付属資料リスト

A. Project proposal for the development and evaluation of quality control on the biological products in the republic of TURKIYE.

B. トルコ国生物製剤の品質管理プロジェクト事前調査団帰国報告会会議報告および会議資料（部分）

C. The National control of vaccines and sera (A guide to the provision of technical facilities), WHO TRS 658 (1981).

D. Turkish Pharmacopia ; 1974（部分）および翻訳英語

E. Guideline for vaccine and serum impremention ; 1980

F. Dr. Serden SAVAS (Deputy Undersecretary of Ministry of Health) 面談要旨 ; 1992. 4. 29

G. トルコ国保健省組織図 ; 1992, 1989およびRefik Saydam Hygiene Center組織図 ; 1991.

H. Summary protocols for measles vaccine(Live): Based on requirements for measles vaccine ; WHO TRS 771 (1988).

I. 実施計画案 (Tentative Schedule of Impremention), 1992/06/12.

J. 供与機材リスト

K. 営繕改装計画平面図

L. 供与予定の力価作業参照品 (Laboratory working reference) の仕様書

M. 国産機材のトルコ国 (Ankara) 代理店の調査資料

PROJECT PROPOSAL FOR THE DEVELOPMENT AND EVALUATION OF QUALITY CONTROL ON THE BIOLOGICAL PRODUCTS IN THE REPUBLIC OF TÜRKİYE

PROJECT PROPOSAL BETWEEN REPUBLIC OF TÜRKİYE AND
GOVERNMENT OF JAPAN

COUNTRY	: TÜRKİYE
NAME OF THE PROJECT	: The development and evaluation of quality control on the biological products in the Republic of Türkiye
RESPONSIBLE ORGANIZATION	: Refik Saydam Hygiene Center
MANAGING ORGANIZATION	: GOVERNMENT
DATE PRESENTED	: July 1991
INITIAL DATE	: January 1992,

1. INTRODUCTION

The immunization programs,which constitute an important part of the preventive health services, are carried out by the Ministry of health.The most prominent factor in the achievement of these programs is the application of effective and safe vaccines.The quality control of the biological products such as vaccines,sera,blood products,etc.is carried out by the Biological Control and Research Department of Refik Saydam Hygiene Center.This department tries to meet the control demands with its small laboratories taking over the responsibility of State control.However,this department is not furnished with sufficient equipment and also provided with adequate and efficient staff so that it can not meet the needs of contemporary biological controls.Satisfactory results could not be obtained in the attempts to compensate the specified shortcomings.

In May 1991,it was announced that the World Bank would contribute to the modernization and development of Refik Saydam Hygiene Center as whole.On the other hand,in order to construct a new State Biological Control and Research Laboratories Center,a certain amount of financial source has been spared in 1991 budget.All these efforts are only for the physical structure,namely for the building.The shortcomings about the sufficient equipment and the trained manpower still remain unsolved.By the help of this project,we expect to overcome the difficulties in this respect.

2. OBJECTIVES

2.1 Long-term Objectives:

2.1.1 The first long-term objective of this project is to increase the immunization level in the country by applying adequate quality control analysis on the biological products in the well equipped modern laboratories, so that it will also be possible to carry out scientific researchs for the determination of the immunization level.

2.1.2 The second long-term objective is to decrease the external-dependence for the standard biological products such as vaccines, sera and toxins by preparing them in our laboratories.

2.2 Short-term Objectives

Among the short-term objectives of the project are:

2.2.1 To contribute to the efforts for the establisment and upgrading of national quality control laboratories.

2.2.2 To carry out in-service training for the present staff in the biological control laboratories by inviting experts form Japan.

2.2.3 To carry out the quality control activities using modern and effective methods.

2.2.4 To give chance to the key personnel related with the activities to attend in-service training at abroad.

3. BACKGROUND

The national health policy of Türkiye consists of following items:

- To reduce the regional differences in respect of health,
- To promode the health level of the people throughout the country
- To rationalize the primary health care
- Hygienic environment
- Healthy life-style
- Healthy Türkiye in 2000 s, much lower maternal and infant mortality rates,
- South-east Anatolia Project.

Since the infant mortality rete is very high in Turkey, (59.3%0-1990)

the immunization programs included in this policy were expanded with the Accelerated Vaccination Campaign started in 1985.

Later on,the EPI program,the purpose of which is to prevent the epidemics of 6 major infectious diseas that cause frequent deaths and disabilities among the children under 5 years and to decrease the mortality rate of these diseases by breaking their infection chain,was also started by the Ministry of Health.In order to accomplish this purpose;

-The immunization level of the high risk group of 0-11 month babies should be increased up to 90% and the continuity of the increased immunization level should be maintained.

-All young babies should be regularly vaccinated and the vaccination of the children under 5 years should be completed.

- EPI should not be only an immunization program,at the same time, it should be a disease control program.

In this direction,in 1989 a program for eradication of Polio was started and in the same year to start another program for elimination of Neonatal Tetanus was accepted.These activities which have been carried out by the General Directorate of Primary Health Care,Ministry of Health,are mainly committed in the health houses,health centers, mother child health and family planning centers,tuberculosis eradication dispenseries and in some private practices.

All vaccination services are carried out as a routine activity. The annual need for the vaccines is estimated according to target population.According to this estimation,main part of the vaccines are produced in Refik Saydam Hygiene Center,and some of them are procured from abroad.The amounts of the produced and imported vaccines and sera are shown according to years.(App.1-5)

All these biological products are controlled by the Biological Control Department of Hygiene Center,in terms of quality and safety. This department was an independent department before 1983.In this year this department was administratively attached to the Vaccine and Serum Production and Research Directorate of Refik Saydam Hygiene Center.The biological products produced in the Center are directly delivered to this department.On the other hand,all kinds of import products have a sample-flow through the General Directorate of Primary Health Care of Ministry Health,Refik Saydam Hygiene Center,Directorate of Vaccine and Sera Production and Research,and finally Biological Control Department.The results of the analysis are sent back to the Ministry through same way.The General Directorate of Primary Health Care makes the final decision about the distribution of the import biological products.

The control tests which can be carried out in biological control laboratories are as follows:

A-The control tests applied to the biological products produced in the Hygiene Center:

-Plain Diphteria-Tetanus(DT)and Tetanus Toxoid(T):Sterility, innocuity,potency,toxicity,pH degree,formaldehyde and identity tests in both bulk and final products.

-Plain Diphtheria-Tetanus-pertussis Vaccine(DPT): Sterility,innocuity,potency(except pertussis),identity,pH degree in the final product.

-Dried BCG vaccine and Tuberculin(PPD):Sterility in the final product.

-Semple type Rabies Vaccine: Sterility and innocuity in the final product.

-Purified-concentrated antitoxins of Diphtheria,Tetanus and Gas Gangrene;Sterility,innocuity,pH degree,potency,Purified and Concentrated

Sera of Scorpion,Anthrax and Rabies:Sterility,innocuity and pH degree in final product.

B- The control tests applied to the biological products imported by the Ministry or by the private companies :

- Adsorbed vaccines of Tetanus,Diphtheria-Tetanus,Diphtheria-Pertussis-Tetanus : Sterility,innocuity,antigenicity(potency except pertussis),pH degree,identity and formaldehyde tests are carried in the biological control laboratories,but control tests for adjuvant and presarvative are done in the Drugs Analysis laboratories.

- Viral vaccines(Vaccines for Poliomyelitis,Measles,Rubella,Mumps, Influenza,Yellow Fewer and HDCV Rabies Vaccine): Only sterility,innocuity and pH degree tests are carried out in the biological control laboratories; identity and potency tests are done in the Virology Laboratories; Residual moisture and the other tests are committed in the Drug Analysis Laboratories.

- BCG vaccine is mainly controlled in its production laboratory.

- Meningococcal Polysaccarit Vaccine: Sterility and innocuity tests are carried out in Biological Control Laboratories, Protein ,residual moisture,pyrogenicity ,protein tests are done in the other related laboratories.

- Immune Sera of Animal Origin : Sterility,innocuity,potency and pH degree are carried out in the Biological Control Laboratories, Pyrogenicity,presarvative and protein controls in the other related laboratories.

(The chart of control tests is shown on the appendix 6.)

When the samples of the products specified above are brought to the Biological Control Laboratories,they are classified according to the needed tests.Some samples are also sent to other related laboratories for the necessary tests.Final report is prepared when all the needed tests have been completed.

Samples of blood products are sent to the Biological Control Laboratories for only sterility and toxicity tests.The production department prepares the reports for the controls of blood products.

The staff and work distribution of the Biological Control Laboratories are as follows :

- Chief of the laboratories, Bacteriologist (1): Evaluation of the tests,preparing the final reports,follow up the literature,coordination of the activities.
- Microbiologist (1): Programing,controlling and deciding of the sterility tests,method identification for the potency tests.
- Biologist (3) :Commitment of the sterility test,control of the media,identification of the bacteria in the cultures,identity tests.
- Pharmacist (1) : Formaldehyde controls,identity tests,physical controls,innocuity and toxicity tests.
- Veterinarian (1): Potency tests,innocuity tests,sample taking, control and otopsy of experimantal animals.
- Chemistry Technician (2): Media preparation,pH degree controls, preparation of the steril rooms.
- Secretary (1) : Typing and filing the final reports.
- Auxiliary staff (3): Cleaning the equipment and all laboratory items.
- Experimental animal keeper (1) :Feeding and keeping the experimental animals.

The Biological Control Laboratories occupy 2 laboratories, 1 kitchen, 2 animal breeding rooms, 1 office, 3 rooms for the experts (Appendix 7).

Some devices in the laboratories are listed below:

1 Lamin-air flow

1 Sterility tests devic

1 Spectrofotometer

1 Microscope

1 Autoclave

2 Sterilizators

2 Balances

1 Centrifuge

1 pH Meter

6 Incubators

1 Benmary

1 Deep-freeze

4 Refrigerators

1 Automatic Pipette

4. ACTIVITIES TO BE IMPLEMENTED

4.1. To establish the Biological Control Laboratories apart from the production laboratories according to recommendations of WHO.

4.2. To construct an adequate building to accumulate the laboratories in a center which is appropriate in terms of GMP.

4.3. To carry out the control activities at the same level of world standarts.In order to accomplish this purpose, the following laboratories should also be established :

- Chemical-Biochemical-Immunochemical Control Laboratory
- Bacteriological Control Laboratory
- Mycoplasma Control Laboratory
- Virological Control Laboratory
- Special unit for the controls of the experimental animals

Beside this,the national standarts for the quality control of the biological products should be established.The training of the staff to be employed in the new laboratories should be carried by the foreign experts either in the country or in abroad.

Required Equipment

	Number
Lamin-air Flow	4
Microscope	2
Fluorescence Microscope	1
Inverted Microscope	1
Deep-freeze	2
Electrophoresis equipment	1
Spectrophotometers	1
Mercury autoanalysor	1
Freeze -drying apparatus	1
High -speed centrifuge	1
Micro Kjeldahl	1
Balances	4
Pure water apparatus	1
Autoclave	2

Spectrophtometer including a scanner for ELISA	1
Fume cupboard with an exhaust fan	1
Multi-headed centrifuge with a cooling system	1
Scintillation counter	1
Incubator with CO2	1
Incubator	6
Liquid nitrogen tanks	4
pH meter	3
Centrifuge	2
Egg incubatör	1
Pyrometer	1
Coagulator	1
Vortex	3
Magnetic mixer	3
Filtration tanks	4
Compressed air pump	1
Cytometer	1
Vacum detector	1
Drying oven	2
Water bath	4
Shaker	3
Sealing equipment	1
Dot-blot apparatus	1
Coulo meter	1
Resistivy meter	1
Osmo meter	1
Automatic pippets	10
Refrigerator	4
Filters	4

Approximate cost of these equipment amounts to $ 1.365.000 (6.000.000.000 TL)

5. JUSTIFICATION

According to the recommendations of WHO ;

- if the production and control units are in the same complex, the control laboratories should be apart from production laboratories.

- the staff in the control laboratories should be well trained to apply the methods matching the world standarts, for testing domestic and import biological products. The staff should regularly undergo in-service trainings for continuous developments in this field.

- Quality control laboratories are expected to carry out some related researchs beside their routine control work. Research activities should be reinforced to develop the analysis methods.

Since the international standarts can only be obtained by adjusting the national standarts, first of all the national standarts should be established.

- The experimental animals should be kept in optimal conditions and fed properly not only during the experiment but also before it. All the required conditions should be established for the maximum safety.

- The control laboratories should be authorized to determine the control methods and their application. For this reason all the control activities in the other laboratories should be gathered in one the control center.

- The Biological Control Laboratories should be supported technically and administratively to keep pace with the developing technology and the needs of growing population.

Most of the specified requirements for the Biological Control Laboratories will be possible by the help of this project.

6. PHASES OF THE PROJECT

Phase	Input: Expertise/ Consultation Services	Input: Man-power Training	Input: Equipment Facilities	Output
1. Project Preperation	X			Foundation of Cooperation Project
2. Built up of İnfrastructure (Establishment of a new control center)	X	X	X	Expansion and upgrading of the quality control activities
3. Quality grade-up of the control activities	X	X	X	Better quality of the control activities
4. Establishment of the national standarts for the quality control	X	X	X	Matching with the world standarts
5. Evaluation of the project	X			Recommendation for future accivities

02/8/91 Sekr.Ş.AÇIKGÖZ

APPENDIX - I

PRODUCTION STATISTICS OF VACCINE AND SERA

PRODUCTION OF BACTERIAL VACCINES

VACCINES	1983 Dose	1984 Dose	1985 Dose	1986 Dose	1987 Dose	1988 Dose	1989 Dose	1990 Dose
D-B-T (Diph.-Pertus.-Tetanus) (Plain)	4.005.400	4.058.400	1.546.400	1.661.200	-	2.264.000	561.000	958.800
D-T (Dipht.-Tetanus) (Plain)	1.202.945	1.620.500	2.427.000	2.846.000	1.200.000	1.465.000	2.248.050	1.905.000
T. (Tetanus) (Plain)	3.025.500	3.269.000	2.731.000	2.900.000	920.000	3.391.000	3.344.000	2.696.000
TİFO (Typhoid Vaccine)	106.800	267.000	129.000	-	114.800	-	31.200	182.800
KOLERA (Chlorea Vaccine)	30.000	-	23.000	-	-	-	-	-

APPENDIX : 2

BCG VACCINE AND TUBERCULIN P P D PRODUCTION

YEARS	BCG (Liquid)	Freeze-Dried BCG Vaccine	Diluent for Freeze-Dried BCG Vaccine	(Tuberculin) PPD
1983 Production (Dose)	4.882.300	345.000	-	3.205.950
1984 Production (")	4.918.400	472.500	-	5.292.300
1985 Production (")	2.497.350	3.693.190	-	3.656.200
1986 Production (")	-	3.881.500	-	4.825.500
1987 Production (")	-	3.178.000	-	4.415.750
1988 Production (")	-	3.977.000	4.507.350	4.521.350
1989 Production (")	-	2.444.000	1.080.400	4.572.600
1990 Production (")	-	1.624.000	2.008.500	818.150

APPENDIX : 3

SERA PRODUCTION

SERA	1983	1984	1985	1986	1987	1988	1989 1990
Tetanus Antitoxin (Ampoule)	32.175	52.790	108.735	146.960	62.130 (X)	30.705	27.945 20.500 xx
Diphtheria Antitoxin(")	16.725	3.610	7.780	8.325	2.000	2.820	2.870 2.675
Mixed Gas Gangrene Antitoxin Vial (15 cc.)	7.301	6.164	5.325	6.049	5.480	6.839	8.271 4.359
Anti antrax Serum (Vial 15 cc.)	710	1.760	1.620	2.380	1.060	1.848	2.007 1.720
Anti Scorpion Serum (Vial 15 cc.)	17.290	28.615	30.880	42.985	36.135	16.995	27.576 86.540
Anti Rabies Serum (Vial 100 cc.)	1.634	1.231	1.777	2.021	2.304	1.848	1.396 2.474

(X) Tetanus Antitoxin 1500 İ.Ü.

(XX) Tetanus Antitoxin 5000 İ.Ü.

