Virus)**
  - **Adenovirus**
  - **Foamy virus**
  - **Enterovirus**

- **Microcarrier culture system**

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POLIOVACCINE IPV
VERO CELL OF PMsv

Registered in :

Europe	France	July	1982
	Austria	October	1991
	Belgium	March	1986
	Finland	October	1990
	Luxembourg	May	1985
	Sweden	September	1994
Eastern Europe	Georgia	December	1992
	Hungary	August	1992
	Kirghiztan	March	1995
	Lithuania	February	1995
	Poland	August	1992
	Czech Republic	December	1992
	Rumania	January	1993
	Russia	January	1994
	Slovakia	December	1992
	Ukraine	January	1995

PASTEUR MERIEUX

POLIOVACCINE IPV

VERO CELL OF PMsv

Registered in :

Middle-East	**Israel**	**August**	**1991**
Far-East	**Hong-Kong**	**July**	**1993**
Oceania	**Australia**	**May**	**1994**
America	**Argentina**	**March**	**1983**
	Canada	**February**	**1995**
	Chile	**February**	**1995**
	Colombia	**December**	**1986**
	Ecuador	**November**	**1991**
	Peru	**November**	**1992**
	USA	**December**	**1990**
	Venezuela	**January**	**1990**
	Aruba	**June**	**1992**
	Curaçao	**April**	**1993**
Africa	**Benin**	**April**	**1991**
	Burkina Faso	**March**	**1991**
	Ivory Coast	**January**	**1983**

PASTEUR MERIEUX

POLIOVACCINE IPV (VERO)

STATE OF THE ART OF QUALITY CONTROL OF VACCINE

- **Working cell bank (VERO)**
  - **Sterility (Microbial - Fungi - Mycoplasma)**
  - **Absence of virus**
    - **Cytopathic** (Subculture and co-culture)
    - **Retrovirus** (After induction by BUDR)
    - **SIV**
    - **D-Retrovirus** (Mason - Pfizer)
    - **Electronic microscopy**
  - **Absence of tumorigenicity**
  - **Inoculation in animals**
  - **Absence of reverse transcriptase activity**

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POLIOVACCINE IPV (VERO)

STATE OF THE ART OF QUALITY CONTROL OF VACCINE

- **Primary virus seed - lots**
  - ✧ **Control cells** : • No cytopathic change
  - ✧ **Viral suspensions** : • Sterility tests (Bacteria - Fungi - Mycoplasma)
    • Absence of mycobacteria
    • Tests in rabbits - Guinea pigs
    • Tests in PMKC (After neutralisation)
    • Identity test
    • Infectious titre
- **Working virus seed-lots**
  - ✧ **Control cells observation - No haemadsorption - Identity supernatants** : • Subcultivation on cell culture
    • Absence of cultivable mycoplasma
  - ✧ **Viral suspension** : • Sterility tests (Bacteria - Fungi)
    • Test for absence of cultivable mycoplasma
    • Test in rabbits
    • Test in cell cultures
    • Identity test
    • Infectious titre

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POLIOVACCINE IPV (VERO)

STATE OF THE QUALITY CONTROL OF THE VACCINE

- **Control cells**
  - ✧ **Cell** : • **Observation**
    • **No haemadsorption**
    • **Identity**
  - ✧ **Supernatant** : • **Subcultures**
    • **Absence of cultivable mycoplasma**
- **Virus harvest (Crude)** : • **Identity**
  • **Infectious titre**
  • **Sterility**
  • **Absence of cultivable mycoplasma**

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POLIOVACCINE IPV (VERO)

STATE OF THE QUALITY CONTROL OF THE VACCINE

Concentrated and purified viral suspension :

- Protein content
- D-Antigen content
- Purity test
- Sterility

Monovalent concentrated inactivated vaccine :

- Residual formaldehyde
- Residual calf serum
- Sterility test
- D-Antigen content } Purity
- Kinetics of inactivation
- Tests for effective inactivation

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POLIOVACCINE IPV (VERO)

STATE OF THE QUALITY CONTROL OF THE VACCINE

Concentrated trivalent vaccine (active substance)

- Sterility
- Effective inactivation
- LAL Test (Endotoxin content)
- pH
- Residual formaldehyde content
- D-Antigen content

Final bulk vaccine :

- Appearance - pH - Protein content
- Residual formaldehyde - 2-Phenoxyethanol
- Sterility test
- D-Antigen content
- Potency (chicken test as Ph. Eur.)

Finished product :

- Appearance - pH - Volume (extractable)
- 2-Phenoxyethanol - Formaldehyde
- Protein content
- Sterility test
- Abnormal toxicity
- D-Antigen content (Identity test)

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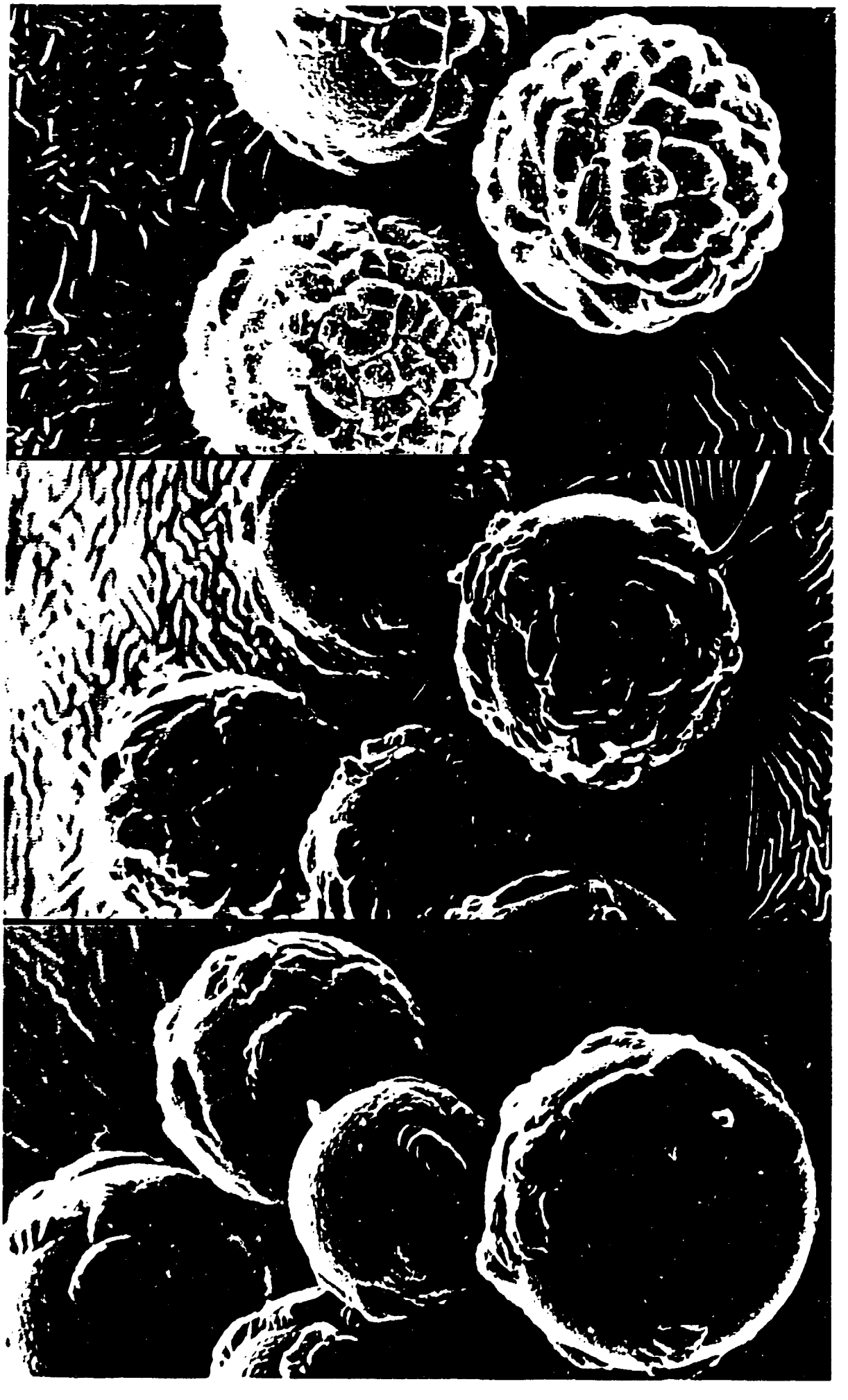
POLIOVACCINE IPV / OPV
An example of an industrial achievement

- **Vero cell line**
  - ✧ **Master cell bank** — **129th passage**
  - ✧ **Working cell bank** — **137th passage**
  - ✧ **Production Vero cell** — **142nd passage**
- **Virus seed lot**
- **Microcarrier culture system (CYTODEX 1)**
- **Virus cultivation**
- **Virus harvest + clarification / concentration**
- **Virus purification**

PASTEUR MÉRIEUX
Sérums & Vaccins

POLIOVACCINE IPV

- **Purification : 3 different stages**
  - Ion exchange chromatography
  - Gel filtration
  - Ion exchange chromatography
- **Inactivation**
  - 12 days at 37°C
  - Formaline at 1 . 4000
- **Monovalent concentrated vaccine**
- **Concentrated trivalent vaccine**
- **Final bulk** { Plain Polio Vaccine (IPV) or Combined vaccines
- **Finished product**

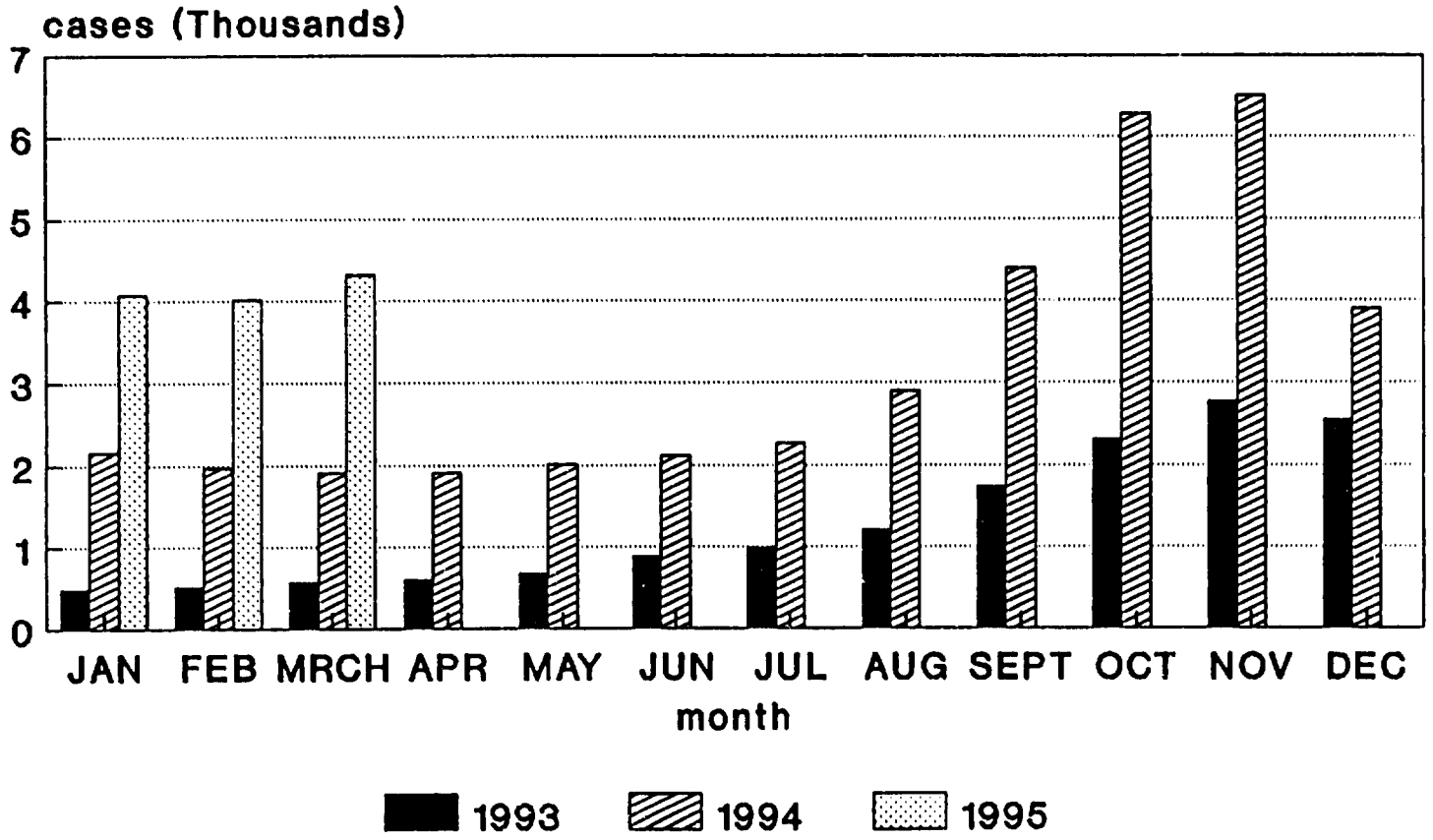


EPIDEMIC DIPHTHERIA IN THE NEWLY INDEPENDENT STATE OF THE FORMER USSR

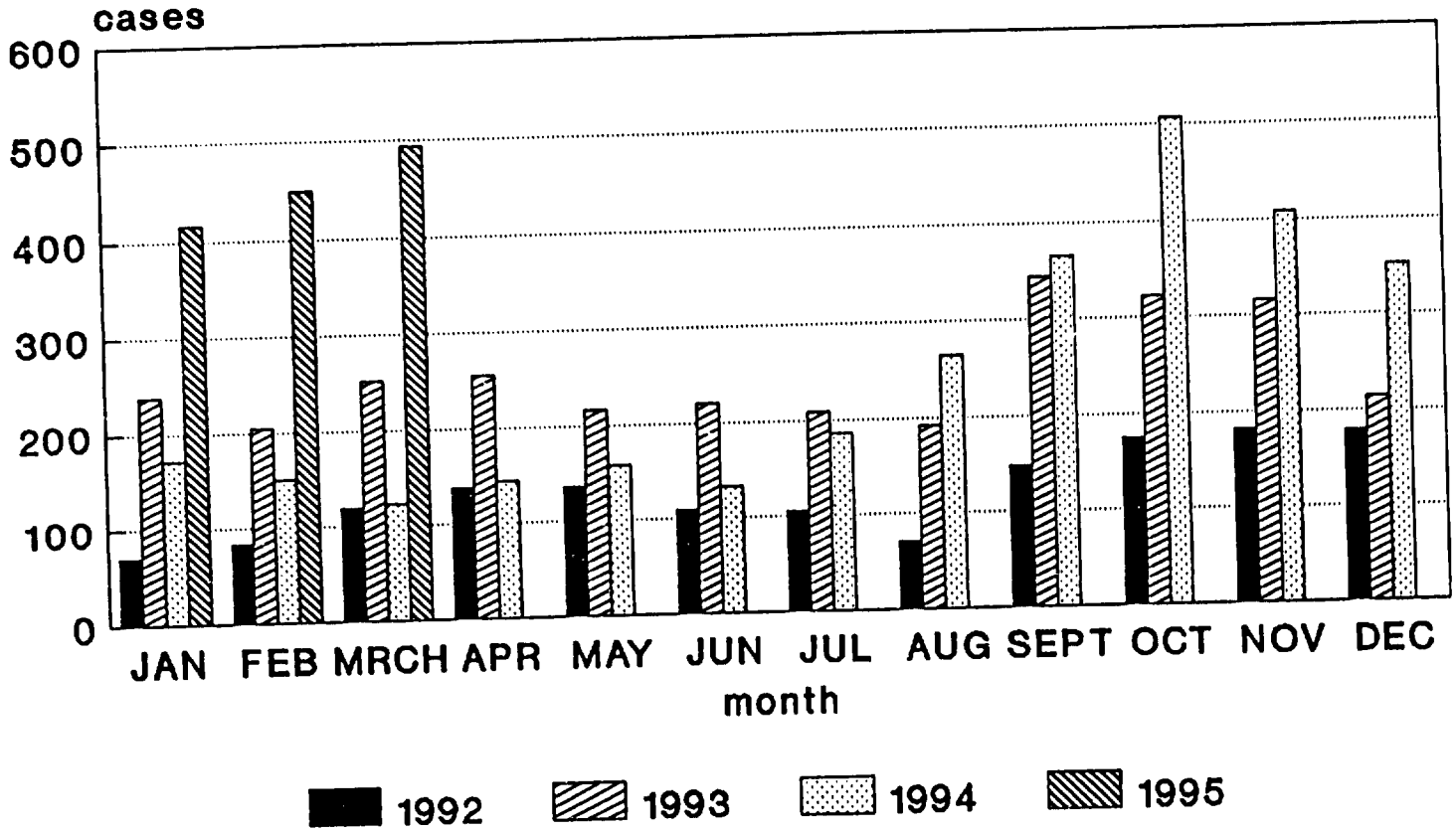
by

Prof. S. Dittmann, Chief
WHO Regional Office for Europe

Diphtheria in Russia
by month - 1993/1994/1995



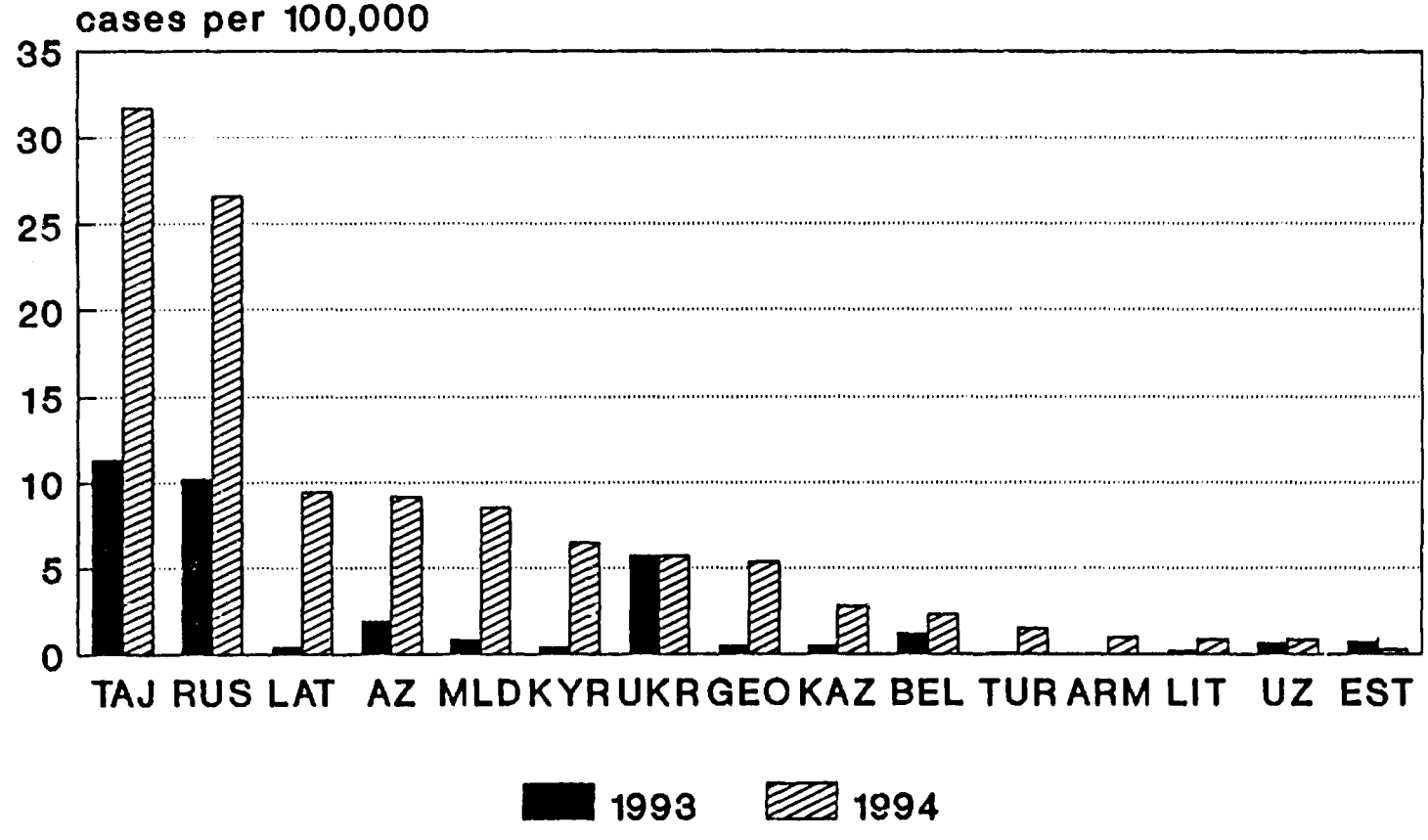
Diphtheria in Ukraine
by month - 1992-1995



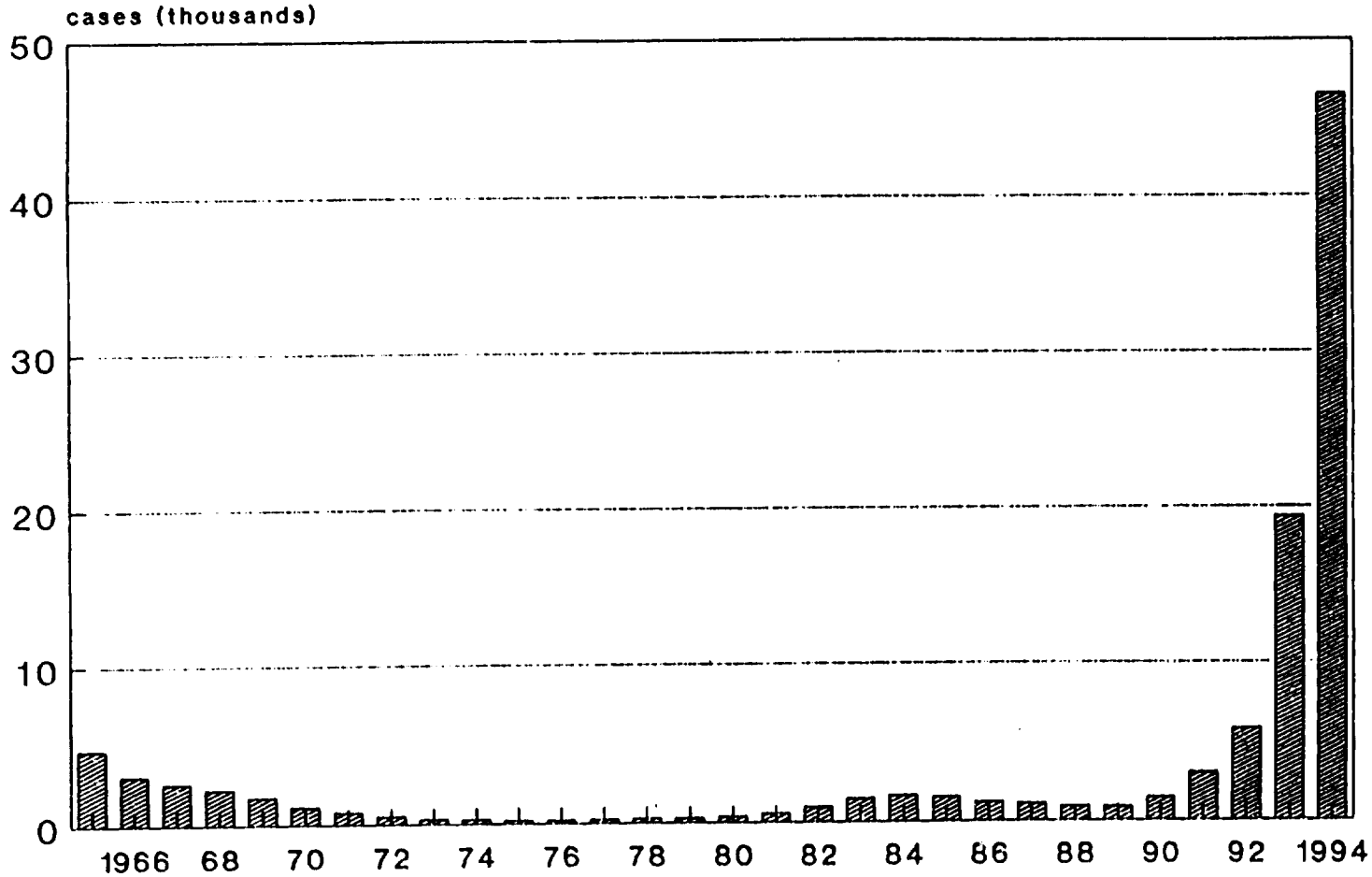
Diphtheria Epidemic in New Independent States (NIS) of Former Soviet Union

- Epidemic began in Russia in 1990
- 14 of 15 NIS now have epidemic diphtheria
- Annual 2- to 10-fold increases in cases in most affected countries
- 1994 NIS overall: 47,808 cases and 1746 deaths
- From 38% (Azerbaijan) to 82% (Latvia) cases aged >15 years
- In Transcaucasian and Central Asian Republics, many cases among displaced persons

Morbidity Diphtheria
NIS 1993 and 1994



DIPHTHERIA USSR/NIS
1965 - 1994



Age distribution

Two main patterns could be distinguished:

- **diphtheria cases occurring mainly in adolescents and adults > 14 years of age,**

  e.g. in Latvia (85 %), Ukraine (80 %, peaks in 15-17-years-old and 40-49-years-old), Belarus (peaks in 15-19- and 30-50-years-old, but also in 5-7-year-old children), Russia (in 1993: 71 % > 14 years of age; but the trend is changing: 66 % during Jan - Oct 1994, only 60 % in October 1994, and the age group 7 - 14 has now the highest morbidity)

- **diphtheria cases occurring mainly in children < 14 years of age,**

  e.g. in Georgia (66 - 75 %), Armenia (58 %, no cases in adults > 40 years of age), Azerbaijan (65 % children, 50 % schoolchildren, 30 % adolescents and young adults), Moldova (50 % schoolchildren, only 1 case in an adult > 50 years of age), Tajikistan (60 % children), Kyrgyzstan (2/3 children, mainly schoolchildren).

The epidemiological situation with respect to age groups must be monitored carefully.

Case fatality rates

Case fatality rates differ between 2 - 3 % (Ukraine, Russia), 6 to 10 % (Armenia, Kazakhstan, Moldava, Latvia), and 17 - 23 % (Georgia, Azerbaijan, Turkmenistan).

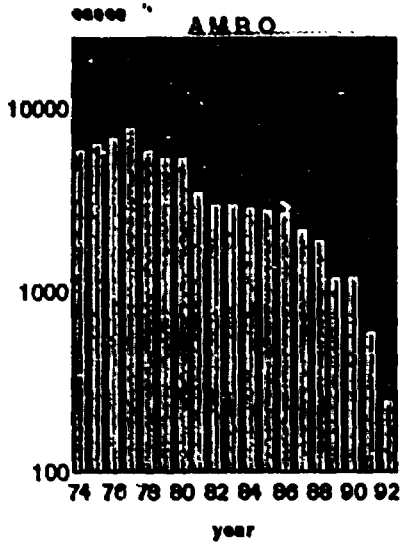
The very low rates are influenced by the occurrence of many mild cases in immunized persons and the availability of resources for proper treatment. On the other hand the lack of antitoxin and other drugs badly influences the prognosis of diphtheria.

