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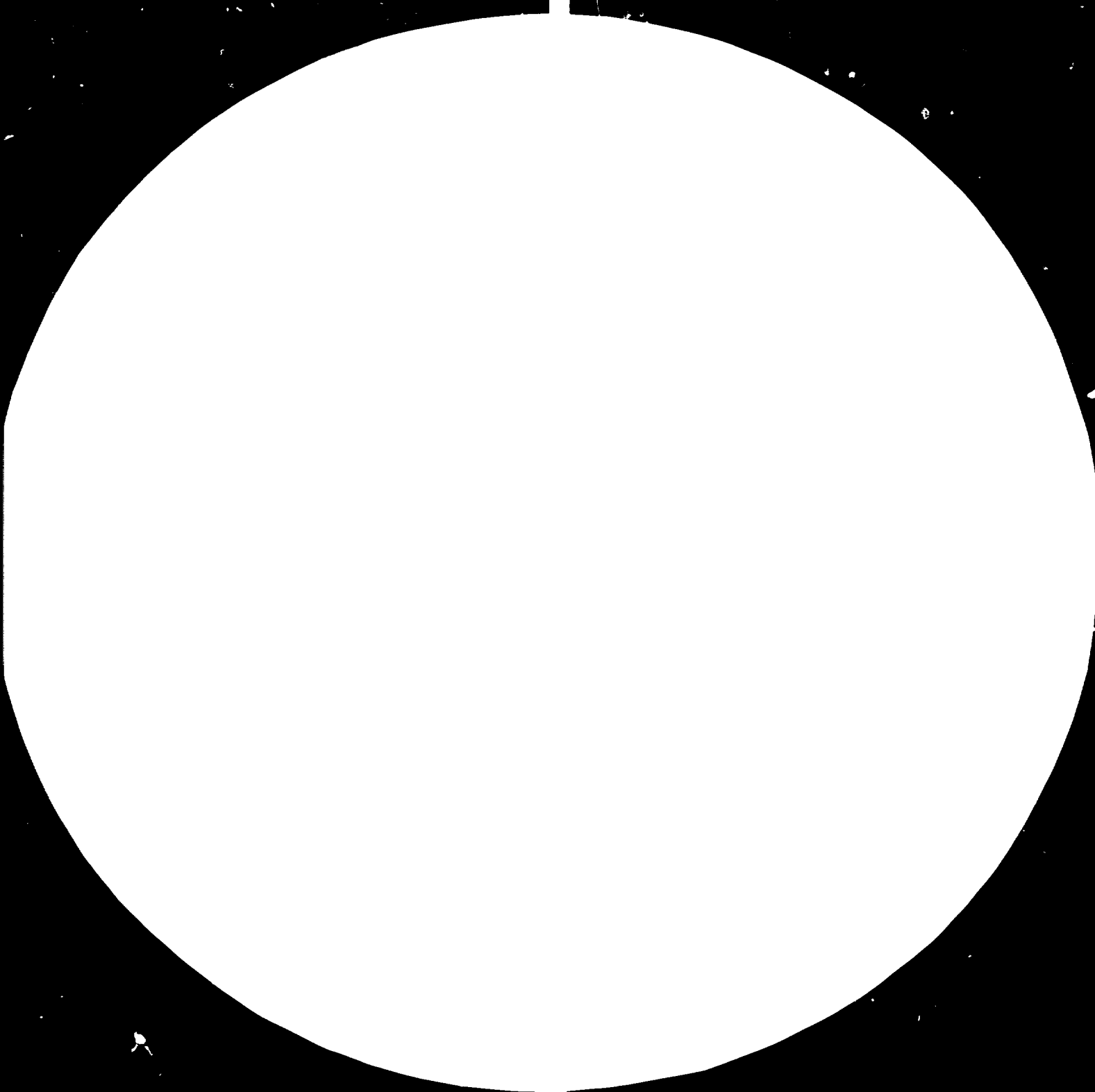

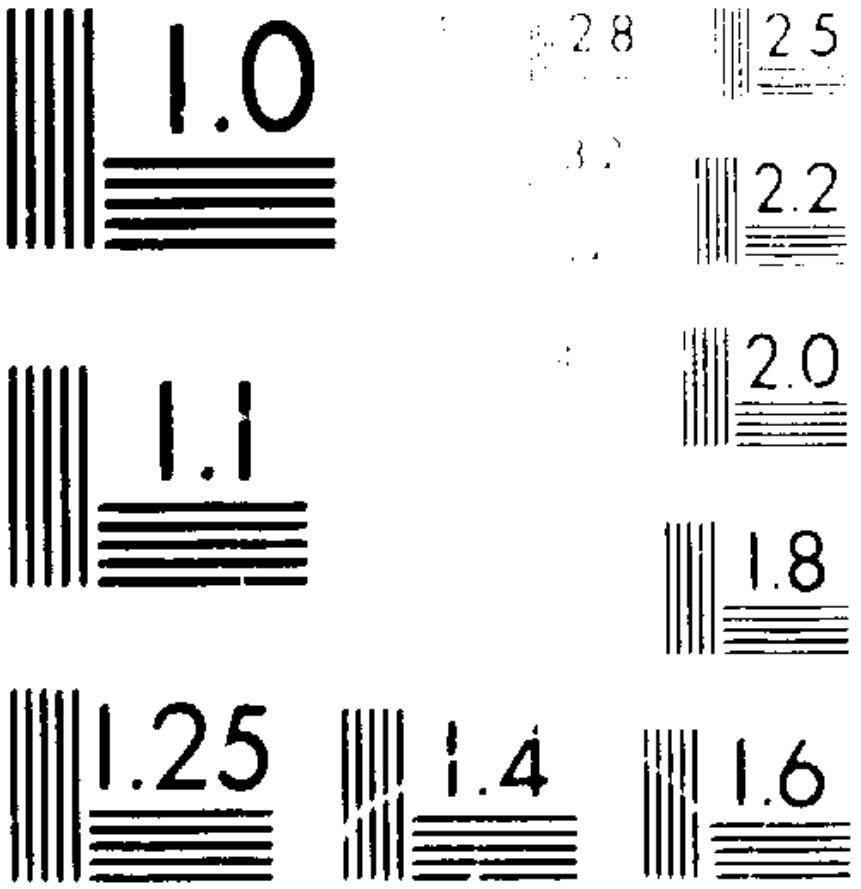
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UNITED NATIONS INDUSTRIAL
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ASSISTANCE TO GIHOC PHARMACEUTICAL DIVISION, PHASE II - ADVISER IN VACCINE PRODUCTION.