APPENDIX : 4

PRODUCTION OF VIRAL VACCINE

YEARS	RABIES VACCINE
1983	1.559.275 Dose
1984	1.331.050 Dose
1985	1.191.925 Dose
1986	1.339.825 Dose
1987	1.394.900 Dose
1988	1.108.700 Dose
1989	717.900 Dose
1990	844.900 Dose

APPENDIX : 5

IMPORTED VACCİNE AND SERA

(DOSE)

		1988	1989	1990	For six months 1991
Tetanus Vaccine (Adsorbed)	İ:	3.000.000	4.420.000	-	-
	U:	1.072.000	3.284.860	3.006.000	341.140
Diphtheria, Pertussis and	İ:	5.710.000	6.500.000	6.000.180	-
Tetanus Vaccine Adsorbed	U:	5.245.000	5.451.000	3.064.400	3.007.000
Oral Poliomyelitis	İ:	10.643.660	11.046.800	3.500.000	4.500.000
Vaccine	U:	7.682.600	10.218.760	7.270.000	3.998.000
Measles Vaccine	İ:	481.500	4.423.100	1.500.260	100.000
	U:	991.400	3.835.100	1.717.030	542.230
Rabies Vaccine	İ:	-	11.111	80.554	100.000
(on Human diploid cells)	U:	39.046	22.866	78.031	21.661
Yellow Fewer	İ:	50	380	-	-
	U:	123	177	83	37
Hepatit B	İ:	-	-	-	-
	U:				1.800
Tetanus Sera	İ:	250.000 Ampoule	309 Ampoule	-	-
(1500 Ü.)	U:	98.940 "	57.985 "	56.375 Ampoule	20.261 Ampoule.
Tetanus Sera	İ:	100.000 "	-	-	-
(5.000 Ü.)	U:	27.554 "	46.021 "	42.810 "	15.074 "
Snake Sera	İ:	4.000 "	-	3.000 "	1.500 "
	U:	3.480 "	3.197 "	2.967 "	1.533 "
Rabies Sera	İ:	-	700 "	-	-
	U:	1.200 "	700 "	-	-
Gas-Gangrene	İ:	-	-	-	3.740 "
Antitoxin	U:	-	-	-	-

İ: Imported U: Utilized

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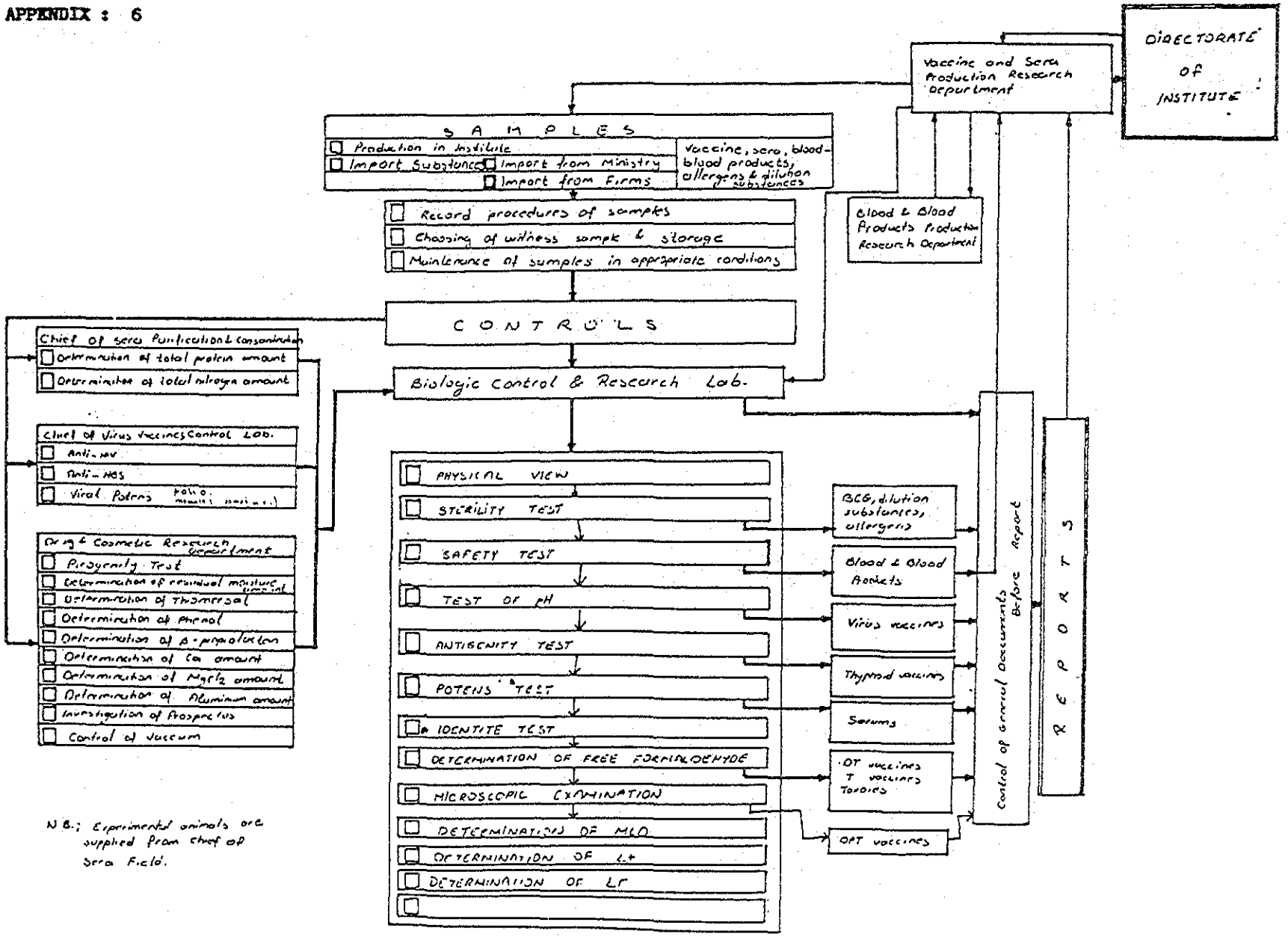
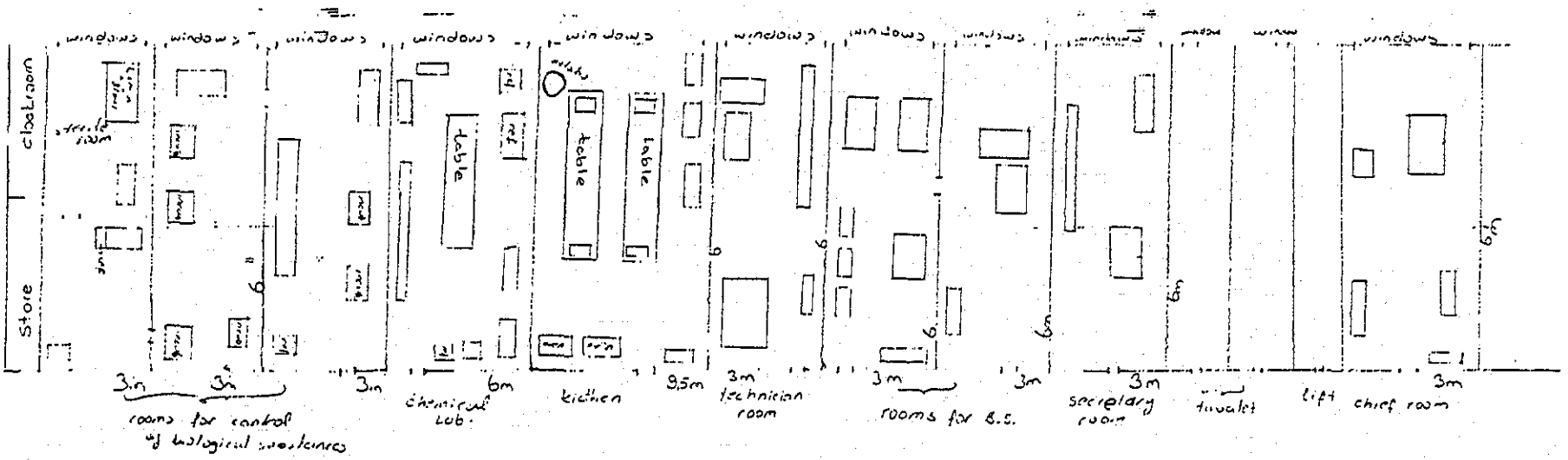
APPENDIX : 6



N.B.: Experimental animals are supplied from chief of Sera Field.

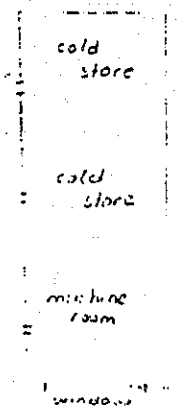
APPENDIX : 7

SETTLEMENT PLAN OF BIOLOGICAL KONTROL AND RESEARCH LABORATORYES

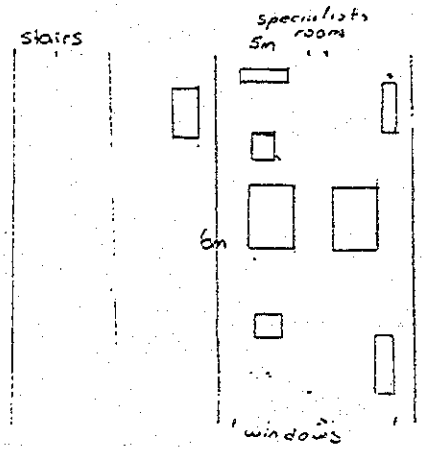


CORRIDOR

ENTRANCE



ANTISERA & ANTISERA LAB.



資料　B

平成４年３月２３日
医療協力部医療協力課
担当者：川上　兼弘

会　議　報　告

会議名	トルコ国生物製剤の品質管理プロジェクト事前調査団帰国報告会
日　時	平成４年３月１２日（木）　13:30 ~ 15:00
場　所	国際協力事業団第１１会議室
参加者	深井孝之助（財・阪微生物研究会理事長）、中川久雄（社・細菌製剤協会常務理事）、木原光城（バイオメディカルサイエンス研究会学術運営委員長・編集長）、亀山昭一　松山繁夫（武田薬品工業株式会社嘱託）、小浜友昭（国立予防衛生研究所麻疹ウィルス第三室長）、高橋元秀（同研究所体液性免疫部主任研究官）、三宅真二（厚生省国際課国際協力専門官）、大宮（外務省技術協力課事務官）、西野世界（国際協力事業団理事）、曽我紘一（同医療協力部長）、長谷川敏彦（同医療協力課長）、鈴木達男（同課長代理）、川上兼弘（同課職員）
討議内容	１．帰国報告概要： （１）レフィク・サイダム中央衛生研究所は、我が国の国立予防研究所のような中心的な機関であるが、過去８年間に保健大臣交替10名、そのたびに局長から課長までが替わっており、同研究所の安定した運営がなされていない嫌いがあるも、本要請を機会に長期的な展望で建て直す気運が窺われた。 （２）世銀がCo-fund に同意していたが、詳細な内容が世銀の満足するものでなかったこと、政変等によりこれからプランニング、８～９月頃原案が固まる予定とのことで、世銀との関係は白紙に戻っている。 （３）ワクチン製産は民営化を進めている。 （４）現有機械は旧式の機材でやっているレベルも低い。高級な機材を導入した場合メンテナンスのレベルが危惧される。 （５）ワクチンの品質の確保が問題 ２．今後の対応： （１）生産部門の将来の見通しがつかないので問題がある。 ワクチンの検定をして品質管理をするのは可及の必要性があるとし、長期調査員を４月上旬より１ケ月派遣、協力の細部を調査することとする。 （２）協力範囲はワクチン生産部門（生産技術、In-process control技術）を除く、検定部門の協力に限定、対象品目はEPI 関連６ワクチンとする。 尚、トルコには不可欠の中心部門になるAuthority がどこにできるのか　現在未決定。８月に計画策定、完全に出来上がるまでに３年間位かかるので、現在の研究所で本プロジェクトを実施予定とする。 （３）技術協力の規模： ⓐ専門家派遣：長期　３～４名、上限10名程度 短期　　５人程度／年 ⓑ研修員受入：２～３名／年×３年間 ⓒ機材供与：１億数千万円程度 （４）実施協議調査団の派遣 平成４年７月上旬派遣を目途 但し、R/D 発効日は、平成５年１～３月頃に設定。 以上
検討事項	

トルコ国生物製剤品質管理プロジェクト

分担報告

事前調査団

団　員　　亀　山　昭　一（バイオメディカルサイエンス研究会）

団　員　　松　山　繁　夫（武田薬品工業株式会社）

1．緒　　論

（別　途）

2．要請の背景とトルコ国のＥＰＩの取り組みに関する調査結果

（別　途）

3．生物製剤製造に関する調査結果

3．1　Refik Saydam Hygiene Center（以下Hygiene Center）

Hygiene Centerは1928年、Dr. Refik Saydamが「Center Hygiene Institute」として開設し、ワクチンおよび抗血清の生産、化学および薬理学分析、伝染病予防、公衆衛生学校経営、などの事業を行ったことに始まる。現在は、トルコ国の保健分野における、科学、技術、行政などを支援するための国立総合センターとして機能し、次の11部門で構成されている。

(1) Vaccine and Sera Production and Research Department
(2) Blood and Blood Products Production and Research Department
(3) Drugs and Cosmetics Research Department
(4) Food Safety and Nutrition Department
(5) Environmental Health and Research Department
(6) Contagious Diseases Research Department
(7) Toxicology Department
(8) Health Progress Training Department
(9) Publication and Documentation Department
(10) Administrative and Financial Services Department
(11) Personal Services Department

Hygiene Centerは首都Ankara市街の略中央に位置し、約35,000㎡の敷地に14の主要建屋を持つ（資料１）。別に市街地の北東（車で所要時間約50分）空港近くに、血清製造と動物繁殖の施設（Sera Production Ranch）を付属する。

3．2　生物製剤のトルコ国内需要現況

3．2．1　トルコ国国内生産

トルコ国のワクチン生産は、唯一Hygiene CenterのVaccine and Sera Production and Research Departmentが担当している。当該部門は施設内の複数の建屋に分散しているが、組織としては次の7研究室から成る。

(1) Bacterial Vaccines Production Laboratories

(2) BCG Vaccine and Tuberculin Production and Control Laboratories

(3) Virus Vaccines Production Laboratories

(4) Sera Production Laboratories (Ranch)

(5) Experimental Animals Breeding Laboratories (Ranch)

(6) Antigens and Antisera Production Laboratories

(7) Biological Control and Research Laboratories

生産しているワクチンの種類と生産実績を資料2に示す。

1990年には破傷風トキソイド（以下T）、ジフテリア・破傷風混合トキソイド（以下ＤT）、ジフテリア・破傷風・百日せき三種混合ワクチン（以下ＤＰT）のいずれも plain製剤と、ＢＣＧおよびSemple型狂犬病ワクチンが生産されていた。また、ワクチン以外の生物製剤として、各種の抗血清（破傷風、ジフテリア、ガス壊疽、炭疽、さそり毒、狂犬病）や診断血清などが製造されている。

3．2．2　Hygiene Centerのワクチン製造技術

正確な評価にはさらに詳細な調査を必要とする。視察した範囲では、ＢＣＧ生産工場はコンパクトにまとめられ、それなりの技術の蓄積が感じられた。トキソイド作業室は閑散とした感じで、設備、器具は清潔ではあるが、いづれも古典的で、かなり長期間設備、技術の投資が途絶えていたと思われた。

技術者集団との短期間の交流ではあったが、優れた指導者が見当たらず、Hygiene Centerのワクチン製造部門は近年、少なくとも我が国と比べて30年間、進歩が止まっている印象を受けた。百日せきワクチンの力価測定技術を持たずに生産を続けたり、トキソイドのハプトグロブリン除去工程を欠き褐色の色濃い原液のままであったり、アルミニウムアジュバント技術を持たないなど製造の近代化にはかなりの努力と期間が必要と思われた。

なお、トルコ国の一般医療品の生産技術を理解する目的で私企業のI.V.Solution Factoryを見学した。注射用（蒸留）水の取り扱い、その他、一応ＧＭＰの型を踏まえた設備になっており、民間のレベルの高さを窺うことが出来た。

3．2．3　輸入ワクチンの種類と需要実績

輸入ワクチンの需要実績を資料2に示す。また、入手した一部の輸入薬品のSummary Protocolを資料3に示す。製剤容器が注射筒またはアンプルの一人用であること、T，ＤT，