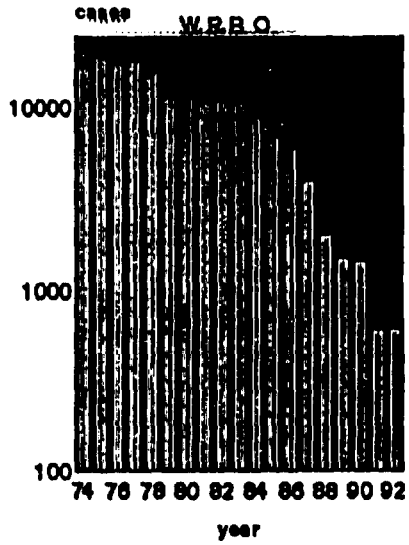
Diphtheria Epidemic in NIS
Importation to other countries

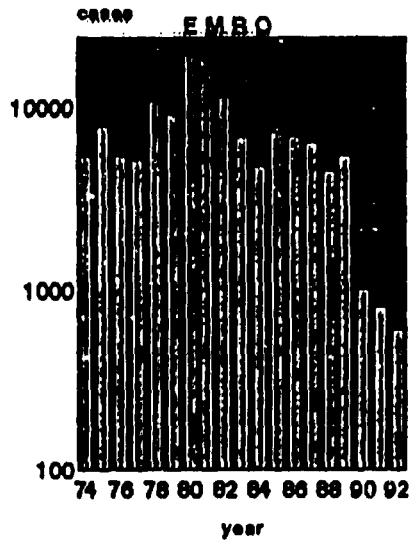
- At least 20 associated imported cases reported in Bulgaria, Finland, Germany, Norway and Poland

- No cases yet imported to U.S., however: two cases were reported in late 1994 among U.S. citizens:
  - A 22 year old woman working in Ukraine
  - A 42 year old woman visiting Russia

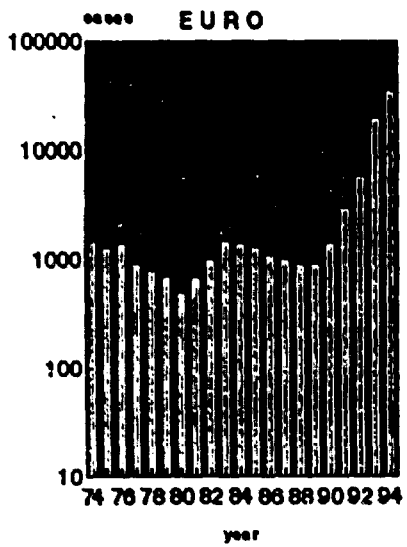
- 20%–60% of adults in Western countries are susceptible to diphtheria

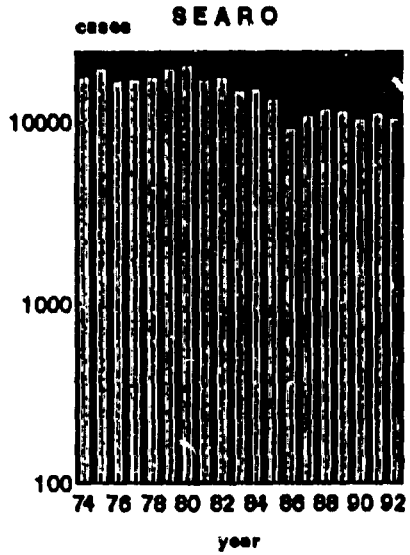


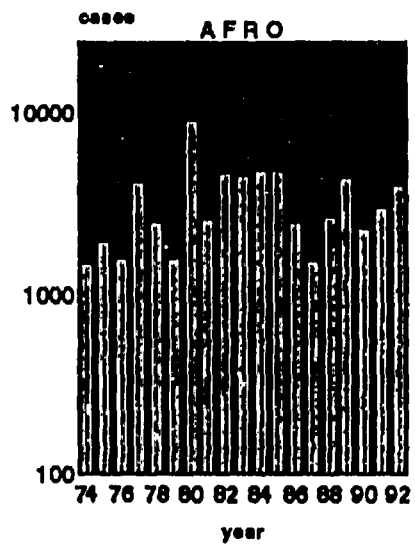




Trends Diphtheria Incidence by WHO Region







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27 March 1995

DIPHTHERIA
PROJECTION for 1995
DELPHI METHOD

Country	Population	Cases 1993	Cases 1994	Incidence 1994	Fold Increase 1993/1994	Cases Jan-March 1994 : Jan-March 1995	Fold Increase 1/94:1/95	Cases 1995 Lower Projection	Cases 1995 Average Projection	Cases 1995 Upper Projection
ARM	3.74	1	36	0.96	36.00	0/ 6		100	150	200
AZ	7.46	141	685	9.18	4.86	93/ 130	1.4	1 300	2 000	2 700
BELA	10.33	120	236	2.28	1.97	40/ 82	2.0	450	725	1 000
EST	1.57	11	7	0.45	0.64	0/ 7		50	75	100
GEO	5.49	28	294	5.36	10.50	44/ 128		600	900	1 200
KAZ	17.46	82	489	2.80	5.96	46/ 259	5.5	2 000	2 500	3 000
KYR	4.70	6	303	6.45	50.50	12/ 227	18.9	1 200	1 500	1 800
LAT	2.65	12	250	9.43	20.83	30/ 107	3.6	500	750	1 000
LIT	3.77	8	39	1.03	4.88	3/ 12		100	150	200
MOL	4.36	35	372	8.53	10.63	26/ 218 (J-A)	8.4	1 500	1 900	2 300
RUS	149.90	15 211	39 907	26.62	2.62	6036/ 12408	2.1	80 000	120 000	160 000
TAJ	6.02	680	1 907	31.68	2.80	161/ 525 (J,F)	3.2	7 500	9 000	11 000
TUR	4.16	3	61	1.47	20.33	5/ 10		100	200	300
UKR	52.47	2 987	2 990	5.70	1.00	446/ 1360	3.0	6 000	9 000	12 000
UZB	22.83	137	232	1.02	1.69	41/ 173	4.2	900	1 150	1 400
TOTAL	297.00	19 462	47 808	16.10	2.46	6939/15524	2.2	~100 000	~ 150 000	~ 200 000

WHO/UNICEF STRATEGY for DIPHTHERIA CONTROL in the NEWLY INDEPENDENT STATES

Epidemic diphtheria can be controlled

by the following three well-recognized measures:

(1) *primary prevention* by ensuring high population immunity through immunization as the most effective measure to control epidemic diphtheria

(2) *secondary prevention* of contact cases of diphtheria by the rapid investigation of close contacts and their standardized treatment

(3) *tertiary prevention* of complications and death from diphtheria by early diagnosis and proper management of diphtheria cases

WHO/UNICEF STRATEGY
for the CONTROL of DIPHTHERIA
in the NEWLY INDEPENDENT STATES
Immunization

1. Routine Immunization

- 95 % coverage with DTP4 by 2 years of age
- backlog immunization

2. Immunization Campaigns

Population Group	Administer 1 dose immediately	Completion of primary series requested
Children		
- preschool age (3-6 yrs of age)	DT	if needed
- at school entry including 1st grade	DT	if needed
- schoolchildren	Td	if needed
Adolescents attending higher educational institutions	Td	
all other adolescents	Td	
adults	Td	persons in distinct age bands need 2 doses (4 wks interval) and 3rd dose 6-12m later

Summary for 1995

Countries having an epidemic:	Armenia Azerbaijan Belarus Georgia Kazakhstan Kyrgyzstan Latvia	Lithuania Republic of Moldova Russian Federation Tajikistan Turkmenistan Ukraine Uzbekistan
Countries having imported cases:	Finland Germany Norway Poland	
Population affected since 1990:	• about 296 million people at risk of becoming infected; • about 80,000 people suffered from the disease; • over 2,500 deaths.	
Strategies:	• immunization of the entire population; • early diagnosis and proper case management; • identification of close contacts and their immediate treatment.	
Funds contributed to date:	over US$ 7 million	
Further funding needed:	US$ 31.7 million US$ 13.9 million for vaccines US$ 14.3 million for other supplies US$ 1.2 million for training US$ [illegible] million for programme implementation	

The Austrian Experience from the perspective of National Quality Control Authority

by Dr. Wolfgang Maurer, Director
Bundesstaatliches Serumprüfungsinstitut, Vienna

The structure of the Health Authorities has a historical background. The development of the organisation is based on certain necessities at a certain time, may be sometimes under political pressure. So the Health Authorities were not planned like a new manufacturing plant with a state of the art structure of the management. Therefore some important departments and activities are situated within the Ministry of Health, whereas others are located in institutes within the organisation of the Ministry of Health.

In general, this institutes perform the expert work in the licensing procedure according to the drug law. The result of this work is an expert report consisting of an evaluation of the dossier of the applicant and an update of the package insert.

A central point of the expert report is the recommendation to license the product or not. The formal decision is in the licensure department in the Ministry of Health.

Three institutes are performing the expert work (fig.1). As an Austrian speciality an experimental evaluation or analysis is performed prior to licensing, in the field of biologicals this is also to he prepared for batch release.

Biologicals are defined by law and are mostly vaccines and blood products. The legal definition was changed by amendments of the law and is different from the WHO definition. The Bundesstaatliches Serumprüfungsinstitut (BSPI) has the responsibility for the biologicals and performs the expert reports during the licensing procedure and also the batch release (fig.2). Being a small country there is always an urgent need of additional staff. Things are worse due to the poor payment of qualified staff in the public sector compared to industry or hospital. The prices for batch release and licensing are also very low and in the budget they are not calculated as income of the institute or of the Ministry of Health. Some amendments in this direction are discussed since years. The current duties of the BSPI are batch release of blood products (1994 n-1402) and vaccines (1994, n=154), batch release of HIV-diagnostics (n=147) and batch release of neopterin test kits. We give information on the current rabies situation and advice for postexposure prophylaxis. The institute also gives scientific advice to the Ministry of Health and makes the expert reports.

The second part of my presentation deals with possible structures of a National Control Agency or National Control Institute. The development of most health authorities in most counties was a historical one. In the New Independent States (NIS) one has the opportunity to create a new authority based on the experience of other authorities but also based on modern miles of responsibility, decision making and modern management methods.

If one wants to define the product quality covering quality, potency and efficacy the authority has some "circles" of activities, which can be more or less independent from the others (fig.3). If the regulatory activities are performed by one staff in one institution, working close together the undefined areas of quality are small. I would prefer having the inspectorate next door of the person who makes the expert reports.

However as a general rule one can not make a high quality vaccine just by (quality) control. The QC-department of the manufacturer is only of part, another part is maintenance of Good Manufacturing Practice (GMP). It is necessary to produce vaccines with acceptable quality and one should not produce products which by (statistical) chance can be released by the QC.

Fig. 4 shows sonic problems which can emerge with recombinant proteins, which are sometimes also vaccines. This problems have to be solved by a QC according to GLP. As a regulator one has to follow the drug law, which in Austria had some amendments. Some problems of the law are listed in Fig.5. One licensing problem was how to deal with the products which were on the market, when the drug law came into action in 1984. One should perform a mere listing of such products (including main characteristics such as composition, seed lot, production flow sheet, package insert, etc). After this is done one can proceed to a licensing process.

At a WHO seminar on "Licensure and regulation of biological products" which take place at the BSPI, Vienna in Dec. 1993, the following proposal was done on the structure of decision making "it is advisable to delegate decision making responsibilities to those departments within the NCA/NCI, who are competent in biologicals in order to facilitate the licensing/regulation process and make it efficient". If this is done in all health departments dealing with licensing of biologicals one would have a highly motivated staff. This is also a certain guarantee that only products which adhere to the current state of the art are on the market. As a consequence the confidence of the people in vaccination in general can be improved and the goals of WHO/EPI programme can be reached in time.

Figure 1

Ministry of Health and Consumer Protection
Vienna
ADR's department, Licensure department, Inspectorate

3 Institutes which perform the expert work:

I. Pharmaceuticals:

A) medical evaluation:
Bundesstaatliche Anstalt far experimentell-pharmakologische und balneologische Untersuchungen

B) pharmaceutical evaluation:
Bundesanstalt fur chemische und pharmazeutische Untersuchungen

II. Biologicals (Blood Products and Vaccines):

C) medical and pharmaceutical evaluation:
Bundesstaatliches Serumprüfungsinstitut
BSPI

Figure 2

Bundesstaatliches Serumprüfungsinstitut
Possingergasse 38,
A- 1160 Wien
Austria

BSPI

Fax: +43-1-492 02 91

Tel.:+43-1-492 00 70

Staff: 36
Scientists: 9 (education: medicine, pharmacy, molecular biology, biotechnology, biochemistry, biology)
Technicians: 16
Administrative staff: 4
Animal care: 4
Chairwomen: 3

02/1995

Abbildung *3AlFigure 3A*

AGENCIES WITH INTERACTIVE ROLE.

Abbildung 3B/ Figure 3B

AGENCIES WITH INDEPENDENT ROLE.

Figure 4

Drug Law March 1983
Amendments 1987, 1988, 1994 and October (?) 1995

Problems:

* poor definition of variations of a marketing authorization versus new product licensure

* changing definitions of "biologicals"

* no listing of main characteristics (composition, seed lot, production flow sheet) of products on the market in 1984

* structure of decision making

  WHO: "it is advisable to delegate decision making responsibilities to those departments within the NCA/NCL who are competent in biologicals, in order to facilitate the licensing/regulation process and make it efficient"

BSPI 06/1995

Figure 5

Quality Control of Recombinant Proteins

- ☞ Identity
- ☞ Potency
- ☞ Purity

A) **different molecular forms of the protein**

* Dimers
* Aggregates
* Additional MET
* Different Disulfide Bridges (Scrambling SS)
* Reduced Forms
* Oxidized Forms (MET)
* Dimidiation Products
* Degradation Products: Proteolytic Cleavage from N- or C-Terminus
* Wrong Amino Acids (Wobble)

B) **other compounds**

* Endotoxins
* Host cell proteins (e.g. yeast proteins)
* residual DNA
* impurities from the production/purification process (e.g. murine antibodies)

A PROPOSAL FOR TECHNOLOGICAL CO-OPERATION IN THE FIELD OF PRODUCTION AND CONTROL OF VACCINES FOR HUMAN USE

by Mr. Bostvironnois
Pasteur Merieux Serums & Vaccins, France

When establishing their strategy of vaccine protection for their population , all countries wish to have in hand vaccines of good quality , available at a reasonable cost and in an appropriate time schedule.

Many countries have a National Control Authority capable of controlling the quality of the products intended for use, but not every country considers as imperative the presence of a local production unit as long as its procurement criteria are respected.

In spite of an unfavourable environment , some countries wish to reach self sufficiency in the field of vaccine production but being conscious of some weaknesses they ask for the technical support of organisations or companies experienced in the field.

Their attitude is not always motivated by a strict economic approach , although the argument of national emulation can be understood, but sometimes originates from a political desire of independence in some fields considered as strategic.

PMsv is in principle favourable to a technical co-operation but wishes a step by step approach in the frame of a long term co-operation agreement in which the mutual interests of the different partners have been clearly identified, recognised and respected.

Some preliminary considerations:

1. The trend of the private vaccine industry is to concentrate in order to obtain economy of scale for the present production and to obtain a critical mass permitting sufficient investments to develop the new vaccines or combinations. This attitude seems now to reach the "national state producers" which should be attracted by the "Consortium of public manufacturers" or the International Vaccine Institute promoted by the CVI and the UNDP in order to share experience in Quality Control and production.

2. Technology transfers in the field of human vaccines have not been so far extremely successful. This confirms the difficulty of transplanting in a different environment a battery of procedures, equipment and behaviours acquired and developed in an other background.

3. Quality of the vaccine cannot be negotiated : All products distributed by our company all through the world are of the same quality. There are not "second rate vaccines" and Good Manufacturing Practices although somewhat subject to interpretations according to the environment should be enforced and complied at least up to the WHO requirements.

4. The capacity of implication of our company in the field of co-operation or technology transfer is not unlimited. Our involvement would be limited to a restricted number of projects and for specific products or activities only.

5. Presently the production capacity of the major international manufacturers is sufficient to face much bigger demand if there were sufficient anticipation of the needs. During the last UNICEF bid the quantity of vaccine proposed by the bidders was almost three time the allocated amount.

6. Vaccination involves many operations in addition to the production of the immunising agent; On average the cost of a vaccine accounts for a tenth of the total vaccination cost.

   Is the local production the first operation to be considered as money saver? A country should evaluate the true cost of each dose of vaccine locally produced and compare it with an outside supply through contracts of reasonable duration. Of course both vaccines should be of same quality that is meeting applicable WHO Standards.

   Those contracts could be established either directly with producers or through international organisations such as UNICEF or PAHO which , through the huge quantity of vaccines they order and their economical credibility get the lowest conditions of price and through the technical support of WHO bring a guarantee of quality of the product supplied.

7. A phased approach must be taken, allowing time to establish a good mutual perception of the problems and a trustful relationship must appear in order to bring a recognition of the scientific community, of the biological manufacturers which will be the partners and of international organisations which will be the objective judges of the quality.

8. Of course the project must be endorsed by the national authorities which will be ready to set and maintain , if it does not already exist, a national control laboratory fully independent from the manufacturer which should be able to define its technical requirements on the vaccines utilised in the territory and to verify the conformity of the ones presently in use.

   In addition , the authorities should be ready to bring a long term commitment in the financial support of the local manufacturer.

9. The liability issue must be considered carefully. Even if the legal responsibility can be established, the repercussions of a problem originated by a failure in sterility or an inopportune association will not stop at the end manufacturer but may affect the reputation of active principle supplier.

The proposal

The mutual recognition will happen in the course of the three steps of the production of a pharmaceutical operation , including the biological specificity which requires full quality controls at different steps and particularly on batches of finished products.

A vaccine production plant consists of different buildings where various operations are performed:

manufacture of the active ingredient;
finishing of the product;
controls on raw materials, in process and finished products;
supply of the necessary utilities (water, power, steam, gas etc.);
storage of the different phases;
shipment of finished vaccines.

This diagram gives the classical flow for vaccine production (Tab. 1)

You see the different manufacturing phases and the impact of the quality control and of the quality assurance.

Progression through the different steps will be done in a careful way, marked by visits, exchanges and necessary requirements on the quality and good practices for manufacturing and control.

Phase 1 :

Distribution of the finished products, packaged in the country (Tab. 2)

This implies the purchase of the finished vaccine, duly controlled by the manufacturer. The vaccine is in its final container and meets specifications of the purchaser (if they are clearly expressed) or the WHO minimum requirements. The supplier has been chosen based on objective criteria which include of course quality, price and consistency of supply.

During this phase, the pharmaceutical operations to be realised in the final country are operations of quality control checking, packaging and logistics :

Setting up of a minimum internal quality control, limited to the examination of production and quality control protocols remitted by the manufacturer and setting up of the appropriate procedures to successfully implement phase 1.

Labelling according to national requirements : this can be realised utilising the national language and adapting the package to the needs and the economical resources of the country (box containing various vials or utilisation of local devices for instance).
The insert could include recommendations for use adapted to the local conditions or the possible vaccine associations specifically demonstrated as being useful for the country .

Setting up of a distribution network performing with a precise monitoring of the cold chain during storage and transportation .

Setting up of marketing surveillance and adverse reaction reporting;

This means that procedures must be clearly established to permit rapid identification of any recipient of a product, and recall and reconciliation of the doses of any batch distributed.

The national control authorities must control the quality of this product and the "local producer" may participate partially in those controls and thus acquire some practice while establishing relationship of confidence.

The risks are minimal (if appropriate procedures are established and enforced there should be no risk of cross contamination or mixing of products); the cost of partially packaged vaccines is slightly lower than that of finished product.

the investment is limited to :

Locals: a cold room of sufficient size to store the incoming products;
a packaging area and storage for packaging material (including a quarantine area for the incoming material pending release for conformity);
a cold storage area and a shipping area for the final finished products after release by the National control authority.

Equipment: This is a particular point: the manpower local cost may impact favourably if a hand packaging is performed. If the quantities permit it the investment of an automated labelling & packaging machine can be considered but, in addition to this investment, the availability and the cost of the self adhesive labels and printed material with very restrictive size norms utilised by those high speed equipment must be assessed.

Phase 2:

Distribution of finished products filled locally from bulks purchased abroad (Tab. 3)

During this step the following operations will be locally performed in addition to those previously described:

filling of bulk received ready for filling, followed if required by a freeze drying.
preparation of this bulk by dilution and blending of concentrated active principles

The "bulk" delivered must be clearly defined: Its specifications must be expressed by the customer in a clear way to avoid misunderstanding . for instance "quantity sufficient to prepare one dose " is somewhat misleading as long as the amount of active ingredient may vary according to the quality of the other ingredients to be added and the environment in which it will be processed (size of tanks, temperature control etc.).

The best way of experiencing this step is the preparation of ampoules of diluent accompanying freeze dried products which can be autoclaved after filling guaranteeing the sterility of said product together with conducting an efficient leak test.

Important investments have to be performed:

Setting up of a sterile filling including sterile areas requiring high quality and stable environment and satellite units supplying the different necessary fluids.

Purchasing of equipment - An economical study is necessary before deciding a major investment (freeze dryer for instance) here is as example, a comment on the importance of the choice of the adequate size of freeze dryer) **(Tab 4)**

Quality control: An effective quality control is compulsory during this phase Control on the manufactured products and on every ingredient including the active principles involved in the production.

The size and therefore the cost of such a Quality Control unit will vary according to the nature of the controls which will have to be produced.

Some of those controls may at the beginning, be contracted to more experienced laboratories for the first batches thus allowing a progressive "taking over" by the local laboratory.

a) Administrative set up:

Writing of the specifications for the supply of the active principle and verifying of conformity of the protocols received from the supplier;

b) Verification of some of the results given by the bulk supplier and Quality control of the products locally filled, some controls being performed in-situ such as:
- Physico chemical (aspect, pH, etc.;)
- Bacterial and fungi sterility
- In vitro potency tests
- antibody titration

those controls, which do not require laboratory animals, do not generate big installation costs nor necessitate animal facilities; the other controls may be performed by a reputable laboratory accepted by the local authorities.

c) Full quality control : at this step all the controls are routinely performed, including the controls in animals such as safety, pyrogens, potency, etc. This implies an important investment which can be used for an additional purpose, that of public health: such a laboratory can participate in studies to appreciate the impact of a vaccination on the population and eventually permit specific recommendations such as booster immunisation for instance after evaluation of the antibodies level of a defined population following a vaccination campaign under local conditions.

The advantages:

The active principle is purchased at a lower price than the filled finished product. The price will be established according to the specificity of the active principle and will vary according to the level of technological support which is to accompany the supply of the bulk. Concentrated

monovalent bulks will be cheaper than a bulk ready for filling which includes a part of the development expenses necessitated for establishing the appropriate stabiliser or to improve a freeze drying cycle.

The local producer can choose the most appropriate size for its blending vessels and for its equipment

Accompanying products such as the diluent or droppers or disposable syringes can be produced locally (as long as they are adequate and compatible for the use of the vaccine), resulting in substantial savings on the material and in shipping expenses (in hard currencies)

The success of this phase is extremely important to tighten the links between the local producer and the international vaccine suppliers. The bulk supplier, in a first step may only act as a commodity supplier which does not intend to commit its responsibility beyond the quality of the bulk therefore without any warranty on the final product resulting from operations performed out of its premises.

If the local producer wishes a larger implication from its international partner, it must be ready to accept duplicate controls of the finished product with the risk of having to destroy batches found unsatisfactory by its partner, with the consequent economic losses. In another hand these type of relationship should permit to establish links of mutual trust necessary to permit an objective evaluation of the interest of going deeper in the production process.

All the vaccines cannot be supplied in such a form , some products (BCG for instance) are filled and freeze dried immediately after creation of the final bulk.

Phase 3:

Production of the active principle **(Tab5)**

This step which is the production of the biological active principal in the country corresponds to the ultimate phase of co-operation between two laboratories.

The local laboratory must have brought the evidence that it has perfectly mastered the previous steps.

Technical expertise:

The skill of the quality control is proven. It is eventually included in the network of the WHO reference centres.

Production and Quality Control personnel is stabilised and has acquired the biological culture (cGMP and QA).

The equipment and the premises have undergone the production events and the adjustments required by the peculiarities of the local environment have been identified and mastered by the local personnel who are then able to properly maintain the equipment and the working areas.

Commercial expertise:

The products manufactured are sold consistently at reasonable prices thus permitting a credible extrapolation of the sales figures for the future.

Economical feasibility:

An economical feasibility study can be realised from market studies and from figures of the investment cost and the operating cost of such unit.

This cost includes the creation of additional buildings , increase of personnel, addition of utilities but will also include the price of the transfer of the Know How for producing the active principle.

This legitimate price is often subject to disputes; The companies which have finalised a process which has consistently proven its efficacy do not wish to give away without compensation what is part of their patrimony acquired during years of investigation, adjustments and experience. Moreover, in case of failure of the "transplantation" the fault may be attributed to the supplier of the technology which will not only suffer economical sanctions but may also loose its credibility in other markets.

This cost analysis must be performed after years of practise in order to avoid "emotional" factors (political for instance) which might justify inappropriate "Window dressing" of the figures.

Within the frame of those considerations, Pasteur Merieux Connaught which has demonstrated its ability of mastering the scaling up of production of a large range of vaccines of high quality confirms its readiness to collaborate with countries or organisations as long as its economic interests are recognised and respected and that the quality of the productions is in full agreement with the local and international requirements.

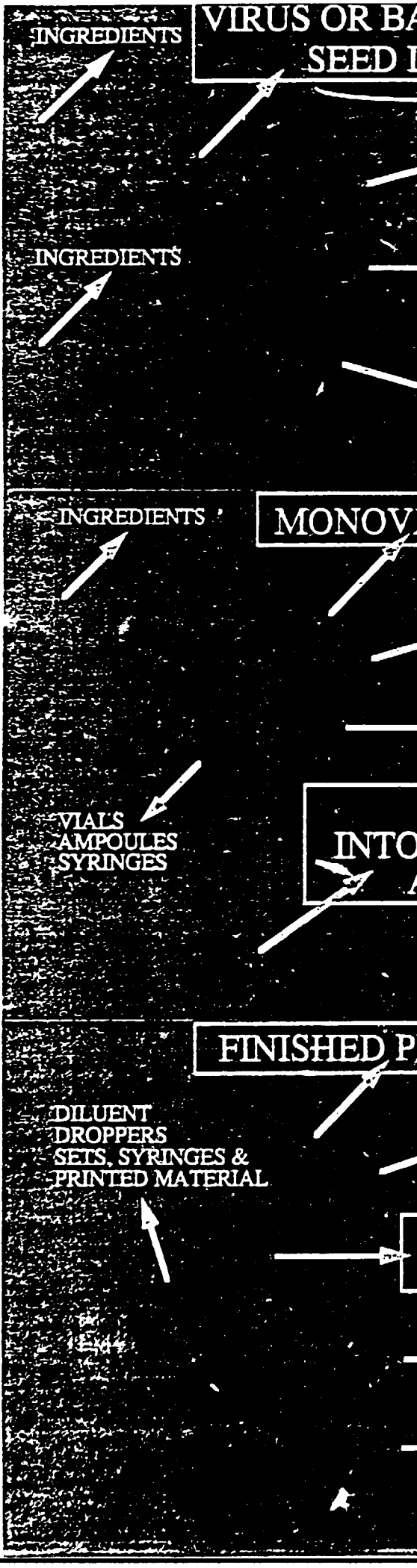
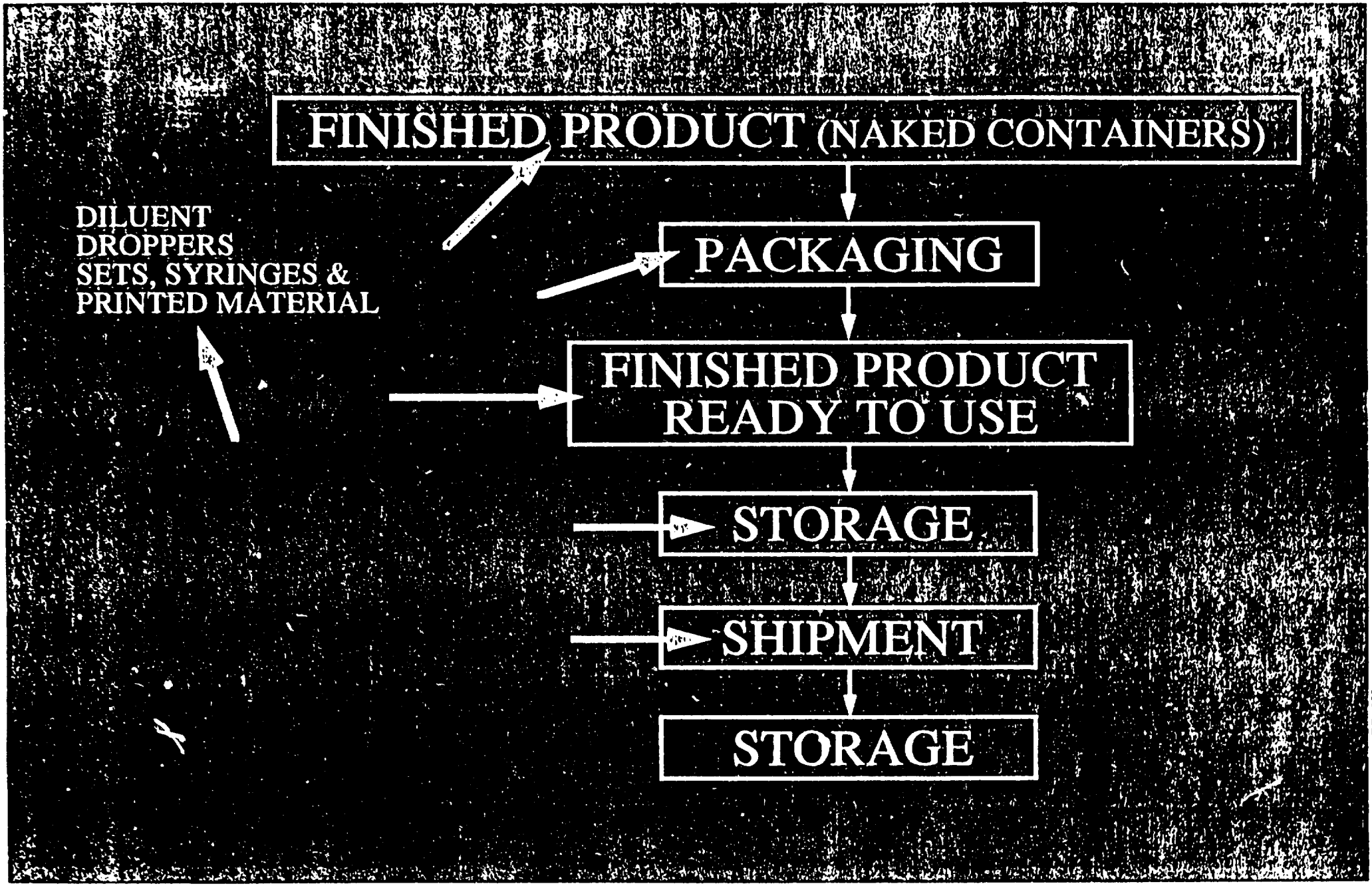

INGREDIENTS
VIRUS OR BA
SEED
INGREDIENTS
INGREDIENTS
MONOV
VIALS
AMPOULES
SYRINGES
INTO
FINISHED P
DILUENT
DROPPERS
SETS, SYRINGES &
PRINTED MATERIAL


TABLE 1
ED LOT
CULTURE)
REDIENT
NGES
S
TAINERS)


FINISHED PRODUCT (NAKED CONTAINERS)
DILUENT
DROPPERS
SETS, SYRINGES &
PRINTED MATERIAL
PACKAGING
FINISHED PRODUCT
READY TO USE
STORAGE
SHIPMENT
STORAGE