TS/GHA/78/002 .

GHANA .

Prepared for the Government of Ghana
by the United Nations Industrial Development Organization,
executing agency for the United Nations Development Programme

Based on the work of Z. Csizer, M.D.,
technical assistance expert for vaccine production

80-32588

Explanatory notes

A slash between dates (e.g 1976/77) indicates a crop year, financial year or academic year.

Use of a hyphen between dates (e.g. 1970-1975) indicates the full period involved, including the beginning and end years.

The following forms have been used in tables:

Three dots (...) indicate that data are not available or are not separately reported.

A dash (-) indicates that the amount is nil or negligible.

The following abbreviations have been used in this report:

ARV	anti-rabies vaccine
ATS	antitetanic horse serum
BCG	bacillus calmette-guérin vaccine
CBPP	contagious bovine pleuropneumonia
DPT	diphtheria, tetanus and pertussis vaccine
GIHOC	Ghana Industrial Holding Corporation
TAB	typhoid-paratyphoid A and B vaccine

CONTENTS

Annexes

INTRODUCTION

The Pharmaceutical Division is one of the 16 Divisions of the Ghana Industrial Holding Corporation (GIHOC). It was built in 1967 on an estate of 110 acres in Accra. The production has risen from year to year, and in 1978 the Division will produce approximately 12 million ampoules, 800 million tablets and 28 million capsules. Recently, the Division has signed co-operation agreements in production with May and Baker Limited, Merck Sharp and Dohme, Ciech Polfa and Glaxo. GIHOC Pharmaceutical Division has approximately 650 employees, of which 40 graduates with university degrees are in charge as managers of the different departments and units.

Because of the steadily growing production the present production areas have become crowded; the restricted space for production and storing has become the limiting factor of further expansion. To solve the problems, the construction of the new Tabletting Department, Main Warehouse and Quality Control Department should start as soon as possible.

The activities of UNIDO in Phase II of project TS/GHA/78/002, "Assistance to GIHOC Pharmaceutical Division, Phase II - Adviser in vaccine production", were with the construction work, installation and furnishing of production and laboratory areas, establishment of new production lines, introduction of new products and, last but not least, training of the staff.

The aim of this mission was (a) to collect basic epidemiological data in Ghana in both the medical and veterinary fields, such as notifiable diseases, amount of vaccines imported and vaccinations performed; (b) to evaluate the existing facilities in the Quality Control Laboratory and production unit of the GIHOC Pharmaceutical Division; (c) to prepare a list of vaccines which could be produced in the Pharmaceutical Division; and (d) to prepare a plan for the establishment of vaccine production and control.

A list of the notifiable diseases in Ghana is given in annex I. The incidence of the principal communicable diseases since 1971 is shown in annex II. The notifications do not in all cases give a correct picture of the incidence of the various diseases. For example, a recent outbreak of yellow fever that caused more than 100 cases, 30% of which were fatal, has not been reported and documented. Annex III shows the vaccinations performed in Ghana since 1969. The vaccines requirements for 1977/78 are shown in annex IV. The requirement and the stock of vaccines in 1978/79 are given in annex V. The demand and availability of vaccines for 1978-79 is shown in annex VI. The veterinary epidemiological data are shown in annex VII.

I. FINDINGS

Before the evaluation of the existing facilities in the Quality Control Department and production unit of GIHOC Pharmaceutical Division which could be used for the production and control of vaccines the implementation of previous recommendations made by Mr. J. Surowiecki and Mrs. A. Tcheknavovian-Asenbauer were investigated. The comments on the implementation of these previous recommendations are given in annexes XIII and IX.

The Injections Department has not enough space for the installation of an aseptic filling unit for vaccines, therefore, the establishment of a vaccine production unit in the existing Injections Department is not practicable. The existing facilities of the Quality Control Department seem to be adequate and sufficient for the sterility, safety and pyrogenicity testing of vaccines. The existing animal house, however, does not meet the minimum requirements for potency testing.

The Quality Control Department has an approximately 10% share in the annual budget of the Pharmaceutical Division. It is divided into an analytical section and a microbiological section. A short review of microbiological tests carried out in the microbiological laboratory is shown in annex X. The description of the sterility test is given in annex XI. The sterility testing as carried out in the Pharmaceutical Division is old fashioned, and therefore tests carried out according to the recent prescriptions (European Pharmacopoeia, FDA Regulations) are highly recommended. The bacteriological environmental control method will be used in the vaccine production unit of the Pharmaceutical Division. The importance of this method, which meets the requirements of good pharmaceutical manufacturing practice, cannot be over-emphasised. A detailed description is given in annex XV.

For Phase II production of the following vaccines is recommended:

Cholera vaccine (fluid or adsorbed, fluid)
Typhoid vaccine (fluid)
Tetanus toxoid (adsorbed, fluid)
DPT vaccine (adsorbed, fluid)

The production of any other human vaccines in the present situation would be completely unrealistic. The cholera and DPT vaccines and the tetanus toxoid

are items of the Ghana National Formulary, 2nd Edition, 1974-76. It is suggested that instead of the TAB vaccine, a single typhoid vaccine be administered. According to the WHO field trials, the conventional TAB vaccine does not protect against S. paratyphi A and B infections.

Before preparing a plan for implementing vaccine production in a properly phased programme, the two recent proposals to establish a vaccine filling unit and a quality control unit for vaccines were investigated. Comments on these proposals are given in annexes XIII and XIV.

The Vaccine Production Department will be installed on the first floor of the new warehouse.[1/] The layout of the department is given in annex XV. The layout is as simple as possible; nevertheless, it meets the requirements of good manufacturing practice. The accesses to the rooms of "white" (aseptic) and "black" (non-aseptic) areas are independent. The aseptic filling unit should be supplied with sterile air under pressure, about 25 mbar higher than atmospheric pressure. The complete automatic filling and sealing machine should be covered by a vertical laminar-air-flow tent. The sterile final containers (ampoules) and the filling armatures should be passed through the double-door sterilizers (autoclave and hot-air oven).