ＤＰＴの使用有効期間を検定合格後３年間としていることが注目された。

３．２．４　トルコ国ワクチンの製造原価と輸入ワクチンの購入価格

1991年のHygiene Center製造原価および輸入ワクチンの購入価格を資料２に示した。原価分析のためには詳細調査が必要であろう。

３．２．５　Hygiene Centerのワクチン生産に関する将来構想とプロジェクトの対応

現在、トルコ国のワクチン供給は１／３が国産、２／３を輸入に頼っている。将来この供給をどのような態勢にシフトするかは、プロジェクトの枠組みを考慮する上で重要な前提となる。

ワクチン生産の経営形態として、官営、公営、民営など各種の選択肢が考えられるが、調査の範囲では将来構想を確認出来ず、国としての方針は未定と思われた。

ワクチンの品質保証には製造の全工程での品質管理、即ちIn-process Controlが不可欠であるとされているが〔The National Control of Vaccines and Sera, ＷＨＯ　ＴＲＳ 658, 1981（以下ＷＨＯ指針)]、Hygiene Centerは製造技術が未完成で、In-Process Controlを言々する以前の状況と思われる。加えて、将来方針が定まらなければ、移転すべき技術も特定する事が難しく、選択肢によっては支援が無駄になることも懸念されるから、将来計画が決まった後、必要があれば、製造技術の改善と平行してIn-process Controlを導入するのが妥当であろう。従って、今次調査団はＷＨＯ指針に準拠し、最終製品の品質管理の技術協力を実施することを想定した調査を重点的に進めることとした。

４．品質管理に関する調査結果

４．１　Biological Control and Research Laboratories（以下ＢＣＲＬ）の現状

４．１．１　ＢＣＲＬのHygiene Center組織上の位置は、３．２．１項で述べたように、Vaccine and Sera Production and Research Department に所属する。ワクチン検体の流れは、資料４に示す通り、Hygiene Centerの生産品はセンターで処理され、輸入ワクチンは、General Directorate of Primary Health Care (Ministry of Health and Social Walfare) が全権を持つ。ＷＨＯ指針によれば、これ等の差別が事実であれば問題であり、運営の詳細についてさらに調査が必要と思われた。

検定の窓口でもあるＢＣＲＬは検定項目に応じて他の４部門に試験依頼をする。定期的試験の流れは資料４に記載の通りで、非定型例としてＢＣＧと血液製剤があり、いずれも製造部門の長が品質管理の責任者も兼ねており、今後改善すべき問題である。

Hygiene Centerで実施されている品目ごとの検定項目、検定部門を資料５に示す。

４．１．２　年間検定実績と検定結果

製造ロットの無菌試験の年間検定実績と結果を調査した。別途、1991年（１～11月）の品質管理試験実施ロット数を入手した。いずれも資料６に示す。両者のロット数のくい違いの

理由は不明である。最近２年間は、年間約160ロット、内輸入品約40ロットの検定が実施されていた。

４．１．３　ＢＣＲＬのマンパワー

職員数14名、内技術者７名である（資料７）。要請に沿って、ウイルス、理化学、ＢＣＧ、その他の試験部門をＢＣＲＬに統合充実するには総員約15名の増員が必要と思われる。

２～３の技術者は、独、佛、などで品質管理の研修を受けていたが、受講者のノートを見た限りでは、品質管理の理論や実際を十分に習得したとは言い難い。また、研修内容がトルコの技術と落差が大き過ぎて、十分活かされていない面も見受けられ、プロジェクトでは現地の実情に則したカリキュラムが重要であることを示唆していた。

一方、技術者は比較的若く、技術的好奇心も旺盛で、よく質問し、今後の技術、技能の成長が期待された。

４．１．４　現有の設備および器機

現在、ＢＣＲＬは第５棟の４階に位置し、無菌試験室、血清試験室を中心に約400㎡（廊下を除く）を専有し、別に第６棟の地下室に約400㎡の試験動物飼育室を使用していた。それぞれの平面図を資料８に示す。

ＢＣＲＬが現在保有する主な器機は次の通りである。

器機名	台数	設置場所	主な用途
クリーンベンチ	1	Steril room	無菌試験
孵卵機	6	Incubation room	〃
顕微鏡	1	〃	〃
冷蔵庫	4	Sera control lab.	汎用
蒸留水	1	〃	〃
ｐＨメーター	1	〃	〃
化学天秤	1	〃	〃
遠心機	1	〃	〃
分光光度計	1	〃	〃
蒸気滅菌機	1	Media preparation	無菌試験
乾燥滅菌機	2	〃	〃
－20℃冷蔵庫	1	Office 4	汎用

孵卵機、恒温槽が使用不能のまま放置されているものもあり、器機整備能力を詳細調査すべきであろう。

４．２　特定技術の現状評価

４．２．１　トキソイド力価試験の現状

力価試験の１例を資料９に示す。ジフテリアおよび破傷風トキソイドともに絶対値を求め

て合否を判定する古典的方法で（合格基準：ジフテリアトキソイドは１：６希釈、破傷風トキソイドは１：４希釈の接種群が80％以上の生存率であること）力価を単位表現できないばかりか、国際的に通用する試験法ではない。また、攻撃毒素量も低く（示された事例の２～３倍量が必要）、低力価の検体を見掛け上合格と判定する恐れがある。ＷＨＯ基準に従って、相対力価試験法を用いようとしてもトルコ国にはまだ国内標準品がなく、国際法は実施できない。この事は技術面から見た本プロジェクト最大の問題点と考えられた。

４．２．２　抗毒素力価試験の現状

１例として破傷風抗毒素について試験記録を調査した。被検抗毒素は６段階で用量反応を試験しているのに対し、対照標準抗毒素は１段階（１単位）のみで、相対力価試験法の統計学的概念の欠落が懸念された。生物検定法の理論的指導が急務と思われる。

４．２．３　無毒化試験の現状

ジフテリアトキソイドの無毒化試験について記録を調査した。モルモット試験法のみで、検出感度のより優れたウサギ試験法の導入が必要と思われた。

４．２．４　無菌試験の現状

1989年から調査時点までの無菌試験実施成績を調査した。更に1991年の試験記録について精査した。また、破傷風トキソイドを例に、個体バルクがどのような（無菌）試験経緯を辿っているかも調べた（資料10)。最終判定では合格とされているが、試験経過の中では再試験および不合格が高率に発生している。このことは、検体（製剤）の汚染率が高いか、無菌試験が不正確かのいづれか、または両者に原因があると考えられ、品質保証の上で由々しき問題であり、早急に原因を解析し、対象を確立することが望まれる。

調査の中でロットの概念が正しく理解されていない事が懸念された。品質保証の基本にかかわることであり、本件プロジェクトが単なるQuality Controlの技術支援に留まらず、ＢＣＲＬのQuality Assurance（管理・運営）にも言及せざるを得ないと考えられた。

４．２．５　試験動物の現状

試験動物（マウス、モルモット、ウサギ）はAnkara空港近くのRanch（Experimental Animals Breeding Laboratories）で自家繁殖していた。供給能力は十分にあるとされ、余剰動物を大学その他の研究機関に分与していると言う。因みに、1990年、1991年（調査時まで）に生物製剤の検定に使用された動物数は次の通りであった。

動　　物	1990年	1991年
マ　ウ　ス	2,655	1,605
モルモット	2,291	1,450
ウ　サ　ギ	5	5

一方、生物検定では動物の種類、系統、飼料、飼育環境など種々の要因が結果に影響することが知られており、Ranchで繁殖されている各動植物が適格かどうかは詳細調査が必要である。また、Hygiene Center内の試験中動物の飼育環境は狭隘で暗い地下室で、マウス30ケージ、モルモット25ケージの収容能力と言う。今後の検定能力充実のために改善を要すると思われた。

5．トルコ国生物製剤品質管理プロジェクト実施体制

5．1　要請内容の確認

1990年8月、トルコ国政府から要請されたプロジェクト方式技術協力の内容は次の数項目に要約される。

(1) Biological Control and Research Laboratoriesを製造部門から独立させ（新しくセンターを建設する計画がある）、分散している検定担当部署を集合して、世界水準に合致する品質管理を実施したい。

(2) 当面、①化学・生化学・免疫化学試験室、②細菌学試験室、③マイコプラズマ試験室、④ウイルス学試験室、⑤実験動物管理室、それぞれの試験研究室を整備確立したい。

(3) 生物製剤の国内標準品を作りたい。

(4) スタッフの技術力向上のため研修をして欲しい。

5．2　実施体制の枠組み

技術協力計画を策定するに当り、調査結果を踏まえて、枠組みとなる諸前提を整備した。

(1) 1985年に開始したトルコ国の免疫拡大計画（ＥＰＩ）は着実に進んでいるとしてよい。法律で決められた予防接種は無料で、Rural Midwivesの指導のもとにHealth station（人口約2,500人単位に設置されている保健医療の基本施設）、Health Unite（Health stationの上部機関）で実施するとされている。冷蔵輸送車、冷蔵庫、搬送アイスボックス、などCold Chainは現場調査の範囲ではよく整備、管理されていた。

(2) 現在トルコ国で流通している生物製剤は、ＥＰＩワクチン以外に治療血清（破傷風、ジフテリア、炭疽、ガス壊疽、狂犬病、さそり毒、蛇毒）、血液製剤、その他ワクチン（狂犬病、腸チフス、コレラ、Ｂ型肝炎、黄熱、風疹、おたふく風邪、球菌性髄膜炎）、など多岐にわたっているが、Hygiene Centerの技術現状から見て、これらを総じてプロジェクトの対象とすることは困難である。まず、ＥＰＩワクチン6品目の最終製品の品質管理試験技術に限って支援を開始するべきであろう。対象品目をこれ等の6品目に限っても、移転技術は汎用性があるから、その他の品目はトルコ国の自助努力で完成すべきである。

(3) 一方、トルコ国でＥＰＩに用いるワクチンは輸入（最終）製品が約2／3を占めるとされ（沈降ＤＰＴ、ポリオ、麻しんなど）、国産品ワクチンはＢＣＧ、トキソイド類に略限られており、技術水準は必ずしも高いとは思われない。トルコ国が今後ワクチンをどのよ

うに調達するか、政府の方針は不明確で、輸入に頼るか国産化を拡大するのか、また、現状のように最終製品の輸入を続けるのか中間半製品（バルク）輸入もあり得るのか、などによって品質管理試験技術、特に生ワクチン関連技術は大きく変わることが予想される。しかし、いずれの選択肢が採用されても、生産の現状を変えるには数年を要すると考えられることから、本プロジェクト実施の枠組みでは、現状のワクチン供給体制を前提に、ＷＨＯ指針に沿って、最終製品のNational Control(Quality Assurance) 確立を支援する立場に限るべきと考える。

(4) 新設が検討されている生物製剤品質管理研究センター構想は、建設予定地を Sera Production Laboratoriesに隣接するRanchに確認した。一方、資金を提供するとされる世界銀行の検討は、Phase Ⅱ段階 (Phase Ⅰ：Proposal, Phase Ⅱ：Budget, Phase Ⅲ：Presentation)で、まだ最終見通しは立っていなかった。また、本計画は1991年国家予算で建設が承認されたとされているが、その詳細を確認することは出来なかった。これらの状況から、新センター構想が実現するとしても、早くとも、３～４年以後になると判断される。

(5) National Control Laboratoriesの確立は、ＷＨＯ指針を待つまでもなく、トルコ国に生物製剤が流通する以上必須であり、新センター構想実現の有無と無関係にトルコ国にとって本プロジェクトは有効であるとしてよい。むしろ、新センターが実現するまでに、技術、設備、機材などが確立していることが望ましく、そのためにも本プロジェクトの早期実現が期待される。

(6) 一方、National Control Authority（一般に厚生大臣を最高責任者とする）が生物製剤の分野でどのように機能しているかは、今後品質保証の骨格として技術移転には不可欠の要件である。調査資料（Activity on Drug in Turky, Drug Control in Turky, etc）によると一般医薬品分野では、National Control Authorityは組織的に体系化され、具体的に管理されて、その機能を発揮していると思われる。しかし、生物製剤ではNational Control Authority が責任を持ってＷＨＯ指針に示されたような国際的な機能が構築されているように見えない（製造規準、製造承認、輸入承認などの基本的法的処置が施行された形跡がない)。

本件プロジェクトを効果的に進めるためには、当該分野のNational Control Authorityの体系的制度の確立、具体的活動が重要となろう。

(7) ＷＨＯ指針のQuality Assuranceを確立するために、現在分散している検定担当部署を集合したいとするトルコ国の当該要請は妥当である。しかし、新設備完成は早期に実現したとしても３年以後と考えられることから、完成以前にプロジェクトを開始するためには、現設備を一部改装して計画を進める以外にはない。現在使用中の第５棟４階、全フロアーを利用し、要望のあった試験研究室を整備することとなろう（約６００㎡、改修費概算見積150,000,000TL)。同時に技術者、技術補助者、計約15名の充員、諸運営費などトルコ国政

府の承認が前提となる。

(8) National Control Authorityが果たすべき役割の１つとして、ＷＨＯ指針には国内標準品の作製を上げている。且つ、生物検定には物差としての標準品は即刻必要となることから、トルコ国の当該要請は妥当である。

一方、国内標準品の作製はＷＨＯのガイドライン（Guidelines for the Preparation, Characterization and Establishment of International and other Standards and Reference Reagents for Biological Substances : ＷＨＯ ＴＲＳ 800 ; 1990）に示されている通り、必ずしも容易ではない。本来、これ等の経験も、技術も、材料も持ち合わせていない開発途上国で、まず必要なのは標準品（参照品）を作れるような技術その他の基礎的背景整備であって、自力で標準品が出来るようになるのはその結果であろう。

フィリピン国（Biological Production Service)では、破傷風のLf用参照品の設定に誤りがあり、製造・品質管理の混乱の原因になっていたし、ジフテリアトキソイド、百日せきワクチンの標準品（参照品）は国際標準品を日常検定に使わざるを得ない状況にあった。

これ等の事例も参考にして、トルコ国の要請をどのように果たすか、１国の支援にとどまらず、将来同じような要望が出るであろうことを踏まえて、総合的に対応を検討する必要があろう。

(9) 生物検定には実験動物が不可欠である。実験動物の適否は試験結果に直接的影響を持つことから、品質管理試験技術の向上に実験動物の改善が前提となる事例が多い。Hygiene Centerの実験動物は一見清潔で良質と判断されたが、当該の生物検定に適するか、或いはさらに良質の動物がトルコ国内で入手出来るかなどさらに調査検討を要する。

また、トルコ国が要望している実験動物管理室の整備確立についても、具体的目標をさらに相手国と詰める必要がある。近代実験動物の繁殖と利用には、高度にして広範な技術、莫大な投資と維持費、加えて生物なるが故の需要調整を含む特殊な経営管理などのノウハウが必要で、望ましくは、途上国における実験動物の段階的改善手順について、この際別途専門家の衆知を整理しておく事を提案する。

６．プロジェクト技術協力の可能性

６．１　技術協力の可能性と方策

プロジェクト方式技術協力の具体的枠組みを以下の各項を前提として作製した。

(1) ＥＰＩ（破傷風、ジフテリア、百日せき、ポリオ、麻しん、結核）関連ワクチンを対象品目とする。

(2) ワクチン生産技術およびIn-process Control技術には関与しない。

(3) ワクチンの調達、供給体制に係わらず、ＷＨＯ指針に準拠して最終製品の品質保証のための検定が実施できるようにする。

(4) トルコ国の基準が公布されるまでの間はＷＨＯ基準を準用する。

(5) トルコ国のワクチン分野におけるNational Control Authorityがさらに体系化し、具体化するようQuality Assuranceの運営管理についても技師的範囲内で助言する。

ＷＨＯ基準による品目ごと検定項目一覧表を資料11に示す(Requirements for Diphtheria, Tetanus, Pertussis and Combined Vaccines, WHO TRS 800;1990. Requirements for Measles Vaccine, Live, WHO TRS 771;1988. Requirements for Poliomyelitis Vaccine, Oral, WHO TRS 800;1990, Requirements for Dried BCG Vaccine, 745;1987)。