S1

TABLE 2

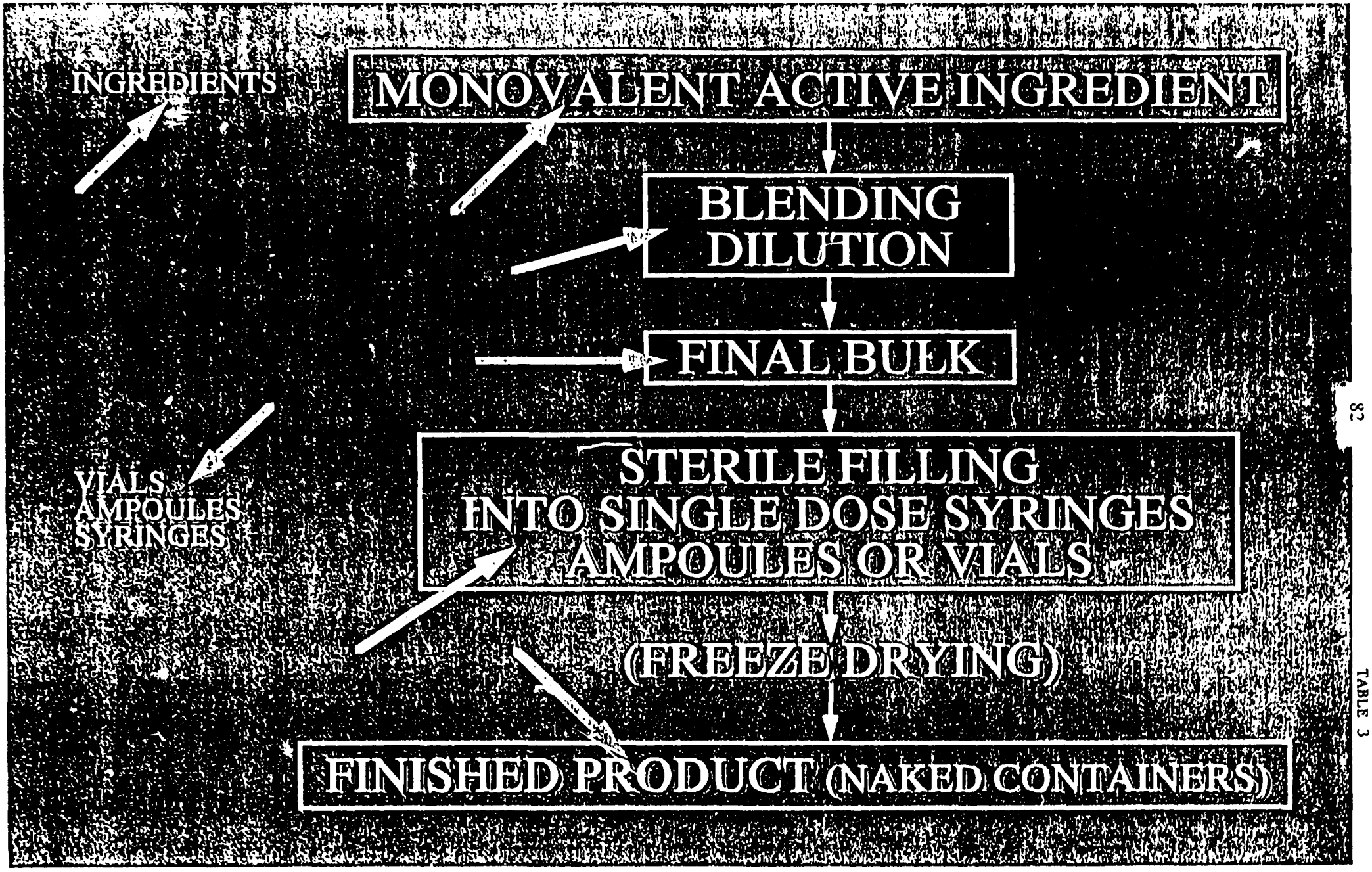
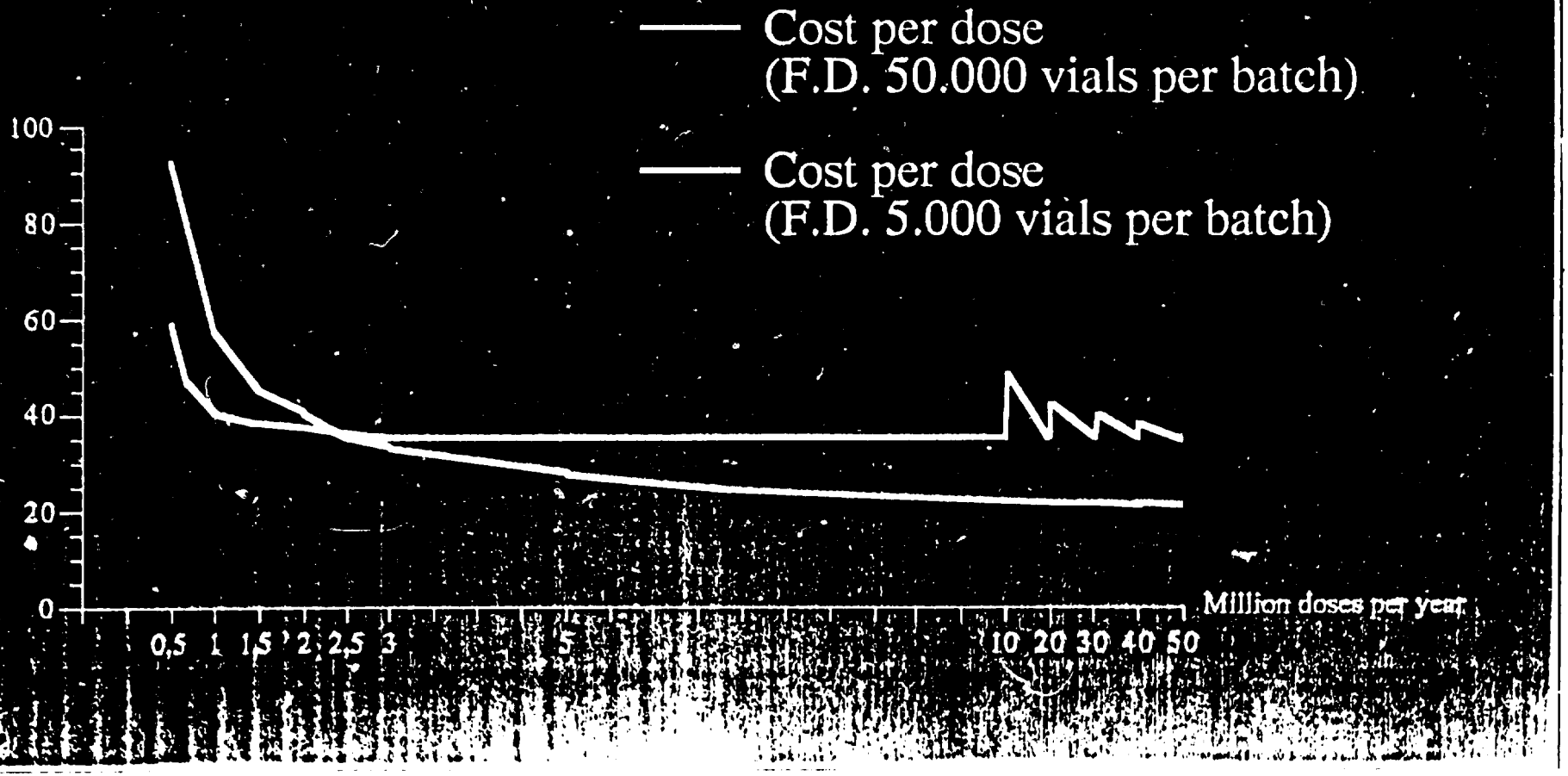

INGREDIENTS
MONOVALENT ACTIVE INGREDIENT
BLENDING
DILUTION
FINAL BULK
VIALS
AMPOULES
SYRINGES
STERILE FILLING
INTO SINGLE DOSE SYRINGES
AMPOULES OR VIALS
(FREEZE DRYING)
FINISHED PRODUCT (NAKED CONTAINERS)

TABLE 3

TABLE 4

Measles Vaccine (10 dose vial)
- Comparative study of the cost per dose for sterile filling, freeze drying and Quality Control according to the size of apparatus and the yearly output-



IMPORTANCE OF THE ADEQUATE CHOICE OF THE SIZE OF A FREEZE DRYER

Hypothesis:

Bulk to be freeze dried : Fixed cost per dose whatever the number of doses (in fact the cost should decrease with the quantities produced)

Quality control : Fixed cost whatever the size of the lot (in fact the sampling penalises the smaller batches) It is considered that the measles control is part of a larger QC. activity

Freeze dryer : amortisation in 7 years.

Labour and consumable for sterile filling : cost considered proportional to the number of doses.

Equipment and SFFP area : considered to be dedicated full time to other SFFP operations when not performing Measles.

Conclusions :

The diagram giving the cost of a dose in function of the number of doses produced, visualizes the facts that :

- The cost of the doses depends obviously on the number of batches produced and on the size of the batch and tends to a lower limit .

- A minimum of doses (2.5 MD in this example) must be produced to reach an acceptable cost of production.

- A large producer able to distribute and sell 50 Million doses per year should be able to reach a product cost half that of a 5 MD/year producer.

- However, if the size of the market is limited it will be more costly to invest in a large capacity equipment.

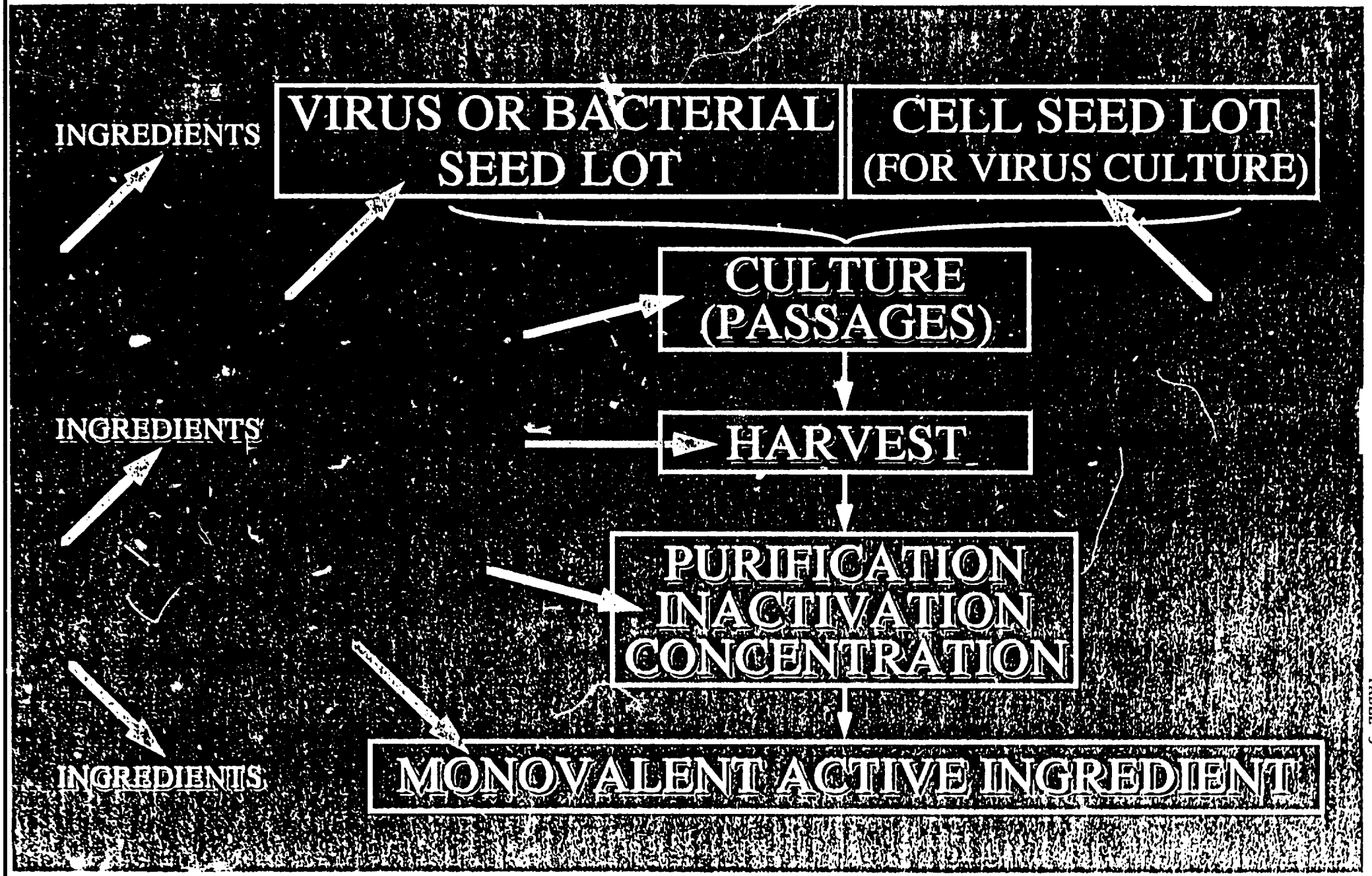

INGREDIENTS
VIRUS OR BACTERIAL SEED LOT
CELL SEED LOT (FOR VIRUS CULTURE)
CULTURE (PASSAGES)
INGREDIENTS
HARVEST
PURIFICATION INACTIVATION CONCENTRATION
INGREDIENTS
MONOVALENT ACTIVE INGREDIENT

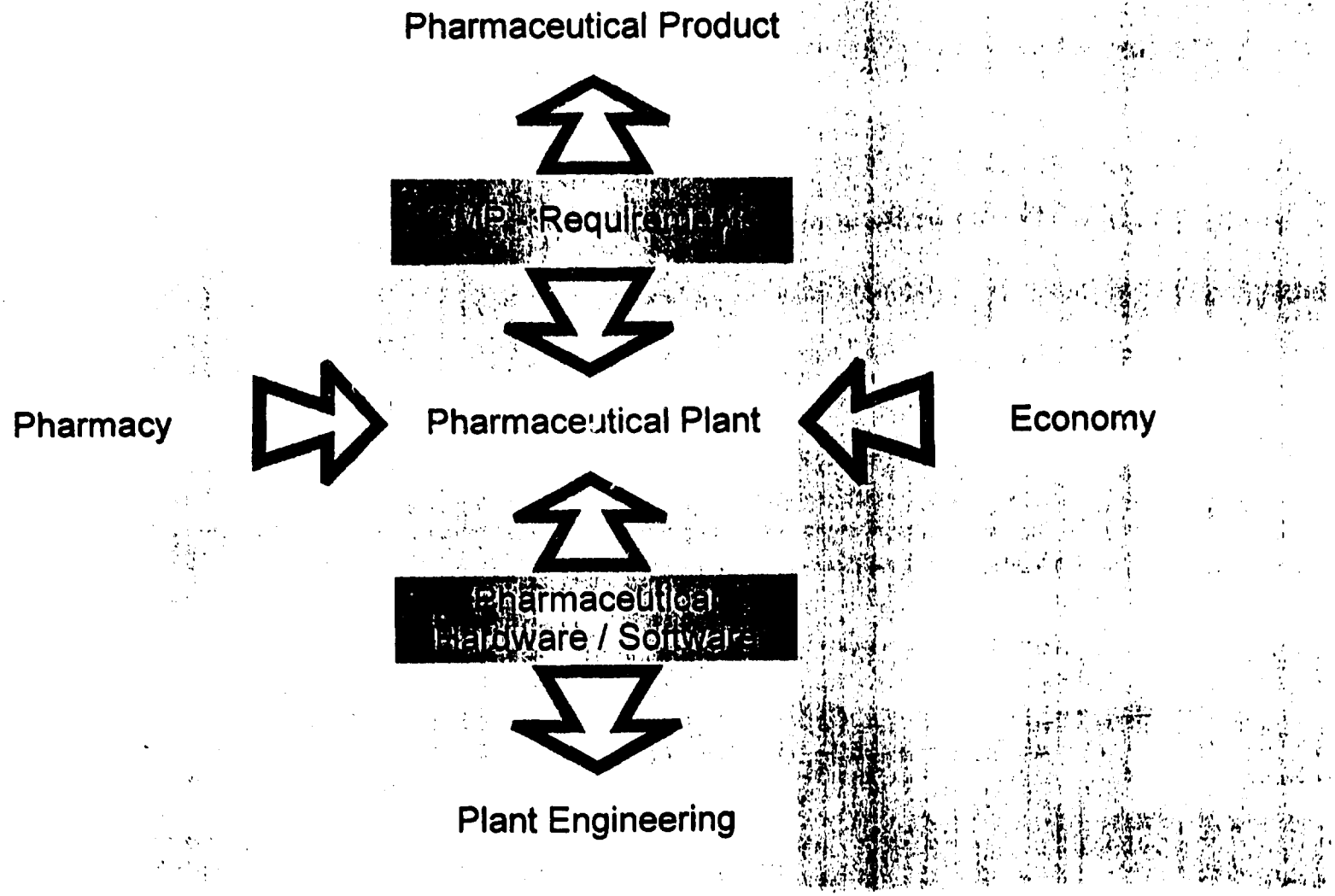
TABLE 5

PRESENTATION ABOUT LINDE-KCA-DRESDEN GmbH

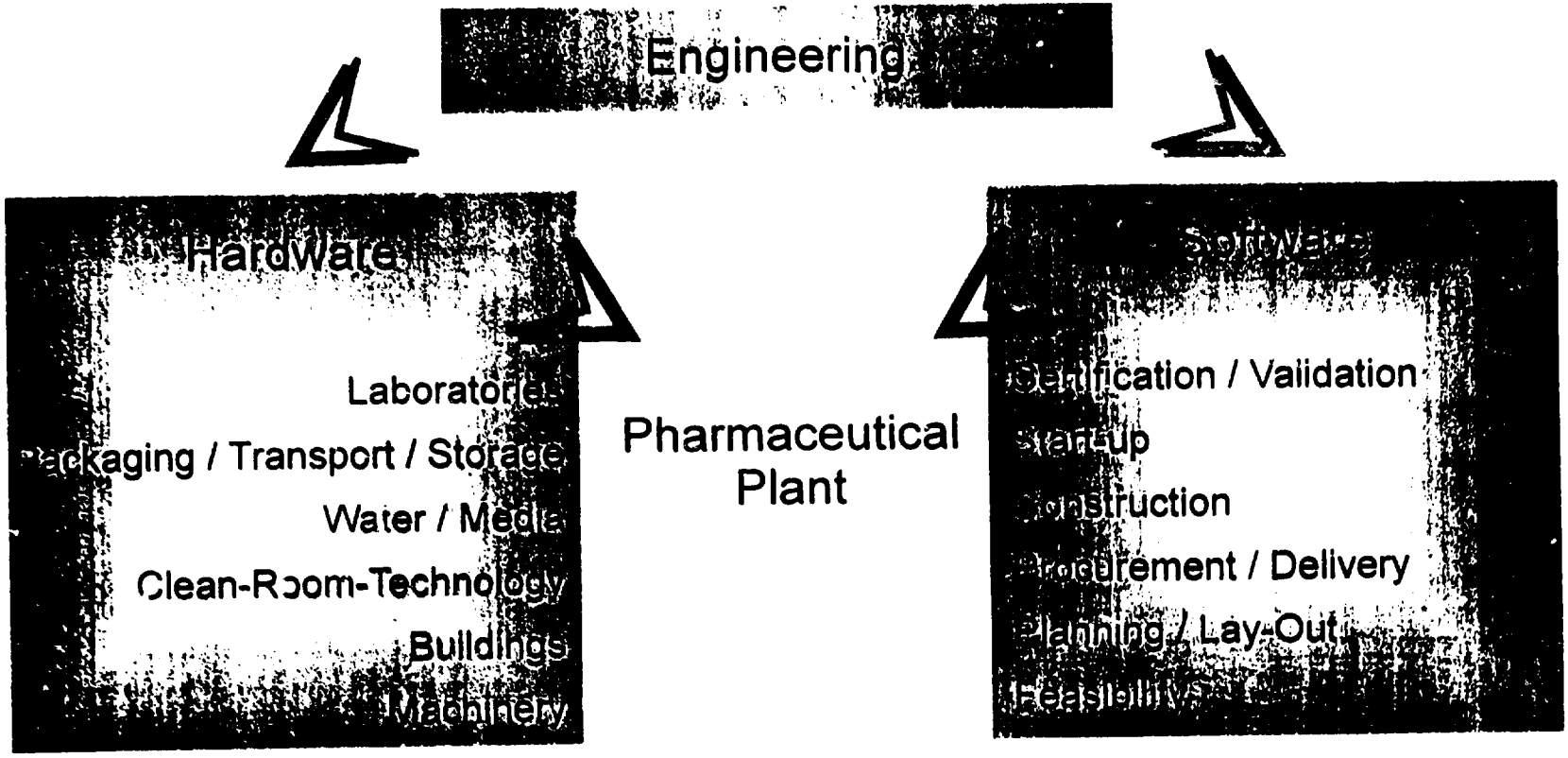
by

Dr. M. Flugge, Project Manager
LINDE-KCA-DRESDEN GmbH, Germany

Engineering for the Pharmaceutical Plant



Thorough Engineering Process - key for Success



OUR OFFER

Plants for production of pharmaceutical products with high quality. Planning and plant construction are effected strictly in accordance with the relevant national and international guidelines, as Pharma Betr. V (Germany), GMP and ECC guide, WHO documents, PIC and FDA guidelines etc.

PLANTS

- Plants for the production of synthetic agents
- Fermentation plants
- Extraction plants for natural agents
- Vaccine production plants
- Plants for formulation and packaging
- Laboratories
- Auxiliary and ancillary facilities, including gas- and waste water purification

SERVICES

- Technical and feasibility studies
- Authority engineering
- General contractor management
- Process- and equipment calculation
- Scale up
- Design
- Delivery
- Site construction and start up
- Civil work
- Validation

CONSULTING

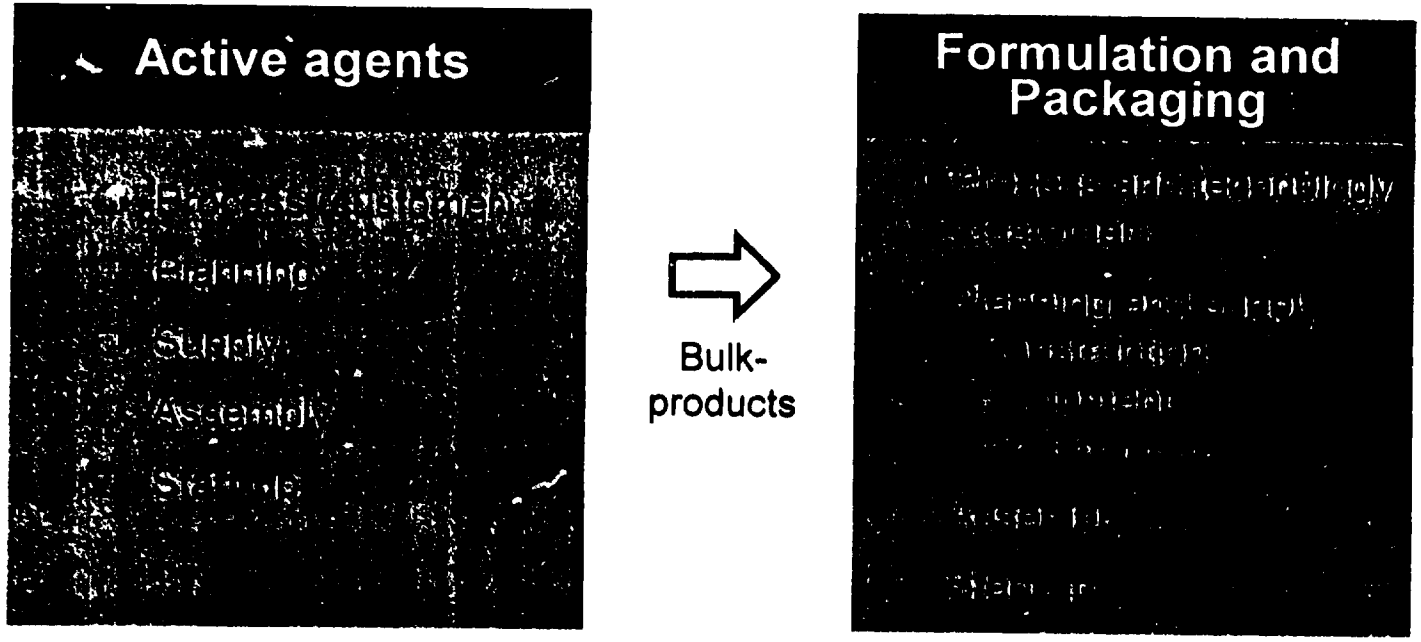
- GMP-concept
  - Quality assurance
  - Validation
  - Self-inspection
- Personnel qualification and -training
- Hygiene program

The LINDE Concept

Planning and realization of pharmacy projects as

General contractor pharmaceutical plants

Planning • Engineering • Supply • Assembly • Start-up



Advantages:
- Cost reduction
- Shortening of construction time
- Standard concepts
- Complete quality assurance

TECHNICAL REPORT - TRIP TO:

RUSSIAN FEDERATION
UKRAINE
REPUBLIC OF MOLDOVA
ROMANIA

by

Mr. N. Cucakovich
UNIDO Consultant

EXECUTIVE SUMMARY

All Governments of the countries visited demonstrated long term commitment for Primary Health Care. Constitutionally every child is entitled to free immunization.

Total yearly requirements of visited countries are estimated to be 100 million doses of EPI vaccines.

Modernization of facilities, equipment and technology is of absolute necessity.

Due to economic hardships all countries faced shortage of funds, and require substantial capital investments.

Established vaccine production industry of the former USSR is no longer capable of providing required EPI vaccines.

Due to shortage of supply and questionable quality of vaccine the effected Governments must consider importing the vaccine, as a necessary temporary measure.

Biological industry of Romania is capable of producing sufficient quantities of good quality EPI vaccines. However some attention to compliance as per WHO guidelines is required.

Further, detailed evaluation of current status and proposed future plans for Russian Federation and Ukraine is required.

KEY RECOMMENDATIONS

Russian Federation

- ***Government of Russian Federation through Ministry of Health must find a way of solving manufacturing problems which are mainly caused by lack of funding and shortage of raw materials.***

- ***In order to successfully protect the population, MOH of Russia ought to consider option of purchase of Human vaccines as a stop gap.***

- ***Considerations should be made to upgrade existing technology. Partial or complete technology transfer would be a step forward for Russian Biological Industry.***

Ukraine

- ***Procurement of the vaccine for Ukraine should be continued for the time being, making sure that the vaccine purchased is of good quality, and produced according to the WHO standards. Liaison with UNICEF is strongly recommended.***

- ***Ukraine should concentrate its efforts and capital to develop portions of the industry, i.e. purchasing the concentrated Bulks, reconstituting and formulating diluted bulks and filling and***

- ***Any planned reconstruction and modernization of the Biological industry should be in compliance as per WHO guidelines.***

- ***National Control authorities must be organized to deal with issues of compliance as per WHO recommendations.***

NOTE:

Incidence of Hepatitis B is reaching endemic proportions. Hepatitis B vaccine may soon be recommended for inclusion in the EPI vaccines. Therefore, yearly requirements for all four countries visited include estimates for this vaccine.

packaging of vaccines. This should be a very selective and planned involvement with the right choices of vaccine.

Republic of Moldova

- *Republic of Moldova should continue its present practice of purchasing vaccine through UNICEF, since this is the most economical way to protect its population.*

Romania

- *Since the quality of the vaccines produced in Romania is good, manufacturing of the human vaccines at the Cantacuzino institute should continue. However, Ministry of Health, National Control Authority and Cantacuzino institute must prepare jointly plans for future modernization and upgrade of the production and quality control facilities and equipment as per European Pharmacopoeia and WHO guidelines.*
- *Ministry of Health of Romania should implement as soon as possible the proposed plans for the establishment of the Agency for purchase and distribution of all human vaccines to the District Health Centers.*

General

- *Governments in the region should consider move towards privatization of the Biological industry. Being private enterprise,*

RUSSIAN FEDERATION

(April 04 to 10 1995)

1.0. GENERAL

Russian Federation has a surface area of about 17,000,000 sq. km. The population, residing equally in urban and rural areas, is estimated to be about 175 million.

Estimated requirements for the EPI vaccines are:

OPV	*20.0 x 10^6 doses*
DTP	*12.0 x 10^6 doses*
BCG	*8.0 x 10^6 doses*
Measles	*6.0 x 10^6 doses*
DT	*6.0 x 10^6 doses*
dT	*6.0 x 10^6 doses*
Hepatitis B	*12.0 x 10^6 doses*

Birth rate is 17/1000 or about 3.0 million children per year.

The above figures include boosters and wastage of vaccine.

2.0. POLITICAL FRAMEWORK

Russian Federation is in the transition period where the control by the state is still very apparent. Constitutionally every citizen of the country is entitled to free health care and immunization. This is not always possible since the country is presently facing very serious economic hardship.

3.0 CURRENT STATUS

3.1. Purchasing

Information obtained from the official sources indicate no purchasing of vaccines for human use from outside suppliers. However, about 10-15% of the population can afford and is purchasing imported vaccine.

Importing of vaccine may become reality in the future, if resolutions for the problems facing the biological industry are not resolved within the reasonable period of time.

3.2. Manufacturing

Russia has a long history of manufacturing of biological products. Prior to the political changes in 1991 enough vaccine was produced to supplly

39,700 cases of Diphtheria recorded in 1994

all needs of former USSR. Since 1991 and predominately due to the severe economic problems only six or seven institutes continued to manufacture vaccine. The economic hardship has effected not only the quantities of vaccines produced but also severely jeopardized the quality. Any further continuation of shortage of raw materials will contribute to closing of the production. It is anticipated that Russia will face severe shortage of EPI vaccines in not to distant future.

only 55-60% of the requirements will be available

3.2.1. Manufacturing facilities

Information obtained from official sources indicates that all manufacturing facilities presently operating in Russia are in a very bad state and would need very significant capital investment to bring them to the level of compliance.

Six manufacturing institutes have been selected for reconstruction. Preliminary plans, with Technical and Investment Studies have been completed, and the cost of reconstruction and purchase of equipment is estimated at about $ 75 million US per site. (Source MOH)

3.2.2. Technology - State of art

Manufacturing technology for production of human vaccines is at least 30 to 40 years old. Plans for urgent and significant upgrades and modernization must be made as soon as possible.

4.0. REGULATORY

National Control Authority reporting to the Ministry of Public Health is responsible for the licensing of the products produced in Russia or imported from outside. The products are normally released on the basis of the production and testing protocols.

5.0. CONCLUSIONS

1. Due to the time allocations for my visit to Russia, and inability of resident UNIDO office to arrange all necessary meetings, some of the conclusions may be to generic. Due to disperse nature and size of the Biological industry in this country further evaluation of the current status will be necessary.

2. *Government of Russian Federation through Ministry of Health must find a way of solving manufacturing problems which are mainly caused by lack of funding and shortage of raw materials.*

3. *In order to successfully protect the population, MOH ought to consider option of purchase of Human vaccines as a stop gap.*

4. *Any planned reconstruction and modernization of the Biological industry should be within a full compliance as per WHO guidelines.*

5. *Apparent immunological problems with some of the vaccines (Diphtheria and Measles) point out towards necessity of investigation and likely replacements of the existing virus seeds.*

6. *Considerations should be made to upgrade existing technology. Partial or complete technology transfer would be a step forward.*

7. *To attract foreign or domestic investors and venture capital, move towards privatization of Biological Industry may be necessary.*

UKRAINE

(April 11 to 16 1995)

1.0. GENERAL

Ukraine has a surface area of about 604,000 sq. km. The population, residing mostly in urban areas, is estimated to be about 52.1 million. Birth rate has been steadily declining since 1985.

Requirements for the EPI vaccines are:

OPV	*5.0 x 10^6 doses*
DTP	*3.0 x 10^6 doses*
BCG	*2.0 x 10^6 doses*
Measles	*1.5 x 10^6 doses*
DT	*1.50 x 10^6 doses*
dT	*1.5 x 10^6 doses*
Hepatitis B	*3.0 x 10^6 doses*

Birth rate is 14/1000 or about 750,000 children per year

The above figures include boosters and wastage of vaccine.