The filling materials should be passed through a window of the corridor of the aseptic filling unit. The staff can reach the aseptic area only through the clean dressing room. If the so-called "grey" area is needed for the actual production work, three independent entrances or passages will be necessary instead of the two which are shown in the draft plan. It is recommended that all the work in the white area be performed by women, since it is light work. The production (grey) area consists of:

(a) A room for washing and sterilizing of glassware and production of distilled water and culture media;

(b) A laboratory for preparing the pre-cultures; equipped with a shaker, a pH meter, a photometer and a microscope;

(c) A laboratory for the mass cultivation; with a fermentor, a separator, centrifuges and water bath;

(d) Two smaller laboratories for freeze-drying the bacterial strains used for production and control and for sterility testing of inactivated cultures and bulk suspensions.

The black area consists of rooms for the sighting, printing, labelling and packaging

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1/ For design and outlay of the warehouse see DP/ID/SER.A/164.

After the construction of the Vaccine Production Department is completed, the filling, sealing and packing of imported vaccines in bulk is recommended as a first step. During this phase, the potency testing of filling lots is recommended to be carried out overseas. The training of a vaccine production manager and staff should be started at the same time. The staff for vaccine production should be reliable and well trained. It is recommended that it be recruited from the existing staff of the Pharmaceutical Division on a voluntary basis. An expert in vaccine production and control should be hired.

The establishment of a national control unit for bacterial vaccines in the Public Health Reference Laboratory, Health Laboratory Services Division, Ministry of Health, is highly recommended. A very brief review of requirements for both the Microbiological Laboratory of the Quality Control Department of GIHOC Pharmaceutical Division and the National Control Laboratory for bacterial vaccines with special reference to the animal breeding house and test room is given in annex XVI. The establishment of a good animal house with adequate sanitary conditions cannot be over-emphasized.

II. RECOMMENDATIONS

A. For GIHOC Pharmaceutical Division

1. The construction of the new production block and the warehouse should start as soon as the financial resources are available.

2. The establishment of a vaccine production unit in the first floor of the new warehouse is highly recommended. The design is attached as annex XV. The estimated budget required for the equipment is approximately $US 300,000.

3. The programme of production should concentrate at first on the four main bacterial vaccines: cholera, typhoid, tetanus toxoid and DPT.

4. The expansion of the Quality Control Department or the construction of a new one is recommended. Quality control can be carried out with the present staff and equipment.

5. The establishment of a new animal house with a mouse colony in accordance with the requirements of Good Manufacturing Practice is essential. A brief review of requirements is given in annex XVI.

6. When production starts an expert in vaccine production and control should be on duty and training of the staff should begin.

7. A sufficiently well trained and reliable staff in the vaccine production and control units should be secured.

8. As a first step to vaccine production, filling and packing of vaccines imported in bulk is recommended.

B. For Health Laboratory Services Division, Ministry of Health

1. The establishment of a national quality control unit for bacterial vaccines in the Public Health Reference Laboratory is highly recommended. The brief review of required test conditions is given in annex XVI.

2. The GIHOC Pharmaceutical Division and the Health Laboratory Services Division, Ministry of Health, should co-operate in the establishment of a mouse colony and breeding house.

Annex I.

THE NOTIFIABLE HUMAN DISEASES IN GHANA

A. Diseases that should be reported immediately by telegram

- Cholera
- Enteric fever
- Plague
- Human anthrax
- Acute poliomyelitis
- Smallpox
- Yellow fever
- Human rabies
- Typhus
- Human trypanosomiasis
- Relapsing fever
- Infectious yaws
- Cerebrospinal meningitis

B. Diseases that should be reported weekly

- Food poisoning
- Tuberculosis
- Leprosy
- Diphtheria
- Pertussis
- Tetanus
- Chickenpox
- Measles
- Infectious hepatitis
- Ophtalmia neonatorum
- Puerperal pyrexia

Annex II

NOTIFICATION OF INFECTIOUS DISEASES IN GHANA, 1971-1976

Year	Measles		Pertussis		Poliomyelitis		Tuberculosis		Tetanus		Diphtheria		Cholera[a]	
	C/D	F/C%	C/D	P/C%	C/D	P/C%	C/D	P/C%	C/D	P/C%	C/D	P/C%	C/D	F/C%
1971	94 870/356	0.4	14 664/24	0.2	119/3	2.5	5 605/100	1.8	1 369/310	22.6	14	-	15 781/821	5.2
1972	95 529/273	0.3	18 261/13	0.1	136/6	4.4	5 201/73	1.4	1 373/321	23.4	23/2	8.7	625/32	5.1
1973	94 918/290	0.3	17 191/14	0.1	194/?	2.5	5 985/106	1.8	1 503/241	16.0	25/3	12	675/37	5.5
1974	91 135/324	0.4	12 486/12	0.1	230/4	1.7	6 354/88	1.4	232/239	19.4	21/2	9.5	483/37	7.7
1975	140 821/388	0.3	22 009/6	0.02	275/3	1.1	6 355/106	1.7	1 520/245	16.1	120	-	63/...	...
1976	131 405/439	0.3	22 348/16	0.1	313/8	2.6	6 174/87	1.4	1 142/204	17.8	44/1	2.3	27/...	...

Year	Yellow fever		Rabies		Cerebrospinal meningitis		Smallpox
	C/D	F/C%	C/D	F/C	C/D	F/C%	
1972	4/4	100	23/23	100	991/102	10.3	Since October of 1968 there have been no cases
1973	4/4	100	31/17	55	671/128	20.7	of smallpox
1974	...	...	16/16	100	787/110	14.3	

Note: C/D = ratio of cases to deaths; F/C% = percentage of fatalities.

a/ In 1977 there were 1,188 cholera isolates; in January-May 1978 there were 416.