これらの各検定項目について、世界の平均レベルで検定が出来るように技術移転、機材供与、技術者研修を行うこととする。また、これ等の実務を通じて、自国基準の作製、国内標準品の確立（又確立するための背景整備）など、National Control Authorityの制度および実施体制の充実を支援する事となろう。

トルコ国の自助努力に期待することも多く、当面プロジェクトの支援期間は３か年とし、National Control Authorityの具体的活動、ワクチン供給体制の方針に応じて、要すれば次のステップ、例えば支援品目拡大、検定項目追加、In-process Control支援などへの進展の適否を協議することとしたい。

６．２　技術協力基本計画の設定

プロジェクト協力基本計画案を資料12に示す。

６．２．１　専門家派遣

現地はりつけの長期専門家（常時）２名を派遣し、基礎技術の移転、周辺技術の整備を進める。

短期専門家を現地の準備状況に応じて派遣する。専門分野を品目別にするか、試験技術分野別にするかは、専門家の出身母体と協議の上決める。

６．２．２　研修生の受け入れ

受け入れ要員はＪＩＣＡ・Schemeに依るが、ここではNational Control Authorityの制度および管理の研修も含め、延べ６～10名の研修員を受け入れる。各人の研修課題は受け入れ機関の実情に合わせ、協議の上決める。

６．２．３　機材の供与

Hygiene Center側の要望器機は資料13に示す通りで、相手国提案の優先順位も付記した。

日本側調査による必要機材、使用調査、年次計画への展望などの詳細検討が必要である。

一方、計画立案と平行して、営繕改善計画、器機配置計画、電力・蒸気・上水・下水など配線配管計画、ユーティリティ、床加重など付属設備の能力調査等が必要である。Hygiene Center作製の営繕改修計画を資料14に示す。

６．３　長期調査団の調査事項案

次の各項について詳細調査が必要と思われる。

(1) トルコ国生物製剤のNational Control Authorityの実施体制、制度の現状および将来計画とＷＨＯ指針（National Control of Vaccines and Sera, WHO TRS 658; 1981）との整合性。

(2) 各ワクチンの製造および試験記録（全文）の確認とＷＨＯ Requirementsとの整合性およびＷＨＯの所謂「Technical adviser」の実体。

(3) 製造および品質管理試験の標準作業法（ＳＯＰ）の現状。

(4) 品質管理諸記録の実情点検。

(5) ＢＣＲＬの組織再編成計画とプロジェクトの整合性。

(6) 各種ワクチンの処方設計と剤型の確認および輸入品の承認、検定制度の実体。

(7) トルコ国国内標準品確立方法の検討と実施計画の策定。

(8) トルコ国実験動物需要の実体とプロジェクト実施計画の策定。

(9) プロジェクト関連営繕改修計画の妥当性。

(10) 器機の詳細仕様作製、日本側提案器機および供与機材の詳細調整。

(11) 器機配置計画作製、配線・配管その他ユーティリティ能力確認。

(12) 研究室の将来計画と供与機材の関連。

(13) 器機の保守・点検・管理能力。

(14) 供与器機、携行機材の年次計画への展開。

(15) 実施計画の妥当性確認。

(16) 製造原価、輸入価格、財務状況の再確認。

(17) 相手国の果たす役割りの立案。

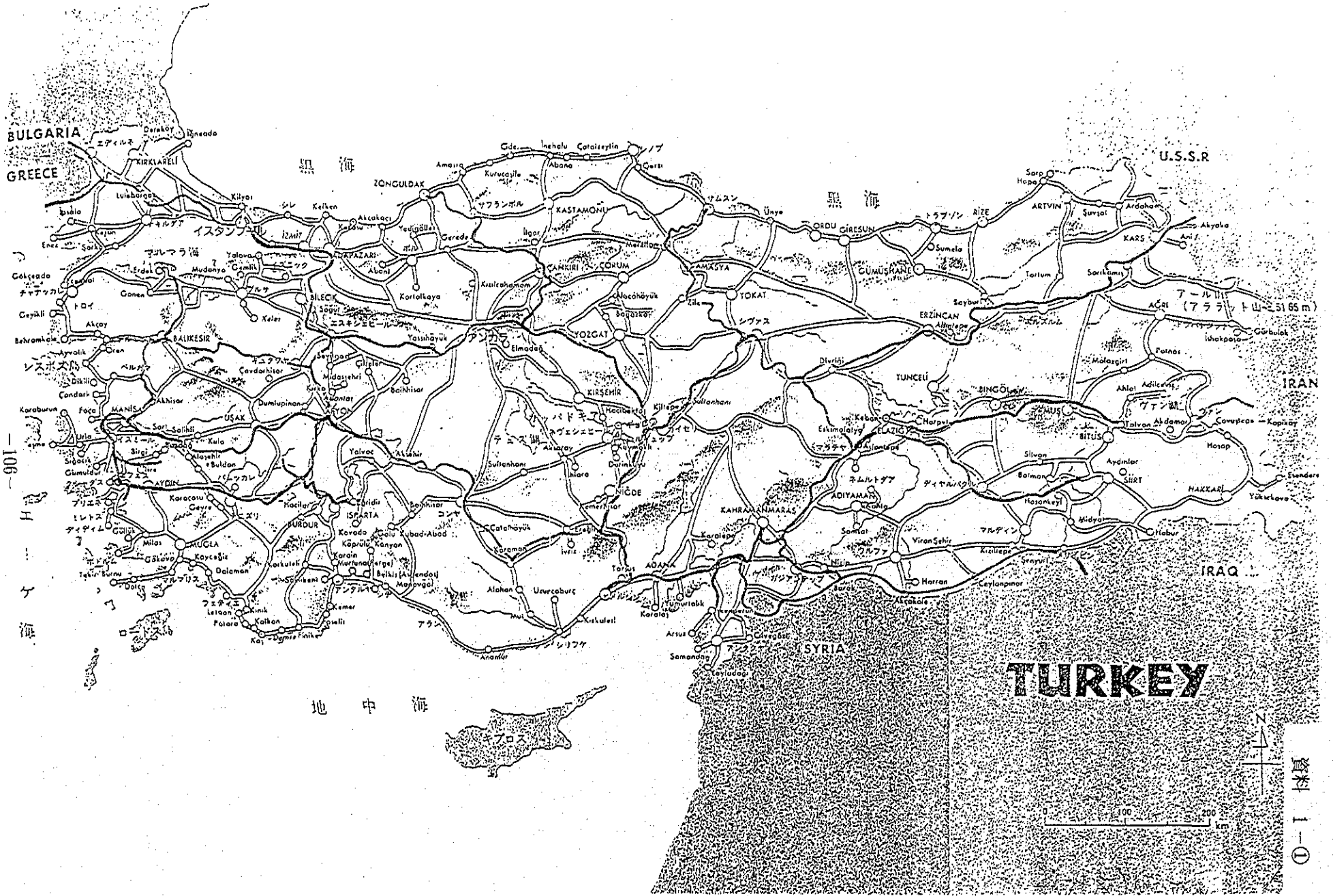
(18) トルコ国、Hygiene Centerの語学障害、専門家の生活環境など、プロジェクト周辺条件の観察と対策検討。

(19) その他。

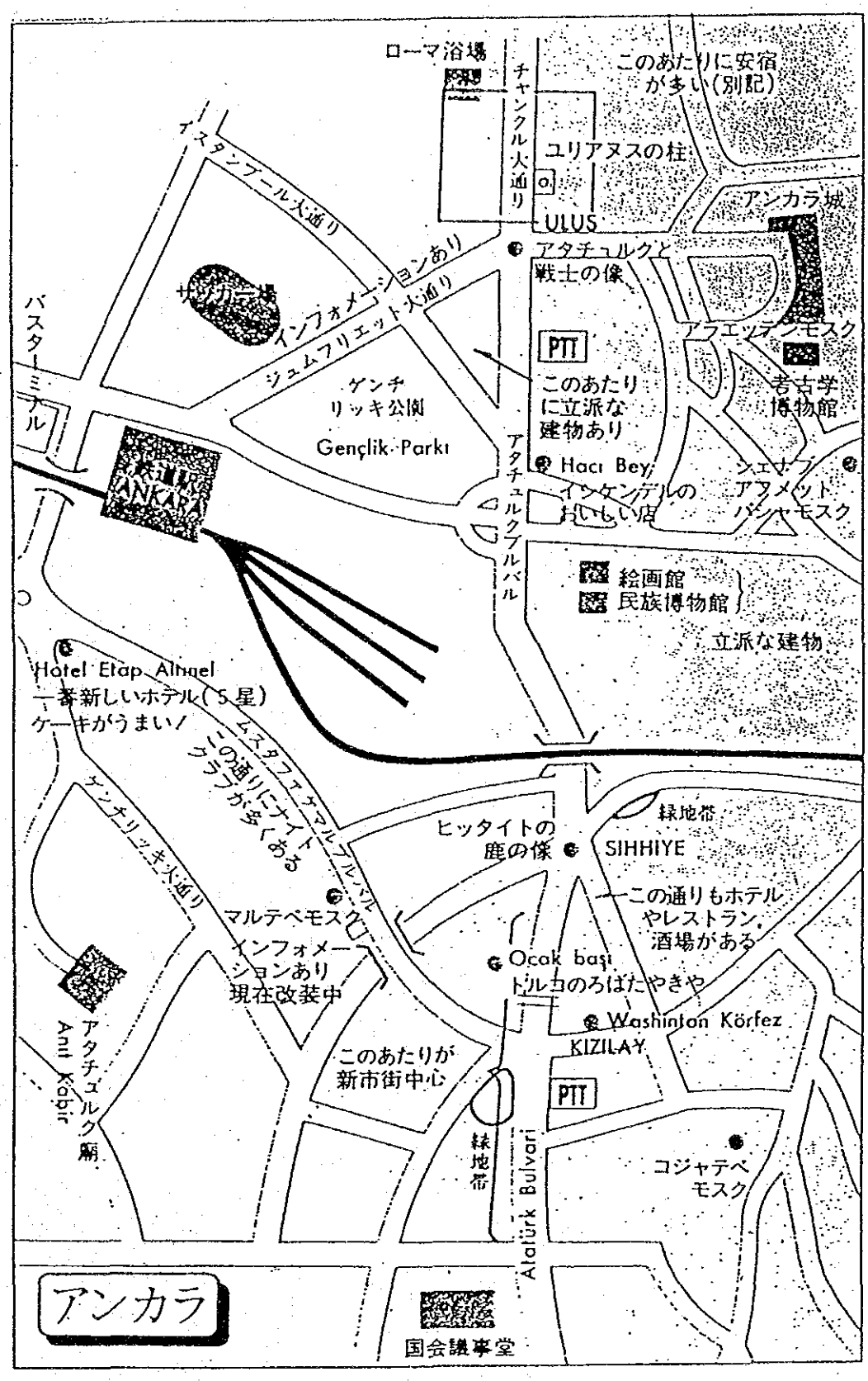
7．結　論

（別　途）

以　上


TURKEY
BULGARIA
GREECE
U.S.S.R
IRAN
IRAQ
SYRIA
黒海
地中海
エーゲ海
マルマラ海
アール山（アララト山 5165 m）
N
0
100
200
km

地図 1－①



Cemal Gürsel Cad. No.18 Sihhiye

4 Fl.
«1940~'72»
Biochemical control. Biological control
Feral control. Antigen antisera
Bacteriology &. Tuberculosis
5
«1928»
Bacterial vaccine production
2
6
Viral vaccine production and Lyophilization. Rabbit prod.
14
7
«1940~'72»
13 Delivery
«1928»
8
BCG Production
Drug & cosmetic control
11
12
Power plant
Pharmacology
Administration
1
Poison & Environmental Control
4
Library
«1928»
3
Personnel
10
9
İsappaşa caddesi
cemal gürsel caddesi
yakıtcılar sokak
yeni yol

Hygiene Centerのワクチン生産実績※

（doses／1月～12月）

ワクチン名＼年（1～12月）	1983	1984	1985	1986	1987	1988	1989	1990
ＤＰＴ　3混　(plain)	4,005,400	4,058,400	1,546,400	1,661,200	0	2,264,000	561,000	958,800
Ｄ　Ｔ　2混　(plain)	1,202,945	1,620,500	2,427,000	2,846,000	1,200,000	1,465,000	2,248,050	1,905,000
破傷風トキソイド (plain)	3,025,500	3,269,000	2,731,000	2,900,000	920,000	3,391,000	3,344,000	2,696,000
腸チフスワクチン	106,800	267,000	129,000	0	114,800	0	31,200	182,800
コレラワクチン	30,000	0	23,000	0	0	0	0	0
ＢＣＧ　(液　状)	4,882,300	4,918,400	2,497,350	0	0	0	0	0
ＢＣＧ　(凍結乾燥)	345,000	472,500	3,693,190	3,881,500	3,178,000	3,977,000	2,444,000	1,624,000
ツベルクリン　(ＰＰＤ)	3,205,950	5,292,300	3,656,200	4,825,500	4,415,750	4,521,350	4,572,600	818,150
狂犬病ワクチン (Semple)	1,559,275	1,331,050	1,191,925	1,339,825	1,394,900	1,108,700	717,900	844,900

※　ツベルクリン（ＰＰＤ）を含む

資料２－②

ワクチンの輸入および使用実績

(doses／１月～12月)

ワクチン名＼年（１～12月）		1988	1989	1990	※1991	備考（輸出メーカー／単価）
沈降破傷風トキソイド	輸入量	3,000,000	4,420,000	0	0	Meriuex, Berna,
	使用量	1,072,000	3,284,860	3,005,000	341,140	Sclavo
沈降ＤＰＴ　３混	輸入量	5,710,000	6,500,000	6,000,180	0	Meriuex, Berna,
	使用量	5,245,000	5,451,000	3,064,400	3,007,000	Sclavo
ポリオワクチン（ＯＰＶ）	輸入量	10,643,660	11,046,800	3,500,000	4,500,000	Meriuex
	使用量	7,682,600	10,218,760	7,270,000	3,998,000	
麻しんワクチン	輸入量	481,500	4,423,100	1,500,260	100,000	Meriuex
	使用量	991,400	3,835,100	1,717,030	542,230	
狂犬病ワクチン（人２倍体）	輸入量	0	11,111	80,554	100,000	Meriuex
	使用量	39,046	22,866	78,031	21,661	
黄熱ワクチン	輸入量	50	380	0	0	
	使用量	123	177	33	37	
Ｂ型肝炎ワクチン	輸入量	0	0	0	0	Meriuex, Berna
	使用量	0	0	0	1,800	

※　１月～６月実績

＜単価：未完成 '92/02/21＞

トルコ国ワクチン製造原価の比較
(参　考)

＜未完成：'92/02/21 ＞

ワクチン名	容量単位 人分	製造原価 TL	単　価 /dose (¥換算) 円	ＢＰＳ 原　価 (¥換算 /dose)	Bio Farma 単　価 (¥換算 /dose)	UNICEF 単　価 (¥換算 /dose)	トルコ国 輸入価格	輸入単価 /dose (¥換算)
ＤＰＴ　3混 (plain)	20	24,000	31.58					
ＤＴ　2混 (plain)	20	12,000	15.49					
破傷風ﾄｷｿｲﾄﾞ (plain)	20	6,000	7.89					
腸 ﾁﾌｽﾜｸﾁﾝ	20	4,000	5.26					
ＢＣＧ (凍結乾燥)	20	12,000	15.79	5.35	3.74	7.15		
ツベルクリン (ＰＰＤ)	200	3,000	0.40					
狂犬病ワクチン (semple)	25	25,000	26.32	33.87				
沈降破傷風 トキソイド	10			7.60	4.26	6.50		
沈降ＤＰＴ３混	10				5.27	11.05		
ポリオワクチン (ＯＰＶ)					9.97	12.35		
麻しんワクチン					22.14	19.50		
狂犬病ワクチン (人２倍体)								
沈降ＤＴ　2混	10				5.27	8.84		

１￥＝38TL，１US＄＝130￥，１US＄＝22.5Ｐ，１US＄＝1,800Rp

INSTITUT MÉRIEUX
Quality Control

****

SUMMARY PROTOCOL FOR

ADSORBED TETANUS VACCINE

Name and address of manufacturer

Institut Mérieux
1541 avenue Marcel Mérieux
69280 MARCY L'ETOILE
FRANCE

Lot number of vaccine	: D0155
Final bulk number	: G754
Volume of final bulk	: 500 liters
Date of manufacture of final lot	: 08.02.89
Nature of final product	: Adsorbed
Containers	: Syringes single dose
Number of containers	: 122540 syringes
Human dose	: 0.5 ml
Potency	: Not less than 40 IU/human dose
Expiry date	: FEB 1992