2.0. POLiTICAL FRAMEWORK

Since Declaration of Independence in 1991, the Government has very strong commitment and support for Primary Health Care.

Declaration was passed in parliament committing the Government of Ukraine to self sufficiency in vaccine supply. Responsibility for detail planning and eventual completion of the ultimate goal of self-sufficiency was delegated to the Committee for Medical and Microbiological Industry.

All people in the country are entitled by law to free health care and immunization.

3.0 CURRENT STATUS

3.1. Purchasing

Presently Ukraine is purchasing its requirement from Russia and may be subject to shortages due to production problem which the Russian institutes could be facing in the not to distant future.

Quality of the vaccine purchased is of grave concern. In the first two months of 1995, 400 cases of Diphtheria have been recorded.

70% of recorded cases occurred in already immunized children.

3.2. Proposed Vaccine Manufacturing

3.2.1. Financial Considerations

For the Med Care plans realization, the credit line of 400 million DM is secured from Germany. The money is to be used for the following projects:

A - Manufacturing of Insulin - 78 million DM
B - Manufacturing of Antibiotics - 32 million DM
C - Manufacturing of Vaccines - 90 million DM

The remaining 200 million DM is to be used for other medical/pharmaceutical needs.

The 90 million DM allocated for the vaccine manufacturing is to provide for engineering and construction of three manufacturing facilities and the purchase of Technology, Production Equipment and Master Seeds:

1. *Facility for production of BCG - Kiev.*
2. *Facility for production of Measles, Mumps, Rubella and Hepatitis B - Odessa.*
3. *Facility for production of Bacterial vaccines - Kharkiv.*

3.2. 2. Proposed industrial capabilities development

In all three manufacturing facilities the plans are for gradual development the industry in two or three phases:

phase I. *Filling from diluted bulks, labeling and packaging.*

phase II. *Reconstitution from the concentrates, fillings, labeiing and packaging.*

phase III. *Complete vaccine manufacturing, dilution, filling, labeling and packaging.*

Plans call for start up of the Phase I by the end of 1996.

The first phase in all three institutes is expected to start by the end of 1996.

3.2.3. Planned Capacities

When manufacturing facilities are completed the planned capacities of production will be:

BCG vaccine	*8.0 - 10.0 million doses/year*
Diphtheria	*5.0 - 6.0 million doses/year*
Tetanus	*5.0 - 6.0 million doses/year*
Pertussis	*5.0 - 6.0 million doses/year*

Measles	***1.5 - 2.0 million doses/year***
Mumps	***0.8 - 1.0 million doses/year***
Rubella	***0.8 - 1.0 million doses/year***
Hepatitis B	***1.5 - 2.0 million doses/year***

3.2.4. Technology - State of art

Ukraine has lost the technical know-how in the 60's and has not been upgrading its facilities or technology for the last 20 - 30 years. To get back, to the capability of producing human vaccines, will be very lengthy and costly proposition.

Until the 60's Ukraine had four institutes for vaccines production.

Selection of the right technology for the future is single most critical task and it needs to be done with the great deal of care.

German Engineering Company has been contracted for planning and management of the project.

4.0. REGULATORY

Ukraine does not have National Control Authority. In the past it was relied on the Russian Regulatory Control Authority to supply the required services. Since the independence Ukraine has made arrangements with the Russian Control Authorities from Moscow to continue and provide product releases and testing of the imported vaccine and other products.

5.0. CONCLUSIONS

1. *Establish an independent National Control Authority responsible for Human Biological products. The agency should be made responsible for establishing of the standards for national licensing procedures. This agency will also review production protocols of vaccine from internal or external suppliers, perform quality assessments of products and conduct inspections of manufacturing facilities.*

2. *Ukraine is too small with about $52x10^6$ people to be able to develop the biological industry and produce human vaccines economically for its own market only. However to be in the position of exporting vaccine outside its boarders the industry*

must be developed in compliance with the WHO standards in mind.

3. *Ukraine should concentrate its efforts and capital to develop portions of the industry, i.e. purchasing the concentrated Bulks, reconstituting and formulating diluted bulks and filling and packaging of vaccines. This should be a very selective and planned involvement with the right choices of vaccine.*

4. *Procurement of the vaccine should be continued for the time being, making sure that the vaccine purchased is of good quality, and produced according to the WHO standards. Liason with UNICEF is strongly recomended.*

5. *To be in the position of making the most appropriate decision in regard to the economics and public health protection, in depth feasibility study must be conducted. Analysis must concentrate on the all options available, including the cost of vaccine when supply purchased or locally produced as well as quality of the product. Appropriate time frames must be set to reflect realistic expectations.*

6. *Ukrainian Government should consider privatization of the Biological industry. If this was done, domestic and foreign investors will be attracted and may be allowed to participate in the re-building of the industry.*

REPUBLIC OF MOLDOVA

(April 17 to 18 1995)

1.0. GENERAL

Republic of Moldova has a surface area of 33,700 sq. km. The population in 1994 was estimated to be about 4.5 million.

Yearly requirements for EPI vaccine are estimated to be:

OPV	*210 x 10^3 doses*
DTP	*210 x 10^3 doses*
BCG	*70 x 10^3 doses*
Measles	*70 x 10^3 doses*
DT	*140 x 10^3 doses*
dT	*210 x 10^3 doses*
Hepatitis B	*210 x 10^3 doses*

Birth rate is 15.5/1000 or about 70,000 children per year.

The above figures do not include boosters or wastage.

2.0. POLITICAL FRAMEWORK

The Government has strong commitment and support for PHC and preventative medicine. Presently, in addition to the routine immunization programs, MOH is very focused on the elimination of Diphtheria among the population. High incidence of Diphtheria within the immunized population is apparent.

203 confirmed cases of Diphtheria in the first three months of 1995.

3.0 CURRENT STATUS

3.1. Procurement

Until 1994, all required vaccine was being purchased from Russia. Last year (1994) requirements were purchased through and with the help of UNICEF, and some small portions of Hepatitis B and MMR were purchased directly from Belgium and Germany. The procurement of the vaccine was made possible by securing a credit of $500,000.00 US through European Bank. Republic of Moldova's preference is to continue purchase of all required vaccines through UNICEF and from the sources which are in compliance with WHO standards.

3.2. Financial and Economic Consideration

Estimated cost of purchase of all required EPI vaccine for Moldova is about $600,000 - $800,000 per year. The cost could increase to about US $1,200,000 in every fifth year for booster programs.

Additional $750,000 *US* required in 1995 for diphtheria booster.

3.3 Vaccine Manufacturing

Republic of Moldova does not produce any of the Human vaccines required, since its requirements have been filled in the past by the Russian manufacturers.

4.0. REGULATORY

Presently Republic of Moldova does not have the National Control Authority responsible for release of imported vaccine. However the intention is to involve the Central diagnostic Center and the Epidemiological Center in the future. In cooperation with these two institutions MOH is planning to establish system for the release of vaccine. The releases will be based primarily on the information available from the Production and Quality Control Protocols and records.

5.0. CONCLUSIONS

1. ***Republic of Moldova should continue its present practice of purchasing vaccine through UNICEF, since this is the most economical way to protect its population.***

2. ***It will be highly recommended to establish National Control Authority with more define mandate for release of all vaccine used in the country.***

ROMANIA

(April 19 to 21 1995)

1.0. GENERAL

Romania has a surface area of about 237,000 sq. km. The population is estimated to be about 23.0 million, with the birth rate being 11/1000 or about 250,000 children per year.

Therefore yearly requirements of the EPI vaccines are as follows:

OPV	*2.0 million doses*
DTP	*1.5 million doses*
BCG	*2.0 million doses*
Measles	*1.0 million doses*
DT	*0.8 million doses*
dT	*1.0 million doses*
Hepatitis B	*0.8 million doses*

Birth rate is 11/1000 or about 250,000 children per year

The figures include boosters and wastage of vaccine.

2.0. POLITICAL FRAMEWORK

Government of Romania has traditionally supported the policy of self - sufficiency of vaccine supply. Since the Revolution in 1990 the support for Public Health and especially for immunization has intensified.

3.0. CURRENT STATUS

Romania has a long history of manufacturing of Biological products for both Human and Animal use. All EPI vaccines are being produced at Cantacuzino Institute, in Bucharest, with the exception of OPV and Hepatitis B which are being purchased through UNICEF.

3.1. Manufacturing

The Cantacuzino institute is the main scientific and technical unit within the ministry of Health. It employs about 1200 people. Of this 215 are Research and Production scientific staff, 85 technical and the rest are auxiliary and administration. The main fields of activity of the institute are: Research, Production, Reference Controls and Public Health, Clinical Biology and Post-Graduate teaching. Production of bacterial and viral vaccines and bacterial immunomodulators represents about 50% of the total production activity of the institute.

3.1.1. Manufacturing Facilities

In the total there are 33 buildings accommodating various activities throughout the complex. In general all buildings are old and need significant capital investment to bring them to the level of compliance. The most modernized unit is for the production of BCG vaccine. However even this unit needs structural modifications and capital investment for equipment.

3.1.2. Technology - State of Art

Manufacturing technologies for production of Bacteria and Viral vaccines need considerable modernization. Some of the more modern and significantly sophisticated equipment has been purchased (i.e. fermenter). It is expected that some of the bacterial vaccines will be undergoing development and will be produced in the future by the fermenter technology.

3.1.3. Capacities per year and cost per dose:

BCG	*6.0 million doses*	*245 Lei = $0.12 US*
Diphtheria	*2.0 million doses*	*205 Lei = 0.10 US*
Pertussis	*1.5 million doses*	*205 Lei = 0.10 US*
Tetanus	*2.0 million doses*	*205 Lei = 0.10 US*
Measles	*1.0 million doses*	*4100 Lei = 2.00 US*
DT	*N/A*	*410 Lei = 0.20 US*
dT	*N/A*	*305 Lei = 0.15 US*

3.2. Procurement and Distribution

Present procurement policy in Romania is as follows:

a. *Imported vaccines are being purchased for MOH by an agent (UNIFARM), for hard currency and distributed to the District Health Centers as per MOH requests.*

b. *Locally produced vaccine is ordered by the individual DHC directly from the manufacturer, and paid for by MOH.*

Present system is creating serious problems in regards to supply, distribution, proper use and correct cold storage. To eliminate some of the difficulties MOH is proposing the following changes: Use UNIFARM company as an agent for all procurement of imported and locally produced vaccine. The Agency will make purchases of the vaccine based on the projection prepared by the Ministry of Health, at the beginning of the year, and to include and cover the requirements of each individual District Health Center through out the country. UNIFARM will also be responsible for distribution of the vaccine to each and everyone of the 41 DHC in sufficient quantities to cover about three months of vaccine requirements. The facility to accommodate planned activities has been renovated and is awaiting installation of cold rooms, freezers and monitoring equipment. The building is equipped with two independent power supplies in addition to a generator for emergency power needs. The facility is expected to be operational by October 1995. With the

SOP for handling, monitoring and distribution have been developed.

money on loan through the World Bank, Ministry of Health has already purchased refrigerators and freezers for all of 41 District Health Centers. With the establishment of this Agency MOH is expecting considerable improvements in the storage, delivery and distribution of the vaccines throughout the country. The new system should have positive financial impact on the cost of vaccine, since it will definitely contribute to improvements of inventories and reduction of waste.

4.0. REGULATORY

4.1. National Control Authority

National Control Authority reporting to the ministry of Health is responsible for Lot to Lot release of vaccines whether they are locally produced or imported. The products are normally released based on the production and testing protocols submitted by the manufacturer. However the State Control Bureau does selective testing to confirm recorded data and test results.
The Control authority also performs periodical visits of the manufacturing facilities for the purpose of GMP inspections.

4.2. Quality Control

Newly renovated Quality control Department is located on the ground floor of the building being shared with the National Control Authority.

Quality Control portion of the building consists of three major sections being used for:

i. Preparation of equipment and decontamination,

ii. Microbiological testing,

iii. Chemical analysis

Presently many of the tests are still being done within the production units, however gradual transfer to QC is expected.

5.0. CONCLUSIONS

1. *The National Control Authority must be physically separated from the Cantacuzino institute. When and if this is accomplished Control Authority will be in a better position to regulate vaccine testing, production procedures and adherence to GMP guide lines for biological products.*

2. *At the Cantacuzino institute, all product release test must be performed by the Quality Control Department.*

3. *Responsibility for release of Final products must be assigned to Quality Control.*

4. *Since the quality of the vaccines produced in Romania is excellent, manufacturing of the human vaccines at the Cantacuzino institute should continue. However, Ministry of Health, National Control Authority and Cantacuzino institute must prepare jointly plans for future modernization and upgrade*

of the production and quality control facilities and equipment as per WHO guidelines.

5. *Ministry of Health should implement as soon as possible the proposed plans for the establishment of the Agency for purchase and Distribution of all human vaccines to the District Health Centers.*

6. *Cantacuzino institute must as soon as possible establish written Standard Operating Procedures for all production and testing activities.*

7. *Development of fermenter technology must be completed as soon as possible. This will significantly increase production capacities of Pertussis, Diphtheria and Tetanus vaccines.*

8. *Complete development work on 10 dose BCG vaccine presentation in order to reduce wastage of vaccine.*

9. *Romanian Government should consider privatization of the Biological industry. As private enterprise, funding for reconstruction and development, may be achieved through domestic or foreign investors.*

LISTS OF PERSONS MET:

Russian Federation:

V. I. Kocherovets	Deputy Minister for Health and Medical Industry
V. P. Ganzenko	President Immunogen
A. V. Mikhailov	National Expert, UNIDO
A. V. Popov	Medical Director Paster Merieux
M. De Vintcha	Managing Director Paster Merieux

UKRAINE:

V. T. Chumak	The First Vice - Chairman, State Committee for Medical and Microbiological Industry
K. V. Kuryshchuk	The Vice - Chairman, State Committee for Medical and Microbiological Industry
E. A. Dorochinsky	Board Member, Head of Management of Scientific and Technology Development and Production Organization, State Committee for Medical and Microbiological Industry

V. V. Khalabuzar	Advisor, Economic Affairs, State Committee for Medical and Microbiological Industry
Y. V. Voloshcenko	Director, Kiev Bacterial Preparation Plant
D. K. Tishcenko	Deputy Chief, Main Sanitary Epidemiclogical Department, Ministry for Public Health
S. Browne	UN Res. Rep.
A. Solovgova	UNDP Programme Officer

MOLDOVA:

M. V. Magday	Deputy Minister, Ministry of Public Health

ROMANIA:

N. Ion - Nedelcu	National Immunization Program Manager Ministry of Health
M. Negut	Deputy Director, Cantacuzino Institute
G. A. Szegli	Scientific Secretary, Head Department of Immunology, Cantacuzino Institute
O. G. Negry	Head,Joint UNIDO-Romania Center

Abbreviations

MOH	*Ministry of Health*
GNP	*Gross National Product*
EPI	*Expanded Programme on Immunization*
DTP	*Diphtheria-Pertussis-Tetanus Vaccine*
DT	*Diphtheria-Tetanus Vaccine*
dT	*Diphtheria-Tetanus Vaccine for Adult*
BCG	*Bacillus Calmette-Guerin (Tuberculosis Vaccine)*
TT	*Tetanus Toxoid*
OPV	*Oral Polio Vaccine*
GMP	*Good Manufacturing Practice*
QC	*Quality Control*
NCA	*National Control Authority*
SOP	*Standard Operating Procedures*
WHO	*World Health Organization*
PHC	*Primary Health Care*
UNICEF	*United Nations Children's Fund*
UNIDO	*United Nations Industrial Development Organization*
GLP	*Good Laboratory Practice*
QA	*Quality Assurance*

INFORMATION ON THE VACCINE PROPHYLAXIS AND THE PRODUCTION OF VACCINES FOR MASS SCALE USE IN RUSSIA

by Dr. V.P. Gantenko, President, IMMUNOGEN

Federal and regional programmes "Vaccine Prophylaxis"

Epidemic situation with infectious diseases in Russian Federation (including controlled infectious of children) is still very tense. Diphteria reached epidemic level. High morbidity is caused by measles, pertussis, mumps, tuberculosis and other infections (Table 1). The coverage of population with prophylactic vaccination is not satisfactory (Table 2).

In view of these circumstances the programme "Vaccine Prophylaxis" was elaborated and adopted by Russian Federal Government.

The targets of this programme are the decrease of children morbidity and mortality caused by infectious diseases controlled by vaccination as well as eradication of poliomyelitis. For reaching these targets the programme includes the increase of the vaccination coverage of children, the support of the modern level of vaccine production and appropriate quality control, the creation of the efficient system of transportation and storage for vaccine preparations, the modernization of the system of epidemiological surveillance, the improvement in teaching and training of personnel and the implementation of applied scientific studies needed for improvement of vaccine prophylaxis.

The programme foresees also for 1993-1997 the appropriate reconstruction of the factories and laboratories produced the vaccines needed for mass scale use - measles, poliomyelitis, BCG, DPT, as well as DP, DP-M, D-M toxoids - to meet contemporary international and national requirements (including GMP and GLP) for production and control of vaccines in seven factories (plants).

1. Production department (plant) of the Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow Region - poliomyelitis vaccine.

2. Production department of the Gamaleya Institute of the Epidemiology and Microbiology, Moscow - BCG vaccine and BCG-M vaccine.

3. Moscow factory for the production of bacterial preparations - measles vaccine.

4. "BIOMED" AS (Mechnicov), Moscow Region - ADPT vaccine, ADP-M and AD-M toxoids.

5. "BIOMED" SPU, Perm - ADP and ADP-M toxoids.

6. State enterprise "Allergen", Stavropol - BCG vaccine.

7. "Immunopreparat" SPU, Ufa - ADPT vaccine, ADP, ADP-M, AD-M toxoids.

Besides Federal Programme "Vaccine Prophylaxis" 72 regional programmes are developed. Sixty-one of these programmes are financed from local budgets.

Certification, registration and licensing of the medical immunobiological preparations produced by national producers as well as imported from abroad

To cover the needs of population in medical immunobiological preparations (MIBP) of guaranteed quality and to improve the procedure of the introduction of newly developed preparations in Russian Federation, the State Committee for Sanitary and Epidemiological Surveillance introduced by official decree No. 5 from 3 June 1994, the system of state registration and certification of medical immunobiological preparations. It includes the expertise of materials, laboratory and field trials, analysis of their results, consideration of norm and techical documentation, registration and issue of special form certificate of state registration and inclusion in the state register.

Besides that to carry on the state control, the fulfilment of the laws and rules securing the state policy in the industrial production and distribution of drugs, the Russian Ministry of Health and Medical Industry by official decree No. 4 from 20 April 1994 stated the order for licensing, manufacturing and distribution of drugs including MIBP. The issue of licenses for production and delivery of drugs is carried on by licensing commission of the Ministry according to the regulations for getting appropriate licenses.

To regulate the importation of MIBP into Russia the Ministry established the procedure of the issue of licenses for buying the preparations. Except that the State Committee for Sanitary and Epidemiological Control by official decree No. 12 from November 1992 introduced compulsory registration for foreign medical immunobiological preparations. It is done for security of the control of the safety and efficacy of foreign preparations and for facilitation of the final decision concerning the use of them in human beings on the territoria of Russian Federation. These rules are also compulsory for the preparations devoted for specific prevention of diseases, for immunological and bacteriological treatment and for diagnostic of infections, parasitic and allergic diseases. The registration of MIBP is carried out by State Committee for Sanitary and Epidemiological Surveillance. It includes the expertise of norm and techncial documentation and laboratory (preclinical) trial(s) and if necessary - clinical trial(s).

In case of satisfactory results, the final report on the study accompanied by the recommendation of Federal Commission is transferred to the State Committee for Sanitary and Epidemiological Surveillance. The Committee issues the registration certificate in Russian and English valid for 10 years and fix the registration number of foreign MIBP.

The registration procedure for MIBP basically does not differ from the registration of pharmaceuticals.

The expertise, trials and registration of MIBP are paid procedures. The cost depends on the quantity of appropriate work.

Vaccination calendar valid in Russian Federation

This calendar includes compulsory vaccination and revaccination of children and adults against following infections:

-	poliomyelitis	children of 3 months to 16 years;
-	measles	children of 12 months to 6-7 years;
-	mumps	children of 15-18 months;
-	tuberculosis	children of 4-7 days to 14-15 years;
-	tetanus	children of 3-6 months to 16-17 years;
-	pertussis	children of 3-6 months to 12-18 months;
-	diphtheria	children of 3-6 months to 16-17 years.

Besides that, to strengthen the measures for diphtheria prevention, the Ministry of Health and Medical Industry and the State Committee for Sanitary and Epidemiological Surveillance introduced the annexes to above calendar (official decree No. 235/130 of 2 Novembe 1994) see table 3.

The production of vaccines in Russia

For mass immunization purposes the following vaccines are produced:

- Measles vaccine (live dry vaccine distributed by 1 or 2 doses per ampoule). In 1995 the experimental batches of measles vaccine with improved thermostabilisation should be produced.

  The producer : A.S. "D. Masai", Moscow
  Production capacity : up to 15 million doses a year.
  GMP standards are to be established.

- Mumps vaccine cultural live dry distributed by 1 or 2 doses per ampoule.

  The producer: A.S. "D. Masai", Moscow
  Production capacity - 8 million doses a year.
  GMP standards are to be established.

- Associated vaccine against diphtheria, pertussis and tetanus (ADPT vaccine distributed by 1 ml - 2 doses per ampoule); Diphtheria toxoid with diminished contents of antigens (AD-M distributed by 1 ml - 2 doses per ampoule); Diphtheria-tetanus adsorbed toxoid (ADT distributed by 1 ml - 2 doses per ampoule); Diphtheria - tetanus adsorbed toxoid with diminished antigen contents (ADT-M distributed by 1 ml - 2 doses per ampoule).

  These preparations are produced by 3 production facilities:
  1. A.S. "Biomed", Mechnicov, Moscow Region
     Production capacity for ADPT vaccine - 5,000 litres a year
     for ADT-M - 12,000 litres a year. The production was not certified

according to GMP requirements but certain sections of production meet GMP requirement (glass washing, sterilization, distribution in ampoules).

2. S.P.S. "Immunopreparat", Ufa.
Production capacity for ADPT vaccine - 8,000 litres a year; for ADT-M - 2,500 litres a year. The production was not certified according to GMP but certified according to national standards for biologicals.

3. S.P.S. "Biomed", Perm
Production capacity for ADT - 1000 litres a year; for ADT-M - 2000 litres a year.
The production was not certified according to GMP but certified according to national standards for biologicals.

- Vaccines BCG and BCG-M. Vaccines against tuberculosis dry for intradermal injection. One set of vaccine is composed of 1 ampoule contained 10 or 20 doses and 1 ampoule of solvent.

The vaccine is produced by 2 facilities:

1. State enterprise "Allergen", Stavropol
Production capacity - 1.8 million sets by 20 doses each

The production was not certified according to GMP but certain sections of production meet GMP requirements (glass washing, sterilization and distribution in ampoules).

2. Production department of Gamaleya Institute of Epidemiology and Microbiology, Moscow.

It produces BCG and BCG-M vaccines.
Production capacity - 0.8 million sets by 10 and 20 doses each.

The production was not certified according to GMP requirements. The project of appropriate modernization is accomplished.

- Poliomyelitis vaccine

The production department (plant) of the Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow Region, produces poliomyelitis oral vaccines contained 1, 2 and 3 types of poliovirus (Sabin strains). Distribution - 10 doses per vial.
Production capacity - 100 million doses a year.

The production standards are close to GMP requirements. Now the project and financial documentation are ready for reconstruction and new constructions started.

Table 1

Dynamics of diphtheria, poliomyelitis, pertussis, meales, mumps and tuberculosis morbidity 1989 - 1994

	YEARS					
	1989	1990	1991	1992	1993	1994
Diphtheria - number - per 100 000	593 0.4	1211 0.8	1896 1.3	3897 2.6	15210 10.3	39917 26.9
Poliomyelitis	11 0.007	16 0.01	17 0.01	10 0.007	5 0.003	8 0.005
Pertussis	27731 18.8	24960 16.9	30876 20.8	24004 16.2	39218 24.4	48309 32.5
Measles	25525 17.3	18370 12.4	20449 13.8	29218 12.5	74336 50.1	29286 19.7
Mumps	72511 49.2	58666 39.2	36513 24.6	34939 23.6	44618 30.08	41391 27.9
Tuberculosis (newly registered per100000)	28.3	29.1	30.5	33.7	34.5	35.7

Table 2

	YEARS					
	1989	1990	1991	1992	1993	1994
Poliomyelitis						
1 year	68.6	69.4	72.1	69.0	82.2	87.5
7 years	78.0	80.0	86.3	88.1	76.2	78.3
14 years	88.7	70.7	86.0	85.5	71.4	98.2
16 years	-	-	84.5	83.2	84.0	96.2
Diphtheria						
1 year	82.7	68.5	69.1	72.6	79.2	88.05
3 years	77.2	77.3	74.6	81.3	83.0	97.5
16 years	-	-	83.4	80.1	86.5	97.5
Pertussis						
1 year	60.3	60.2	59.2	62.0	65.8	71.7
3 years	68.8	67.7	63.0	67.1	66.0	77.9
Measles						
2 years	82.0	81.1	78.4	82.6	88.2	91.2
7 years	67.9	70.2	69.9	61.5	67.6	72.7
Mumps						
2 years	61.3	58.5	56.6	61.7	66.9	71.2
Tuberculosis						
Newborns	-	-	97.0	97.2	97.1	97.5

Table 3

The scheme of immunization against diphtheria, pertussis and tetanus
(According to the decree of Ministry of Health and Medical Industry and
State Committee for Sanitary and Epidemiological Surveillance
No. 235/130, 2 November 1994)

Type of immunization	Time of immunization	Time of reimmunization				Notes
		1	2	3	4	
ADPT-vaccine (diphtheria, pertussis, tetanus)	3 months 4.5 months 6 months	12-18 months after completed vaccination				Vaccination could be combined in time with poliomyelitis vaccination. Revaccination carried out once
ADT toxoid (diphtheria, tetanus)	3 months 4.5 months	9-12 months after completed vaccination				Same as above
ADT-M toxoid (diphtheria, tetanus)			at 6-7 years of age (before entering school)		16-17 years	Revaccination carried out once. Adults are revaccinated once after 10 years
AD-M toxoid (diphtheria)				11-12 years		Revaccination carried out once

Comment: For children immunized according to individual scheme the interval between first and second revaccination must be not less than 4 years; For further revaccination, the interval must exceed 5 years.

The supply of Russia and newly independent countries with the vaccines of mass scale use in 1991-1994

Preparation	Units	1991		1992		1993		1994	
		Total	Russian Federation	Total	Russian Federation	Total	Russian Federation	Total	Russian Federation
Measles vaccine	thousand doses	14000	6016	9803	5636	10163	6406	11500	6972
Mumps vaccine	thousand doses	7701	3334	7400	3524	6453	3932	8000	3793
Poliomyelitis vaccine	thousand doses	69700	30550	68100	24539	49200	27278	44875	32700
Tuberculosis vaccine	thousand sets	2627	1202	3137	1243	2500	1012	2500	1324
DPT vaccine	litres	14265	6290	12900	5272	9962	8208	8392	6972
DT toxoid	litres	336	183	500	274	1718	880	2600	2265
DT-M toxoid	litres	9615	4584	11681	4437	12657	11483	25540	24300
D-M toxoid	litres	2048	1092	2436	775	4533	3296	10940	9782

COUNTRY REPORT ON VACCINE MANUFACTURING IN UKRAINE

by Mr. V. Chumak, First Vice-Chairman of State
Committee for Medical and Microbiological Industry of Ukraine

The State Committee for Medical and Microbiological Industry of Ukraine (Derzhcommedbioprom) is responsible for the output of the medical preparations in Ukraine, including the output of vaccines for the immunological prophylactic measures of the population.

The problem of the immunological prophylactic measures of the population of Ukraine is urgent, taking into consideration consequences of the accident at the Chenobyl nuclear power-station.

At present, Ukraine has no good manufacturing practices on its manufacturing of vaccines which are necessary for the immunological prophylactic measures of the population.

In accordance with the decision of the Government of Ukraine, in the limits of the Germany credit fine, the State Committee for Medical and Microbiological Industry of Ukraine concluded a contract with the firm "Linde KCA Dresden", Germany, as for construction at 3 plants manufacturing the following vaccines:

* DPT
* BCG
* Measles vaccine
* German measles vaccine
* Hepatitis B vaccine.

Means, which are allotted for the organisation of vaccines manufacturing are not sufficient for the accomplishment of the complex of works /acquisition of the equipments, technologies, strains for the manufacture of the above mentioned vaccines.

The State Committee for Medical and Microbiological Industry of Ukraine requested UNIDO to render assistance in the receipt of the strains and the technologies for the manufacture of the above mentioned vaccine, in the form of technical or humanitarian help, through the World Health Organisation. They are ready to provide all the necessary information as for the given question.

THE NATIONAL CENTRE OF INFECTIOUS AND PARASITIC DISEASES IN SOFIA, BULGARIA

by Prof. P. Nenkov, Deputy Director, Ministry of Health

A GENERAL REVIEW

The history of the National Centre of Infectious and Parasitic Diseases began in 1881 when an Antivariola Laboratory was established at the district hospital of the town in Razgrad with a Royal Memorandum of Prince Battenberg. The laboratory was headed by Dr. Boris Ox. In 1888 an Antivariola Institute was opened in Sofia. Later it was transformed into a Bacteriological Institute. In 1890 the Antivariola Laboratory and the Bacteriological Institute merged. Eight years later the Antiplague Institute joined them. The production of antivariola vaccine was started and large-scale studies on its effectiveness and side reactions were performed. The preparation of antisera to diphtheria, rabies and plague was initiated. Antiplague vaccine was also prepared. In 1908, the production of anticholera vaccine, polyvalent antistreptococcal serum and type-specific sera for diagnostic purposes began. In 1910, the united Bacteriological, Antivariola and Antiplague Institutes were given the name Central Institute of Hygiene. In March 1921, the Supreme Medical Council issued a new regulations giving higher status of this Institution. Gradually, the scope of activities had broadened and it turned into a real centre of the prophylactic medicine in Bulgaria. Today the devoted work of the founders of the Centre is greatly admired.

Over the years the activities of the Centre covered a wide area of research and production of preparations for the prophylactic work of the National Health Care.