Annex III

VACCINATIONS PERFORMED IN GHANA, 1969 - 1976

Year	Smallpox	Measles	DPT[a]	BCG[b]	Tetanus	Poliomyelitis	Yellow fever	Cholera	Tab[c]
1969	2 033 128	370 193	- [d]	351 811	-	-	233 492	-	-
1970	1 912 478	412 099	3 838	553 975	2 175	3 116	363 730	-	-
1971	1 [illegible]08 360	277 075	3 230	278 169	1 934	2 183	208 812	3 615 820	-
1972	647 613	228 671	16 441	136 6[illegible]0	7 686	4 908	103 635	-	-
1973	354 904	132 320	31 681	73 183	22 250	18 999	137 691	680 438	209 406
1974	1 037 130	233 115	45 734	161 263	61 431	30 909	-	442 541	21 119
1975	945 179	184 632	41 818	217 830	75 081	22 721	-	261 213	23 344
1976	509 804	131 251	24 111	132 751	47 966	31 533	66 127	303 399	37 756
Average per year:	1 056 075	246 170	20 882	238 205	27 315	14 296	139 186	662 926	36 453

Population census in 1970: 8 559 313

Estimated population in 1978: 10 428 683

Estimated population eligible for vaccination: 0 to 1 year; 344 146 (3.3%); 1 to 4 years, 1 553 873 (14.9%); 5 to 9 years, 1 762 447 (16.9%); 10 to 14 years, 1 220 155 (11.7%)

Note: 1977 data are not available.

a/ Diphteria, tetanus and pertussis vaccine.

b/ Bacillus Calmette-guérin vaccine.

c/ Typhoid-paratyphoid A and B vaccine.

Annex IV

REQUIREMENTS FOR VACCINES IN GHANA, 1977/78

Type of vaccine and dosage	Number of population at risk	Number of required doses	Quantity and type of vials				
			5 doses	10 doses	20 doses	25 doses	100 doses
BCG (0.1 ml)	4 656 452	500 000	-	-	10 000	-	3 000
DPT (0.5 ml)	500 000	300 000	-	30 000	-	-	-
Poliomyelitis (oral) (0.02 ml)	500 000	300 000	-	-	15 000	-	-
Measles (0.5 ml)	1 811 932	1 000 000		10 000	-	-	-
PPD 2TU (Tuberculin)	-	150 000	-	15 000	-		
Smallpox	-	100 000	-	-	-	4 000	-
Yellow fever (0.5 ml)	-	40 000	2 000	-	1 500	-	-
TAB (1 ml)	-	20 000	-	2 000	-	-	-
Tetanus toxoid (0.5 ml)	-	80 000	-	-	4 000	-	-
Cholera (1 ml)	-	100 000	-	10 000	-	-	-
A.T.S.[a] (1.0 ml)	-	100 000	-	10 000	-	-	-
ARV[b] (14 x 1 ml)	-	70 000					

Note: The vaccines should not expire earlier than July 1979.

a/ Antitetanic horse serum.

b/ Anti-rabies vaccine.

Annex V

VACCINE STOCK AND REQUIREMENTS IN GHANA, 1978/79
(Doses)

	Smallpox[a]	Measles[b]	DPT[c]	BCG[b]	Poliomyelitis[d]	Yellow fever[d]	Cholera[b]	Tetanus toxoid[d]	ARV[c]	TAB[b]
Expiry date	-	July 1978	7/12/1978	August 1978	1978/79	October 1978	February 1979	July 1978	July and August 1978	April 1979
Quantity in stock	379 650	117 120	30 541	534 680	282 640	256 100	198 510	279 135	26 250	182 220
Outstanding donations from UNICEF 1977/78	-	525 000	30 000	43 000	-	30 000[e]	-	50 000	-	-
Required for 1978/79	-	-	120 000[g]	-	300 000[k]	30 000[i]	-	50 000[j]	56 000	

a/ 25-dose vials.
b/ 10-dose vials.
c/ 1-dose vials.
d/ 20-dose vials.
e/ 1,500 vials à 20 doses.
f/ 2,500 vials à 20 doses.
g/ 120,000 vials à dose.
h/ 15,000 vials à 20 doses.
i/ 1,500 vials à 20 doses.
j/ 2,500 vials à 20 doses.

Annex VI

PROPOSED UNICEF SUPPLIES OF VACCINES

May-December 1978, Summary Table

(Thousands of doses)

Vaccine	Current stock	Proposed UNICEF supply	Total available	Total required
DPT	37	100	135	220
Tetanus	269	-	269	61
Yellow fever	-	100	200	200
Measles	10	175	185	100
BCG	682[a/]	50[c/]	682[b/]	450
Poliomyelitis	16.8	-	16.8	30
Cholera	88.5	500	698.5	1 000

a/ Including supply from WHO.

b/ Expiry August 1978.

c/ Expected August 1978.

Annex VII

VETERINARY EPIDEMIOLOGICAL DATA

A. Notifiable diseases

Diseases that should be reported immediately by telegram	Diseases that should be reported weekly
Rinderpest	Fowl typhoid
Contagious bovine pleuropneumonia	Fowl pox
Anthrax	Swine fever
Foot and mouth disease	Trypanosomiasis
Black leg	Tuberculosis
Rabies	Bacillary white diarrhoea
Newcastle disease	Fowl paralysis
Haemorrhagic septicaemia	Mange
Fowl plague	Glanders
Swine erysipelas	Epizootic lymphangitis

B. Vaccinations

Year	Rinderpest	CBPP	Anthrax	Rabies	Trypano-somiasis	Black leg	Newcastle disease	Fowl pox	Brucellosis	
									S.19	45/20
1973	204 572	219 461	78 670	117 319	21 642	63 539	4 714 208	1 714 208	24 557	40 333
1974	275 848	89 396	40 850	103 729	22 207	51 160	5 073 731	1 632 920	21 620	89 352
1975	265 947	22 548	43 595	29 714	25 907	30 731	5 395 800	888 499	9 565	62 283
1976	399 325	591 512	31 910	29 385	29 476	26 647	4 596 586	1 094 586	-	1 862
1977	194 268	193 536	36 738	65 088	41 440	5 507	5 671 073	2 030 194	-	-

C. Disease outbreaks

	Rinderpest		CBPP		Foot and mouth disease FMD		Black leg		Anthrax		Haemorrhagic septicaemia		Trypanosomiasis		Rabies	
	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F
1973	149/10+	82	193/25+	158	4 061/33	4	41/7	25	91/27	91	-	-	762/26	2	119/30	119
1974	63/3	49	1 497/47	740	15 399/144	27	25/8	25	232/9	51	-	-	470/16	-	177/40	177
1975	-	-	838/78	641	469/9		31/3	29	30/3	30	-	-	81/5	9	132/38	132
1976	-	-	4 441/40	266	-	-	81/2	9	930/9	45	55/8	54	1 848/12	3	193/53	193
1977	-	-	1 737/59	750	-	-	534/8	43	5 357/9	169	12/2	12	18/4	13	121/36	121

Note: C/O = ratio of cases to number of outbreaks; F = fatalities.