SUMMARY PROTOCOL FOR

ADSORBED DIPHTERIA AND TETANUS VACCINE

Name and address of manufacturer

Institut Mérieux
1541 avenue Marcel Mérieux
69280 MARCY L'ETOILE
FRANCE

Lot number of vaccine	: D0123
Final bulk number	: E753
Volume of final bulk	: 501 liters
Date of manufacture of final lot	: 03.02.89
Nature of final product	: Adsorbed
Containers	: Ampules single dose
Number of containers	: 275684 ampules
Human dose	: 0.5 ml
Potency	
Diphteria	: Not less than 30 IU/human dose
Tetanus	: Not less than 40 IU/human dose
Expiry date	: FEB 1992

UT MÉRIEUX

Control

015 DT COQ Lot n° D0190 page: 2 of 30

****

SUMMARY PROTOCOL FOR

ADSORBED DIPHTERIA, TETANUS AND PERTUSSIS VACCINE

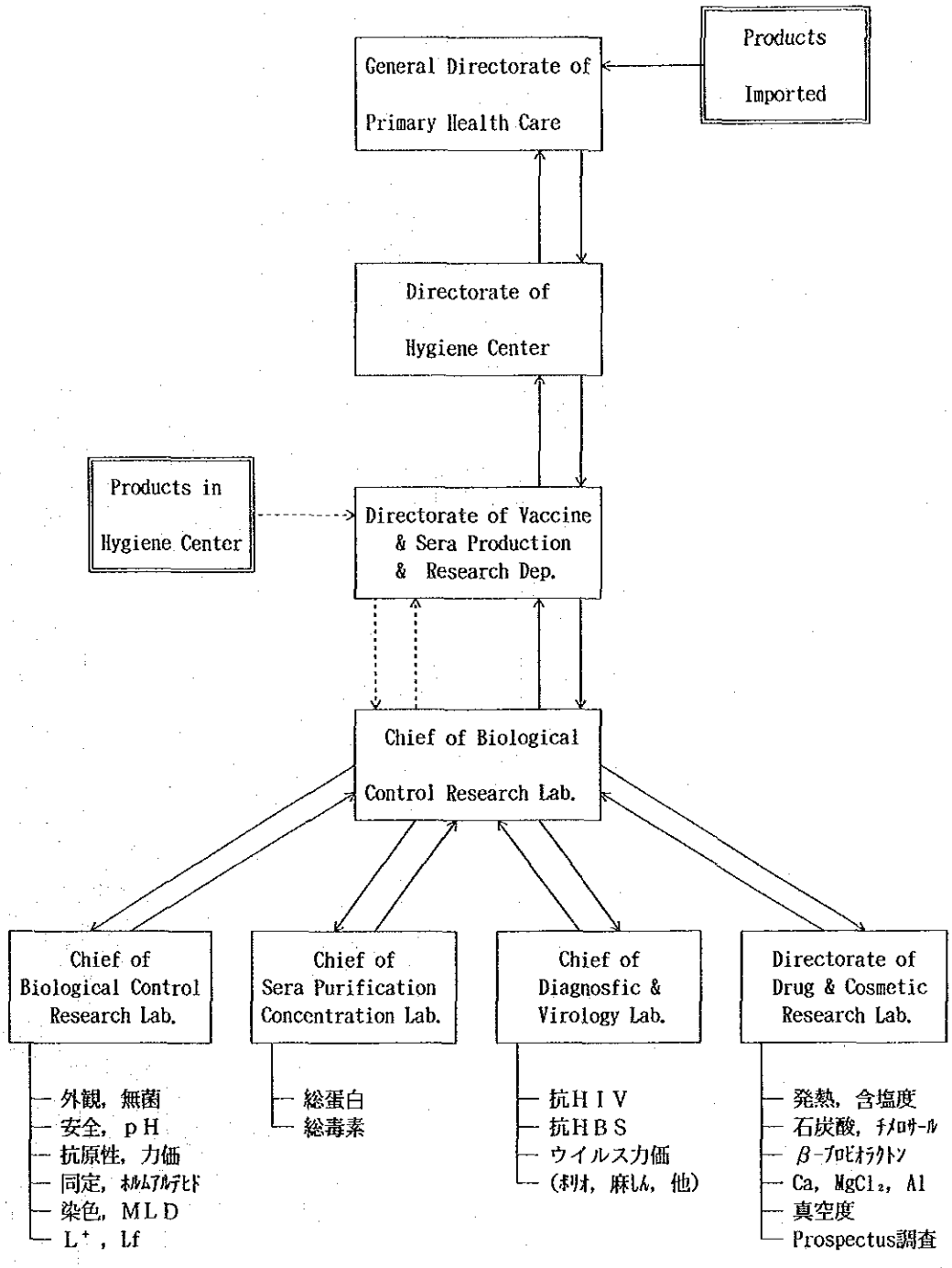
Name and address of manufacturer

Institut Mérieux
1541 avenue Marcel Mérieux
69280 MARCY L'ETOILE
FRANCE

Lot number of vaccine	: D0190
Final bulk number	: B750
Volume of final bulk	: 502 liters
Date of manufacture of final lot	: 17.02.89
Nature of final product	: Combined, adsorbed
Containers	: Syringes single dose
Number of containers	: 152599 syringes
Human dose	: 0.5 ml
Potency	
Diphteria	: Not less than 30 IU/human dose
Tetanus	: Not less than 60 IU/human dose
Pertussis	: Not less than 4 IU/human dose
Expiry date	: MAR 1992

資料 4

試験検体の流れ図



CONTROL TESTS OF BIOLOGICAL PRODUCTS IN TURKEY(Produced in the H.C.)

Biological products	Strl B	Strl F	Inct B	Inct F	Potc B	Potc F	Toxt B	Toxt F	pH B	pH F	Foma B	Foma F	Idnt B	Idnt F	Antg B	Antg F	Test
DT comb(pl)	○	○	○	○	○		○	○	○	○	○	○	○	○			BCLa
Tet(pl)	○	○	○	○	○		○	○	○	○	○	○	○	○			BCLa
DPT(pl)		○		○						○				○			BCLa
Dried BCG		○															BCLa
Tuberculin,PPD		○															BCLa
Semp type Rab		○		○													BCLa
Diph-Ab		○		○		○				○							BCLa
Teta-Ab		○		○		○				○							BCLa
Gas Gang-Ab		○		○		○				○							BCLa
Scorpion-Sera		○		○						○							BCLa
Anthrax-Sera		○		○						○							BCLa

CONTROL TESTS OF BIOLOGICAL PRODUCTS IN TURKEY(Imported products)

Biological products	Strl B	Strl F	Inct B	Inct F	Potc B	Potc F	Toxt B	Toxt F	pH B	pH F	Foma B	Foma F	Idnt B	Idnt F	Antg B	Antg F	Test
Tet(Ads)	○		○						○		○		○		○		BCLa
DT comb(Ads)	○		○						○		○		○		○		BCLa
DPT(Ads)	○		○						○		○		○		○		BCLa
	Adjuvant, Preservative																DALa
Vir Vac(Poli, Meas,Rube,Mump Infl,YelF,Rabi	○		○			○			○					○			BCLa VLa
	Moisture and the other tests																DALa
BCG																	PrLa
Meng Polys Vac	○		○														BCLa
	Protein,Moisture,Pyrogenicity,Protein test																ReLa
Imm Ser-Animal	○		○		○				○								BCLa
	Pyrogenicity,Preservative,Protein controls																ReLa

B : Bulk, F : Final products, BRL : Biological control and research laboratory, DAL : Drugs analysis laboratory, PL : Production laboratory, ORA : The other related laboratory, VL : Virlogy laboratory

注：略号は修正中です

Biological Control and Research Lab.の検定ロット数

（無菌試験）

ワクチン種類＼検定年度（1～12月）		1989		1990		1991	
		検定ロット数	不合格ロット数	検定ロット数	不合格ロット数	検定ロット数	不合格ロット数
国産ワクチン	ＤＰＴ　3混（plain）	28	1	26	0	25	0
	Ｄ　Ｔ　2混（plain）	22	0	23	0	11	0
	破傷風ﾄｷｿｲﾄﾞ（plain）	63	0	26	0	34	※ 2
	ＢＣＧ（凍結乾燥）	60	0	45	0	54	※※ 2
輸入ワクチン	沈降ＤＰＴ　3混	15	0	10	0	3	0
	沈降　ＤＴ　2混	2	0	1	0	0	0
	沈降破傷風トキソイド	26	0	6	0	1	0
	ｵﾘｵﾜｸﾁﾝ（ＯＰＶ）	12	0	6	0	17	0
	麻しんワクチン	27	0	12	0	17	※※※ 2
	ＭＭＲワクチン	4	0	3	0	3	0

不合格理由：　※無菌試験　　※※無菌試験　　※※※力価試験

1991年の品質管理試験実施ロット数
(但し、1月－11月)

製剤名	由来	ロット数	ロットサイズ
Tetanus anatoxin ※	国内	5	Ca 5 L
Diphtheria anatoxin ※	国内	2	Ca 5 L
Tetanus vaccine	国内	26	Ca 75 L
Tetanus vaccine	国外	6	
DT vaccine	国内	29	Ca 75 L
DT vaccine	国外	1	
DPT vaccine	国内	26	Ca 75 L
DPT vaccine	国外	9	
Polio vaccine	国外	6	
Measles vaccine	国外	12	
Dried BCG vaccine	国内	45	

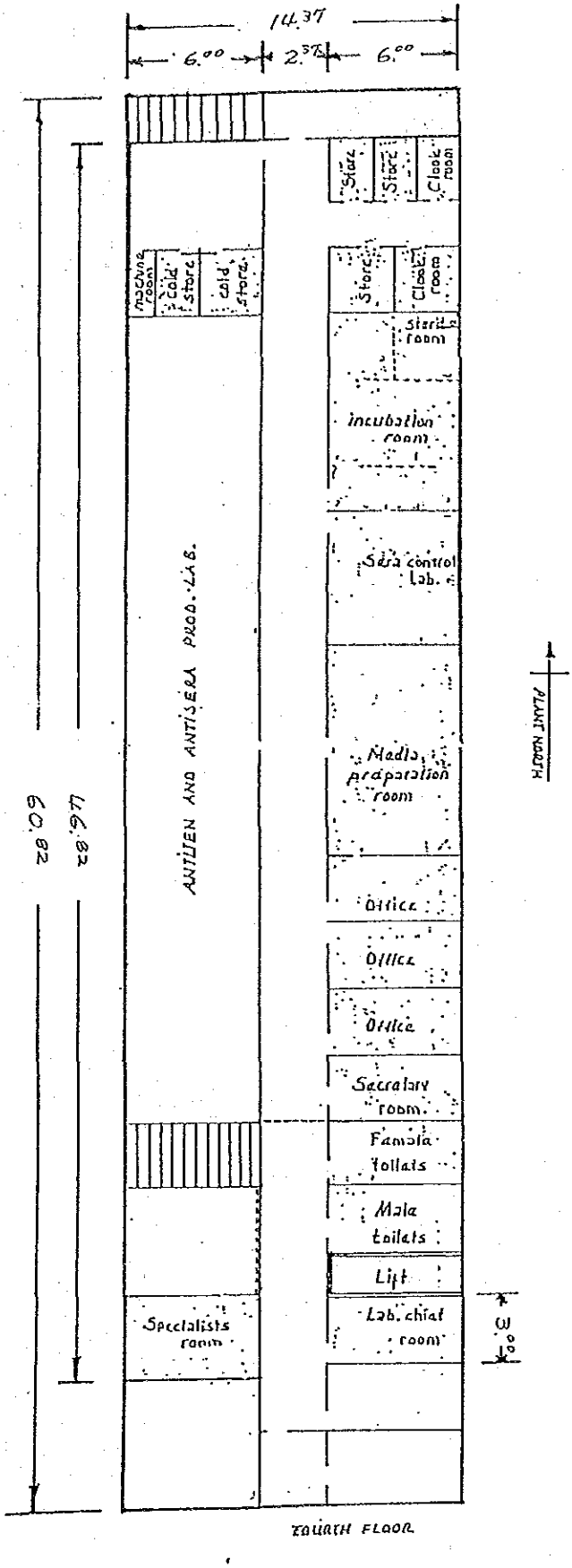
※ Sera Production Lab. で製造された抗毒素製造用トキソイド

Biological Control and Research Lab.構成人員

氏　　名	専攻技術分野	主 担 当 業 務	経験年数（年令）	※ 参考（月給）TL
Mualla ÖZKAN	獣医学，細菌学	ＢＣＲＬ長、部門統括	20	3,100,000
Mine Feray AKKUŞ	微生物学	計画立案（無菌、他）	5（35）	2,800,000
Nermin YENGINGÜÇ	薬　　学	理化学、安全、他	4（36）	2,800,000
Fethiye BROGLU	生 物 学	検定責任（無菌、他）	12（35）	2,350,000
Ahmet ÜNAL	獣 医 学	力価、安全、動物、他	4（30）	2,300,000
Biliz ŞENGÜN	生 物 学	培地調製、他	2（27）	1,870,000
Emine GÜLEÇ	生 物 学	細菌同定、他	1（27）	1,731,000
Mualla ALTOP		化学技術補助(培地他)		1,450,000
Ahmet KARA		化学技術補助(無菌他)		1,289,000
Şerife AÇIKGÖZ		秘書（書類作成、他）		900,400
Ramazan YOZGATLI		技能補助（洗浄準備）		1,119,000
İsmail YAVUS		補助（洗浄準備、他）		1,030,000
Ali KÜÇÜKÇELEBİ		補助（洗浄準備、他）		1,086,000
Yaşar AYDIN		実験動物飼育管理		1,150,000

※ '91.Dec. 為替換算率： 38TL／¥，5,000TL／US $

BIOLOGIC CONTROL AND RESEARCH LAB.



SCALE : 1 : 200

Biologic Control and Research Laboratory
Experiment animals unit.