The Rockefeller Foundation was interested in the work performed here and the visit of its representative Prof. Selektar marked the beginning of a long-term useful co-operation. According to an agreement, signed in 1928, this Foundation granted 19,5 million levs for a new building. Its construction started in 1932-1933. The official opening of the building with well equipped laboratories took place on March 3, 1938. The representative of the Foundation at that time R. Collins, was appointed to be the acting Director of the Institute, serving as an employee of Bulgaria. The Institute was divided into three departments: Microbiology, Chemistry and Hygiene.

A farm was attached to the Institute to take care of the needed animals and to produce sera from them. (This farm is located in the suburbs of Sofia, in the area of the mountain "Lyulin"). The variety of prophylactic, therapeutic and diagnostic sera became greater. Their list included bivalent and polyvalent sera against gas gangrene, typhus, paratyphus, anthrax, botulismus, E.coli, etc. New methods of diagnosis of infectious diseases were widely introduced. The production of nutrient media was enlarged.

During the years of World War II, the Institute worked on solving new problems which arose with the spreading of malaria, tuberculosis, anthrax, syphilis.

In 1949, new departments were included in the structure of the Institute. The department for production of biopreparation was established as a separate unit. A department of

epidemiology started to work and a division took care of the connections of the Institute with the local microbiological laboratories and the introduction of new methods of diagnosis in these laboratories (the division was named "organizational and methodical activities").

In the late fifties, the problem of the viral infections became sharp and a Virology Department was set up.

As the Medical Academy was created in Bulgaria in 1972, the Institute was incorporated into it. It was named Research Institute of Infectious and Parasitic Diseases and about twenty years it belonged to the Academy. In the meantime, the problem of AIDS emerged and the Centre AIDS Laboratory was created.

At present the National Centre of Infectious and Parasitic Diseases is an important institution in the Bulgarian Health Service. About 700 employees work here. The advantage of this large institution is that it can house a wide range of disciplines that can cooperate freely. This is valid for the five departments of the present centre. These departments are of: Microbiology, Virology, Epidemiology, Parasitology, Applied Immunology and Biotechnology, and Organizational and Methodical Activities Unit. Their duties can be summarized as : research, diagnostic work, production of biopreparations, training of specialists of the country's prophylactic network in advanced courses. Thus the National Centre of Infectious and Parasitic Diseases can solve complex problems connected with the control of the epidemiological situation in the country.

The result of the research and the production of valuable preparations is the limitation of many infectious diseases. Here we may quote the strong positive effect of the vaccination programmes against diphtheria, tetanus, pertussis, tuberculosis, typhus, cholera, variola, poliomyelitis and rabies. In recent times, the vaccine against measles, mumps, rubella, herpes and Crimean Haemorrhagic Fever'α-interferon produced in NCIPD have given their favourable effect. The purified and concentrated hyperimmune equine sera (against anthrax, diphtheria, tetanus, gas gangrene, snake venoms, etc.) and the human normal and specific immunoglobulins for intramuscular and intravenous use are valuable preparations for the prophylaxis and treatment of life-threatening diseases. The latest developments in the production of the Centre are in the field of the immunonodulating vaccinal preparations. The polybacterial peroral vaccines "Respivax" and "Urostim" are widely used now for the prophylaxis of respiratory tract and uro-tract infections.

A great number of laboratory methods and diagnostic preparations were introduced in the practice. The modern developments include florescent and electron microscopy, enzyme-linked immunosorbent assays, colicine phagotyping, molecular-biological methods for the studies of Salmonelloses and Shigelioses, AIDS, rota and paraviruses, influenza, papilloma viruses, herpes viruses, etc.

The production of monoclonal antibodies was started. Now they are routinely used in the laboratories in the country for diagnostic purposes. Modern methods for the investigation of the immune status of the patients were introduced.

The Centre produces a large number of diagnostic preparations including saturated and unsaturated sera for the serological diagnosis of Salmonella, Shigella, E.coli, Bordetella, cholera, etc.; discs for antibiotic-resistance determinations; precipitating antiglobulin sera, including

labelled with FITZ and enzymes; a great number of dry and fluid culture media, including differential and selective ones needed for the adequate microbiological diagnosis.

The parasitological laboratories in the country use now the kits for the immunodiagnosis of some parasitises including trichinellosis, echinococcosis, toxoplasmosis, etc. produced at the Centre.

Diagnostic preparations for viral diseases (i.e. herpes infections, influenza enteroviruses, Crimean and other haemorrhagic fevers) were developed and found their application.

Studies of the epidemic processes of viral hepatitis, influenza, nosocomial infections, staphylo-streptococcal diseases were performed. The role of a number of insects and rodents as vectors of infectious diseases was clarified.

The result of the research in the field of allergy-causing factors is the production of a variety of allergens for specific diagnosis and treatment of allergic diseases. The production programme of the Centre includes 160 types of allergens from house dust, bacteria, pollen grains, moulds, foods, insects, industrial pollutants, etc. Recently, a new class of preparations - allergoids (chemically modified allergens) was developed.

A field which also had a good development starting in the late fifties was the fractionation of human blood proteins. The technologies for the preparations of albumin, normal and specific immunoglubolins for intramuscular and intravenous application were worked out by the specialists of the Centre.

Beside the production and practice-directed research, studies of fundamental character have been performed in the fields of : local and systematic humoral immunity, immunochemistry of bacterial and viral antigens, mechanism of action of atopical allergens, antigen-representing cells of the immune system, the cellular metabolism of Bordetellas, certain aspects of virus-cell interactions and the isotopic tracing of the infected cell's metabolism, the molecular hybridization, plasmidology, the mechanisms of antibiotic sensitivity and poly-resistance and chemotherapy of some viral diseases, etc.

The Centre is respected internationally. Scientific projects with institutions mostly in European countries have been implemented on bilateral and multi-lateral basis. The contacts with WHO are effected mainly through the Ministry of Health in the field of the studies of the epidemiological processes. The Laboratory of Allergy and the Laboratory of AIDS are associated to WHO.

In conformity with the world's scientific achievements, personal experience and the research of the specialists, the Ministry of Health and the prophylactic network was given systematic and active help for performing antiepidemical activity and control over the whole country including development of analysis, prognoses and prophylactic programmes for separate or group infectious and parasitic diseases, guide materials for epidemiological investigations, DDD activities and others. Helping the medical practice, periodical, national and regional scientific-methodological conferences, meetings and symposia are held.

There cannot be realized a fruitful and successful work without a broad study of the world's scientific and practical achievements, without using the experience and without the

scientific collaboration with a number of related scientific institutes. Dozens of our specialists obtained new and modern knowledge in establishments in Russia, Czechoslovakia, Germany, France, the UK, Italy, the USA, etc.

A significant help for the NCIPD were the joint scientific projects with institutions of Russia, Czechoslovakia, Hungary, Germany, Greece, Austria, USA.

Our Institute is the place where, needed for the country, profiled specialists in the sphere of infectology - epidemiologists, microbiologists, virologists, parasitologists and infectionists, took an active part in the peripheral units and laboratories in the country, as well as in the medico-biological scientific field.

LIST OF PREPARATIONS
Produced by the National Centre of Infectious and Parasitic Diseases (NCIPD)

VACCINES

Vaccine against Diphtheria, Tetanus and Pertussis
Vaccine against Diphtheria and Tetanus
Vaccine against Tetanus and Diphtheria for adults
Vaccine against Tetanus
Antituberculosis BCG Vaccine for Intradermal Use, Freeze-dried
Vaccine against Typhoid Fever
Vaccine against Cholera, Freeze-dried
Inactivated Vaccine against Crimean Haemorrhagic Fever (CHF)
Freeze-dried Inactivated Antiherpes Vaccines: Types 1, Types 2 and Types 1+2
Live Measle Vaccine - Freeze - dried
Inactivated Cell Culture Rabies Vaccine
Lipovac (Anti-Influenza Vaccine)

IMMUNOSTIMULATORS

Respirax
Urostim

ALLERGENS

Group A, House Dust, Mites and Dandruff Allergens
Group B, Pollen Allergens
Group C, Food Allergens
Group D, Bacterial Allergens
Group E, Fungal Allergens
Group F, Occupational Allergens
Group G, Insect Allergens

HUMAN BLOOD DERIVATIVES

Normal Human Immunoglobulin
Human Anti-Crimean Haemorrhagic Fever Immunoglobulin
Human Antirabies Immunoglobulin
Immunovenin - Intact
Staphovenin
Histaglobin
Human Serum Albumin
Alpha-Interferon

HYPERIMMUNE EQUINE SERA:

- Tetanus Antitoxin
- Diphtheria Antitoxin
- Gas Gangrene Antitoxin
- Botulinus Antitoxin
- Antiviperine Serum
- Anti-Anthrax Serum

IMMUNODIAGNOSTICS

Purified Protein Derivate of Tuberculin (PPD)
Diagnostic Bacterial Preparations for Intestinal Infections
Anti-Salmonella O-polyvalent Sera
- Anti-Salmonella O-Group Sera
- Anti-Salmonella H-Factor Sera
- Anti-Salmonella H-Sera for Sven-Gard

Diagnostic anti-Shigella Sera
Diagnostic anti-E.coli Sera
Anti-Human-Globulin Goat Serum for Antiglobulin Coombs Test
ELISA-Ab Test System Trichinella Spiralis
ELISA-Ab Test System Echinococcus granulosus
ELISA-Ab Test System Toxoplasma gondii
Hemagglutination Kit for Detection of Antibodies to Trichinella spiralis
Hemagglutination Kit for Detection of Antibodies to Echinococcus granulosus
Hemagglutination Kit for Detection of Antibodies to Toxoplasma gondii
IF Kit for Detection of Antibodies to Enthamoeba histolytica
IF Kit for Detection of Antibodies to Toxoplasma gondii
IF Kit for Detection of Antibodies to Echinococcus granulosus
Cardiolypin preparation for diagnosis of syphilis
Kit for assay of cellular immunity

MONOCLONAL ANTIBODIES

Specific for:

Human leucocyte surface antigens : purified,
FITC & PE conjugated (Anti-CD2,3,4,5,7,8,11b,14,15,57,45, DR)
Human blood group antigens
(Anti-A, Anti-B)
Human immunoglobulins
(Anti-IgM and IgG)
Salmonella
(Anti-O and Anti-H)

CULTURE MEDIA

Dehydrated Culture Media - 30 preparations
Prepared Plated, Tubed and/or Bottled Media - 280 preparations

MISCELLANEOUS

Guinea-Pig Complement, Freeze-dried
Phytohemagglutinin
Paper indicator for Checking Dry-Hot Sterilization 160-165°C
Paper indicator for Checking Autoclave Sterilization 121°C
Paper indicator for Checking Autoclave Sterilization 134°C
Freund's Adjuvant

NATIONAL IMMUNIZATION PROGRAMME IN ROMANIA

by Dr. N. Ion-Nedelcu, National Immunization Programme Manager, Ministry of Health and Dr. A. Combiescu, Director, CANTACUZINO Institute

I. INTRODUCTION

Background

The population of Romania is 22.5 million. The annual birth cohort was 248.000 in 1994 with an infant mortality of 26.7%.ooo.

II. NATIONAL IMMUNIZATION PROGRAMME (NIP) STRUCTURE

Organization

NIP is coordinated at the national level by the National Immunization Manager in the Ministry of Health. At the district level (41 districts including Bucharest) immunization activities are the responsibility of a medical epidemiologist from the Preventive Medicine Centre. Technical support for NIP is provided by National Institute of Public Health. Advice on immunization policy is provided to Ministry of Health by the Commission of Infectious Disease. CANTACUZINO Institute manufactures the majority of needed vaccines and is the national reference centre for microbiological research.

Delivery of Vaccination Services

All vaccines are administered by state employees working in primary health centres (5000 dispensaries) and maternity hospitals (n-400).

III. IMMUNIZATION POLICY

All vaccinations are free of charge.

Romania adopted WHO objectives and targets for vaccine-preventible diseases control.

As of November 1989, Romania adopted WHO guidelines for contraindications to vaccinations.

At present Romania has no policy to prevent CRS, or NIB infection by vaccination.

IV. EPI VACCINE COVERAGE

EPI Vaccines Coverage - ROMANIA
(at 18 months of age)

Yearly Generation	DTP3	OPV3	MEASLES	BCG
1991	97.2	91.2	90.4	99.2
1992	97.6	91.3	90.5	99.2
1993	98.2	93.5	91.4	99.8

Source of data : National Immunization Programme

V. NATIONAL IMMUNIZATION PROGRAMME SCHEDULE

IMMUNIZATION SCHEDULE in ROMANIA (PRESENT)

AGE	VACCINES	COMMENTS
Birth	BCG	Continuous
2-7 mo	TOPV	Campaigns March & September
4-9 mo	TOPV	Campaigns April & November
10-15 mo	TOPV	Campaigns April & November
3 mo	DTP	Continuous
4 mo	DTP	Continuous
5 mo	DTP	Continuous
9-13/15mo	Measles	Campaigns February & September
11 mo	DTP	Continuous
29 mo	DTP	Continuous
7 y	DT plus Measles	
9 y	TOPV	
14 y	DT plus BCG	BCG if Mantoux negative

IMMUNIZATION SCHEDULE - (STARTING WITH OCTOBER 1995)

RECOMMENDED AGE	*VACCINES*	*COMMENTS*
Birth	HepB BCG	In the first 24 hours At 4-7 days of age
1mo	Hep B	Simultaneously
2 mo	DTP + TOPV	Simultaneously
4 mo	DTP + TOPV	Simultaneously
6 mo	DTP +TOPV -Hep B	Simultaneously
9 mo	Measles	
12 mo	DTP + TOPV	Simultaneously
30-36 mo	DTP	
7 y	DT Measles	
9 y	VPOT	
14 y	DT BCG	If Mantoux negative
24 y	Td	Every 10 years

VI. VACCINE PREVENTABLE DISEASES SITUATION

Vaccine Preventible Disease 1990 - 1994, ROMANIA

Diseases	Nb. cases per indicated year				
	1990	1991	1992	1993	1994
Measles	4690	1773	6061	28321	6228
Pertussis	817	2463	822	1551	732
Polio Total	8	30	18	10	8
Wild/Unknown	1/0	10/15	1,/1	0/2	0/5
Tetanus Total	34	23	37	30	25
Neonatal	1	1	3	1	1
Diphtheria	0	0	0	0	0

VII. LICENSING AND REGISTRATION OF BIOLOGICAL IN ROMANIA

The Centre for State Control of Biological Product of Human Use is designated as National Authority Control in Romania.

Appliers for vaccines registration are asked to furnish the following:

a) A sample of biological product.

b) Vaccine's technical documentation issued by the manufacturer..

c) Documentation to show that the premises under which product is manufactured meet Good Manufacturing Practices in the form prescribed by WHO standard and are subject to regular inspection by the NCA for every batch.

d) Free Sale Certificate issued by country of origin.

e) Fixed tax of 500 USD plus the values of control tests.
Licensing is provided by the Ministry of Health.

VIII. VACCINES LOCAL PRODUCED AND IMPORTED IN ROMANIA 1990 - 1994

Since 1990 Romania imported annually 2.000.000 TOPV closes. (Sclavo - Italy). The rest of needed vaccines have been produced locally - annual produced and present potential capacity are shown in underneath table. In the interval 1990 - 1994 Romania did not exported vaccines.

In 1995, Romania paid for importation of 1.75 millions paediatric doses and 250.000 doses of hepatitis B vaccine. As soon as vaccine should be arrived the preparations are made to integrate hepatitis B universal infant immunization in the National immunization schedule as a main strategy of hepatitis B control. The additional strategy of hepatitis B control is hepatitis B immunization of the health professionals at risk (in the first 2 years) followed by vaccination of medical students starting with the year 2+1 of the control programme.

VACCINES PRODUCED BY CANTACUZINO INSTITUTE - BUCHAREST IN ROMANIA
1990 - 1995

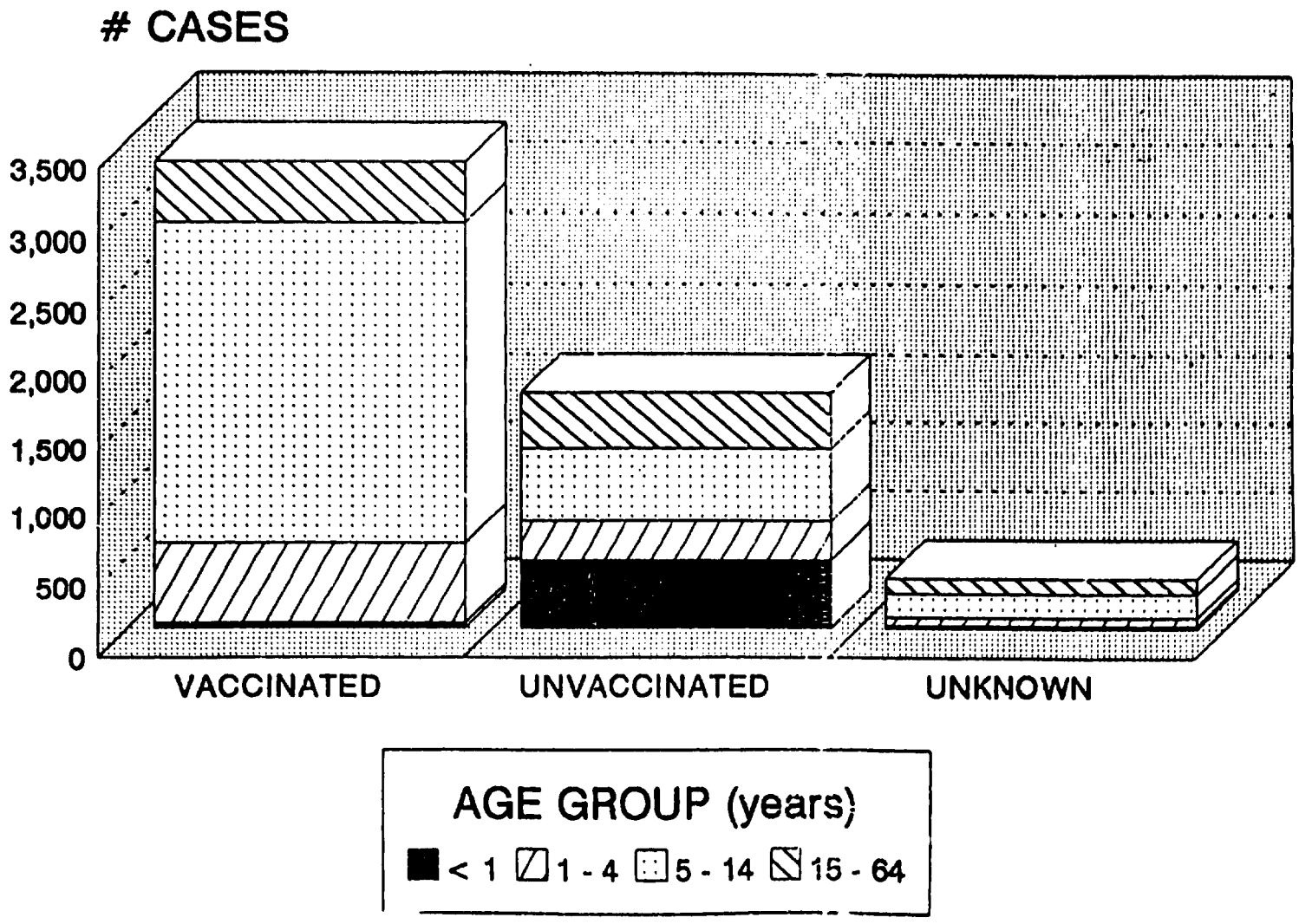
Ord.) No	VACCINE	TYPE	COMPOSITION	PRESENTATION	AMOUNTS PRODUCED (DOSES) 1990	1991	1992	1993	1994	ESTIMATED POTENTIAL CAPACITY (AT PRESENT)
1	MEASLES	Live (s.c.)	1000 $TCID_{50}$	Freeze-dried Multidose	503002	482290	511888	528525	761952	1000000
2	INFLUENZA	inactivated (Trivalent, i.o.)	Purified nucleo-capsidal proteins	Liquid monodose	183800	139890	96250	53040	107360	300000
3	RABIES	B-propriolac-tone inactiv (i.o.)	Newborn mouse brain	Liquid monodose	181040	194260	238120	281330	334440	500000
4	DIPHTHERIA (for adults)*	Purified toxoid (i.e.)	6.25 LF/ dose	liquid monodose	6630	4950	4410	13530	1620	See note
5	TETANUS	Purified toxoid (i.e.)	10 BU/ dose	Liquid monodose	1556550	1741951	2028050	2304500	2131100	2000000
6	DIPHTHERIA-TETANUS	Combined purified toxoids (i.e.)	25 LF D-toxoid 10 BU T-toxoid	Liquid monodose	883560	152740	628890	861380	778860	1000000
7	DIPHTHERIA-TETANUS - PERTUSSIS	Combined (i.e.)	15 LF D-toxoid 6BU T-toxoid 20 IU pertussis	Liquid monodose	1536110	1278210	1159910	989320	936150	2000000
8	TYPHOID	Heat inac-tivated (s.c.)	5.10^9 bact dose	Liquid monodose	389200	502800	406150	316350	482250	3000000
9	BCG	Live (i.d.)	4 mg semi-dried weight/ml	Freese-dried multidose	5428500	4546700	4958400	4715000	4217400	7000000
10	VADIZEN (BACILLARY DYSENRTY)	Live (oral)	10^{11} CFU/ml	Liquid multidose	233100	233900	131200	163200	163800	300000

* Replaced by Td since January 1st 1995 - 1000000 doses annual capacity

ROMANIA - NATIONAL IMMUNIZATION PROGRAMME
EPI Plus Schedule (as of 1995)

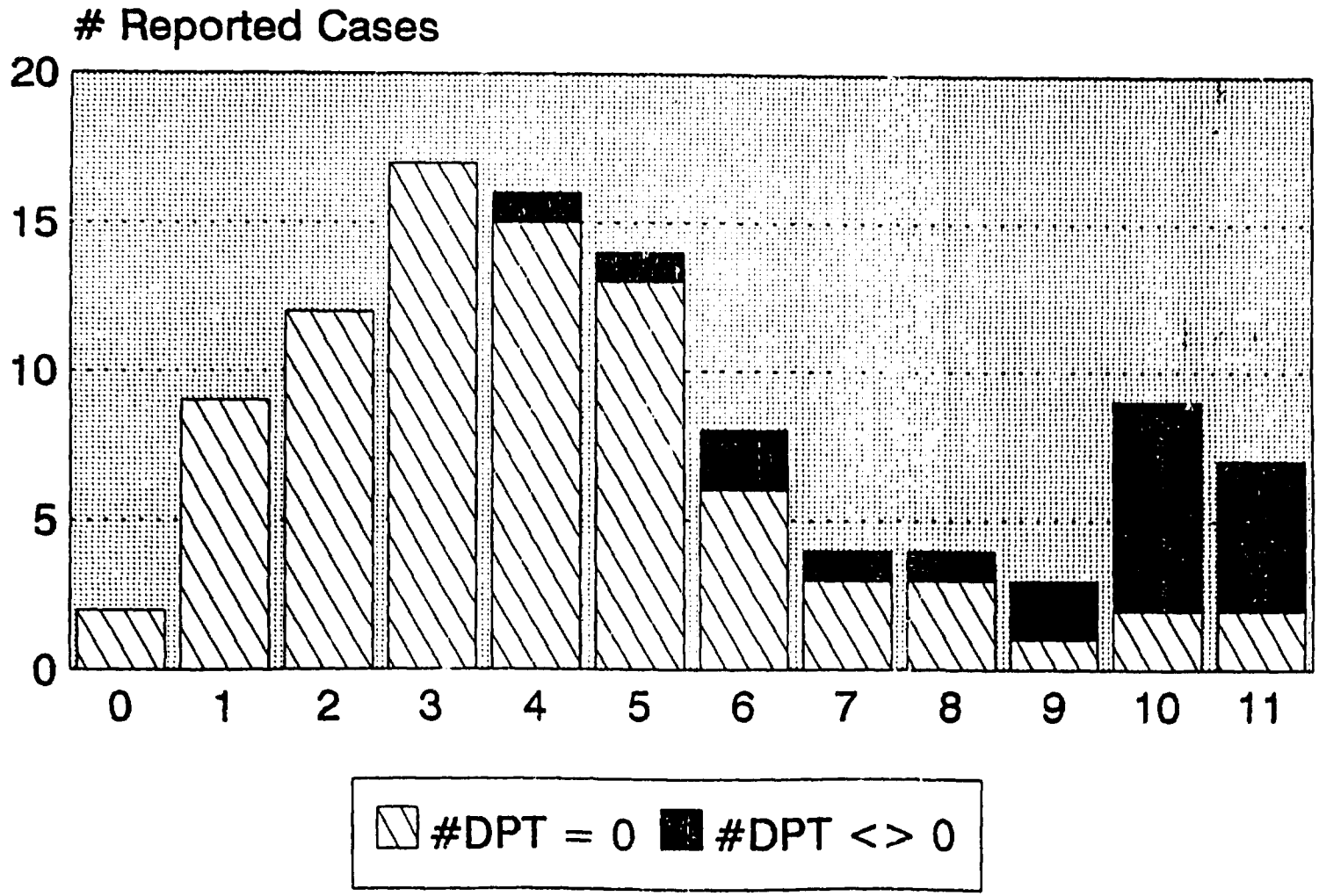
AGE	Diph/Teta Pertussis	Polio	Hepatitis B	TB	Measles
Birth			Hep B	BCG	
2 mos	DTP	TOPV	Hep B		
4 mos	DTP	TOPV			
6 mos	DTP	TOPV	Hep B		
9 mos					Measles
12 mos	DTP	TOPV			
30-36 mos	DTP				
7 yrs	DT				Measles
9 yrs		TOPV			
14 yrs	DT			BCG	
24 yrs +	dT				

MEASLES - CASES BY IMMUNIZATION STATUS AND AGE GROUP ROMANIA/1ST SEMESTER 1994 N = 5411



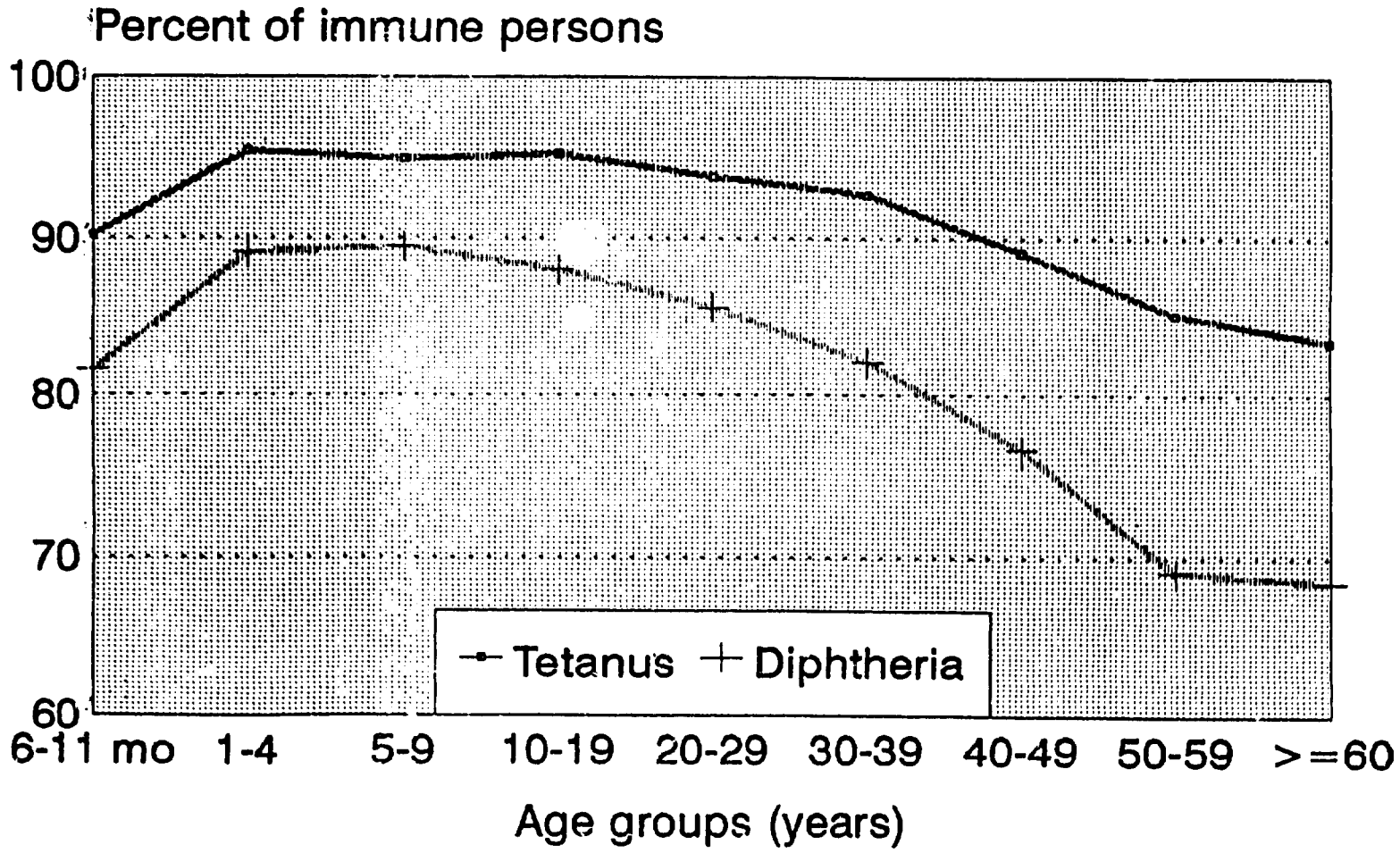
Source : National Immunization Programme

Pertussis - cases under 1 by onset age (months)
Romania - 1st semester 1994 (N = 104)



Source : National Immunization Programme

Tetanus and Diphtheria Immunity (HA) by age group ROMANIA - National Serorosurvey 1993-1994



Source: National Immunization Programme

NATIONAL VACCINATION PROGRAMME IN POLAND

by Prof. W. Magdzik, National Institute of Hygiene
and Dr. E. Kaczurba, Sera Vaccines Central Research Laboratory

Programme of vaccination

National vaccination programme in Poland is realized on the basis of calendar of vaccination, which is actualized once yearly by the Ministry of Health according to the advices of Epidemiological Committee.