C. Disease outbreaks (continued)

Year	Newcastle disease		Fowl pox		Fowl typhoid		Bacillary white diarrhoea		Mange		Tuber-culosis		Swine erysi-pelas		Fowl cholera	
	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F	C/O	F
1973	74 295 / 55	25 431	3 371	469	-	-	1 812 / 66	1	40 / 2	12	630 / 4	28	-	-	-	-
1974	10 988 / 41	6 203	8 975 / 44	559	-	-	-	-	5 853 / 110	-	2 / 1	2	6 / 1	6	-	-
1975	11 106 / 159	9 803	1 256 / 51	265	1 730 / 5	1 730	25 / 1	25	305 / 35	-	1 / 1	1	110 / 3	4	-	-
1976	20 532 / 85	19 087	1 590 / 23	507	122 / 6	122	-	-	-	-	1 / 1	1	73 / 1	40	-	-
1977	27 904 / 100	25 340	6 925 / 30	3 929	2 460 / 10	1 060	4 344 / 11	1 385	-	-	2 / 2	2	-	-	31 / 2	

D. Imports of vaccines

Year	Newcastle disease						Infectious bronchitis	Fowl pox
	HBI	Lasota	Komarov	Inactivated	Combivac	Gumboro		
1973	4 250 000	4 500 000	1 700 000	200 000	1 498 000	-	750 000	4 500 000
1974	3 000 000	3 078 200	1 830 000	250 000	500 000	1 580 000	200 000	3 500 000
1975	4 298 600	2 250 000	2 000 200	25 000	1 500 000	2 000 000	-	1 146 400
1976	1 240 000	1 939 500	-	725 000	1 500 000	4 000 000	-	2 660 900
1977	5 866 000	1 888 500	1 200 000	500 000	4 682 000	2 267 500	-	2 267 500

D. Imports of vaccines (continued)

Year	Fowl cholera/ typhoid	Rabies	Haemor-rhagic septicae-mia	Anthrax	TCRV	Black leg	CBPP	Covexin	Brucella S.19	Brucella 45/20	Tetanus antitoxin
1973	-	90 000	10 000	350 000	400 000	5 000	390 400	261 000	44 235	50 000	-
1974	-	110 000	45 000	-	400 000	-	140 600	52 200	90 000	100 000	6 000
1975	200 000	30 000	399 000	100 000	200 000	-	479 100	-	-	-	-
1976	200 000	100 000	-	-	400 000	-	878 200	550 000	-	-	-
1977	-	100 000	-	40 000	400 000	-	250 400	-	-	-	-

Annex VIII

FOLLOW-UP OF THE RECOMMENDATIONS MADE BY J. SUROWIECKI, UNIDO EXPERT, IN 1976

A. Production

1. The construction work of the new production building and the new main warehouse should start before the end of 1978.

2. Since 1975, nine graduates and four technicians were sent for overseas training to gain experience in production and control processes. Their courses in different countries (Federal Republic of Germany, Hungary, Sweden and the United Kingdom of Great Britain and Northern Ireland) varied from 10 weeks to 1 year in length.

3. The Development Section (Department of Production Development) was organized but its progress is not encouraging. It is hoped that in the second phase, when a development manager is appointed, the R and D work will become effective.

4. There is a constant co-operation with the Korle Bu Teaching Hospital in Accra, from time to time a representative of the Medical School takes random samples of the pharmaceuticals manufactured in GIHOC Pharmaceutical Division for control. Refresher courses for graduates are organized in different departments of the University of Ghana Medical School.

5. The quality of packaging materials for use in tropical climates has been improved. Polyethylene bags in pilfer-proof plastic containers are used.

6. For production, four fluid-bed spray granulators, one automatic filling and sealing machine to process reduced-vacuum closed ampoules, and one high capacity autoclave were bought.

B. Quality control

1. The Quality Control Manager visited a 10-week course of quality control in Stockholm, Sweden in 1977. The staff of Quality Control Department is well-trained.

2. The construction work of the new Quality Control Department is believed to start before the end of 1978.

3. The Microbiological Laboratory of Quality Control Department has made progress, its work if efficient, a new bacteriological environmental control method has been introduced. The Microbiological Laboratory (4 rooms) has been equipped with new incubators, dry-heat sterilizator, autoclave and analytical balance.

C. Maintenance

At the moment there are only three senior technicians in the Maintenance Department. They have all had training courses in Hungary.

Annex IX

FOLLOW-UP OF THE RECOMMENDATIONS MADE BY A. TCHEKNAVORIAN-ASENBAUER IN 1975

1 (a) In August 1977, a consultancy service of the United Kingdom set up a system of cards to control the everyday situation of machines and spare parts in the Maintenance Unit.

1 (b) Recently the Maintenance Unit lacks an engineer.

2. An air-conditioning machine has been installed in the pyrogen testing room, but because of the unpredictable break-downs,better service or a stand-by machine is needed.

3. The responsible person in the Packaging Unit, a trained nurse, had a six-month course in Hungary. She has been in charge since June 1978.

4. Of late years, Miss Muriel D. Gilbertson, Quality Control Manager, Miss Jane Rose Onny, Production Manager/Injection Unit and Mr. R.B.K. Kissi-Asomaining, Manager-In-Charge, Tabletting Unit had overseas training in several European countries for longer period. In this phase there is no need for foreign experts in the above-mentioned departments of GIHOC Pharmaceutical Division.

Annex X

MICROBIOLOGICAL TESTS

Sterility testing

Sterility testing is done on all injections to ensure that they are free from micro-organisms.

Random sampling is done in the Injections Department on the previous day's work and sterility testing is dome in an area free from contamina ion. Tests are carried out under aseptic conditions using the following media:

Cooked meat
Thioglycollate } anaerobic

Nutrient broth - aerobic
Selenite broth - pathogenic baccilli, e.g. S. typhi
Sabouraud - fungi

The above media are controlled once a month.