トキソイド（バルク）の力価試験例

	ジフテリアトキソイド	破傷風トキソイド
免疫期間	4 週	6 週
攻撃毒素量	10 MLD／1 mℓ	5 MLD／2 mℓ
検体のLot No.	50－94	VI
検体の希釈	1/6 1/4	1/4 1/2
注射量	1mℓ 1mℓ	1mℓ 1mℓ
モルモット数	10 10	10 10
死亡数	1/9 0/10	1/9 0/10
生残率（%）	90 100	90 100
試験毒素対照	ジフテリア	破傷風
	1 MLD 10 MLD	1 MLD 10 MLD
2日目	s s d d	s s d d
4日目	d d	d d
力価試験の結果	合格	合格

トルコにおける無菌試験一覧（Nov. 29, 1991 - Dec. 17, 1991）

製剤名	初回試験結果			再試験の内訳		
	合格	再試験	試験中	合格	不合格	試験中
破傷風トキソイド（検体数66）	33	19	14	9	9	1
ＢＣＧワクチン（検体数９）	1	6	2	2	2	2
ツベルクリン（ＰＰＤ）（検体数１）	1					
狂犬病ワクチン（検体数15）	4	8	3	4	1	3

バルク間で比較した破傷風トキソイド無菌試験状況

バルク番号	検体数	再試験数	試験中数	合格数	不合格数（%）
53	8	3	0	5	3 (37.5)
54	8	2	0	7	1 (14.3)
55	8	2	1	7	0
56	8	2	0	6	2 (33.3)
57	8	0	0	8	0
58	8	4	4		

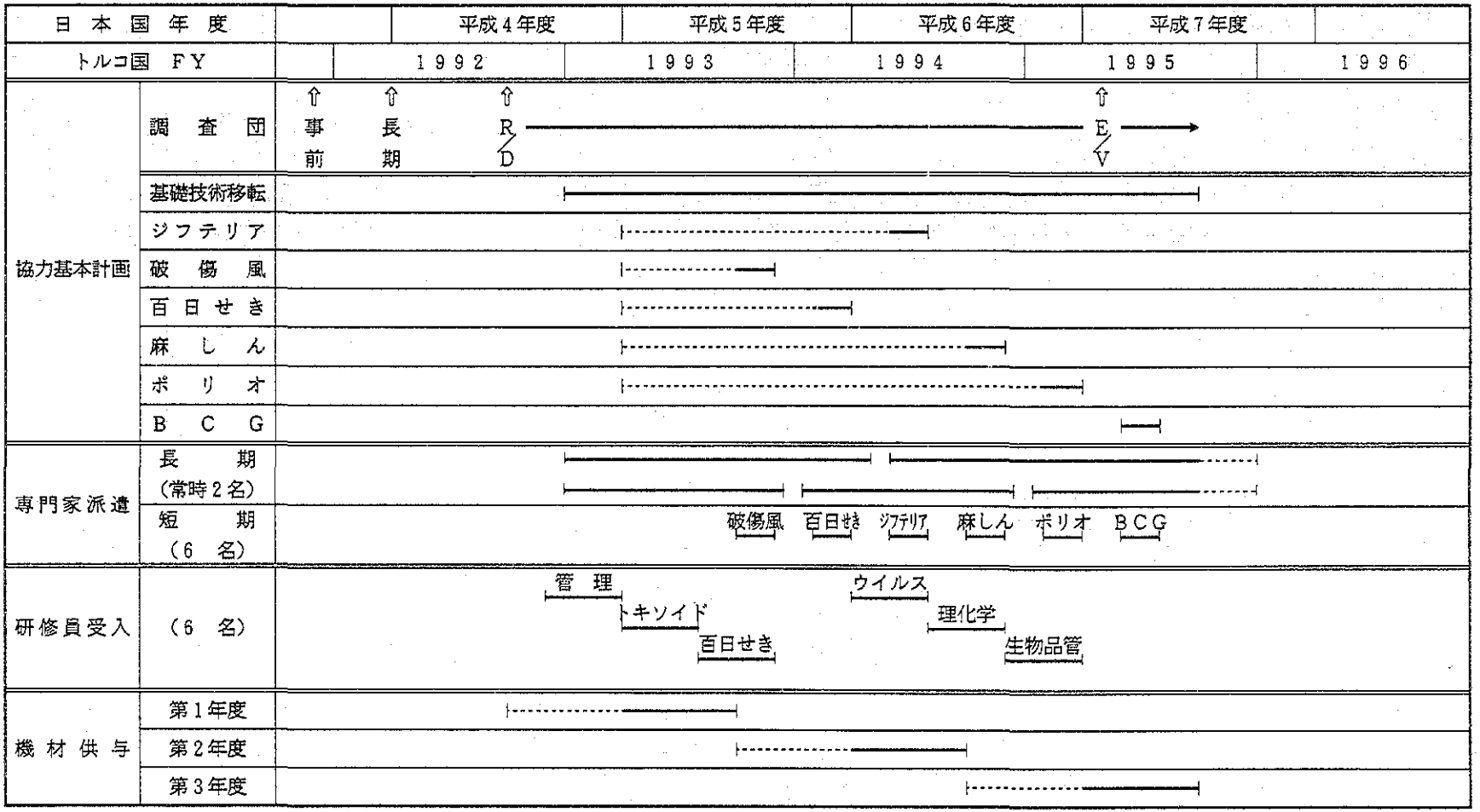
WHO基準による最終製品の検定項目

検定項目 / EPI関連ワクチン	Identity	Sterility Test for bact.& fungi	Potency Virus concent. Virustitrat.	Innocuity General safety	Accelerated degradation	Residual moisture	Adjuvant content	Preservative content	pH	Inspection final conti. ainers
破傷風トキソイド (plain)	○	○	○※	○				○	○	○
D T 2 混 (plain)	○	○	○※	○				○	○	○
DPT 3 混 (plain)	○	○	○※	○				○	○	○
BCG (凍結乾燥)	○	○	○	○	○					
沈降破傷風トキソイド	○	○	○※	○			○	○	○	○
沈降DT 2混	○	○	○※	○			○	○	○	○
沈降DPT3混	○	○	○※	○			○	○	○	○
ポリオワクチン (OPV)	○	○	○		○					
麻しんワクチン	○	○	○	○	△	○				○

※ 最終バルクについて実施の場合は省略することが出来る。 △Potency testに同じ目的の試験を含む

1992.01.29

トルコ国生物製剤品質管理プロジェクト協力基本計画案



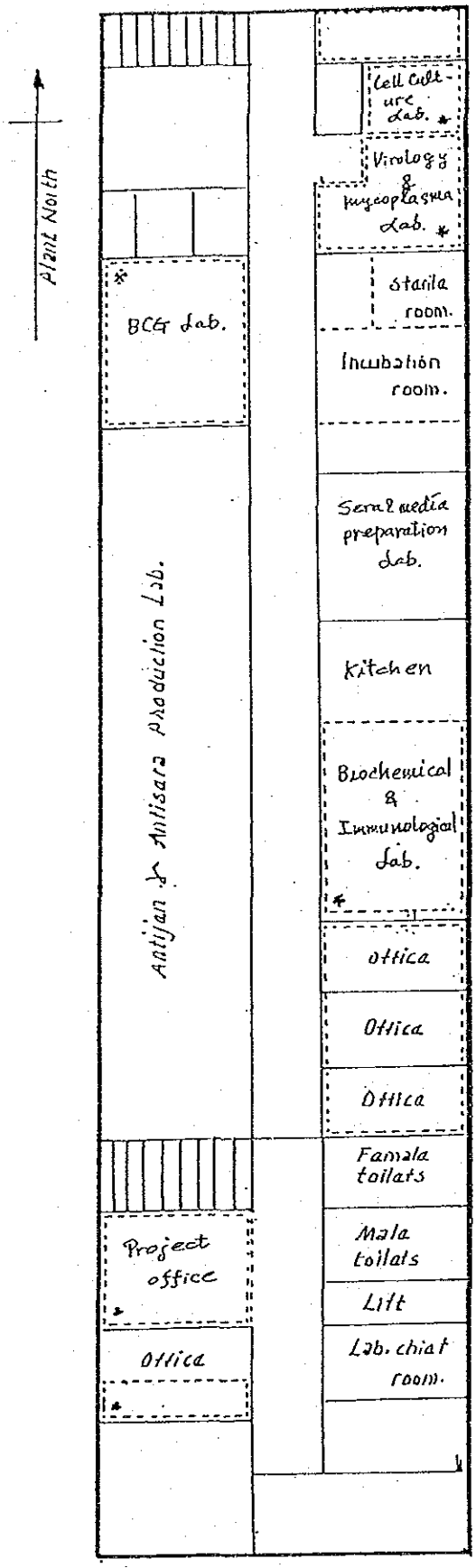
資料12

（トルコ国要請による）供与機材リスト

＜未完成,'92/02/21＞

Priority	機器名	台数	単価		金額	備考
			トルコ調べ	日本調べ		
			M-TL			
1	Lamina air Flow	2	80			
2	Microscope	1	20			
3	Fluorescence Microscope	1	50			
4	Inverted Microscope	1	50			
5	Deep-freezer (−70℃)	1	80			
6	CO_2 Incubator	1	45			
7	Centrifuge with Chiller	1				
8	Fume Cupboard	1	30			
9	Balance	2	40			
10	Incubator	3	20			
11	Dry-heat Sterilizator	2	20			
12	Spectrophotometers	1	50			
13	Freezedrying Apparatus	1				
14	Distiled water Apparatus	1				
15	pH Meter	2				
16	Centrifuge	1				
17	Water Bath	2				
18	Coagulator	1				
19	Vacuum Detector	1				
20	Automatic Pippets	10				
21	Drying Oven	1				
	Electrophoresis Equipment					
	Mercury Autoanalyser					
	High-speed Centrifuge					
	Micro Kjeldahl					
	Autoclave					
	Scintillation Counter					
	Liquid-nitrogen Tank					
	Egg Incubator					
	Pyrometer					
	Magnetic Mixer					
	Filtration Tank					
	Compressed Air Pump					
	Refrigerator					

Biologic Control and Research Lab.



※ Tadilat (Repairing) (restoration) ≅ 150.000.000 TL.

Add the following new footnotes:

[11] Cefamandole and cefoxitin have a wider spectrum of activity against Gram-negative bacilli than do the cephalosporin antibiotics for which the cefalotin disc is used. Organisms resistant to cefalotin may be susceptible to cefamandole and/or cefoxitin. Therefore, the cefalotin disc cannot be used for testing susceptibility to cefamandole and cefoxitin. Further, the spectra of cefamandole and cefoxitin are dissimilar enough to justify tests using both cefamandole discs and cefoxitin discs.

[12] The carbenicillin disc is used for testing susceptibility to carbenicillin and ticarcillin.

The reference to footnote 12 is to be inserted after the two carbenicillin entries in the table.

Annex 11

THE NATIONAL CONTROL OF VACCINES AND SERA

(A guide to the provision of technical facilities)

INTRODUCTION

Biological Substances and their Control

The biological substances referred to here are vaccines and sera for administration to humans. Assurance of their safety and potency requires in-process controls and tests, as well as tests on the final product—procedures necessitating specialized biological knowledge and competence. These substances may be of microbiological origin (vaccines and diagnostic reagents) or of animal or human origin (sera).

The ministry of health is responsible for the suitability of the biological substances used in a community. It is important, therefore, for all such ministries in all countries to establish or recognize pharmacopoeial standards or have access to a means of exercising quality control over biological substances. Such control is generally the

responsibility of a legally constituted national control authority which may differ from one country to another. The authority may be:

(*a*) the minister of health or other appropriate minister;
(*b*) a designated national controller; or
(*c*) the director of a national laboratory concerned with the control of biological products.

The national control authority should be empowered:

(*a*) to establish criteria or recognize pharmacopoeial requirements for the acceptability of the products;
(*b*) to establish standard preparations to be used as reference materials in biological assays;
(*c*) to license manufacturers of biological products, and to license their products for use in the country or for export; and
(*d*) to establish the technical facilities and other mechanisms needed for implementing the requirements.

The facilities that can be established by a national control authority will depend on the technical and financial resources available. It is important, however, to have some facility, no matter how modest, or to make the necessary arrangements with a country with a comprehensive control system.

In many countries the necessary facilities would have to be created and advice could be obtained from national experts in universities, hospitals, research institutes, public health bodies, or local pharmaceutical companies. Although in some countries controls for food and even for some drugs may exist, the techniques for the control of biologicals differ so markedly from those of chemical analysis that their control will demand a separate facility.

A great need in a developing country is for facilities for the control of immunological products (e.g., vaccines and toxoids, sera and antitoxins, and antivenoms). This Annex therefore deals with the technical arrangements for the separate control of such products.

One of the ways in which WHO assists Member States in the control of immunological substances is through its international biological standardization programme. This programme has two main features:

(1) the establishment of international standards and reference preparations for use as reference materials in biological assays, thus permitting the potency of biological products to be expressed in uniform terms (international units or their equivalents) throughout the world;

(2) the provision of sets of international requirements for biological substances, which are intended to provide guidance to those concerned with the production and control of such substances. An important part of this WHO programme is to promote the use and application of international standards and requirements as widely as possible.

Where international standards and reference preparations are needed, these are provided through the Organization's biologicals programme.

Another way in which WHO can assist Member States is by giving advice on the suitability of products from manufacturing establishments and by reading protocols of the results of in-process and final tests of the manufacture and control of particular batches of vaccine for use in a particular country. WHO is assisted in checking the potency and safety of vaccines and sera by those countries that have comprehensive quality control facilities. Such arrangements can be of immediate assistance to countries that, at the moment, cannot contemplate the establishment of a national control facility, but the aim should be to establish the control of biologicals where feasible.

There are two important reasons why quality control should be established before any manufacture of biologicals is contemplated.

(1) A comprehensive quality control facility can:
(*a*) check the potency and safety aspects of vaccines on importation, which involves the checking of manufacturers' protocols, including in-process quality control;
(*b*) check the potency of vaccines on storage;
(*c*) check the antibody responses to vaccines; and
(*d*) carry out serological surveys to check the immunity of a community to infectious diseases.

(2) When a country wishes to become involved in manufacture, which, in the first instance, may consist of the importation of unfinished bulk materials with dilution, blending, filling, and packaging done locally, then the final product must be subjected to quality control. The establishment of a quality control facility, therefore, must precede manufacture.

In some countries the manufacture of biologicals is in progress without any national control, and in some instances there is inadequate testing by the manufacturer. Such situations should be corrected as soon as possible, and steps taken to ensure that only safe and potent vaccines are used in the future.

The national control laboratory furnishes the necessary technical services to the national control authority for the implementation of national regulations relating to biological products. In some cases the director of the laboratory may also be the legally empowered authority.

It is part of the task of the national control authority, in collaboration with the technical staff of the national control laboratory and the manufacturing establishments (if appropriate), to formulate the requirements to be used in a country. In carrying out this task, the international requirements published by WHO and existing national requirements should be taken into consideration. The advisory functions of the laboratory also relate to the various technical questions involved in the application of these requirements. The evaluation of batches of products, based on the interpretation of test results and on other technical information, can be adequately done only if the person making the evaluation has the necessary technical knowledge. The advisory service of the national control laboratory will also provide advice based on the results of the research carried out in the control laboratory for the development of better methods of control.

The release of products may be based on a three-tier system:

(1) Products in the production and testing of which there may be inherent dangers (for example, poliomyelitis vaccine and BCG vaccine), or any product from a new manufacturer. These would need batch-by-batch control with the submission of protocols and samples, which may include bulk materials and samples taken during processing, as well as final filled containers.

(2) Products for which the test methods are not giving reproducible results or have only just established consistency. These would require the submission of protocols for each batch.

(3) Products that have been marketed by the manufacturer for many years without any break in consistency. These could be marketed after the manufacturer had shown the batch to be satisfactory and without further formality.

The scheme outlined in this Annex has been drawn up for the purpose of providing Member States with a guide to the steps that may be followed in providing the technical facilities needed to establish or develop a functioning national control authority for biological substances. The simplest and least expensive step would be to appoint a technical adviser to the national control authority. Although such a service would have its limitations, it is worth while in countries with no suitable laboratory facilities.

The next step would be to set up laboratory services, though not necessarily with animal facilities since these are very expensive. Much can be achieved by *in vitro* tests, particularly in checking the maintenance of live virus vaccines that can be used as an index of the continuity of refrigeration facilities (cold chain) and the antibody responses of the community to these vaccines.

The ultimate step is the comprehensive quality control facility that is capable of carrying out all tests on all vaccines and sera.

In some countries the manufacture of biological products is carried out in a governmental institute or one sponsored by the government. Even in such a situation, a national control authority should be established. It may sometimes be the case that, in order to make use of facilities already available (e.g., equipment), manufacture and national control are done in the same establishment. If this is so, the control laboratory should be an independent unit directly responsible to the national control authority (*1*, pp. 19–22).

STEP 1

Technical Adviser

At this stage, all that is envisaged is that a competent person should be available to act in an advisory capacity. He may be designated a "technical adviser".

His advice will be in the form of recommendations to accept or reject particular batches for use, to demand further information, or to require the repetition of tests.

In order to fulfil his functions he should be empowered to:

(1) Establish that a product has come from a suitable source. (Advice in this respect may be obtained from WHO or the national control authority of the country of origin.)

(2) Ensure that each batch of the product conforms to the relevant international and national requirements, where these exist.

(3) Evaluate the protocols of manufacture and testing required from the manufacturer; the WHO requirements include the format of a protocol for the purposes of reporting these data. If the product is manufactured in a country where there is only a technical adviser and

no quality control facilities, the adviser should arrange through WHO for samples to be tested independently. The checking of protocols is a most important part of the control of biological products. It requires meticulous attention to detail and a knowledge of the methods used in the production and control of each of the products under consideration. The information provided in the protocols must make it possible to trace all steps in the manufacture and testing of each batch of a particular product, including all required in-process controls and control tests on the final product. The study of protocols also enables an assessment to be made of the consistency of production of each manufacturer. Such consistency is a great safety factor in the manufacture of biologicals and should be established by all new producers. Before recommending the acceptance of a product from a new source, evidence should be provided that the product is safe, stable, and efficacious.