The calendar for 1995 is divided into three parts. Obligatory vaccination of children and adolescents with mentioned in calendar doses of particular vaccines and age of children are included to part A. In the first year of life primary vaccination against tuberculosis at birth and vaccination at 12th month of life for the second time only for children with no scar or scar smaller than 3 mm after first vaccination, vaccination by 3 doses of DTP and simultaneously against poliomyelitis by OPV are included to the calendar. Above it in the half of country all newborns and infants and in the second half only newborns and infants born from HBV infected mothers are vaccinated four times against hepatitis B in the scheme 0, 1, 2, 12. In next two years it is since 1997 all newborns and infants in the whole country would be vaccinated against hepatitis B. In the first half of the second year of life vaccination against measles - mumps and rubeola by vaccine MMRII and in the second half fourth dose of DTP and simultaneously OPV is included to the calendar.

Children and adolescents in the age between 6 and 19 are vaccinated by the booster doses:

- three times against tuberculosis (at 7, 12 and 18),
- twice against diphtheria and tetanus by vaccine DT (at 6 and 14),
- once against diphtheria and tetanus by vaccine Td (at 19),
- twice against poliomyelitis by OPV (at 6 and 11),
- once against measles (at 7),
- once against rubeola (at 13).

Obligatory vaccinations mainly adults from the risk groups against hepatitis B, typhoid fever, diphtheria and tetanus, as well as against rabies are included to the part B of Polish calendar of vaccination.

Recommended vaccinations against influenza, tick born encephalitis, yellow fever and other vaccinations mentioned in International Health Regulation for travellers as well as against hepatitis B for persons not included to the part A and part B are mentioned in the third part of calendar.

Vaccination coverage

Coverage for the most of vaccinations are above 90% and even above 95% (Fig.1). Several months delay of some vaccination in comparison with calendar are observed. The coverage below 90% is observed only in one district (in Poland - 49 districts).

Figure 1

Vaccination coverage on 31 December 1990-1994 for children born in the years 1988-1992 of basic immunization against diphtheria, tetanus, pertussis, poliomyelitis (OPV), measles and primary vaccination against tuberculosis performed soon after birth.

Vaccination against	1990 (born 1988)	1991 (born 1989)	1992 (born 1990)	1993 (born 1991)	1994 (born 1992)
diphtheria	98,4	98,2	98,0	98,2	98,2
tetanus	98,5	98,2	98,0	98,2	98,2
pertussis	97,3	97,7	97,6	97,6	97,6
poliomyelitis (OPV)	98,4	98,1	97,9	98,1	98,2
measles	94,6	93,5	94,9	95,3	95,6
tuberculosis	96,9	94,0	94,5	94,3	93,2

Licensing and registration of vaccines

According to Polish legislation each vaccine used in the country imported as well as produced inside has to be registered. Each lot of produced inside the country and imported vaccine has to be controlled by State Control Laboratory, which is organized at National Institute of Hygiene in Warsaw.

Epidemiological situation of injections diseases preventable by vaccination

Diphtheria and poliomyelitis may be evaluated as eliminated diseases. The last epidemic and last deaths causes by diphtheria was noted in 1973. Four cases of diphtheria were noted eighties years. Thirteen cases of diphtheria were noted in 1992-1994 (Fig.2). All of them were imported from Ukraine, Russia and Byelorussia.

The last poliomyelitis cases caused by wild polio viruses were noted in 1982 and 1984. Yearly between 0 and 3 poliomyelitis cases associating OPV vaccination are registered (Fig.2).

No tetanus cases are observed among children and youths yearly 50-65 cases are registered among older adults, mostly at villages in southeast part of country.

In the 80s up to 1991 - 200-300 pertussis cases were noted in Poland. Increasing of number of cases up to 600-700 was noted in 1992, 1994 (Fig 2) and also in 1995. Observation has to be performed very carefully and the reason of this situation should be explained.

Decreasing of number of measles and hepatitis B cases is observed in last years. Especially programme of vaccination against hepatitis B has been significantly enlarged because of big numbers and big incidence rate noted in the country. Health care workers, students of medical faculties and at nurses' and laboratories' schools, persons with chronic diseases, persons with dose

contact with HBV infected as well as persons before planned surgical operations are vaccinated free of charge. Also vaccination against hepatitis B of all newborns and infants are spread step by step, to cover the whole country in 1997.

Tuberculosis cases in the years 1990-1994 for the first time since the last war increased between 16136 and 16653 (3.1%). New cases of tuberculosis are observed especially among adults.

Figure 2

Number of cases and incidence rate per 100 000
of infectious diseases preventable by immunization

Diseases	No. of cases					Incidence rate per 100 000				
	1990	1991	1992	1993	1994	1990	1991	1992	1993	1994
Diphtheria	-	-	1	10	2	-	-	0.03	0.026	0.01
Tetanus	65	58	52	51	54	0.17	0.15	0.14	0.13	0.14
Pertussis	292	302	590	314	697	0.77	0.79	1.54	0.82	1.81
Poliomyelitis	1	-	2	3	1	0.003	-	0.005	0.008	0.00
Measles	56471	2419	3695	1410	864	148.1	6.3	9.6	3.7	2.24
Hepatitis B	15116	13603	13237	13296	10924	39.7	35.6	34.5	34.6	28.34
Tuberculosis	16136	16496	16551	16828	16653	42.3	43.1	43.1	43.8	43.2
(New cases)										

Production and import of vaccines to Poland

In Fig.3.a and Fig.3.b vaccines produced in Poland according to number of doses and years 1990-1994 and in Fig.4 vaccines imported to Poland are mentioned.

Figure 3.a Vaccine production in Poland

Serum and Vaccine Manufacturer	Product	Pack	Number of doses by year				
			1990	1991	1992	1993	1994
"BIOMED" - Lublin	BCG Vaccine freeze-dried	ampoules of 20 doses	About 1.500.00 doses by year 1990-1994				
	BCG Vaccine freeze-dried	ampoules of 10 doses (from 1994)	-	-	-	-	7.000
"BIOMED" - Warszawa	Tetanus Toxoid Adsorbed	ampoules of 1 ml	183.273	175.026	386.604	324.339	589.353
	Tetanus Toxoid Adsorbed	vials of 10 ml	611.700	372.800	321.960	232.400	350.000
	Typhoid Vaccine	vials of 10 ml	56.050	-	-	-	-
	Typhoid-Tetanus Vaccine	vials of 10 ml	106.000	65.800	60.600	-	113.400
	Cholera Vaccine	vials of 10 ml	117.050	83.250	-	71.850	79.100

Figure 3.b Vaccine production in Poland

Serum and Vaccine Manufacturer	Product	Pack	Number of doses by year				
			1990	1991	1992	1993	1994
"BIOMED" - Krakow	Diphtheria-Tetanus-pertussis Vaccine DPT Adsorbed	ampoules 25x1ml	1.750.000	1.607.500	2.102.575	1.949.400	2.437.175
	Tetanus Toxoid Adsorbed Te	ampoules 5 x 1 ml	175.000	575.000	604.000	470.500	551.215
	Tetanus Toxoid Adsorbed Te	vials of 10 ml	500.100	620.000	574.250	250.970	296.760
	Diphtheria-Tetanus Toxoid, Adsorbed DiTe	vials of 10 ml	380.000	561.000	542.090	521.470	727.220
	Diphtheria Toxoid Adsorbed Di	vials of 10 ml	-	10.000	6.630	5.810	13.820
	Diphtheria-Tetanus Toxoids, Adsorbed Td	ampoules 15 x 5 ml	-	345.000	829.620	1.220.025	1.618.545
	Diphtheria Toxoid Adsorbed for adults "d"	ampoules 5 x 0,5 ml	-	-	-	-	27.500
	Diphtheria Toxoid Adsorbed for adults "d"	ampoules 15 x 0,5 ml	-	-	-	-	184.470
	Typhoid Vaccine Ty	vials of 10 ml	-	-	24 200	27.870	30.940
	Typhoid-Tetanus Vaccine Ty-Te	vials of 10 ml	152.700	30.000	198 900	125.000	172.960

Figure 4
Type and amount of vaccines imported in the years 1990-1994

Vaccines imported to Poland	Number of doses				
	1990	1991	1992	1993	1994
Poliomyelitis	4997600	4100000	4400000	5600000	4500000
Measles	350000	500000	1222000	1250000	1350000
Hepatitis B					
for children	24983	34000	35000	190000	680000
for adults	336950	152000	120000	560000	700000
Influenza	-	50000	100000	79460	74618
Tick born					
encephalitis	4800	1500	154	1254	42652

THE SCHEME OF VACCINATION IN THE CZECH REPUBLIC

by Ing. J. Jansa, Managing Director, SEVAC

B C G VACCINE

manufacturer: BEHRINGWERKE (Germany)

- for primary vaccination in children of the age of 4 days up to 6 weeks

the inspection of the result of vaccination the injection site and nodules - after 3-6 months following the vaccination

Vaccination dosage and administration:

a of dose 0.5 ml. intracutaneously
- revaccination at the age of 11 years in the tuberculin negative subjects with a dose of 0.1 ml intracutaneously

ALDITEPERA SEVAC

manufacturer: SEVAC a.s. (Czech Republic)

- for primary vaccination of the subjects from the age of 12 weeks, 3 doses

dosage and administration:

0-4 (exceptionally 8) weeks - 4 weeks (exceptionally 6 months)

0.5 ml. intramuscularly

boosters:
- at the age of 18-20 months
- at the age of 5 years

with a dose of 0.5 ml intramuscularly

POLIO VACCINE

manufacturer: SmithKline Beecham (Belgium)

- for primary vaccination of subjects from the age of 2-5 months, with 2 doses at interval of 2 months the vaccine contains all 3 types of Sabin strain of the attenuated virus of poliomyelitis

dosage and administration:

1 dose = 2 drops, perorally

boosters:

1 year after the primary vaccination - 2 doses at interval of 2 months
- at the age of 13 years - 1 dose

nation-wide term for the primary vaccination and boosters:
2 weeks in March and 2 weeks in May by a dose = 2 drops, perorally

MOPAVAC SEVAC

manufacturer: SEVAC a.s. (Czech Republic)

- for primary vaccination from the lst day of the age of 15 months

dosage and administration:

a dose 0.7 ml. subcutaneously - primary vaccination

boosters:

- after 6 - 10 months following the primary vaccination (or as close after the term as possible) by a dose of 0.7 ml. subcutaneously

ERVEVAX

manufacturer: SmithKline Beecham (Belgium)

dosage and administration:

dose at the age of 2 years in children of both sexes
dose in girls at the age of 12 years
dose 0-5 ml. subcutaneously

ALTEANA SEVAC

manufacturer: SEVAC a.s. (Czech Republic)

dosage and administration:

- for primary vaccination with 3 doses, according to the same vaccination schema as in the case of ALDITEPERA a dose 0-5 ml, intramuscularly

boosters:

- in children at the age of 14 years by a dose
- in adults with a dose of 0-5 ml always after 10 years, intramuscularly

At present vaccines ALTEANA by IMUNA (Slovakia) and TETAVAX by Pasteur Merieux (France) are also used.

FLUARIX

manufacturer: SmithKline Beecham (Belgium)

dosage and administration:

a dose is applied always in autumn, in children up to the age of 6 years 2 doses at interval of 4 - 6 weeks, the vaccination is repeated each year

a dose 0.5 ml, to children up to 6 years, 0.25 ml intramuscularly or subcutaneously

ENGERIX B

manufacturer: SmithKline Beecham (Belgium)

dosage and administration:

for primary vaccination 3 doses: 0 - 1 - 5 months
a dose 0.5 ml - 1 ml, intramuscularly

boosters:
after 4 - 6 years following the primary vaccination in the workers working under the increased risk of infection - a dose 0.5 ml, intramuscularly

F S M E

manufacturer: IMMUNO A.G. (Austria)

dosage and administration:

for primary vaccination - 3 doses: 1 - 1 to 3 months - 9 to 12 months
a dose 0.5 ml, intramuscularly

boosters:
by a dose of 0.5 ml always after 3 years, intramuscularly

MENINGOCOCCAL POLYSACHARIDE VACCINE A+C

manufacturer: Pasteur-Merieux (France)

dosage and administration:

a dose, subcutaneously or intramuscularly in subjects up to 2 years

TYPE AND AMOUNTS OF VACCINES MANUFACTURED IN CZECH REPUBLIC from 1990 - 1994

Bacterial Vaccines

Name of vaccine	1990 (doses)	1991 (doses)	1992 (doses)	1993 (doses)	1994 (doses)
ALDITEPERA vaccinum diph., pertussis et tetani	1.330.210	1.196.520	1.123.300	1.191.210	1.186.680
ALDITEANA anatoxinum diphtericum et tetanicum	50.970	1.260	21.170	26.320	45.260
ALDIANA anatoxinum diphtericum	1.520	1.560	2.280	4.540	4.870
POLYSTAFANA anatoxinum staphyl.	27.220	29.960	43.860	28.840	26.430
ADNEXBA bacterinum adnexitidicum	47.292	22.776	48.612	48.552	49.140

Viral Vaccines

Name of Vaccine	1990 (doses)	1991 (doses)	1992 (doses)	1993 (doses)	1994 (doses)
MOPAVAC vaccinum morbillorum at parotitis	568.420	371.350	375.740	307.460	290.900
MOVIVAC vaccinum morbillorum	51.330	524.200	581.920	425.700	237.490
PAVIVAC vaccinum parotitidis	-	80.070	2.160	960	2.010

The manufacturers of vaccines used in the regular vaccination scheme

B C G VACCINE Tuberculosis	BEHRINGWERKE, GERMANY
ALDITEPERA SEVAC Diphtheria, tetanus and pertussis	SEVAC a.s., CZECH REPUBLIC
POLIO VACCINE Poliomyelitis	SMITHKLINE BEECHAM, BELGIUM
MOPAVAC SEVAC	SEVAC a.s., CZECH REPUBLIC

Measles and mumps

ERVEVAX Rubella	SMITHKLINE BEECHAM, BELGIUM
ALTEANA SEVAC Tetanus	SEVAC a.s., CZECH REPUBLIC
ALTEANA Tetanus	IMUNA, SLOVAKIA
TETAVAX Tetanus	PASTEUR MERIEUX, FRANCE

VACCINATION BEFORE TRAVELLING ABROAD

For all travellers to the countries with a lower standard of hygiene:

TETANUS
HEPATITIS A
DIPHTHERIA
POLIO
MEASLES

The duration of stay: The standard of hygiene:	short		long
	high	low	no
Hepatitis B	-	-	+
Typhus, India, north, west Africa	+	+	+
Typhus, other countries	-	+	+
Rabies	-	-	(+)
Cholera	-	-	-
Jap.Enc.B	-	+ (endemic countries)	
Meningitis	epidemics, trekkers, pilgrims		
Yellow fever	a WHO list of epidemic countries		
Influenza	if a risk is assumed		

NO VACCINES PRODUCED IN THE CZECH REPUBLIC ARE CURRENTLY EXPORTED ABROAD (EXCEPT TO SLOVAKIA, A PART OF FORMER CZECHOSLOVAKIA)

TREND: a new trivaccine against measles, mumps and rubella will be included into the regular vaccination schema

Extra vaccinations:

Vaccination against influenza

- the groups of health stigmatized persons remain the same

Vaccination against hepatitis

- the groups will not be extended

Vaccination against meningococcal diseases

- the recruits starting the active basic military service are currently vaccinated

Vaccination with haemophilus vaccine

- the vaccination of the risk group of children is under consideration

FOREIGN VACCINES REGISTERED IN THE CZECH REPUBLIC

ACT-HIB	Institut Merieux, France, haemophilus vaccine conjugated on tetanus toxoid
BCG	Behringwerke, Germany, vaccine against tuberculosis
BCG VACCINE SSI	Statens Seruminstitut, Denmark, vaccine against tuberculosis
BIMMUGEN	The Chemo-Sero-Therapeutic Research Institute, Japan, recombinant vaccine against hepatitis B
ENCEPUR	Behringwerke, Germany, vaccine against tickborne encephalitis
ENGERIX-B	SmithKline-RIT S A., U.K., recombinant vaccine against hepatitis B
ERVEVAX	SKB, Belgium, live attenuated vaccine against rubella
FLUSHIELD	Wyeth Laboratories Inc., USA, subunit vaccine against influenza

FSME-IMMUN	**IMMUNO,** Austria, vaccine against tick-borne encephalitides
GEN-H-B-VAX	Merck Sharp Dohme, USA, recombinant vaccine against hepatitis B
H-B-VAX	SmithKline, U.K.vaccine against hepatitis B
CHOLERA	Berna, Switzerland, vaccine against cholera
IMOVAX POLIO	Pasteur Merieux, France, inactivated vaccine against infectious poliomyelitis in children
IMOVAX RABIES	Institut Merieux, France, vaccine against rabies
INFLUSPLIT SSW 93 I.M.	Sachsisches Serumwerk, Germany or
FLUARIX	SmithKline, Belgium, subunit vaccine against influenza
LYOPHILIZED BCG VACCINE	Pasteur Merieux, France, vaccine against tuberculosis
LYSSAVAC N	Serum-und- Impfinstitut Bern, Switzerland, vaccine against rabies
M-M-R II	Merck Sharp Dohme, Switzerland, vaccine against measles, mumps and rubella
ORAL POLIOMYELITIS VACCINE	Pasteur Merieux, France, live vaccine against infectious poliomyelitis in children
PEDVAX HIB lyoph.	Merck Sharp Dohme, Switzerland, vaccine against haemophilus infection
PLUSERIX	SmithKline-RIT S.A., Belgium, vaccine against measles, mumps and rubella
POLIO SABIN ORAL VACCINE	SKB, Belgium, live vaccine against infectious poliomyelitis in children
ROTELN-LEBEND-IMPF-STOFF	Serotherapeutisches Institut, Austria, vaccine against rubella
RUBEATEN	Serum-und- Impfinstitut, Bern, Switzerland, vaccine against rubella
RUDIVAX	Sero Merieux, Austria, vaccine against rubella
SUBINVIRA	IMUNA, Slovakia, subunit vaccine against influenza

TAB VACCINE	Berna, Switzerland, inactivated vaccine against typhoid fever
TRIMOVAX	Sero Merieux, Austria, vaccine against measles, mumps and rubella
VACCINUM TUBERCULOSICUM (BCG)	Medexport V/O, Russia, vaccine against tuberculosis
VAXIGRIP	Institut Merieux, France, subunit vaccine against influenza
YELLOW FEVER	Wellcome, U.K., vaccine against yellow fever

FIGURE 1

The occurrence of some diseases in the Czech Republic

Disease	in the year					
	1989	1990	1991	1992	1993	1994
TETANUS	0	3	1	1	2	3
DIPHTHERIA	0	0	0	0	1	0
PERTUSSIS	5	48	33	10	72	75
POLIOMYELITIS	0	0	0	0	0	0
MEASLES	2	2420	839	416	18	9
MUMPS	21856	3780	1192	1197	1538	1575
RUBELLA	2086	1307	11014	2222	562	1873

FIGURE 2

Regular vaccination scheme in the Czech Republic

Disease	Vaccine	Age of child
TUBERCULOSIS primary vaccination boosters:	BCG	 from the 4th day 11 years tuberculin negative
DIPHTHERIA, TETANUS and PERTUSSIS primary vaccination: 3 doses at intervals of 4-8 weeks boosters:	ALDITEPERA	 12th week 16th-20th week 20th-24th week 18th-20th month 5 years
CHILDREN INFECTIOUS POLIOMYELITIS primary vaccination: boosters:	POLIO-VACCINE	 from the 2.5 months from the 4.5 months from the 15th month from the 17th months 13 years
MEASLES and MUMPS primary vaccination: boosters:	MOPAVAC	 from the 15th months from the 21st months
RUBELLA	ERVEVAX	2 years 12 years - girls
TETANUS	ALTEANA	14 years

BRIEF INFORMATION ON THE ACTIVITIES OF HUMAN CO. LTD., HUNGARY

by Dr. Zsolt Nagy, R&D Director, HUMAN

The vaccines form one of the numerous product groups manufactured by HUMAN*.

Several kinds of vaccines which are applied for immunization to prevent several kinds of illnesses of bacterial origin (e.g. Typhus, Pertussis, Diphtheria and Tetanus) were produced.

In this field, Hungary was among the first in Europe, where in the early fifties the compulsory vaccination of D, P and T was introduced. The necessary vaccines were produced already at that time by HUMAN.

At present HUMAN produce and sell 7 vaccines:

Diphtheria-Pertussis-Tetanus Vaccine (adsorbed)
Diphtheria-Tetanus Vaccine, forte (adsorbed) for pediatric use
Diphtheria-Tetanus Vaccine for adults
Cholera Vaccine (freeze-dried)
Tetanus Toxoid Vaccine (adsorbed)
Typhoid-Tetanus Vaccine (freeze dried)
Typhoid Vaccine (freeze dried)

in 15 presentations.

The clinical trials of the eighth vaccine - the Td for adult - will be completed in the near future and production and sales will start immediately thereafter.

All steps of the vaccine production take place in HUMAN from preparing the culture media necessary for fermentation of the bacteria until packing of the vaccines including QC works for qualification of the vaccines.

The production of the antigens is going on in the new Vaccine (Fermentation) Plant built in 1992. In this plant the anaerobe and aerob sections are able to produce purified antigens sufficient for the production of 200 million doses and the Injection II plant has a capacity to formulate and fill all of these.

Due to the very low vaccination needs in Hungary, the HUMAN CO. LTD. is exporting 98% of its vaccine production, mainly to WHO/UNICEF.

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* HUMAN Serum Production & Medicine Manufacturing Co. Ltd. (2100 Gödöllö. Tánsics M.u. 82, Hungary. Phone (36-280 320 733, Fax (36-28) 320 177

You can find HUMAN CO. LTD. in Gödöllö, 30 kilometres from Budapest.

Besides the vaccines, our main product groups are the following:

Derivatives of blood plasma
Infusions
Diagnostics
Pharmaceutical specialities

The majority of the shares of HUMAN CO. LTD. is owned by Novopharm, Canada.

HUMAN CO. LTD. is stock listed on the Stock Exchange.

Gödöllö, June 1995

VACCINATION CALENDAR IN HUNGARY

(Compulsory vaccinations)

AGE OF ELIGIBLES	VACCINES ADMINISTERED	APPLICATION
0-42 days	BCG	Continuous
3 months	DPT I/a+eIPV	Continuous
4 months	DPT I/b+TOPV	Continuous
5 months	DPT I/c+TOPV	Continuous
15 months	MMR+TOPV	Continuous
36 months	DPT II+TOPV	Continuous
6- 7 years	DPT III+TOPV	Campaigns at school entry
10-11 years	BCG revaccination for those negative to PPD 5 TU	Campaigns
11 years	DT	Campaigns in September in schools
11 years	Measles	Campaigns in October in schools
16-18 years	BCG revaccination (as above)	Campaigns
18-30 years	BCG revaccination (as above)	Campaigns for those living in communities

HUNGARY: COMPULSORY IMMUNIZATIONS OF PERSONS EXPOSED TO INFECTIONS

IMMUNIZATION WITH	ELIGIBLE PERSONS
TYPHOID VACCINE (Ty, TyT, Vivotif)[x]	Contacts of patients with typhoid fever Contacts of S. typhi carriers Health care workers
DIPHTHERIA VACCINE (DPT, DT)[x]	Contacts of patients with diphtheria
PERTUSSIS VACCINE (DPT I or II)[x]	<6 years old contacts of patients with pertussis
TETANUS VACCINE and/or ANTITOXIN [x]	Patients with injuries
RABIES VACCINE	Persons possibly exposed to rabies infection
MEASLES VACCINE or GAMMA GLOBULIN [x]	Contacts of patients with measles
GAMMA GLOBULIN	Contacts of patients with hepatitis A
HEPATITIS B VACCINE + IMMUNOGLOBULIN	Newborns of HBsAg positive mothers

[x] Depending on actual circumstances

HUNGARY: IMMUNIZATIONS ON VOLUNTARY BASIS

IMMUNIZATION WITH	OFFERED TO	REMARKS
TETANUS VACCINE (DT)	Persons borne before 1941	Free of charge
	Persons traveling to countries with epidemics	Free of charge
HEPATITIS B VACCINE	Health care workers	Free of charge
	Persons at risk	Subsidized ˣ
INFLUENZA VACCINE	Elderly persons	Free of charge
	Persons with chronic diseases	Free of charge
	Health care workers	Free of charge
	Anybody	Subsidized ˣ
TICK-BORNE ENCEPHALITIS VACCINE	Anybody	Subsidized ˣ
HAEMOPHILUS INFLUENZA B VACCINE	Children between 2 and 60 months of age	Subsidized ˣ
PNEUMOCOCCUS VACCINE	Patients > 2 years of age with chronic diseases	Subsidized ˣ
HEPATITIS B IMMUNOGLOBULIN	Health care workers exposed to hepatitis B	Free of charge

ˣ

40 % is paid by the Health Insurance

ANNEXES

Annex I

UNIDO ONUDI

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
ORGANISATION DES NATIONS UNIES POUR LE DEVELOPPEMENT INDUSTRIEL

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7 April 1995

AIDE-MEMOIRE

Regional Meeting on Industrial Support for Pilot Regional Programme on Biotechnological Vaccines in Central and Eastern Europe

Organized under the auspices of the
United Nations Industrial Development Organization

to be held at
UNIDO Headquarters, Vienna, Austria
7-8 June 1995

AIDE-MEMOIRE

1. Background

As a result of the collapse of USSR, the structures for supply, marketing and distribution of healthcare products are in a state of general confusion in the former Soviet Union due to the different decrees and regulations being issued whilst, in the mean time, various organizations carrying out their own policies. In broad terms, the old structures remain in place in all the newly emerged independent republics and continue to be used as procurement, supply and distribution channels for government purchases particularly for hospitals. In parallel, however, semi-commercial organizations associated with government structures have been created both within the republics and overseas to act as supply channels and profit centers. Local commercial companies are also being formed to act as distributors and may form the basis for future wholesale organizations. To date, this has not in any way improved the distribution efficiency and availability remains at a level comparable to some developing or even least developed countries.

Due to the near collapse of the healthcare delivery system, major epidemics threaten the Eastern European region. In the early 1990s a major epidemic of diphtheria emerged in the European part of the Russian Federation and in Ukraine due to non-availability of vaccines for the immunization programmes. The situation has become worse since in many instances the medical personnel could not diagnose the disease, the incidence of which was
practically negligible in the last 50 years. In the last two years more than 100,000 diphtheria cases have been notified, that is the magnitude of the epidemic has become comparable to that of the era before the immunization against diphtheria started in Europe (in 1938 in France and in 1939 in Hungary).

In addition to the diphtheria epidemic, there is a very high incidence of hepatitis A and B infections in the region. The tuberculosis incidence is steadily increasing and cholera is also re-appearing and reaching at a stage what can be defined as epidemic situation in Romania and Ukraine. Recently there have been several reports of different sources which were later reconfirmed by virological laboratories that in Moldova and Ukraine not only the surface waters but the municipal water lines of certain cities are contaminated with polio virus. In Romania the vaccine-related cases of poliomyelitis is unacceptably high (8 cases reported in 1993).

It should be noted that in USSR the quality of vaccines included in the Expanded Programme on Immunization (EPI) of WHO, namely diphtheria-pertussis-tetanus (DPT), poliomyelitis, measles and BCG against tuberculosis in many cases did not meet the international requirements. The quality of the vaccine manufactured in the former Soviet Union did not often meet the requirements of WHO either.

It should also be noted that the manufacturing technologies used for the production of the above vaccines did not comply with the Good Manufacturing Practices (GMP) and their purity did not in all cases meet the international requirements, e.g. residual bovine serum content in the viral vaccines, residual chloroform content in the bulk diphtheria and tetanus toxoid, etc.

To improve the situation and start to rebuild and strengthen a new system of delivery, the Fondation Marcel Merieux with the Fondation Karol DaVilla, a Romanian and the Association Bioassistance, a French/Romanian foundation has jointly started to organize and deliver training courses to medical personnel in vaccinology in Romania. The Centers of Disease Control of the United States and the Rotary International have recently joined the efforts. Since the epidemics do not respect frontiers, the main reason of these courses is to build capacity, to create awareness and preparedness in case of an epidemic and to obtain information on the modern vaccines in the market, which has, if at all, been included very peripherally in the syllabus of medical schools. This very basic knowledge of modern vaccinology is necessary to fully utilize the advantages of the biotechnological vaccines available in today's market compared to those which were traditionally prepared by bench-scale technologies on a trial and error basis.

The support to be provided by UNIDO should therefore address four main industrial issues of this very complex interdisciplinary sub-sector of the pharmaceutical industry, e.g.

1) Issue of quality operations

The issue would cover areas such as the introduction of Quality Assurance (QA) and Good Manufacturing Practices (GMP) in the manufacturing systems, and Good Laboratory Practices (GLP) in the quality control systems; the state of the art in control and administration of vaccines (cold chain); and introduction of safe vaccines with low incidence of adverse reactions;

2) Issue of vaccine production

This issue covers modern, state of the art vaccine manufacture, with specific reference to the feasibility to establish financially sustainable manufacturing facilities in Central

and Eastern Europe; new trends in vaccine manufacture; and cleaner technology in vaccine manufacture;

3) Issue of diagnostics production

Covering the surveillance of the epidemiological situation by modern biotechnological diagnostics; monitoring of the efficacy and the effectiveness of the vaccines by modern biotechnological diagnostics; and production of in vitro or in vivo diagnostics;

4) Issue of vaccine marketing

Covering the availability and distribution of vaccines, with specific reference to domestic and/or regional production; vaccine market, with specific reference to the size of the market which could sustain a financially viable vaccine manufacture; and financing of immunization programmes.

The main issue is how to finance efficient immunization programmes. The question to be answered is what should be preferred: (i) to purchase vaccines from a reliable source of consistent quality or (ii) to promote local/regional manufacture? If local manufacture is the decision of choice, would projects of greenfield development be preferred or should the existing facilities be upgraded? The subject project will make an attempt to address the technological and financial issues of an industrial support for a pilot regional programme on biotechnological vaccines.

The main conclusions and recommendations of the Working Group on "Biotechnology and World Health: Vaccines and Other Medical Products Produced by Genetic Engineering: Review of Risks and Benefits" held in Geneva, 6 - 8 November 1994 recognized that the most pressing global need in the immediate future is the provision of safe and effective vaccines for the prevention of infectious disease. Therefore, the Group recommended that enhanced, timely equity of access to vaccines and therapies on a worldwide basis be accepted as a key principle.

By organizing a regional meeting to be held in UNIDO, Vienna, 7-8 June 1995 on industrial support, at national and regional level, for new biotechnological vaccines of high safety, quality and efficacy, UNIDO is ready to launch a pilot regional programme (i) to assess and review of existing industry, (ii) to evaluate the technical and economic feasibility of technology transfer and investment and (iii) to provide advice and guidance to restructure and/or privatize the sub-sector. By also inviting other interested parties, e.g. UN organizations, financial institutions and multinational and bilateral donor agencies, the subject pilot programme will carry out its multiplying effect; the XP funding as "seed money" will most probably raise further funds for the implementation of a full scale programme in the region.