Five cc of the drug is inoculated and the media incubated for 10 days. If no growth of organisms is detected the sample passes for sterility. If there is a growth the test is repeated and the final report made to the Quality Control Manager.

Pyrogen testing

Pyrogens are by-products of bacterial metabolism that give rise to increases in temperatures, accompanied by feverish reactions which last for several hours upon intravenous injection.

Since certain bacteria produce pyrogens any condition that permits bacterial growth might lead to the existence of pyrogens. Pyrogens may be developed in H_2O left in stills or distilled H_2O left overnight.

The test is carried out on healthy rabbits with a temperature range of 38.9° - $39.8^{\circ}C$ and weighing not less than 1,500 g. The water for injection is rendered isotonic by the addition of NaCl before the injection test. The dose does not exceed 10 ml per kg of the body weight of test animal.

Intravenous injection of rabbits is done using the marginal ear vein. If there is no rise in temperature the particular batch passes pyrogen test and final report is made.

Antibiotic assay

Potency tests are determined by comparing the dose of the test that inhibits a susceptible organism with the standard of that antibiotic which produces the same degree of inhibition. Steel cylinders filled with uniform amount of antibiotics are placed on a media seeded with an organism. As the antibiotic diffuses into the media it inhibits the growth of the organisms in a ring like pattern. After 16-18 hours the zones of inhibition are measured and potency calculated.

Environmental testing

The number of organisms in a production area is always controlled to give a good picture of the level of contamination, so that the necessary measures are taken to bring the number of organisms to the permissible level of contamination.

This is done by exposing the plates for a certain period to allow the organisms in the area to fall into the plate. After incubation the number of organisms per plate is counted to give the level of contamination.

Annex XI

TESTS FOR STERILITY IN THE MICROBIOLOGY SECTION OF THE QUALITY CONTROL DEPARTMENT

Tests for sterility are performed on all parenteral solutions. These tests are performed using aseptic techniques in an area as free from contamination as is possible to achieve. The tests are not performed under direct exposure to ultraviolet light or in areas under aerosol treatment. Environmental tests to assess the suitability of testing conditions are frequently made to assure the validity of test results.

Since the whole of a batch of injections cannot be tested for sterility, the test is made on a randomly selected representative portion of the batch and inference about the sterility of the whole batch is made from the result of the sterility test of the sample. If the sample passes the test for sterility and we know that the whole of the batch from which the sample was drawn has been subjected to a recognized sterilization procedure, the batch is declared safe for issue. This does not mean that the whole of the batch is sterile beyond doubt. Statistically, there is always the chance of an extremely resistant organism having survived somewhere in the batch. The probability of such an event occuring is very low, and in the case of our factory products that have been through a recognized heating process, approaches zero.

The fluid media used for the tests are always examined to ensure that they are capable of promoting vigorous growth of small numbers of the commoner contaminating aerobic and anaerobic organisms. For aerobic organisms we use a media containing either meat extract containing peptone or a protein digest. For anaerobic tests we use thioglycollate medium. Before the test, this latter medium is heated at 100°C to drive off dissolved oxygen and cooled to 37°C or lower, before the final inoculation. For the moulds and yeasts we use Sabourand Agar.

Procedure

Dust particles are removed from the ampoules with sterile cotton wool saturated with alcohol. The ampoule is then flamed adequately at the same time avoiding undue heating of the contents. The ampoule is then opened using a sterile file.

The contents for culturing are removed with a sterile pipette and placed in 0.5 ml portion into the media listed above in duplicates. Control tests are performed for each of the media used.

The test and controls are incubated at 37°C (liquid media) and at 25°C (Sabourand Agar) for 10 days.

If a bacteriostatic agent is present in the preparation to be tested, it is diluted to a concentration that will not inhibit the growth of any organisms that might be present.

The following organisms are used to inoculate our control tubes: Staph. aureus (aerobic tests); Clostridium sp (anaerobic tests); Candida albicans (fungi); Proteus or Salmonella (Tetrathionate and Selenite Broth).

Results

If no growth of micro-organism is found in any tube the sample is declared to have passed the tests for sterility. If growth is visible the tests are repeated on further samples and, if necessary, done a third time. If growth is seen in each of these or if the same organism is seen in more than one test, the sample fails to pass the test.

Annex XII

BACTERIOLOGICAL ENVIRONMENTAL CONTROL IN PRODUCTION OF INJECTABLE SOLUTIONS

A. Measuring of airborne micro-organisms

Object

The number of micro-organisms in the air under activity in a room with a controlled environment gives a good picture of the impurity level within the area and gives a measure of the effect of the steps taken to keep a certain hygiene level. The simplest method is to expose open Petri dishes with nutriment agar during a fixed time in specified places. Measuring of fallout does not give any quantitative measure, but is a simple method which can give important information when regularly used.

Principle

Determination of the number of sedimented airborne micro-organisms in exposed petri dishes with nutriment culture medium.

Culture medium

Soya trypton agar (Oxoid or Difco)

Plates

Petri dishes with a diameter of approximately 9 cm

Procedure of analysis

The plates are incubated at about 30°C during four days, after which final reading is made of the number of micro-organisms occured. A reading of the number of bacteria colonies should also be made after two days. At ample occurrence of mould spores those can spread and hide the growth of bacteria at the reading after four days.

Taking of specimen

1. Laying out plates in production premises

For each production unit a number of test places are decided. These should in the first place be areas with open handling of the product or sterile product packing. The plates should be exposed during 60 minutes while activities are going on. Taking of specimen should be done at least once a month at each test place.

2. Laying out plates in LAF-benches

The plates should be exposed about 60 minutes under activity. Tests should be made after new installations and every or every other month depending on the activity level.

3. Control of air filters

The plates should be exposed about 20 minutes near the filter for incoming air. Specimen should be taken when there is no activity in the room. These controls should be made about three times annually.

Estimate of results

The results from plates exposed at fixed places in the different production units for production of injectables should on the average be less than five colonies per plate. Values of five-ten colonies per plate could be accepted in certain places occasionally. Values above ten colonies per plate indicate that a controlled environment is not maintained. Occasionally high values essentially above normal values should give rise to an extra bacteriological control of the products manufactured at the time for the test. A great number of micro-organisms at repeated measuring should give rise to measurements to increase the hygiene level. When deciding on suitable steps, the types of microorganisms isolated from the plates can be of help. High values of staphylococci on the plates indicate that the personnel is the source of the impurities. Ample occurrence of mould spores and spore-forming bacteria might cause high contents of gram-negative bacteria, fungi etc.