(4) Inspect samples of the products, their labelling, and accompanying documentation. Visual inspection of a number of samples of each batch may give useful information on the particular product and on the container. The labelling should comply with international and national requirements and enable the batch to be identified in relation to the protocol. The directions on the package inserts must give adequate information on the reconstitution, if appropriate, and mode of administration of the product, recommended storage conditions, and contraindications for use.

(5) Inspect premises and all processes of manufacture including control in the technical adviser's own country and elsewhere when feasible. This is to verify that the products conform with the general requirements for manufacturing establishments contained in the revised Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories) (*1*, p. 11); it also enables independent checks to be made at in-process stages of manufacture. Control activities at this point also include approval of the technical staff manufacturing and testing the products as well as those who are responsible for signing protocols. It cannot be overemphasized that inspection by persons knowledgeable in the manufacture of biologicals contributes greatly to ensuring the quality of biological products. For imported products the technical adviser of the importing country should have the right to demand certificates of conformity with any existing national requirements of the country of origin. Each certificate should be signed by the appropriate government official.

Much of the information provided to the technical adviser is of a confidential nature and must be treated as such.

STEP 2

Laboratory Facilities for in vitro Tests

Every national control laboratory should deal with biological products manufactured in the country itself as well as those that are imported. The national control laboratory should be autonomous and administered by, or on behalf of, the national control authority, even though, as in some countries, the national control laboratory is housed in a national laboratory that has other functions—e.g., teaching, pathology, diagnostic microbiology, and reaearch.

A limited control laboratory could provide a good measure of technical service for the control of certain biological products.

In addition to the activities previously described, such a laboratory would:

(1) Carry out the following control tests:
(*a*) virus titre of live virus vaccines in cell cultures;
(*b*) determination of viable units in BCG vaccine;
(*c*) monitoring of virus titres of live virus vaccines and viable units in BCG vaccine during distribution and use;
(*d*) estimation of antibody content of certain antisera—e.g., diphtheria antibody in cell cultures, and poliomyelitis antibody by neutralization tests in cell cultures;
(*e*) flocculation tests;
(*f*) identity tests; and
(*g*) safety and other tests, as applicable—e.g., protein, residual moisture, and pH.

Sterility testing has been omitted deliberately from this list because, unless a full sterility test is carried out, its interpretation will have little meaning. The inclusion of a full sterility test would markedly increase the size of the staff and facility required. In a limited quality control facility, therefore, it will be necessary to rely for proof of sterility on the manufacturer, whose results will be reported in the protocol, bearing in mind that in-process control of sterility is of greater importance.

(2) Advise the national control authority regarding inspection of manufacturing establishments or, possibly, carry out inspections of such establishments if assigned this responsibility.

(3) Provide some national standards and calibrate them against the appropriate WHO reference materials for antibody content and virus titres.

Details of staff and facilities are given in Appendix 2.

STEP 3

The Comprehensive Facility

For fully comprehensive national control, a laboratory to carry out all essential laboratory and animal tests prescribed in the WHO Requirements must be provided.

Some of the control tests are performed in animals. For this reason the availability of good-quality laboratory animals (guinea-pigs, mice, rabbits) and of a well-equipped animal house are absolutely essential (*2*).

In addition to those mentioned above, the functions of a comprehensive laboratory should include performance of the following control tests:

(*a*) *Sterility.* The tests specified in the revised General Requirements for the Sterility of Biological Substances apply here (*3*, p. 40).

(*b*) *Identity.* Identity tests can be done for many vaccines and sera. These may be based on the morphological appearance of organisms in stained smears or of colonies on growth media. For other vaccines or sera, specific antigens or antibodies are necessary—e.g., for agglutination of pertussis and typhoid vaccines and flocculation of diphtheria and tetanus toxoids.

(*c*) *Innocuity and pyrogenicity.* Tests of bacterial vaccines and of most serum products for innocuity require a limited number of guinea-pigs and mice. Tests for pyrogenicity require an adequate supply of rabbits.

(*d*) *Safety.* Specific safety tests are carried out on some products, such as diphtheria and tetanus toxoids and pertussis vaccine, using guinea-pigs and mice. With other products such as virus vaccines, more elaborate tests are required, involving the use of monkeys and histological techniques.

(*e*) *Potency.* Facilities to carry out all the tests as formulated in the specific WHO Requirements shall be provided. These require an adequate source of good-quality mice, guinea-pigs, and rabbits, as well as fertile hen's eggs.

(*f*) *Stability.* Stability tests based on potency determinations shall be included, particularly for vaccines stored within the country.

A list of the WHO requirements for the specific vaccines and sera is included in Appendix 1. A summary of the appropriate tests for the various vaccines, as far as they are performed in animals or tissues, is given in the accompanying table.

In vivo and *in vitro* tests for specific vaccines

Vaccine	Potency: animal or tissue[a]	Specific safety: animal or tissue[a]	General innocuity (guinea-pigs and mice)
Polio (killed)	mo, gp, or other	mo?	+
Yellow fever	tc	—	+
Cholera	mi	—	+
Smallpox	ra + fe	—	+
Polio (live)	tc	mo + gp + mi + ra + tc	+
Pertussis	mi	mi	+
Diphtheria	gp	gp	+
Tetanus	gp or mi	gp	+
BCG	vc	gp	+
Measles	tc	gp + mi + tc	+
Immune sera	depending on serum titration	—	+
Typhoid	mi + ra	—	+
Influenza	fe	fe	+
Rabies	mi	—	+

In vivo and *in vitro* tests for specific vaccines (*continued*)

Vaccine	Potency: animal or tissue[a]	Specific safety: animal or tissue[a]	General innocuity (guinea-pigs and mice)
Meningococcal polysaccharide	—	—	+
Rubella	tc	—	+

[a] fe = fertile eggs; gp = guinea-pigs; mi = mice; mo = monkeys; ra = rabbits; tc = tissue culture; vc = viable count.

The only vaccine subjected to tests for pyrogenicity is meningococcal polysaccharide vaccine; immune sera are tested for pyrogenicity.

In addition, provision should be made for research on and development of new and improved methods in quality control.

Details of staff and facilities are given in Appendix 2.

AUTHORS

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Dr J. W. G. Smith, Director, National Institute for Biological Standards and Control, London, England

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1. WHO Technical Report Series, No. 323, 1966.
2. *Manual for the design, equipping and staffing of facilities for production and quality control of bacterial vaccines* (unpublished document WHO/BLG/UNDP/78.1).
3. WHO Technical Report Series, No. 530, 1973.
4. WHO Technical Report Series, No. 345, 1966.
5. WHO Technical Report Series, No. 638, 1979.

Appendix 1

LIST OF WHO REQUIREMENTS FOR VACCINES AND SERA[a]

No. of requirement	Year of establishment or last revision	No. in Technical Report Series
1. General requirements	1965	323
2. Polio (killed)	1965	323
3. Yellow fever	1975	594
4. Cholera	1968	413
	1973[b]	530
5. Smallpox	1965	323
7. Poliomyelitis (oral)	1971	486
	1980[b]	658
8. Pertussis	1978	638
	1980[b]	658
10. Diphtheria/Tetanus	1978	638
	1980[b]	658
11. BCG	1978	638
12. Measles	1966	329
14. Human immunoglobulin	1967	361
15. Typhoid	1967	361
16. Tuberculins	1968	384
17. Influenza (inactivated)	1978	638
18. Immune sera of animal origin	1969	413
21. Snake antivenins	1971	463

No. of requirement	Year of establishment or last revision	No. in Technical Report Series
22. Rabies (human)	1973	530
	1980	658
23. Meningococcal polysaccharide	1976	594
	1977[b]	626
	1980[b]	658
24. Rubella	1977	610
	1980[b]	658
27. Human blood and blood products	1978	626
28. Influenza (live)	1979	638
31. Hepatitis B	1980	658

[a] These documents may be obtained from WHO on request.
[b] An addendum that should also be referred to.

Appendix 2

STAFF AND FACILITIES REQUIRED FOR THE CONTROL OF VACCINES AND HUMAN AND ANIMAL SERA

The size of the staff and the facility will depend on the extent of the quality control contemplated. Advice can be obtained from WHO concerning particular needs. There should be adequate maintenance services and provision for spare parts.

1. Director or officer in charge (steps 2 and 3); technical adviser (step 1)

The director or officer in charge (steps 2 and 3) should be a medical or science graduate (or, if appropriate, a graduate in veterinary medicine) with qualifications in microbiology and immunology. The director should have a broad technical knowledge of the production and control of biological substances and should have had one to two years' practical experience in a production and/or control laboratory.

Further periods of laboratory experience may have to be completed when the control of certain biological products is undertaken; this may be necessary also in order to keep abreast of the latest advances in laboratory techniques. Such experience may be gained from time to time by visits to one or more scientists in other countries working in the same or related fields so as to exchange ideas, discuss techniques and problems in the work, or analyse the results of studies.[1] The director should be aware of the administrative aspects of control.

A technical adviser (step 1) should have the same qualifications and experience as a director.

2. Scientific officer

The qualifications and experience desirable for a scientific officer are the same as those described above for a director, although the experience required may be limited to a particular control discipline.

3. Technician

A technician should have had a general education up to 16 years of age, and thereafter have obtained a qualification in microbiological techniques (*2*, *4*).

Certain of the special technical skills needed would have to be developed by actual work in the laboratory under the supervision of the higher-qualified staff. It is the responsibility of the director to ensure that his staff receive suitable training.

4. Facilities for the laboratory

(*a*) *Facilities for a step-2 laboratory*

As a minimum, a step-2 laboratory should have adequate laboratory space and services (running water, electricity, and/or gas) and some arrangement for working under sterile conditions.

The equipment must include:

— glassware and equipment suitable for general laboratory services;
— an autoclave for sterilizing glassware and media and facilities for membrane-filtration sterilization;
— a refrigerator or other cold-storage facilities, and incubators; and
— equipment and materials for cell-culture procedures.

[1] Assistance can be obtained from WHO (and/or other international agencies such as UNDP) in the form of fellowships, research training grants, and grants for exchanges of research workers. Applications for fellowships should be made to the World Health Organization, Geneva, Switzerland. National governments may also find opportunities for developing consultant services through other international organizations.

(*b*) *Additional facilities for a step-3 laboratory*

Arrangements should be made for a regular supply of good-quality animals and for adequate accommodation for them (including facilities for quarantine and conditioning (2)), and possibly for animal-breeding facilities if there are no suitable sources of good-quality animals outside the facility. The extent of the accommodation and the number and species of animals required will depend on the number and variety of tests to be done, including potency tests. Appropriately trained personnel for animal care will also be necessary.

5. Documentation, clerical, statistical, and epidemiological services

In every national control laboratory adequate documentation is essential. This should include at least:

(*a*) All relevant international requirements for biological substances published by WHO—i.e., general requirements for manufacturing establishments and control laboratories, general requirements for sterility, and requirements for specific products (5, p. 196).

(*b*) Other relevant specifications and recommendations in WHO publications.[2]

(*c*) The current national requirements and standard operating procedures of the country itself and of the countries from which biological products are imported.

The laboratory should possess, or have access to, library facilities appropriate to its field of activity.

Suitable clerical facilities are needed for correspondence, preparing reports, issuing certificates and other documents, and keeping accurate records.

Statistical services would be needed if potency tests were being performed. The minimum required would be access to simple calculating equipment and to individuals familiar with experimental design and evaluation of data from biological assays.

Since it is essential to confirm both the quality of biological substances and the efficacy of immunization schedules, close cooperation with an epidemiological service is highly recommended.

[2] For example: *Specifications for the quality control of pharmaceutical preparations. Second edition of the International Pharmacopoeia* (Geneva, World Health Organization, 1967) and the reports of expert committees and other international groups of experts published in the WHO Technical Report Series. Workers and institutions who wish to be kept informed of new reports in these series can do so by regular reference to the summaries of these reports published in the *WHO Chronicle*. Some further information may also be found from time to time in occasional publications of the Organization. In addition, the *Journal of biological standardization* (New York, Academic Press) deals with this subject.

Annex 12

REQUIREMENTS FOR RUBELLA VACCINE (LIVE)

(Requirements for Biological Substances No. 24)

Addendum 1980

The WHO Expert Committee on Biological Standardization, at its twenty-eighth meeting, adopted the Requirements for Rubella Vaccine (Live), which were annexed to its report (WHO Technical Report Series, No. 610, 1977, pp. 54–87). One section of those Requirements concerns the chromosome monitoring of human diploid cells where such cells are used for the growth of the virus.

Similar sections are to be found in the Requirements for Rabies Vaccine for Human Use (revised) (see pages 81–87) and the Requirements for Poliomyelitis Vaccine, Oral (revised) (see pages 157–168).

There are some differences in the karyology requirements, however, because the more recent requirements were able to take into account the report of the *Ad Hoc* Committee on Karyological Controls of Human Cell Substrates (Lake Placid, NY, 1978).

As it is desirable for the requirements for chromosome monitoring to be the same for all vaccines produced in human diploid cells, the relevant paragraphs in the Requirements for Rubella Vaccine (Live) have been revised.

VACCINUM TETANICUM

TETANOZ TOKSOİDİ

Sinonim : Toxoidum tetani

Tetanoz Toksoidi, *Clostridium tetani* nin üretilmesiyle elde edilen tetanoz toksinine belirli oranda formaldehit TS ilâve edilerek hazırlanmış steril bir sıvıdır.

Vasıflar. Renksiz veya sarımsı-kahverengi, şeffaf sıvı; hususi karakteristik

Toksisite. 300 ilâ 400 g ağırlığında 4 kobaya, derialtı veya periton içi yolla, en az 5 insan dozu enjekte edilir, hayvanlar şimdi bir gün süre ile gözlenir; bu süre içinde tetanozla ilgili hiç bir simptom görülmez.

Antijenik değer. 300 ilâ 400 g ağırlığında 10 kobayadan her birine insanda bağışıklık sağlayan total dozun üçte birinden fazla olmayacak hacimde tetanoz toksoidi, derialtına enjekte edilir. Altı hafta sonra kobayların her birine tetanoz test toksininden 2 ml hacim içinde 10 MLD (minimum letal doz), derialtına enjekte edilir, kobaylar en az on gün gözlenir; bu süre içinde hayvanların yüzde 80 i sağ kalır.

Saklama. Tetanoz Toksoidi, 2° ilâ 8° de saklanmalıdır.

Etiketleme; Diğer şartlar. "Vaccina" monografisindeki şartlara uyar.

Kullanma süresi. Yukarıda bildirilen saklama şartlarında, son kontrol tarihinden itibaren iki yıldır.

Etki ve kullanılış. Tetanoza karşı koruyucu olarak (aktif bağışıklık sağlar).

Doz. Dört ilâ altı hafta ara ile, 3 defa, derialtına veya kasiçine enjekte edilir. Prospektüsünde veya etiketinde başka bir kayıt yoksa, bir uygulama dozu, yaş ayırımı gözetilmeksizin 1 ml dir. Üçüncü enjeksiyondan bir yıl sonra 1 dozla rapel yapılır.

TOXOID OF TETANUS

Synonym: Toxoidum tetani

Toxoid of tetanus is a steril liquid prepared by adding formaldehyde in a certain amount to tetanus toxin which is obtained by producing clostridium tetani.

Qualities : Colourless or somewhat yellow-brown, transparent liquid and characteristic odour.

Toxicity: At least 5 human doses are injected as subcutaneous injecttion, or into peritoneum of 4 guinea-pigs (animals used in scientitic experiments) that weight 300-400 grams, guinea-pigs are observed for 21 days and any symptom related to tetanus is not seen during this period.

Antigenity: Toxoid of tetanus of which volume is not more than one third of total dasage producing immunity in human, is infected as subcutaneous injecttion to 10 guineapigs that weight 300-400 grams. After 6 weeks, subcutaneous injection of 10 MLD (minimum letal dose) within tetanus test toxin of 2ml are made to guinea-pigs and these animals are observed for at least 10 days. 80% of the animals survive during this period.

Storing: Tetanus toxoid should be kept at 2°C- 8°C

Labeling: Other contitions.Conforms to the conditions in the "vaccine" monography.

Term of use: Two years as from the date of the last control, on the above storing conditions.

Effect and use: As a protection against tetanus (produce active immunity)

Dosage: Subcutaneous or intramuscular injecttion is made three times with intervals of 4-6 weeks. Dosage for one administration is 1 ml whatever the age is. 1 dose is administered once again after 1 year from the third injection.

