OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

RESTRICTED

15889

DP/ID/SER.A/760
13 October 1986
ENGLISH

(R) INDIA: MODERNIZATION OF FACILITIES FOR THE MANUFACTURE OF ANTI-MALARIAL DRUGS.

DP/IND/81/028

INDIA

Technical report: Transfer of technology*

Prepared for the Government of India
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Backstopping officer: C. Chari, Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

28

* This document has been reproduced without formal editing.

V.86 60793

35.60 204

TABLE OF CONTENTS

ANNEXURES

1. Introduction

The technology involved in the production of pharmaceuticals in dosage form is relatively simple and is well diffused in several developing countries specially in the Asian and Latin American regions. This type of industry is also characterized by licencing arrangements, foreign subsidiaries and joint ventures. However, the technology in the case of manufacture of pharmaceutical chemicals or bulk drugs is rather sophisticated and is held by a limited number of technology holders. This is one of the reasons why only a few developing countries have been able to make some head way in this area. India is among such countries.

The availability, pricing and transfer of technology for the bulk drugs formed one of the major issues of both the UNIDO consultations on the Pharmaceutical Industry held in 1980 and 1983 respectively [1]. The first consultation recommended that mutually acceptable transfers of technology should be facilitated through UNIDO providing reference information relevant to the transfer of technology, including technical aspects, such as level of production, magnitude of investments, inputs, infrastructure etc..., which could be significant aid to individual developing countries in bilateral negotiations for transfer of technology.

The second consultation recommended that in respect of offers of technology for the production of bulk drugs and intermediates, UNIDO should in cooperation with technology holders prepare feasibility studies at the request by interested countries.

In the above context, the project entitled "Modernization of facilities for manufacture of anti-malarial drugs" is a very interesting example of development and transfer of technology in the area of manufacture of pharmaceutical chemicals based on chemical synthesis and constitutes an important milestone in the development of Pharmaceutical Industry in India and has significance for other developing countries in this field. This also highligha the importance of the indigeneous Research and Development effort in

[1]. First consultation on the Pharmaceutical Industry, UNIDO/ID/259, 1980; Second Consultation, UNIDO/ID/311, 1983

developing a viable technology for the Industrial Scale manufacture of bulk drugs. In this particular case, Bengal Immunity Co. Ltd (BICL) the Government implementing agency in cooperation with the Regional Research Laboratory, Jorhat, India has optimised the process technology for scaling up and a project proposal for setting up of a 80 tonnes per annum chloroquine phosphate plant was approved by the Government to be created at their factory site at Baranagar, Calcutta. The execution of the project was entrusted to Krebs & CIE (I) Pvt Ltd; a project engineering firm of Calcutta on a turnkey basis. The process required certain key equipments and sophisticated instruments not available in India for improving the technology and quality of the drug. Significant contribution was made by UNIDO through UNDP through the supply of the above equipment and instruments, assigning experts to instal and commission those equipments and training local technicians in operation and maintenance of the equipment and instruments both at the works of the fabricator abroad and at site. Thus an indigenous Research and Development effort supplemented by assistance by the international organizations in certain key areas resulted in the development and transfer of viable technology for the commercial manufacture of chloroquine phosphate. This will form an important element of the national program to eradicate malaria in the country and to meet the increased demand of this drug with indigenous technology.

The project was approved in november 1981 for implementation over a period of one year and eight months. Soon after starting of the programme, the scope of the project was increased substantially both in technical and financial aspects. This has resulted in a delay of the completion of the project. The testing and commissioning of various equipments were started in march 1984 and extended till March 1985. The initial production runs commenced in April 1985 and extended to the first half of 1986.

2. Objectives and logic of project

The development objective of the project is the expansion of domestic production of anti-malarial drug-chloroquine and to this extent reduce dependency upon import and freeing the anti-malaria campaign from foreign exchange constraints.

The immediate objective is to improve and optimize the indigeneous technology developed by BICL from locally available raw materials through:

(i) the introduction of new techniques of separation and subsequent material handling avoiding manual handling;

(ii) rigid process control to improve the product quality.

BICL in the course of the development of technology carried out extensive studies on process and equipment optimization for scaling up and observed that mechanization of unit operations was necessary, which in turn required some sophisticated equipment and instruments not available in India. Technical expertise was also required for the installation and commissioning of such equipment and it was important to train BICL scientists/engineers in the operation and maintenance of these instruments. The provision of sophisticated equipment and instruments and the technical assistance necessary for the installation, commissioning and initial operation of such equipment and training were taken over by UNIDO through UNDP.

3. Activities carried out and outputs produced

(i) Provision of equipment and instruments

The following equipment and instruments were procured and provided to the project by UNIDO.