On plates exposed under activity in LAF-units during 60 minutes there should not after culture be any micro-organisms. Values above 5 colonies per plate indicate that the environment in the bench is not satisfactory.

When checking air-filters with laying out plates according to 3 above no microorganisms should occur. Values above 10 colonies per plate indicate that the filter is out of function.

B. Surface control

Object

For checking the cleaning of the working area, tests with contact plates can be made. This method can also be used for control of apparatus, equipment and the clothes of the personnel. Use of the results as a basis for an estimate of the effect of used sanitation methods can however be made only after a long period of regular testing.

Realization

Plates (Rodak plates) of 5 cm diameter are totally filled with soya tryptone agar. When casting the plates it must be watched that the culture medium is filled to the brim, so that the surface of the medium is situated above the edge of the dish. This is possible due to the surface tension of the liquid culture medium. The surface of the agar is pressed directly against the surface which shall be tested. The plate with micro-organisms which have been transferred from the test surface to the agar surface is then incubated at 30°C. After 4 days, the number of developed micro-organisms colonies is read. As this test means that culture media are transferred to the test surface it is of outmost importance that the surface is disinfected after the test with e.g. 70% alcohol.

Estimate of products

When testing objects which might come in direct contact with the product, the number of colonies should not exceed 0-5 per plate. For other surfaces the value should be 0-10 colonies per plate.

C. Bacteriological hand control

Object

Control of the hand hygiene of the personnel

Realization

Petri dishes with soya trypton agar or blood agar could be used. The tester presses the finger tips against the agar surface. After the test it is of outmost importance that the hands be cleaned to remove the nutriment substratum. The plates should be incubated at 37°C for 2 days before reading.

This control should be done about once a month and in the first place comprise personnel who might come in contact with the product, e.g. personnel on the filling lines. In cases when the routines prescribe use of gloves at work, samples should be taken on those after use.

Estimate of results

No E. coli shall occur, as presence of those indicates, that satisfactory sanitation of the hands after going to the lavatory, has not been done. Standards for the highest allowable number of staphylococci colonies per sample are not possible to stipulate. As a rough objective however 0-20 staph. Colonies per sample can normally be acceptable. The value of the hand controls is also that they have a psychologic effect and could contribute to it that the rules regarding hand hygiene are followed.

D. Broth filling in the production

Object

Control of filling equipment and aseptic working technique in production of injectable solutions.

Realization

With the same equipment, package and working technique as for the injectable solution a number of units are filled with broth. The test could preferably be made immediately after the filling of the injectable solution is finished. The units should not be gased with nitrogen or carbon dioxide and should only be filled to about 2/3 because the absence of oxygen influences the growth of bacteria in the broth solution. After filling it is extremely important that all parts which have come in contact with the broth are carefully cleaned.

After filling and sealing the units are incubated at 30°C for 7 days, after which growth if any can be seen as a muddiness in the nutriment solution.

Frequency

Routine controls of the filling machines for aseptic filling should preferably be made 1-2 times annually. When using injection vials at least 300 vials should be filled and when filling cartridges at least 1,000 per test.

Bacteriological media instead of product should also be used when testing new filling equipment and at the introduction of new or modified methods. In the latter case the nutriment solution can pass the whole production process and samples be taken from different points in the process for estimate of hygienic risks.

Estimate

Normally no growth should occur in filled units. If 1% of the units are infected, steps should be taken. For derivation of the contamination source, knowledge of the kind of micro-organisms can be of help. Occurrence of staphylococci indicates that the personnel is the source of contamination. Occurrence of spore-forming bacteria might be due to the medium or the equipment not being sterile.

Annex XIII

EXPERT'S COMMENTS ON PROPOSALS MADE BY ANDRE AND CIE, S.A.
ON 3 APRIL 1978

1. The second room is very small for an aseptic filling unit.

2. The accesses between the dressing rooms with shower and the second room will not prevent the air flow from being polluted by aerosols and dust particles.

3. The proposal does not include completely automatic ampoule filling and sealing equipment. The advantage of this equipment is not that it saves labour but that it reduces contamination to a minimum; it therefore should be regarded as essential.

4. In Ghana there is a great demand for vaccines in single-dose ampoules. In this respect the proposal does not contain details.

5. Because of the cross-immunity between the classical and eltor biotypes, according to the WHO requirements for cholera vaccine, this vaccine should only contain the strains of V. cholera Inaba 35A3 and Ogawa 41. Administration and dosage: a single dose of 8,000 million bacteria in 0.5 ml is acceptable for all age groups.

6. According to WHO field trials, the duration of immunity after the complete primary immunization with adsorbed DPT vaccine in the case of diphtheria and pertussis is 5 and 4 years, respectively.

Annex XIV

EXPERT'S COMMENTS ON PROPOSALS MADE BY PRUTSCHER
LABORATORY EQUIPMENT
ON 17 JUNE 1977

1. The drawings of the new Quality Control Department prepared by Mr. Fritz Brennig, UNIDO Construction Expert (February 1977 - April 1978) meet the requirements of good pharmaceutical manufacturing practice (GMP).

2. It is a good idea to place the Development Section (Department of Production Development) in the new building of Quality Control Department (ground floor, Room Nos. 25-26, 28, 30-32). The most important advantage is that in this case the Quality Control Department and the Development Section can share the same storerooms and instrument rooms. The largest pharmaceutical factories have independent quality control laboratories for production and research and development, but in the relatively small GIHOC Pharmaceutical Division, the experimental (laboratory or pilot-scale) products prepared by the Development Section should be tested by the Quality Control Department.