The problems to be addressed within this regional programme would be both industrial and policy issues by nature. Industrial aspects would cover the insufficient production of vaccines, the low quality of vaccines, inadequate information on modern vaccinology, etc. Besides those, there are a number of policy issues such as financing of immunization programmes, national versus regional production of vaccines, upgrading versus new production facilities, etc. which should thoroughly be considered.

2. Objectives of the Regional Meeting

To raise awareness for the priority issues of the industrial support for a pilot regional immunization programme on biotechnological vaccines at the decision makers' level.

3. Programme of the Regional Meeting

The programme of the Meeting will be as follows:

Morning session of the 1st day:

Opening Session (Opening addresses given by UNIDO, Fondation Marcel Merieux and the representatives of the participating countries)

Presentation of the country specific papers on Romania, Moldova, Ukraine and the Russian Federation

Afternoon session of the first day:

Presentation of the issue papers prepared by the consultants on the industrial support for a pilot regional programme on biotechnological vaccines

Discussion on the presentations

Morning session of the second day:

Discussion on the issue papers

Presentation of the conclusions and recommendations as well as plan of action of the Meeting

Afternoon session of the second day:

Discussion of the conclusions and recommendations as well as plan of action of the Meeting

Endorsement of the conclusions and recommendations as well as the plan of action of the Meeting

4. Expected Outcome of the Regional Meeting

Specific recommendations and plan of action on industrial support for a pilot regional programme on biotechnological vaccines in the Central and East European countries in order to harmonize their healthcare development strategies and to develop their technological capabilities compatible with those of the European Union keeping in mind that the epidemics do not respect frontiers.

5. Date and Venue

The Meeting will take place at UNIDO Headquarters, Vienna, Austria from 7 to 8 June 1995.

6. Participants

The Governments of Belorus, Bulgaria, the Czech Republic, Hungary, Moldova, Poland, Romania, the Russian Federation, Slovakia and Ukraine will be invited to nominate two (2) participants to represent their countries at the Expert Group Meeting.

The participants should be selected from the highest management and decision making level of the national immunization programmes and vaccine licensing/registration authorities, e.g. Director of Preventive Medicine Division of the Ministry of Health, Chief Medical Officer/Surgeon General of the country, Director of the National Quality Control for Vaccines, Director of national vaccine manufacturer or Professor of Preventive Medicine of a Medical School, etc. The Governments should give consideration to professional qualifications, level of experience in this particular subject when selecting participants representing their countries.

The Governments should communicate to UNIDO via the local UNDP office the names of the participants nominated for the Meeting with their titles and positions, contact addresses, phone and fax numbers. The closing date for receipt of the nominations is 5 May 1995.

The participants of each country are expected to jointly prepare a country paper on the national vaccination programme with vaccination coverage, licensing and registration of vaccines in the country, immunization schedule, current epidemiological data on infectious diseases preventable by immunization (from 1990 to 1994), local vaccine manufacture (vaccine manufacturer, type and amounts of vaccines manufactured from 1990 to 1994), vaccine export and import data (type and amounts of vaccines exported and imported from 1990 to 1994) and on any information and/or trend relevant to the establishment of a regional immunization programme. For reproduction purposes two (2) copies of the country paper must be sent in advance and not later than 26 May 1995.

The representatives of local/regional office of WHO as well as the Children Vaccine Initiative (CVI) will be invited as observers. Representatives of financial institutions (World Bank, EBRD) and multinational donor organizations (Rotary International) will also be invited.

7. Language Requirements

Since the programme and the discussions of the Regional Meeting will be conducted in English, it is a prerequisite that the participants must have a good working knowledge of the English language. Inspite of this and in order to facilitate the meeting, simultaneous interpretation from English to Russian will be provided.

8. Financial and Administrative Arrangements for the Regional 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, bus tickets, or mileage between home country and Vienna, Austria.

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

Hotel reservations in Vienna, Austria 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 Regional 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 Vienna, Austria and back.

Before leaving their home countries, they are urged to contact the nearest Austrian 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 Vienna not later than Tuesday, 6 June 1995, and to depart on Friday, 9 June 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 UNIDO.

12. Enquiries and Correspondence

All enquiries and correspondence should be addressed to:

Mr. M. A. Youssef, Head

attention: Mr. Zoltán Csizér

Chemical Industries Branch
Industrial Sectors and Environment Division
UNIDO
Vienna International Centre
P. O. Box 300
A-1400 Vienna, Austria

Telex: 135612 Fax: 43-1-230-9615 Phone: 43-1-21131-3948

directly or through the office of the Resident Representative, United Nations Development Programme (UNDP) in the participant's home country.

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Regional Meeting on industrial support for pilot regional programme on biotechnological vaccines
7-8 June 1995, UNIDO Hqs., Vienna

AGENDA

Tuesday, 6 June 1995

Arrival of all participants in Vienna
Hotel accommodation to be fixed
Dinner organized at Hotel Reichshof

Wednesday, 7 June 1995

09:00 - 09:15 Introduction
DR. J. BOECKMANN
Translation English/Russian

09:15 - 10:00 ***DR. O. RAYNAUD***
Clinical experience of the DTP/IPV combination
New trends and future aspects of combos

10:00 - 10:15 Discussions

10:15 - 11:00 ***PROF. I. DÖMÖK***
The OPV/IPV mixed schedule in Hungary
Interest of such a programme - Clinical aspects

11:00 - 11:15 Discussions

11:15 - 11:30 Coffee Break

11:30 - 12.15 ***DR. B. MONTAGNON***
* IPV/OPV - An example of an Industrial Achievement
* Choice from primary monkey to Vero Cell Technology
* Registration status of IPV
* State of the art of quality control of vaccines

12:15 - 12:30 Discussions
12:30 - 14:00 Lunch

14:00 - 15:00 ***PROF. S. DITTMAN***
Diphtheria epidemics in Central and Eastern Europe

15:00 - 15:30 ***DR. W. MAURER***
The Austrian Experience from the perspective of National Quality Control authority

15:30 - 16:15 ***MR. C. BOSTVIRONNOIS***
State of the art vaccine production
* The Private Industry point of view
* Industrial Aspects
* Economical Feasibility
* Alternatives to industrial implementation

16:15 - 16:30 Presentation by ***DR. M. FLUGGE***
LINDE-KCA-DRESDEN

16:30 - 17:00 Discussions

17:00 - 18:30 ***DR. NIK CUCAKOVICH***
Status of current vaccine production in Central and Eastern Europe

18:30 - 19:00 Discussions

19:00 End of session
Dinner organized outside the city

Thursday, 8 June 1995

9:00 - 12:30 Conclusions and recommendations
Action programme for industrial support for pilot regional programme on biological vaccines.
Round table discussions

Departure of participants

Annex 2

Third Consultation on the
Pharmaceutical Industry

Madrid, Spain, 5-9 Ocotober 1987

THE CHALLENGE OF BIOLOGICAL TECHNOLOGY TRANSFER TO DEVELOPING COUNTRIES

Background Paper

Prepared by

the UNIDO Secretariat

CONTENTS

PREFACE

This paper deals with the transfer to developing countries of technology related to the manufacture of biological products.

Since the Second Consultation on the Pharmaceutical Industry in November 1983 and the creation of UNIDO's Advisory Panel on Preventive Medicine in December 1983 much progress has been achieved in the understanding of the various aspects of biological technology transfer. In March 1986, a Model Programme for the Production of Vaccines in Developing Countries was finalized and adopted by the Advisory Panel on Preventive Medicine. The present background document serves as an introductory paper to the Model Programme, highlighting the opportunities and risks presented by the transfer of technology in the field of conventional vaccines. It raises three key issues in this area: the availability of the technology, the feasibility of its transfer and the advisability of actually proceeding with such technology transfer.

INTRODUCTION

Recognizing that immunization programmes are an essential component of primary health care, especially in developing countries, the Second Consultation on the Pharmaceutical Industry, held in Budapest, Hungary (21-25 November 1983) agreed on a number of points of major importance concerning biological technology transfer (1):

1) The transfer of biological technology should be offered in stages:

- The first stage must be the creation and the running of a validated national quality control facility and a quality assurance programme;

- The second stage could be the transfer of technology of vaccine packaging, blending and filling. A precondition for that type of technology transfer is often the purchase of bulk vaccine from the supplier of the relevant technology. As a preliminary stage, the setting up of an infusion and reconstituting fluids plant could be crucial in order to assure the transfer of technology for the water treatment process and sterile operation;

- The third stage would be a step by step approach assimilating technologies from packaging and filling to actual manufacture and from the production of conventional vaccines to modern ones. Joint ventures were deemed advisable only if they covered industrialized production technologies. It was further postulated by the Second Consultation that production facilities could be developed at subregional or regional levels to achieve economic feasibility.

2) The vaccine produced must comply with WHO specifications.

It was recommended by the Second Consultation that UNIDO should take a series of actions including:

- Adopt a step-by-step approach for establishing a control and production capability of vaccines in two ways:
  - . From packaging and filling towards actual manufacture;
  - . From production of conventional vaccines towards modern ones.
- Implement long term continuous technical assistance and support programmes for effective assimilation of technology and control procedures to be transferred.

To this end, shortly after the Second Consultation, UNIDO created an Advisory Panel on Preventive Medicine to make recommendations on the technical and economic aspects of the establishment of the Organization's programme of Industrial Production of Biologicals (IPB). It is the Panel's current role to oversee and give advice on the implementation activities of the IPB programme.

The Advisory Panel has met four times since its inception: in Vienna, Austria (27-28 February 1984); Bogota, Colombia (22-23 November 1984); Bilthoven, The Netherlands (6-7 June 1985); and Ottawa, Canada (11-12 March 1986).

The main conclusions and recommendations of the Advisory Panel are embodied in the chapters that follow, in so far as they relate to the transfer of technology as described in the Model Programme for the Production of Vaccines in Developing Countries (2).

PRESENT STATUS OF THE BIOLOGICAL INDUSTRY

There are, worldwide, some 20 producers of polio vaccine and measles vaccine, 31 manufacturers of BCG, over forty laboratories that make diphtheria - pertussis - tetanus vaccine and nearly 70 that produce tetanus toxoid (3).

However, only a dozen or so biological manufacturers compete regularly in the UNICEF and PAHO tenders that provide the bulk of vaccines for WHO's Expanded Programme on Immunization (EPI). These companies are all located in Western Europe or in North America (4). As a reminder, the objective of the EPI is to provide immunization for every child in the world against diphtheria, whooping cough, tetanus, measles, poliomyelitis and tuberculosis, by the year 1990.

It was feared, a few years ago, that there would be a decreased interest in manufacturing conventional vaccines in the industrialized countries and hence a shortage of supply for the vaccination programmes of developing nations (5). This fear has not materialized. While it is true that in the United States, the number of biological manufacturers declined from 11 in 1966 to only 5 in 1981, this phenomenon did not occur in other parts of the industrialized world. The very serious problem of

product liability turned out to be a greater disincentive for American producers than diminishing local demand or low profit margins on sales of vaccines in the international market.

To quote from UNIDO Sectoral Studies Series No. 4: "Nevertheless, the supply situation is satisfactory and there is keen price competition amongst the bidders of international tenders" (6).

Manufacturers in the industrialized countries have repeatedly stated that, provided certain conditions are met, there should be no major difficulty in continuing to supply high quality products, in the required quantities, and at competitive prices, for the vaccination campaigns of developing countries organized under the EPI. The conditions cited include: realistic quantity forecasts by the international procurement agencies (UNICEF and PAHO), reasonable lead times and the adoption of a multi-supplier sourcing policy for each of the EPI vaccines.

Most of these basic conditions currently prevail and there should therefore be no shortfall in the foreseeable future.

This does not mean, however, that the option of local manufacture of biological products should be disregarded by developing nations. As a first step, each country must examine its own supply and demand situation and study the benefits and risks involved. These considerations are covered in the following chapters.

THE SUPPLY SITUATION IN DEVELOPING COUNTRIES

The pros and cons of local manufacture, following the step by step strategy recommended by UNIDO's Second Consultation, should be evaluated against the current supply situation for the EPI vaccines and future expectations.

The goal of relative self-reliance so far as conventional vaccines are concerned is a laudable one. However, existing procurement possibilities, economies of scale and public health considerations should not be overlooked.

Many developing countries are currently receiving their EPI vaccines free of charge through donor agencies. Others, who are supplied through the PAHO Revolving Fund or by similar arrangements, purchase the products they need at international tender prices calculated on the basis of worldwide requirements. Countries without the required infrastructure and trained manpower contemplating the production of EPI vaccines for their own needs alone, must accept that local manufacture is, or is likely to be, the least economical solution of the three. One of the possible long term effects of donation programmes is the "free of charge" concept of vaccine supply which undermines, from a financial standpoint, future policies of vaccine purchase or local production.

The subject of vaccine donation, within the scope of the Expanded Programme on Immunization of WHO, was touched upon at the Fourth Meeting of UNIDO's Advisory Panel on Preventive Medicine. The Panel remarked that the donation of vaccines may be considered by the responsible authorities of many developing countries as a permanent solution for supply to their national immunization programmes. If free donation is regarded as a final

long term solution for the supply of vaccines, local production will never be feasible for the recipient countries since the cost of donation is zero. The UNIDO Secretariat considered that it would be useful if UNICEF could provide, on a yearly basis, a statement on its donation programme with regard to its size and duration, the conditions required for participating as recipient in the programme, and the market situation for each EPI vaccine with particular reference to the adequation of offer and demand. Such a statement would be of great importance, not only for the authorities of developing countries responsible for planning and implementing national immunization programmes, but also for the biological industry currently supplying the EPI campaigns. This information could also play a key role in UNIDO's IPB programme.

So far as economies of scale are concerned, countries wishing to engage in local production of vaccines, through technology transfer, should first consider the potential of their own national territory with regard to its population, birthrate, etc. Then, provided all the necessary competitive criteria are met, and if contractual arrangements permit, these countries may look at the possibilities offered by the international export or tender market.

It was suggested, at the Second Consultation on the Pharmaceutical Industry, that production facilities could be developed at subregional or regional levels to achieve economic feasibility. Although it is reasonable to expect that larger production batches would lead to a lower cost per dose, special requirements by neighbouring countries might well negate such savings. Above all, political considerations, nationalistic attitudes and unpredictable payment situations could constitute insuperable obstacles to such regional initiatives. There are, it is true, a few instances of regional bulk procurement for essential medicines and one or two examples of successful regional manufacture of pharmaceuticals. In the vaccine field, PAHO's Revolving Fund is a good example of regional procurement for the EPI. So far as regional manufacture in the developing world is concerned, yellow fever vaccine produced in Senegal is used in the vaccination campaigns for several West African countries.

The main public health concerns relating to pharmaceuticals in general, and to vaccines in particular, are quality, safety and efficacy, whether these products are received free of charge, purchased or locally produced. This implies, of course, the existence of a distribution system and a cold chain capable of ensuring that a vaccine which is safe, potent and of high quality at the end of the production cycle, or upon reception in the country, presents the same indispensable characteristics at the time it is ready to be administered.

The quality control aspects of vaccine production, already identified by the Second Consultation, were highlighted in the Advisory Panel's discussion on the IPB Programme at its First Meeting, held in Vienna in February 1984. It was noted that quality assurance was important in the production of safe and effective biologicals, and also that the quality control of EPI vaccines in particular is of major concern to the World Health Organization. All vaccines used in the Expanded Programme must be safe, effective and stable, and in compliance with WHO's Requirements for Biological Substances. The latter condition is stipulated in WHO's Model List of Essential Drugs, in the section devoted to immunologicals (7).

In its successive meetings and deliberations, UNIDO's Advisory Panel on Preventive Medicine has stressed the importance, from a public health standpoint, of establishing an independent national quality control authority and making sure that this authority is linked up with WHO's network of collaborating quality control centres.

Once it is envisaged to package, fill and ultimately produce vaccines locally, added requirements are the implementation of quality assurance programmes, and the application of Good Manufacturing Practices (GMP). The most recent reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (8) and the WHO Expert Committee on Biological Standardization (9) are useful guides to developing countries in this respect.

CURRENT AND FUTURE DEMAND FOR EPI VACCINES

A few years ago, it was estimated that not more than 20% of the 90 million children born in the developing world each year were fully immunized against the six infectious childhood diseases targeted by the Expanded Programme on Immunization. For lack of protection, some 5 million children under the age of five reportedly died each year and another 5 million were handicapped for life.

The latest Global Status Report on the EPI, however, indicates that all WHO regions, with the exception of Africa, show an immunization coverage of over 50% for at least one of the EPI vaccines (10). The level of coverage for the African region is currently about 20%. The Regional Committee, considering that there was reasonable hope of providing immunization for at least 75% of African children by 1990, proclaimed 1986 "Africa Immunization Year". Appropriately, at its second meeting, in November 1984, UNIDO's Advisory Panel on Preventive Medicine focused on the situation in Africa and made a series of recommendations. The Panel recommended that UNIDO should respond positively to requests for rehabilitation or expansion of existing production facilities in Africa, and that a more comprehensive approach to the production of biologicals in Africa should be taken. In this respect, the Panel discussed a working paper on the Programme for Production of Vaccines in Africa, which stresses, amongst other things, the need for political support involving regional and subregional organizations (11).

Although the overall immunization situation is improving, a lot remains to be done. Almost 3.5 million deaths are attributable, annually, to the six EPI diseases. There are still over 250,000 cases of paralytic poliomyelitis each year. At its eighth meeting, in November 1985, the EPI Global Advisory Group formulated a series of recommendations for the global EPI programme, with a view to achieving greater immunization coverage and setting targets for reductions in morbidity and mortality (12). If these objectives are to be reached, it goes without saying that greater quantities of vaccine will be required. The problem is how to gauge future demand and determine how much vaccine will be needed between now and the end of the century.

The present and projected demand for immunizing agents included in the EPI were thoroughly analyzed in UNIDO's Sectoral Studies Series No. 4 (6). A comparison of 1980 consumption estimates with 1990 and the year 2000 demand projections for EPI vaccines showed a doubling of worldwide requirements by the end of the century, with the developing regions requiring approximately two and a half times the 1980 uptake by the year 2000.

These estimates may well be on the low side, especially in view of PAHO's goal for 1990, i.e. the eradication of poliomyelitis in the Americas, and the hopes, in Europe, of eliminating polio, respiratory diphtheria and neonatal tetanus before the end of the century.

Current trends in UNICEF and PAHO's purchasing patterns do, in fact, reflect the acceleration of vaccination campaigns and the demand for increasing quantities of EPI vaccines.

In view of the above, countries with a large population, a high birthrate and a firm commitment to the Expanded Programme on Immunization may wish to study the option of local production of EPI vaccines. It is with these countries in mind that the Model Programme for the Production of Vaccines was developed.

THE MODEL PROGRAMME FOR THE PRODUCTION OF VACCINES IN DEVELOPING COUNTRIES

At its very first meeting, in February 1984, the Advisory Panel on Preventive Medicine recommended that UNIDO, with the advice of the members of the Panel, should start the preparation of a master plan for projects for industrial production of vaccines in developing countries which should include technical and economic details for the implementation of such projects, at different stages.

At its second meeting, ten months later, the Panel discussed a working paper presented by the Director-General of the Rijksinstituut voor Volksgezondheid en Milieuhygiene (National Institute of Public Health and Environmental Hygiene, The Netherlands) further referred to as the RIVM. The working paper described a model programme for the preparation of BCG vaccine, pertussis vaccine, purified diphtheria toxoid, purified tetanus toxoid; the controls required for these vaccines and also those for cell culture rabies vaccine, measles vaccine, inactivated poliomyelitis vaccine; with additional notes on buildings and services, staff members and qualifications, equipment, maintenance and costs. The Panel accepted this first draft and recommended that additional sections be prepared with more detailed reference to training of personnel, animal accommodation, quality control, chemical engineering, local constraints, management, maintenance, priority criteria and cost effectiveness.

Subsequent drafts of the RIVM document were studied and reviewed by Panel members and further items were either added or expanded. These include the addition of standard-cost data relating to the vaccines produced by the unit-processing method with an indication of the cost per immunized child and the importance of on site training for production and control personnel.

The document, in its final form which includes a short Explanatory Memorandum, was adopted by the Advisory Panel in March 1986.

The Model Programme is intended primarily for use by government officials and directors of institutes who are responsible for structuring and implementing national immunization programmes. It may also be of general guidance to the professional staff members in charge of vaccine production. It may, in addition, serve as a basis for comparing different technologies applied in other laboratories for the manufacture and quality control of conventional vaccines.

The Model Programme for the Production of Vaccines in Developing Countries constitutes a summary of the RIVM's experience in the production and control of a series of conventional bacterial and viral vaccines currently used in national immunization programmes. The production of oral poliomyelitis vaccine is not included in the document. The Model Programme therefore offers only one option among a number of technologies: the unit-processing principle as proposed by van Hemert.

The Model Programme comprises 5 sections covering:

1) Vaccine Production Technology;
2) Quality Control of Vaccines;
3) Economic Aspects of Vaccine Production and Control;
4) Lay-out of Technical Facilities for Production of Vaccines;
5) Staff Training in Production and Control.

The basic information contained in the Model is being completed by a series of UNIDO technical documents covering the production and quality control of BCG vaccine produced on surface culture; the production and quality control of oral poliomyelitis vaccine; a paper on technology transfer for biological production and a directory of potential partners in transfer of technology for biological production.

CONDITIONS FOR SUCCESSFUL TECHNOLOGY TRANSFER

Because of the complexities of biological production itself and the difficulties of successfully transferring the relevant technology, the list of prerequisites and conditions is necessarily longer than it would be for the transfer of less sophisticated or non health-related manufacturing procedures.

Some of the basic and preliminary conditions have already been mentioned: a long term commitment to the EPI programme, the acceptance of a stepwise progression in the production process starting with quality control of imported finished goods, and a potential market large enough to justify the investment.

The specific characteristics of biological manufacture were fully recognized by the Second Consultation on the Pharmaceutical Industry, in November 1983. The Consultation noted that the production of conventional vaccines differs significantly from that of other pharmaceutical products. For example:

- The problems of storage and distribution are crucial and a continuous cold chain is essential;

- The products are rarely subject to patent protection, and established production facilities have the capacity to ensure an adequate supply to the developing world;

- In an immunization programme, the cost of the product is a minor item in relation to the overall cost of vaccination, and the success of such a programme is entirely dependent on an adequate infrastructure for distribution and administration.

The Explanatory Memorandum to the Model Programme mentions a number of conditions which must be met before, during, and after the actual transfer of the technology. To start with, a preliminary analysis of the local industrial infrastructure and of prevailing economic conditions must be made. Appropriate scientific and technological educational programmes must be devised. A good organizational and managerial infrastructure with the optimal use of human resources is essential for the success of such an undertaking. Additional aspects include the guarantee that the supplier himself shall install the purchased equipment and ensure that all machinery performs according to specifications. Maintenance and training of maintenance personnel are key considerations. As mentioned earlier, the complete understanding of the concept of quality assurance is of vital importance.

A continuing support services plan should be envisaged at the termination of the execution stage of the project. Such a plan may comprise, on a yearly or two-yearly basis: a GMP audit, spare part procurement, performance of parallel quality control tests, training of new senior staff, raw material testing and implementation of new WHO requirements.

So far as WHO requirements are concerned, the recipient in the developing country and the supplier of technology must make sure that the buildings foreseen for production and control activities, the vaccine seed strains (bacterial or viral), the substrates and the manufacturing processes involved, all meet WHO requirements or specifications.

Finally, two important aspects which should not be overlooked: the political and financial commitment to such an investment project and the marketability of the products manufactured locally.

Political will must be demonstrated from start to finish: from the moment the project proposal is drawn up and presented for approval, through the execution of the project plan, to the time when the quality of successive batches of vaccine is consistently verified by independent audit.

So far as financing is concerned, governments must accept that these are long term projects for which long term funding arrangements have to be sought. A ten-year financial commitment is not exaggerated. UNIDO's Advisory Panel has recommended the establishment of an IPB Fund, suggesting that contributions should come from UNIDO, through its industrial funding, UNDP, World Bank, interested governments and UNICEF which is currently the major supplier of EPI vaccines to the developing countries.

It is commonly believed that the manufacture of goods in developing nations is an economically viable proposition. This does not seem to be the case for vaccines. Although manpower and building materials may be available locally at low cost, up to 80% of the necessary equipment, raw materials and components will have to be purchased abroad, with hard currency. Vials, stoppers and leucosis-free eggs are cases in point.

This brings us to the aspect of marketability of the products. If marketing is defined, concisely, as "achieving consumer satisfaction", this means that the locally manufactured products must be competitive.

They should be of comparable quality, safety and efficacy to the imported products with which doctors, other health care personnel, and patients have become familiar over the years. Although some concessions may be made, for example so far as packaging esthetics are concerned, no compromise on supply and delivery requirements should be tolerated. The locally-made products must always be available in the required quantities, at the right time, and in good condition if national immunization campaigns are to be conducted efficiently and effectively.

- It must be highlighted that the costs of vaccines are only one fifth of those of the immunization, and the lives of some 800,000 infants are only saved while approximately 3.5 million children die every year in developing countries because of the six EPI diseases, the above mentioned competitiveness should therefore not necessarily mean comparable vaccine prices at the international and domestic markets.

UNIDO PROGRAMME ON INDUSTRIAL PRODUCTION OF BIOLOGICALS

The Model Programme is intended primarily for use by Government officials and directors of institutes who are responsible for structuring and implementing national immunization programmes including domestic production of vaccines. There are approximately 50 developing countries whose EPI vaccine requirements are being provided totally from outside sources, and this situation seems unlikely to change during this decade. In many countries of the Third World only one EPI vaccine is produced, and no developing country except China and Yugoslavia is self-sufficient in vaccines. Although UNICEF, PAHO and other donor agencies are generally fulfilling current vaccine requirements, acceleration of coverage and the recent addition of poliomyelitis and measles vaccines to the immunication schedules of several large countries of Southeast Asia may threaten to exhaust these outside financial resources. As a consequence of the growing demand of measles vaccine, the lead time of procurement and the cost of measles vaccine have recently increased.

The commitment of Rotary International, the contribution of Canadian and Italian Governments, the grant of the Inter-American Development Bank to UNICEF and PAHO indicate that the resource requirements of the universal child immunization can be met. However, it also shows that without the above considerable donations many developing countries would be constrained in their efforts to reduce childhood morbidity and mortality by shortage of vaccines.

The free donation of EPI vaccines cannot be the final long term solution for the supply of vaccines, and the importation of them is regarded as the first step forward to self-reliance. Developing countries contemplating the production of EPI vaccines, must look into the techno-economic feasibility and commercial profitability but should not neglect the social and political benefit of this venture. The social and political considerations of domestic vaccine production in several cases outweigh the economic ones. The contributions of domestic production of vaccines to a number of inter-related, social and economic objectives of the developing countries are among others as follows: reduction of dependance on supplies requiring foreign currency, more efficient use of national resources, increase of domestic stocks of technical know-how and human capital in many disciplines used in development of biologicals, creation of employment, and creation of infrastructure and logistic, etc.

In most of the European countries vaccine production cannot be justified on purely economic ground, in spite of this it develops dynamically and it is hardly influenced by the recent standardization tendencies either in Western or Eastern parts of Europe.

The strategy of the IPB programme is based on an industrial approach characterized by the concept of unit processing and homogeneous culture system. This approach also secures the consistency in the consecutive production lots by means of a built-in quality assurance. It advocates the required transfer of technology through a long-term support programme enabling the recipient to adopt and assimilate the technology as well as assisting in the promotion of new products.

In addition to the Model Programme which is intended primarily for use by the more advanced developing countries, UNIDO advocates a rehabilitation and restructuring programme of existing vaccine production units. If adequate national support is received, the main criterion for the implementation of a rehabilitation project is only the technical feasibility of the technology to be transferred. By rehabilitation the infrastructure is strenghtened and the personnel are properly trained for absorbing new technolgy. The importance of these projects, that comply with the quality assurance and quality control requirements, is that they create a nucleus of know-how of production technology which can then be scaled up at a later stage.

To economize on production, even at small scale, UNIDO promotes the production of human and veterinary vaccines and other biologicals, in an existing facility with ample capacity either sharing only the same services and infrastructure or even using the same production equipment on time sharing basis. The introduction of either human vaccines in an existing production unit for veterinary vaccines, or vice versa, should be carried out by application of good manufacturing practices and quality assurance in line with the requirements of WHO.

A further advantage of the industrial approach in vaccine production, contrary to the conventional bench-type technology still in use in many developing countries, is that it can be developed towards the new biotechnological applications where fermentation is an indispensable element of biotechnology's support system. The IPB programme also intends to motivate the staff of centres of academic research in the Third World to turn towards applied research and in such a way may widen the scope of activity of production units of EPI vaccines.

Through its IPB programme, UNIDO can play the role of catalyst for the transfer of technology between holders and recipients, and with technical expertise, competence and resources available at its disposal would assist developing countries in assimilating new technologies and achieving a viable production of standard quality products.

CONCLUDING REMARKS

After the preceeding chapters which dealt mainly with "caveats" and promises, it would seem appropriate to mention that several developing or newly industrialized nations have already launched into extensive programmes of domestic manufacture of vaccines (13). Amongst

them: Algeria, Argentine, Brazil, Colombia, Cuba, Egypt, India, Indonesia, Mexico, Pakistan, Philippines, Thailand and Venezuela. Some of these countries are even able to contemplate moving from the production of conventional vaccines towards the manufacture of modern ones, using the advances of biotechnology.

It is the role of UNIDO's Advisory Panel on Preventive Medicine to advise and offer guidance to developing countries on the technical and economic aspects of the establishment of UNIDO's programme of Industrial Production of Biologicals. The Model Programme is proof of the availability of appropriate vaccine technology and the feasibility of the stepwise and comprehensive transfer of such technology (2).

The various aspects developed in the other chapters of this paper are submitted to governments as "points to be considered" when assessing the advisability of local manufacture of vaccines and other biological products in countries of the developing world. It must be stressed that, in order to launch, at any time that exigencies may require, an endeavour of local manufacture of vaccines in such countries, governments have to devise incentive measures to develop the required capabilities for such an undertaking. These capabilities cover infrastructure and logistics, trained manpower, a quality control authority and facility, university institutes, research and development institutes, etc.