(a) Funda-Filter - Type A - 5 m^2. Skidmounted with Fundatrol process controller, supplied by Chemap Ag, Switzerland - one piece.

(b) Bottom discharge batch centrifuge Type 46 A 1200 mmd. x 750 mm depth supplied by Thomas Broadbent and Sons Ltd., UK - two pieces.

(c) High pressure liquid chromatograph model 244 W/M 6000A - U6K supplied by Waters Associates, U.S.A.

(d) Hitachi Double-Beam UV-VIS spectro-photometer, 200 - 0025 model 200-20, supplied by Nissei Sangyo Co. Ltd, Japan.

(e) Aquameter Titrator, Beckman . mod. KF-4B, supplied by Beckman Instruments International, Switzerland.

(f) FOXBORO pH Recorder-controller supplied by Ing. Stahl G.M.B.H, Austria.

(g) NMR High resolution spectrometer. Varian EM model 360 L supplied by Varian Ag., Switzerland.

(ii) Assignment of experts

The following experts were assigned by UNIDO:

a) Mr. Guido Brem, engineer of Chemap Ag (suppliers of Funda Filter) supervised the installation of Funda Filter during two weeks in October 1984. He paid a return visit to the project site in March 1985, when the above equipment was commissioned, run with the actual material and was found to function satisfactorily. He also trained BICL technicians in the operation and maintenance of the above equipment.

b) An erection engineer from Thomas Broadbent and Sons Ltd. U.K (suppliers of bottom discharge centrifuges) assited in November 1984 in the installation of the centrifuges. The engineer paid a return visit to the project during April 1985 and assisted in commissioning the centrifuges.

(iii) Training

The training of BICL personnel was organized in Europe as well as at project site by UNIDO.

Study tour of three week's duration was arranged during April 1983 in the field of production and maintenance management for the following BICL officials in Europe.

(a) Dr. S. Bhattacharya - Team Leader (Research and Development)

(b) Mr. D.N. Mazumdar - Electrical engineer (Projects)

(c) Mr. S. Bhattacharya - Senior Maintenance Officer

(d) Mr. A.K. Dutta - Senior Production Officer

(e) Mr. B.C. Pai - Chargeman

BICL technicians were also trained at project site by the engineers of CHEMAP and Thomas Broadbent and Sons in the installation, operation and maintenance of equipment supplied by these firms.

(iv) Commissioning and initial production runs

The testing and commissioning of equipment were started in March 1984 and extended till March 1985. The initial production runs commenced in April 1985 and extended to the first half of 1986.

4. Achievement of immediate objectives

The immediate objectives of the project have been achieved as described below:

i) The introduction of new techniques of separation and subsequent material handling avoiding manual handling through the use of Funda Filter and bottom discharge centrifuges respectively resulted in the improvement and optimization of the indigenous technology developed by BICL in cooperation with RRL.

ii) Rigid process control through the use of UV-visible Spectrophotometer, Aquameter, HPLC and NMR spectrometer resulted in improvement of the product quality which is vital for a drug conforming to the Pharmacopoeial quality standard. NMR spectrometer is needed for the detection and identification of the undesirable by-product in various steps of the process. This would improve the overall quality of the end product as well as key intermediates. The process flow sheet of chloroquine phosphate is shown in Annex A. The load test data of the entire plant are presented in Annex B. The load test data for the separation technology are shown in Annex C. The rigid process control data are given in Annex D.

5. Utilization of project results

The technology for the production of chloroquine phosphate has been optimized through the use of modern equipment for separation and mechanized material handling. The quality of intermediates and final product has been improved and standardized with the use of sophisticated instrumentation and rigid process control. These are made an integral part of the manufacturing operations in the BICL plant.

6 Conclusions

1) The BICL plant with an annual production capacity of 80 tons has been commissioned and operations have commenced. Through this the development objective of expanding domestic production of anti-malarial drug-chloroquine has been achieved and to this extent, the anti-malaria campaign has been freed from foreign exchange constraints.

2) The project is an important milestone in the development, optimization and transfer of indigenous technology for the production of pharmaceutical chemicals based on chemical synthesis. BICL has developed the technology, optimized and scaled up the process in cooperation with RRL and rendered the technology viable through the introduction of modern equipment for separation and mechanized material handling and rigid process control using sophisticated instrumentation provided by UNIDO through UNDP. BICL scientists and engineers have acquired the know-how through training in the operation and maintenance of sophisticated equipment and instruments.

3) The successful completion of the project demonstrates that developing countries can develop indigenous technology, optimize and scale-up the process in cooperation with local research institutions and transfer viable technology through the assistance of international organizations and in this case UNIDO/UNDP. This is an important advance in acquiring viable technology for the manufacture of pharmaceutical chemicals or bulk drugs, which is vital for increasing domestic production of essential drugs to meet health needs.