VACCINUM MORBILLORUM

KIZAMIK AŞISI

Canlı attenue Kızamık Aşısı, attenue edilerek, insan kullanmasında uygun görülmüş kızamık virüsünün, civciv embriyonu veya köpek böbreği kültürlerinden üretilerek hazırlanmış steril suspansiyonudur. Uygun miktarda antibiyotik ihtiva edebilir.

Vasıflar. Donmuş olarak kurutulan madde, şişenin dibinde krem veya pembemsi bir topak görünümündedir.

Saklama. Kızamık Aşısı, tercihan bir dozluk ampullerde veya birkaç dozluk kaplarda, 2° ilâ 8° de saklanmalıdır.

Etiketleme. "Vaccina" monografisindeki şartlara uyarı; ayrıca kap üzerindeki etiketle 1) aşının kurutulmuş olduğu; 2) hazırlanacak seyreltme sıvısı miktarı; 3) virüs titresi yazılı olmalıdır.

Diğer şartlar. Üretimi ve kontrolleri, Dünya Sağlık Teşkilâtı Eksper Grubunun saptadığı minimum standartlara uyar.

Saklama süresi. Yukarıda bildirilen saklama şartlarında bir yıldır.

Etki ve kullanış. Kızamığa karşı koruyucu olarak.

Doz. Derialtına 0.5 ml enjekte edilir.

MEASLES VACCINE

Live-attenuated measles vaccine is a sterile suspension of attenuated (weahened) measles viruses, that is prepared by producing it from chick embryo or dog kidney culture. It might contain antibiotic in an appropriate amount.

Qualities (appearence) : Subtance that is dried as frozen appears a lump somewhat pink (pinkish) or cream when it is in a vial.

Storing (keeping) : Measles vaccine should be kept at 2 °C – 8 °C within preferably an ampul of o dose or within cups of some doses.

Labeling : conforms to the conditions in the "vaccina" monography. Followings should be writtin in the label on the cup:

1) " Vaccine is dried out"
2) Rarefying liquid amount to be used.
3) Virus Titer

Other conditions: Production and control comply with the minimum standards determined by WHO Expert Group.

Duration for storing: 1 year in the above (storing) condition.

Effect and use: As a protection against measles

Dosage: Subcutaneous in injection of 0.5 ml is made.

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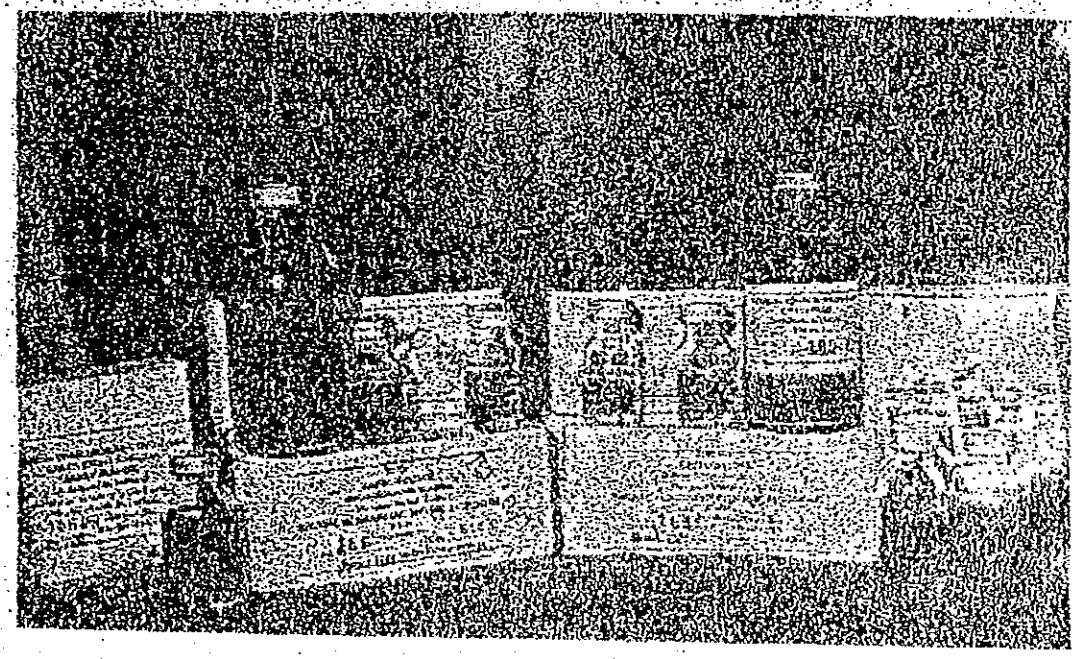
TETANOZ AŞISI (TETANOZ TOKSOİDİ)
(TOXOIDUM TETANI)

NİTELİĞİ :

Tetanoz aşısı, antijen niteliği uygun Clostridium tetani suşunun özel sıvı besi yerlerinde üretilerek, elde edilen Tetanoz toksininin belirli oranda formaldehid'le muamele edilmesiyle hazırlanmış tetanoz toksoidi ya da tetanoz anatoksinidir.

Tetanoz toksininin, formaldehidle toksisitesi giderildiği halde, antijenik değeri büyük ölçüde kalır.

Tetanoz aşısı, esmer sarımtrak renkte, kendisine özgü kokusu olan saydam bir sıvıdır. Şekil'de görülmektedir.



DOZU :

Yaş farkı gözetmeksizin, bir uygulama dozu 1 ml. dir.

UYGULAMA ÇAĞI ve İNVERVALLER :

Tetanoz aşısı, Difterideki gibi iki aylık dolduran ve üç aydan gün alan bebeklere ve her yaşta çocuk ve yetişkinlere güvenle uygulanabilir.

Tetanoz aşısı, normal aşı kursunda her defasında bir doz olmak üzere 6-8 hafta aralıklarla iki üç kez uygulanır.

Üçüncü enjeksiyonu izleyen 12 ay sonunda, bir dozla rapel yapılır. Rapellere, yine bir dozla 5-10 yıl aralıklarla, bütün hayat süresince devam edilir. (Askerler, avcılar kırsal alanda çalışanlar gibi)

Daha önce yeterli karma aşı yapılmış çocukların yaralanmalarında bir doz tetanoz aşısı yeterli koruma sağlar. Gebelere aşısızsa 2 kez, önceden aşılı ise 1 kez tetanoz aşısı uygulanır.

UYGULAMA YERİ ve TEKNİĞİ :

Tetanoz aşısı, asepsi ve antisepsi kurallarına uyularak cilt altına veya adale içine yapılır. Adsorbe aşılarda, adale içi yol önerilir.

BAĞIŞIKLIK SÜRESİ ve RAPELLER :

Hayatında ilk kez ve bir doz Tetanoz aşısı uygulanan bir kimsede, spesifik antikorlar düşük titrede olmak üzere ancak dört hafta sonra oluşur (Birinci stimulus). Bu durumdaki bir kimse muhtemel tetanoz enfeksiyonundan korunamaz.

Birinci enjeksiyondan, 6-8 hafta sonra uygulanan ikinci dozu izleyen 7-10 gün içinde, spesifik antikorlar hızla çoğalarak (İkinci stimulus), kişiyi enfeksiyondan koruyabilecek üniteye yükselebilir. Aynı ara ile uygulanan üçüncü enjeksiyonda bağışıklık kuvvetlenerek, 12-18 ay devam eder. Bu sürenin sonunda uygulanan birinci rapel, bağışıklığın 3-4 yıl daha uzamasını sağlar.

Uygulamalar arasındaki 6-8 haftalık süreler kısaltılmakla, bağışıklığın meydana gelmesi hızlandırılamaz; bu şekil uygulama yanlıştır.

Hastalık veya unutma gibi nedenlerle, aşılamalara ara verilmişse aşağıda belirtilen kurallara uyulmalıdır :

1. Birinci enjeksiyonla ikinci arasındaki sürenin 6 ay'ı geçmemesine özen gösterilir.
2. İkinci ve üçüncü enjeksiyon arası 12 ay'ı geçmemelidir.
3. Üçüncü enjeksiyonla, birinci rapel arası iki yılı geçmemelidir.

Tetanoza karşı aşılanmış ve rapellerini zamanında yaptırmış bir kimse, enfeksiyon tehlikesi olacak biçimde yaralanmışsa, bir doz tetanoz aşısı uygulanarak, mevcut aktif bağışıklığı desteklenir. Burada en önemli sorun kişinin tetanoza karşı aşılı olup olmadığının doğru olarak saptanmasıdır. Aşılı kişiye tetanoz serumu yapılması yanlıştır.

TETANUS VACCINE (TETANUS TOXOID)

Quality:

Tetanus vaccine is toxoid of tetanus or tetanus maintoxin prepared by treating tetanus toxin with formaldehyde in a certain amount.

Although toxicity of tetanus toxin is reduced by formaldehyde there is still considerable antigenity.

Tetanus vaccine is a transparent liquid with somewhat dark yellow and unique odour.

- Dosage : 1 ml for one administration, whatever the age is.
- Age for implementation (vaccation) and intervals : Tetanus vaccine as in the case of diphtheria, can be safely implemented to infants complated the second month in their life and entered to their third months , to children at all ages and to adults.

In the course of normal vaccine tetanus vaccinè is implemented two or three times as 1 dose (one dose- every time) with 6-8 weeks intervals.

At the end of 12 months after, the third injection 1 dose is administered again (rapel) . Administration of 1 dose with 5-10 years intervals continue in course of life.

Tetanus vaccine is implemented to pregnants two times if they have not vaccinated before and one time if they have vaccinated.

- Implementation Technique:

Tetanus vaccine, in accordance with the rurels of asepsis and antisepsi, is implemented , by intramuscular or subcutaneaus injections for adsorbed vaccines intramuscular is advided.

- Immunity (duration) and Repeats (of vaccination) spesific anticors at low titer occur after 4 weeks in a person whom tetanus vaccine of 1 dose is implemented for the first time and this person can not defend himself /herself against possible tetanus infection.

Within 7-10 days following the second dose administered after 6-8 weeks from the first infection specific anticors rapidly increase (2 nd stimulus)

and can reach to level that protect the person from infection. In the third infection implemented at the some intervals immunization strengthen and continues for 12-18 months.

The first repeated implementation of the vaccine at the end of this period leads to a lasting immunization for 3-4 years . It is not possible to accelerate the occurance of more immunization through shorten the 608 weeks intervals between implementations, such implementations are not appropriate (they are wrong)

If there is a gap between vaccinations because of illness or ignorance following rules should be obeyed:

1) Interval between the first infection and the second one should be not more than 6 months.

2) Interval between the second infection and the third should be not more than 12 months.

3) Interval between the third infection and the first repeat (of vaccination) should be not more than two years.

If a person who has been vaccination against tetanus and who has repeated vaccination in due course, is wounded and there is a threat of infection administration of 1 does of tetanus vaccine supports the present active immunity. The most important problem in this case is to find a right answer to the question of whether the person has been vaccinated before against tetanus. It is wrong to give tetanus serum to a person vaccinated.

KIZAMIK VİRUS AŞISI
(Canlı Attenue)
(Measles Virus Vaccine, Live Attenuated)

NİTELİĞİ:

Kızamık aşısı, steril koşullarda yetiştirilen civciv doku kültürlerinde, ya da uygun diğer besi yerlerinde üretilmiş, attenüe virus süspansiyonudur.

Virus, aşılanandan kasına bulaşmaz, aşılanan çocukta ateş ve döküntü yapsa da hastalığa görülebilen komplikasyonlara rastlanmamıştır. Halen ülkemizde üretilmeyip dış alımla sağlanmaktadır.

DOZU:

1 doz aşı 0,5 ml. dir ve 1000 den az olmamak üzere TCID 50 (Doku Kültürü İnfektif Partikül) ihtiva etmelidir. Kızamık aşısı 1 dozluk ampullerde ya da 5-10 dozluk ampul ya da şişelerde liyofilize halde ve beraberinde sulandırma sıvısı ve özel enjektörü vardır.

Aşı ambalâjı üzerinde kullanılacak sıvı miktarı ve kullanma süresi belirtilmiştir. Genellikle, başta kızamık aşısı olmak üzere, bütün canlı virutik aşılar, uygulanacak örgüt tarafından alındıklarından itibaren en geç iki ay içinde kullanılmalıdır.

UYGULAMA ÇAĞI VE İNTERVALLER:

Aşı 12 aylıktan büyük yani 12-15 ayını doldurmuş ve kızamık geçirmemiş çocuklara bir defada uygulanır. Kızamık epidemisi süregiden yörelerde, yurdumuz koşulları gereği 6 ayını doldurmuş ve hastalığı geçirmemiş tüm çocuklara kızamık aşısı yapılır. Bunlardan 12-15 aylıktan küçük olanların aşıları, 15 ayı doldurmalarından sonra yinelenir.

UYGULAMA YERİ VE TEKNİĞİ:

Bir dozluk aşı 0,5 ml. sıvı ile karıştırılır ve hemen erir; koldan cilt altına zerk edilir.

BAĞIŞIKLIK SÜRESİ VE RAPELLER :

Aşı hastalığı geçirenlerde olduğu gibi uzun süre bağışıklık sağlar. Şimdilik rapel düşünülmemiştir. Yeni bilgiler ve bulgular konuya açıklık getirecektir.

ENDİKASYONLARI :

a) Sistematik uygulama :

1) 12-15 aylıktan büyük kızamık geçirmemiş çocuklara,

2) Kızamığa yakalandığında, hayati tehlike ihtimali bulunanlara,

a) Aktif tüberküloz,

b) Solunum yolları hastalığı,

c) Kardiyopati,

d) Ensefalopati,

gibi hastalıkları olan çocuklara öncelikle uygulanmalıdır.

b) Endemik bölge :

Yukarıda belirtilen çocuklara sistematik aşı uygulanmalıdır.

c) Epidemik bölge :

1. Enfeksiyonu alan aşısız bebek ve çocuklardan zayıf bünyelilere hastalığı hafif geçirmeleri için GG verilebilir.

2. Hastalığı geçirmemiş çevredeki 6 ay ve yukarı yaştaki çocuklar aşılanır. Bir yaş altında olup epidemi nedeni ile kızamık aşısı yapılan bebeklere aşıları 15 aylık devreden sonra tekrarlanır.

AŞI TEPKİLERİ VE ÖNLEMLER :

Aşı çoğunlukla reaksiyon vermez, fakat 7-9 uncu günlerde 38°-39°C ateş ve hafif, gastroentestinal rahatsızlık ve rinofarinjit görülebilir. Bu gibi hallerde aspirin verilmesi yeterlidir.

HANGİ AŞILARLA BİRLİKTE UYGULANABİLİR :

BDT ve polyo aşıları ile birarada uygulanabilir.

MEASLES VIRUS VACCINE, LIVE-ATTENUATED

-Quality:

Measles vaccine is attenuated virus suspension which is produced in chich's tissue culture in the sterilized conditions or in other appropriate.

Virus do not contaminate any other person except the person who is vaccinated Much as the virus causes fever and skin eruption in child we have not encountered with any complication which may seem in case of disease. The virus is not produced in our country and it is imported.

-Dosage:

1 dose vaccine is 0.5 ml and contains TCID50 (Tissue Culture Infective Particle) not less than 1000.

Measles vaccine is held in ampuls of 1 dose or in ampuls or vials of 5-10 doses in a lyophilized form, with a solution to make it watery and it has own injector.

Amount of solution to be used and term of use is indicated on the vaccine package. All the live-virutic vaccines, particularly measles vaccine should be used within two months at the latest as from (the date of their procurement by the organization which will use them.

-Age for implementation (vaccination) and intervals: Vaccination is implemented once to children older than 12 months i.e. completed 12-15 months of their life. All children older than 6 months who have not suffered from the disease (measles) and who live in area where epidemic measles is seen , are vaccinated. Vaccination of those who are younger than 12-15 months is repeated after they complete 15 months of their life.

- Implementation Technique: Vaccine of 1 dose is mixed with liquid of 0.5ml and it dissolves immediately; subcutaneous infection through arm is made.

- Immunity (duration) and Repeats (of vaccination): The vaccine produces immunity as in the case of those who have suffered from the disease. Repeat of vaccination has not been considered for the present. New findings would lighten the issue.