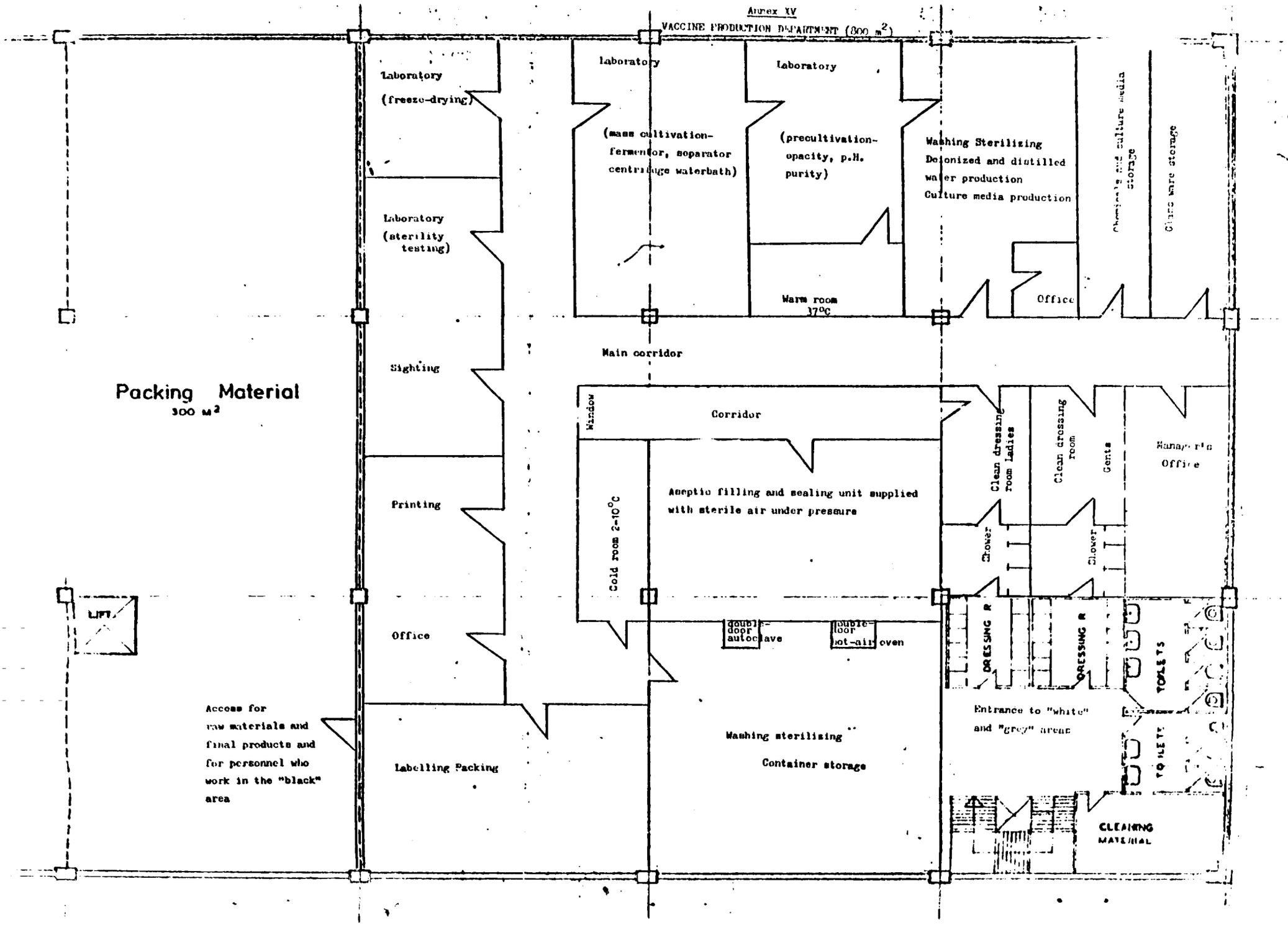
3. Room No.11 (cool room, 20°C) and Room No. 12 (warm room, 37°C) on the ground floor of the Microbiological Laboratory of the Quality Control Department possess common accesses as is shown on the drawing. Opening the doors allows warm air to get into the cool room and cool air to get into the warm room. That will waste energy by overworking the conditioning machines. Independent accesses to these two rooms are needed.

4. The first floor is occupied by the Analytical Chemical Section of the Quality Control Department. There are rooms for testing of raw materials, phase products and final products (with the exception of injections). That is neither rational nor economic. If the quality control of any raw material, phase product or final product is carried out by the same analytical method, it should be done in one and the same room.

5. The offer for the laboratory furniture (laboratory benches, storage cupboards, fume cabinets, energy cells, media hydrants etc.) is adequate. The price of the total consignment and that of the installations, however, seems to be very high, especially for 1977.

Annex XV

VACCINE PRODUCTION DEPARTMENT (800 m²)



Annex XVI

CONDITIONS STIPULATED BY THE PUBLIC HEALTH REFERENCE LABORATORY FOR QUALITY CONTROL TESTS

Potency test

For the potency tests of cholera, tetanus, and pertussis vaccines, mice are used. The potency of the vaccines is determined in comparison with that of the appropriate standard preparations. The attendants for animals used for the potency testing of products must be sufficient in number and experience to insure adequate care. Animal quarters shall be kept free of flies, insects, and lizards, and have sufficient ventilation or air-conditioning and abundant water supply. All the challenged mice and the cages shall be sterilized in autoclaves at the end of observation period after the challenge.

Safety test

For the safety test (innocuity test), guinea pigs and mice are used. Only overtly healthy animals shall be used, and they shall not have been used previously for any test purpose. For each test, at least two mice and two guinea pigs shall be used.

Sterility test

The sterility tests should be carried out in an appropriate laminar-air-flow bench. For products containing a mercurial preservative, the sterility test shall be made on Fluid Thioglycollate Medium. For products without mercurial preservative the medium shall be Soybean Casein Digest Medium.

Bacterial content

The number of bacteria in final container material shall be estimated by opacity determination in comparison with the International Opacity Reference Preparation or by nitrogen-content determination.

Mouse colony

A mouse colony shall be established for the potency tests. As for a single potency test of cholera vaccine about 300 mice, half male and half female,

weighing 14-16 g are needed, a breeding room of at least 60 mouse families shall be established. Mice shall be ordered from one of the laboratory animal breeding farms. The animals shall be fed by artificial pellets containing the essential amino acids, vitamins, and trace elements. An abundant supply of clean drinking water is essential. The animals shall be inspected daily. Animals that become ill shall be isolated from other animals and not used for tests until recovery is complete. To prevent the contamination of the animals in the breeding room, the breeding room shall be independent of the test room. Competent veterinary care shall be provided as needed.