4) The above project is a good example of indigenous Research and Development effort leading to the development and transfer of viable technology for the industrial scale manufacture of pharmaceutical chemicals for which there are a limited number of technology holders.

5) The project is yet another illustration of the capability and competence of the Indian scientists and engineers in the development and transfer of sophisticated technology in the area of bulk drug manufacture.

6) Through this plant, India can extend technical cooperation to other developing countries in this important field of development and transfer of technology.

7. Recommendations

a) BICL should take up regular production of chloroquine phosphate and attain the rated capacity, yields, time cycles and quality on a regular and continuous basis.

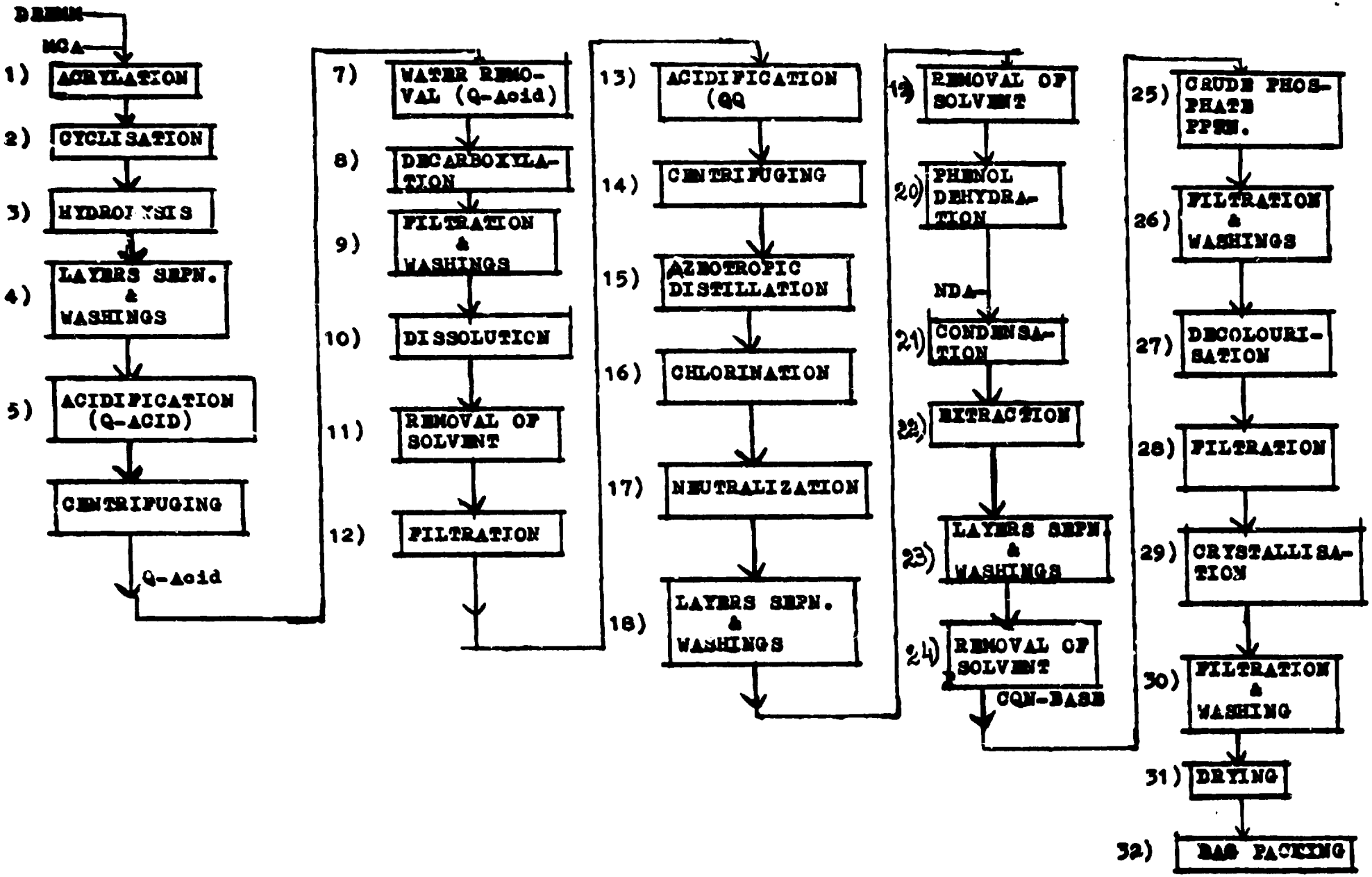
b) The scientists and engineers of BICL should monitor the process closely and take measures to effect cost reduction.

c) Follow-up projects such as "Seminar on development of technology of established and new anti-malarial drugs" or "Regional group training programme on technology transfer for chloroquine production" could be formulated by BICL and international organizations approached for assistance.

d) BICL in cooperation with Bengal Immunity Research Institute could utilize the facilities and know-how acquired for the development and transfer of technology for other synthetic pharmaceutical chemicals.

e) Technical cooperation can be extended to other developing countries in this vital field.