To conclude, it should be understood that the final decision with regard to initiating local production of vaccines must rest with national governments, particularly where a definite immunization programme is to be implemented to achieve definite goals. Considering that fluctuations of price and availability of vaccines may drastically change the policies of local production of immunizing agents, governments have to keep abreast of national, regional and international developments that may affect their long term immunization plans.

REFERENCES

(1) Report of the Second Consultation on the Pharmaceutical Industry (UNIDO/ID/311, 1983).
(2) Model Programme for the Production of Vaccines in Developing Countries (UNIDO/IO.2, 1986).
(3) International List of Availability of Vaccines and Sera (WHO/BLG/84.2, 1984),
List of Availabil ... of Human and Veterinary Vaccines Produced in Latin America (PAHO/WHO, 83-114, 1982).
(4) The Biological Industry and World Health (IFPMA, 1985).
(5) The Manufacture of Vaccines in Developing Countries (UNIDO/ID/WG.393/13/Rev.1, 1983).
(6) Prospects for Production of Vaccines and Other Immunizing Agents in Developing Countries (UNIDO/IS/402, 1983).
(7) WHO Technical Report Series, No. 722, 1985.
(8) WHO Technical Report Series, No. 704, 1984.
(9) WHO Technical Report Series, No. 725, 1985.
(10) Weekly Epidemiological Record, 60 (34), 1985.
(11) Programme for Production of Vaccines in Africa (UNIDO/IO/R.148, 1985).
(12) Weekly Epidemiological Record, 61, 13-20, 1986.
(13) New Trends for Vaccine Production and UNIDO Programme on Industrial Production of Biologicals (UNIDO/IO.630, 1986).

Annex 3

REGULATIONS OF THE "EUROPEAN VACCINES MANUFACTURERS"

Article 1: Name

Between the subscribers to these regulations is founded an international group, by the name of "European Vaccine Manufacturers" (in French : "Fabricants Europeens de Vaccins"), hereafter: EVM: EVM is part of the European Federation of Pharmaceutical Industries Associations (EFPLA), and will consequently respect EFPLA statutes. In case of conflict between the present regulations and EFPLA statute. EFPLA statutes will prevail.

Article 2: Purpose

In line with public health interest, EVM, which has no lucrative purposes, will endeavour to contribute to the improvement of the status and the development of European Vaccine Manufacturers.

EVM will act on behalf of its members as their representative body.

EVM principally pursues scientific goals, in support of the European vaccine industry.

In particular, EVM will:

* represent its members with international government bodies, e.g. by signifying points of view of members in all matters of their concern with respect to public health, and with respect to international law and regulations;

* establish close liaison with government bodies as well as with nongovernmental organisations to abet understanding of issues of interest to its members;

* study its members' standpoints on scientific, socio-economic, and legal issues of their concern;

* organize, between its members, the exchange of information and standpoints in a manner compatible with EC competition rules;

* supply counsel and services to its members.

Article 3 : Field of application

The activities of EVM address all matters related to the purpose of EVM described in Article 2 and that are of interest to its members.

Article 4 : Office

EVM has its office at the European Federation of Pharmaceutical Industries' Associations (EFPLA) in 1050 Brussels, 250, avenue Louise. The office can be transferred in Belgium by decision of the General Assembly.

Article 5: Members

The founding members of EVM are:

Behringwerke A.G., Postfach 1140, D3550 Marburg, Germany
Immuno AG, Industriestrasse 87, A-1221 Wien, Austria
Medeva plc, 10, St. James' street, London SWA IEF, United Kingdom
Pasteur Merieux, 58, avenue Leclerc, F-69007 Lyon, France
Biocine Sclavo S.p.A, via Fiorentina 1, I-53100 Siena, Italy
SmithKline Beecham Biologicals, 89, rue de l'Institut, B-1330 Rixensart, Belgium
Swiss Serum and Vaccine Institute, Rehhagstrasse 79, CH-3018 Berne, Switzerland

Article 6: Admission, Resignation, Exclusion

New members can be admitted by the General Assembly; the list of members shall be kept updated by the Bureau and available for consultation at the office of EVM. Decisions by the General Assembly about admission, refusal of admission, resignation, exclusion, to or from EVM are of without appeal.

The General Assembly is under no obligation to justify its decision.

However, any member must at least fulfill the following conditions, which can be amended by the General Assembly at any time :

a) be a manufacturer of vaccines, it being understood that "manufacture" means all of production activities of at least one vaccine;

b) be lawfully established in Europe;

c) be a public company;

d) be a member of the professional pharmaceutical industry association of the member's home country.

Membership is lost by:

a) resignation;

b) non-fulfilment of the conditions described in this Article 6;

c) exclusion by decision of the General Assembly, taken by secret vote and by a qualified majority of two thirds, for non-payment of the subscription fee, or for any grave matter, after the Bureau will have asked by registered mail that the member state his case, within ninety days of having been so requested. The excluded member is notified by registered mail.

In the case of loss of membership, paid subscription fees are not refundable, except as provided for in Article 13.

Article 7: Duration

EVM is constituted for an indefinite period of time.

Article 8: Financial Management

Resources of EVM come from the members' subscription fees, donations and legacies, subsidies obtained public or private, national or international organisations, companies, and from all proceeds resulting from the activity of EVM.

Accounts of EVM are kept per calendar year, within the accounts of EFPLA. Annual accounts are closed by the Bureau and submitted to the first ordinary General Assembly following the year to which the accounts pertain.

Accounts will at least include the account of revenues and expenditures of the previous year.

Article 9: Organization

EVM will comprise the following bodies:

* The General Assembly
* The Bureau
* Ad hoc Working Parties, established and empowered by the Bureau or the General Assembly.

Article 10: The General Assembly

The General Assembly is constituted of all the members. Each member is entitled to two representatives at the meetings of the General Assembly. Member's Representatives are designated for a period of two years. Representatives have themselves replaced. Members of the General Assembly have one vote. Power of attorney may be given to another member for the purpose of voting.

10.1. Powers

* The General Assembly has the powers foreseen by the Belgian law.

* The General Assembly has the broadest powers to order, do or ratify all acts concerning EVM;

The ordinary General Assembly meets once yearly, at the venue indicated in the convocation.

Mandatory agenda items are:

a) submission of the annual report of the Bureau;

b) approval of the accounts of the previous year and discharge to the Bureau;

c) approval of the budget and determination of the subscription fees of the current year.

All meetings are subject to minutes. Excerpts or affidavits are signed by the President.

10.2. Convocation

Extraordinary General Assemblies are held at the Bureau's request, acting through its President, or in his absence through the Vice-President, or at the request of a simple majority of the members.

Ordinary or extraordinary meetings of the General Assembly are convoked in writing (letter, fax, etc..). The convocation will specify the venue, the date and the time of the meeting of the General Assembly.

10.3: Vote

The validity of the deliberations of the General Assembly is not subject to a minimum quorum of attending or represented members; decisions are taken by simple majority except when the Belgian law or the Statutes require otherwise.

In the case of parity of the votes, the vote of the, President, or in his absence, the Vice-President, will carry the decision. Members of the General Assembly may request a 10 (ten) days moratorium to cast their vote, to allow for consultation with their Management in the case they deem the issue on which to vote beyond their powers of attorney; they will then let their vote be known in writing to the other members.

Article 11: The Bureau

The Bureau is elected by the General Assembly among its members, and is comprised of:

* the President, elected for a period of two years; ending at the second ordinary General Assembly following his appointment;

* the Vice President and the Treasurer, elected for a period of one year, ending at the first ordinary General Assembly following their appointment.

Appointments can be renewed and are not renumerated.

The Bureau meets upon written convocation by the President, every time the interests of EVM so require, or upon written request to the President by three members, at the seat of EVM.

Valid deliberations and decisions by the Bureau require at least half of the Bureau members attend or are represented at the meeting.

* Decisions by the Bureau are by simple majority. In the case of parity of the votes, the vote of the President, or in his absence of the Vice-President, will carry the decision. members of the Bureau may request a 10 (ten) days moratorium to cast their vote, to allow for consultation with their Management in the case they deem the issue on which to vote beyond their powers of attorney. they will then let their vote be known in writing to the other members.

* All meetings are subject to minutes. Excerpts or affidavits are signed by the President.

11.1: Powers

The Bureau has the broadest powers of administration and management of EVM. Powers include, but are not limited to, to make all agreements or acts; acquire, exchange, sell goods or estates, mortgage, borrow, conclude leases of any duration, receive any legacies, subsidies, donations, transfers of funds.. forsake rights; give power of attorney to mandates of its choice, whether associated or not, represent EVM in court, either as a respondent or as claimant.

The Bureau can hire and dismiss personnel of EVM, at the exclusion of EFPLA personnel allocated to activities related to EVM; receive all sums and valuables; open and close bank accounts, effect all operations on such accounts such as withdrawals of funds by cheque, payment or transfer of orders or any other type of payment instruction; hire a safe; pay all amounts due by EVM; receive from the Post Office, customs, railroads mail and parcels, registered or insured or not effect and receive payments through the Post Office. EFPLA rules and regulations will prevail for dealing with the matters described in Article 11.1, in as far as they are effectively handled by EFPLA or its authorized personnel.

11.2 Representation

Documents binding EVM, other than those of EVM's day-to-day management, are signed by the President or by two members of the Bureau, except when the Bureau has given a particular power of attorney. Documents related to the day-to-day management are signed by the authorized delegate.

11.3. Liability

Members of the Bureau do not contract any personal liabilities by the carrying out of their duties; they are only responsible of their mandates.

Article 12

The General Assembly may establish standing rules. These rules will see various issues not dealt with in the present regulations and relating to the administration of EVM.

Article 13: Dissolution

EVM can be dissolved at any time by decision of the General Assembly. The General Assembly will then appoint one or several liquidators and determine their powers.

In the case of dissolution, the net assets of EVM will be restituted to the members, in proportion to the average subscription paid over the last three years.

Article 14: Working language

EVM shall use English as its working language.

Annex 4

"... we agreed to avoid
all kind of empty phrases
... and to talk realistically
on specific jobs to be done ..."
Prof. T.J.M. Madsen,
President of the Health
Committee of the League
of Nations, 1921. 1/

REGIONAL QUALITY CONTROL LABORATORY FOR BIOLOGICALS OF HUMAN USE - AN INTRODUCTION*

1. Historical Background

In 1975, Frank Perkins was appointed as Chief of Biologicals, WHO, Geneva. It was his vision and drive which resulted in a long list of new and revised requirements for a wide variety of vaccines and other biological products. He also gave tremendous help and encouragement to enable developing countries to check the quality of imported vaccines and to start local production 2/. It was also his vision that the promotion of regional self-reliance in matters of vaccine quality control and vaccine production should be given a priority 4/.

The first regional quality control reference laboratory was established in Mexico City in 1979 4/. Potential sites for Reference Laboratories were identified in other regions as well and it was expected that regional quality control systems could be initiated before the end of 1980 5/.

It seems to be easy to criticise his ideas after twenty years but to date it has become obvious that Dr. Perkins' goal to establish and certify a global system of vaccine quality control 6/ was over-optimistic and due to several reasons of technical, marketing, political and financial nature its creation has yet to be awaited.

It should be noted that the idea of a programme on biological standardization was born in 1948, in the year when the WHO was established. As for many other programmes and initiatives in the biological industry it was fostered by Dr. Charles Merieux. In line with the original proposal of Dr. Merieux in 1948, the programme was actually commenced with the foundation of Uniserum in Madrid, on April 4, 1950 by the representatives of four vaccine manufacturing institutes: Institute Llorenta, Madrid, Spain; Sclavo, Siena, Italy; Swiss Serum Institute, Bern, Switzerland; and Institute Merieux, Lyon, France. The principal objectives of the group were:

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* This paper has been prepared as a project concept for establishing a regional quality control laboratory for human vaccines in Africa, however, the thoughts presented in it have certain relevance for the national control laboratories in CEE.

1) to develop research in the field of serums and vaccines both for man and animals.
2) to set up a collection of strains and a documentation centre, and
3) to create a central control laboratory.

Two important assets were missing:

1) liaison with the WHO, and
2) liaison with the International Association of Microbiological Societies (IAMS).

However, March 15, 1954, Dr. Merieux succeeded in bringing together, around the same table in Bern:

- the members of Uniserum,
- a delegate of WHO,
- the Secretary General of IAMS, and
- Government delegates entrusted with the control of human and veterinary products.

As a results of this round table, the First European Meeting of Biological Standardization was organized in Lyon by Dr. Charles Merieux in 1955. This meeting brought together representatives of WHO, FAO, and the IAMS, in all, more than 100 participants from 20 countries 7/.

In 1983, during the preparation for the UNIDO Second Consultation on the Pharmaceutical Industry held in Budapest, an Advisory Panel on Preventive Medicine was set up to give advice and guidance to the Secretariat to discuss the issue of vaccine production in developing countries an to facilitate the Technical co-operation Programme of the organization to establish the programme on industrial production of biologicals (IPB). The Panel consisted of representatives of governments and industry and Dr. Charles Merieux was invited to accept the Chairmanship 8/.

On 27-28 February 1984, the UNIDO Advisory Panel on Preventive Medicine convened for its first meeting in Vienna, Austria. Great personalities, legends in their lifetimes attended the meeting. Dr. Frank Perkins whose vision first of all was quality said that the major difference between drugs and vaccines was that while the drugs were given to sick people, the vaccines were administered to healthy infants. No-one should occupy a hospital bed with a disease that could be prevented by immunization, he added. Dr. Charles Merieux, who created an industry from dubious benchscale techniques had the dream that people could work together coming from all corners of the world to achieve this humanitarian objective. But it was Dr. Hans Cohen, Director General of the very highly reputed RIVM at Bilthoven, the Netherlands, who challenged both of them and UNIDO by stating that the technology transfer for biologicals was a reality if an industrial approach had been applied. He, then, recommended that UNIDO should prepare a model programme for the production of vaccines in developing countries 9/.

The Model Programme was prepared and published in 1986 as a result of a genuine team work led by Dr. A.L. Toon van Wezel, a tremendously gifted Dutch engineer in RIVM, who invented the microcarrier system for industrial scale production of viral vaccines 10/. The Model Programme together with the Challenge of Biological Technology Transfer to Developing Countries, to which Dr. Mike Phillip, Director of Public Affairs, SmithKline RIT contributed

significantly 11/ were presented and adopted by the UNIDO Third Consultation on the Pharmaceutical industry held in Madrid in 1987 12/. The Model Programme in 1989 was extended to the BCG vaccine prepared from surface culture by Prof. L. Lugosi, most probably the top BCG-ologist of the world 13/.

The Model Programme was intended primarily for use by Government officials who were responsible for structuring and implementing national immunization programmes including domestic production of vaccines. There are more than 50 developing countries where EPI vaccine requirements are being provided totally from outside sources, and this situation seems unlikely to change during this decade. In many countries of the Third World, only one EPI vaccine is produced, the quality of which is highly questionable and there are very few developing countries like China that are self-sufficient in all six EPI vaccines.

The first step towards self-reliance should be the importation of vaccines instead of the acceptance of free donation of EPI vaccines that cannot be the final, long term solution for supply. Developing countries, contemplating the production of EPI vaccines, must look into the techno-economic feasibility and commercial profitability but should not neglect the social and political benefits of this venture. The social and political considerations of domestic vaccine production in several cases outweigh the economic ones. The contributions of domestic production of vaccines to a number of inter-related, social and economic objectives of the developing countries are among others as follows:

1) reduction of dependence on supplies requiring foreign currency;
2) more efficient use of national resources;
3) increase of domestic stocks of technical know-how and human resources in many disciplines used in development of biologicals;
4) creation of employment; and
5) creation of infrastructure and logistic, etc.

The WHO laid down the requirements for the national control of vaccines and sera in 1981. In many developing countries controls for food and even for some drugs may exist, but the techniques for the control of biologicals are significantly more sophisticated and more expensive, therefore manufacture of biologicals is often carried out without any national control. In some instances, the testing by the manufacturer is also inadequate.

One of the problems of an independent national quality control laboratory particularly in a developing country without domestic manufacture of vaccines arises from the fact that the performance of the quality control tests is hampered by the lack of experience gained in manufacture. In the industrialized countries one can find very often that professional and technical personnel of the national quality control laboratories have previous manufacturing experience. Financial contraints pose another major problem. The costs of full fledged quality control of vaccines are in the same magnitude as those of the production. The governments of developing countries without vaccine production would find good reasons enough to avoid to establish national quality control. The decision might be taken only at a time when the government decides to buy vaccines instead accepting donation. The national quality control can be an option to obtain an objective opinion on the value of a vaccine purchase.

Ten years ago UNIDO made a survey on human vaccine production in 10 African countries with manufacturing facilities 14/. At that time, the survey found a paradoxical situation

which was characterized on one hand by projects on establishment of vaccine manufacturing facilities in several African countries being developed but on the other hand by existing laboratories facing difficulties in marketing their vaccines and consequently closing down. With reference to EPI vaccine manufacture in Africa, the situation has since then become even worse. In the sub-Saharan Africa, South Africa excluded, there has remained only 4 manufacturers of EPI vaccines but they are facing serious difficulties. The manufacturers and their difficulties with the product quality are as follows:

1) Yellow fever vaccine - Institute Pasteur, Dakar, Senegal. The vaccine is included in the EPI of West African countries where yellow fever is endemic, but only the manufacture of bulk material is carried out. At a certain period of time the bulk prepared in Dakar used to be filled at PMsv, Val de Reuil, France and marketed from there.

2. Yellow fever vaccine - Vaccine Production Laboratory, Yoka, Nigeria. The vaccine in only used in Nigeria. The quality of the vaccine is questionable.

3. Tetanus Vaccine - Lanavet, Bockle, Garoua, Cameroon. No national quality control exists but the vaccine is used domestically.

4. BCG vaccine - Institute Pasteur, Antananarivo, Madagascar. The quality of the vaccine is not consistent. No national quality control exists.

2. Concept of a Regional Quality Control Laboratory for Biologicals of Human Use

In cooperation with the French Government and the Foundation Marcel Merieux, UNIDO organized a regional meeting in Dakar, Senegal in 1987 on the production and distribution of biologicals for human and veterinary use in Africa 15/. The government of Senegal housed the meeting and WHO and FAO were invited to attend, reflecting the multidisciplinary nature of the agenda.

The objectives of the meeting were as follows:

- To discuss the best way to develop and promote the production of vaccines and other biologicals against "exotic" and "tropical" diseases in Africa;
- To discuss the best way to develop and promote quality control units for vaccines and other biologicals at national and regional level;
- To discuss the best way to promote the quality to the products of the existing units and to enlarge their market in Africa to achieve an economic scale of production.

The objectives of the meeting were in line with the recommendations of the Advisory Panel on Preventive Medicine 16-18/ and the UNIDO Second Consultation on the Pharmaceutical Industry 19/. Reference was made to former regional meetings on blood derivatives held in Cartagena, Colombia in 1984 and in Macau in 1986 20/.

Sixty five participants attended the meeting in Dakar, representing governmental institutions and industry, with 41 representatives from 24 African Countries, namely: Algeria, Botswana, Burundi, Cameroon, Chad, Cote d'Ivoire, Egypt, Ethiopia, Gabone, Ghana, Guinea, Kenya, Madagascar, Mali, Morocco, Mozambique, Niger, Nigeria, Rwanda, Senegal, Tanzania, Tunisia, Zaire and Zambia.

One of the main recommendations of this meeting, which was in fact the Fifth Meeting of the Advisory Panel, was that a system of total quality control should be the first stage in the establishment of biological industry. Quality should be maintained consistently throughout all stages of product preparations in conformity with GMP and quality assurance.

The meeting agreed that quality control should be envisaged at national and regional levels and a system of controls devised for imports, production and distribution. Training programmes should be available in analytical control, quality control and production. Logistic problem, such as transport, cold-chain, storage, etc. should also be examined, i.e.:

- accessibility of site (road, railways, communications);
- services and supplies (electricity, water, waste disposal);
- layout of buildings;
- housing and breeding of animals;
- local resources;
- ancillary industries (glass, stoppers, chartboard, paper, etc).

It was recommended that in case if it might prove difficult to establish national quality control laboratories, the feasibility of establishing a regional quality control laboratory should be investigated.

3. The Project

A regional quality control laboratory for biological products for human use should comply, if established, with all of the recommendations and requirements published by WHO. Since no specific requirements have been published for a regional laboratory, all requirements of WHO for a national quality control laboratory and for quality control laboratories for manufacturers of biological products should apply 21-27/.

The project should, preferably, be developed in a step-wise way.

Phase I

At the Phase I the administrative sections of the regional laboratory would be established. The responsibilities of the administrative sections could be as follows:

- Establish the source of supply of the product such as
  - manufacturer,
  - exporter,
  - donor agency,
  - international organization, etc.

- Obtain samples of the product with certificate issued by the national control authority of the exporting country.

- Obtain evidence that the product is licenced/ registered/ approved for use in the exporting country.

- Obtain evidence that the manufacturer of the product is a licenced establishment that conforms with the principles of GMP and quality assurance.

- Obtain all relevant additional information on the manufacturer such as
  production volumes,
  product quality,
  consistency of quality,
  quality assurance and validation,
  quality control procedures,
  licence of production and control buldings,
  animal facilities,
  environmental measures,
  safety measures,
  segregation of operations,
  sources of critical raw materials or
  any other, relevant non-confidential information.

- Obtain information on the product such as
  source materials and their validation,
  critical raw materials (eg. foetal bovine serum) and their sources,
  brief desciption of production processes,
  manufacturing protocols,
  brief description of quality control techniques,
  quality control protocols,
  consistency of manufacture,
  consistency of quality control,
  samples of packaging materials, labels and package inserts,
  potency,
  safety,
  specific and non-specific toxicity,
  stability,
  brief report on preclinical studies,
  clinical trials,
  list of countries in which the product is licenced for use.

- Establish a databank on the suppliers based on the above listed information.

- Obtain all relevant information on the cold chain such as
  quarantine, storage and despatch of the manufacturer,
  receiving, storage and despatch of the exporter,
  receiving, storage, loading/unloading and shipment conditions during forwarding,
  receiving, customs clearance, storage at the recipient country.

sampling and conditions of transporting samples to national quality control laboratory,
sampling and conditions of transporting samples to regional quality control laboratory,
central, provincial and municipal storage facilities,
mobile units,
cold chain products,
sampling and conditions of transporting samples from the site of use.

- Establish personal contacts and a system of communication with
  all relevant government authorities in the region,
  suppliers in the region,
  national quality control authorities and laboratories in the region,
  the most important suppliers outside the region,
  international donor agencies and organizations,
  bilateral donor agencies.

- Inspect samples of the products.

- Review documentation accompanying the samples.

- Inspect premises of the manufacturers in the region.

- Establish an auditing system for the manufacturers in the region.

- Disseminate all relevant information in the region related to the procurement, transport, production and quality control of biologicals to government officials and directors of institutions who are responsible for structuring and implementing national immunization programmes, professional staff in charge of vaccine production and control, personnel of central medical stores, personnel involved in cold chain operation, personnel involved in transportation of vaccines, and field staff involved in vaccination.

- Promote proper registration/licencing for biologicals to be used in the region.

- Organize training courses in procurement, registration/ licencing, shipping and controlling of biologicals in the region to
  responsible staff of national control authorities,
  directors of national quality control laboratories,
  directors of vaccine manufacturing establishments,
  and
  goverment officials assigned to purchase of vaccines.

Phase 2

At Phase 2 a priority list of biologicals would be prepared in consultation with representatives of relevant government offices in the region, members of UNIDO Advisory Panel on Preventive Medicien, representatives of the main suppliers, United Nations agencies (WHO,

UNICEF, World Bank) and international/bilateral donor agencies. The terms of reference of this consultation meeting would include the identification of criteria based on which a priority list of biologicals could be prepared.

The priority of introduction of any biological product into the work program of the regional control laboratory should take into consideration at least the following aspects:

1) Vaccines
   a) Is the vaccine included in the EPI of WHO?
   b) Is the vaccine included in the Essential Drug List of WHO?
   c) Is the vaccine included in the EPI of the region/country?
   d) Is the vaccine used for universal immunization?
   e) Is the vaccine used for specific groups of individuals?
   f) Epidemiological data (morbidity and mortality) on diseases preventable by immunization.
   g) Stability data.
   h) Specific requirements for shipping and storage.
   i) Heat sensitivity.
   j) Expiry time in general and actual expiry date.
   k) Certified/validated source of supply.
   l) Nature of vaccine: live or inactivated.
   m) Formulation of the vaccine: liquid or freeze-dried.

2) Sera and immunoglobulins
   a) Is it a live-saving product such as an antivenom sera?

3) Diagnostic agents
   a) Is it for in vivo tests in human?
   b) Is it for in vitro tests?
   c) Is it a critical test that might indicate a live-saving medical intervention?

4) Blood products
   a) What is the stability of the product?
   b) Is it liquid or dried?
   c) Is it safe?

The consultation meeting should, according to its terms of reference, discuss and decide by concensus which are those few products that should be included in the work programme of the regional control laboratory.

The second main item in the terms of reference of this consultation meeting would be to decide on the quality control tests to be performed on the selected priority biologicals. It should be noted that only validated test procedures should be accepted. At this point at least the following questions should be considered:

   a) Type of tests to be performed.
   b) Number of tests to be performed.
   c) Validation of the tests.
   d) Specifications/requirements for the product.
   e) Statistical analysis applied for the evaluation of the tests.

f) Specifications/requirements for the tests.

The third item of the terms of reference of the consultation meeting should be the preparation of a report on the above.

Based on the report of the consultation meeting a detailed study can be prepared on the regional laboratory including all technical requirements such as

- buildings,
- equipment,
- personnel,
- laboratory animals,
- chemicals, biochemicals,
- consumables,
- reagents,
- reference preparations, standards, etc.

This detailed technical study, then, would be submitted with some preliminary estimate of investment requirements to possible donor agencies.

The investment requirements would only cover the costs of equipment since it has been assumed that the construction costs would be covered by the government of the host country or alternatively an adequate office and laboratory space would be provided within an existing institution. If this assumption with regard to the availabitity of the building(s) for the regional control laboratory was not valid, other alternatives should be sought. These could be as follows:

- The participants of the consultation meeting will make an attempt to identify an adequate institution/facility and to arrange to obtain an agreement from the government of the host country where the regional control laboratory would be located.

- The participants of the consultation meeting will recommend bilateral donor agencies, banks, companies, etc who would be, in principle, interested to finance the project including the construction costs of new facilities or the costs of remodelling/renovation of available existing facilities.

The laboratory buildings and the animal houses should meet the requirements of international standards and, if required, they should be validated. Therefore, one should be very careful when makes decision on the acceptance of an existing facility. Since the new requirements become very strict in many cases the costs of remodelling/renovation required for an existing building, being not designed as a biological control laboratory, would be in the same range or could even be more expensive than the costs of a new, green-field construction. It should be emphasized that no compromise related to the requirements can be made in the quality of the laboratory for sterility testing and the animal facilities.

5. References

1. Cockburn, W.C.: The international contribution to the standardization of biological substances. I. Biological standards and the League of Nations 1921-1946. Biologicals 19: 161-169, 1991.

2. Magrath, D.: Obiturary. Frank T. Perkins Ph.D., F.I. Biol. FZS, FRSA, 1925-1984. J. Biol. Standards 13: 1-2, 1985.

3. Progress Report by the Director General: Expanded Programme on Immunization. WHO A31/21, Page 2, 31 March 1978.

4. Report of the Expanded Programme on Immunization Global Advisory Group Meeting. New Delhi, India, Page 6. WHO EPI/GAG/79/REPORT.

5. Report of the Expanded Programme of Immunization Global Advisory Group Meeting. Geneva, Page 19, WHO EPI/GEN/80/1.

6. ibid. Page 19-20.

7. Csizer, Z.: WHO - World Health Organization - Where, What and Why. Connaught Laboratories, Willowdale, Ontario, Canada, Conntact, Vol. 4, No. 1, Page 6, 1991.

8. UNIDO Programme for Industrial Production of Biologicals (IPB).UNIDO/IO.590, 1984.

9. Report on the Meeting of the Advisory Panel on Preventive Medicine. Vienna, Austria. UNIDO/IO.583, 1984.

10. Model Programme for the Production of Vaccines in Developing Countries. UNIDO IO.2. 1986.

11. The Challenge of Biological Technology Transfer to Developing Countries. UNIDO ID/WG.466/10(SPEC.), 1987.

12. Report of the Third Consultation on the Pharmaceutical Industry. Madrid, Spain, UNIDO ID/356, 1987.

13. Model Programme for the Production of Vaccines in Developing Countries: Manufacturing and control methods of the Hungarian freeze-dried intradermal BCG vaccine prepared form surface culture. UNIDO DP/ID/SER.A/1206, 1989.

14. Report of the Second Meeting of the Advisory Panel on Preventive Medicine. Bogota, Colombia, UNIDO/IO.617, 1984.

15. Report of the Regional Meeting on Production and Distribution of Biologicals for Human and Veterinary use in Africa. Dakar, Senegal, 1987. UNIDO - Fondation Marcel Merieux, Lyon, France, 1988.

16. Report of the Third Meeting of the Advisory Panel on Preventive Medicine. Bilthoven. The Netherlands. UNIDO/IO.624. 1985.

17. Report of the Fourth Meeting of the Advisory Panel on Preventive Medicine. Ottawa. Canada. UNIDO/IO.631. 1986.

18. New trends for vaccine production and UNIDO Programme on Industrial Production of Biologicals. UNIDO/IO.630. 1986.

19. Report of the Second Consultation on the Pharmaceutical Industry. Budapest. Hungary. UNIDO ID/311. 1983.

20. Asiatic Symposium on Blood and Its Derivatives. Part I-II-III. Macau. 1986. UNIDO - Fondation Marcel Merieux. Lyon. France. 1987.

21. The national control of vaccines and sera. WHO Techn. Rep. Ser. 658. Annex 11. 1981.

22. Guidelines for national authorities on quality assurance for biological products. WHO Techn. Rep. Ser. 822. Annex 2. 1992.

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

24. General requirements for manufacturing establishments and control laboratories. WHO Techn. Rep. Ser. 323, Annex 1, 1966.

25. WHO certification scheme on the quality of pharmaceutical products moving in international commerce. WHO Techn. Rep. Ser. 1990. Annex 5. 1990.

26. Good manufacturing practices for pharmaceutical products. WHO Tech. Rep. Ser. 823. Annex 1. 1992.

27. Good manufacturing practices for biological products. WHO Techn. Rep. Ser. 822. Annex 1. 1992.

Annex 5

XP/RER/94/102
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