BLOCK-DIAGRAMME PROCESS-FLOWSHEET OF CHLOROQUINE PHOSPHATE



Annex B

SUB: LOAD TEST DATA OF ENTIRE 80 TPA CHLOROQUINE PHOSPHATE PLANT AT BENGAL IMMUNITY LIMITED

In the manufacturing of Chloroquine Phosphate there are 32 unit operations/processes.

A Block Diagram is shown at Annex A for the entire process. Detail of the Load Test is given below:

Sl No.	Unit operation/ Process	Load given	Performance	Remarks
1.	Acrylation	Full load	Good	Tested for 2 times
2.	Cyclisation	"	"	"
3.	Hydrolysis	"	"	"
4.	Layers Separation & washing	"	"	"
5.	Acidification	"	"	Tested for 2 times. Problem faced for the removal of the Slurry rectifications already suggested
6.	Centrifugation	"	"	Tested for 2 times. This equipment has been supplied by UNIDO. Load data is enclosed in Annex B.
7.	Water removal (Q-Acid)	"	"	Tested for 2 times
8.	Decarboxylation	"	"	Tested for 2 times
9.	Filtration & Washing	"	"	Tested for 2 times. This equipment has been supplied by UNIDO and load tested for 2 times. Details of load data enclosed in Annex B.

10.	Dissolution	"	"	Tested for 2 times
11.	Removal of solvent	"	"	Tested for 2 times
12.	Filtration	"	"	Tested for 2 times
13.	Acidification (OQ)	"	"	Tested for 2 times
14.	Centrifuging	"	"	Tested for 2 times. This equipment has been supplied by UNIDO and the load data enclosed in Annex B.
15.	Azeotropic distillation	"	"	Tested for 2 times
16.	Chlorination	"	"	Tested for 2 times
17.	Neutralisation	"	"	Tested for 2 times
18.	Layers sperartion and washing	"	"	Tested for 2 times
19.	Removal of solvent	"	"	Tested for 2 times
20.	Phenol Dehydration	"	"	Tested for 2 times
21.	Condensation	"	"	Tested for 1 time 2 batches of the earlier product is to be carried out in 1 operation as the residence time of the reaction is more than 24 hours.
22.	Extraction	"	"	Tested for 1 time
23.	Layers separation and washings	"	"	Tested for 1 time
24.	Removal of solvent	"	"	Tested for 1 time
25.	Crude phosphate PPTN	"	"	Tested for 1 time
26.	Filtration and washings	"	"	Full load test is in progress
27.	Decolourisation	"	"	Full load test is in progress
28.	Filtration	"	"	Full load test is in progress
29.	Crystallisation	"	"	Full load test is in progress
30.	Filtration and washing	"	"	Full load test is in progress
31.	Drying	75%	"	Tested for 3 batches to get optimum drying time. The material was taken from the existing Pilot Plant.

Annex C

Load test data for the equipments supplied by UNIDO for introduction of better separating technology:

(A) Load test of Broadbent Centrifuge No. 1 for Q-Acid:

1) Quantity of Q-Acid Slurry - 1000 kg.
2. Total time required for Centrifuging including Feeding, Spinning and Ploughing - 6 hours.
3. Total Q-Acid obtained - 235.8 kg.
4. Percentage of moisture in the Cake - 54.2%.

The basic object of the introduction of the Centrifuge was to eliminate the human contact during the Centrifugation operation. Immediately after removal of the Cake, the material was discharged into the next reactor for further process and thus eliminating the manual handling and human contact. The performance has been found very good and there was no problem for the entire operation for both the load tests. Apart from this, 2 load tests along with the materials prepared from the same plant the Centrifuge was also tested during commissioning of the same with the material received from existing Pilot Plant.

(B) Load test for Broadbent Centrifuge for OQ Slurry:

1. Quantity of OQ slurry 600 kg.
2. Total time required for Centrifuging including Feeding, Spinning and Ploughing - 5 hours.
3. OQ Cake obtained after Centrifuging - 121.5 kg.
4. Moisture presence in Cake 44.5 %.

The basic object of the introduction of the Centrifuge was to eliminate the human contact during the centrifugation operation. Immediately after removal of the Cake, the material was discharged into the next reactor for further process and thus eliminating the manual handling and human contact. The performance has been found very good and there was no problem for the entire operation for both the load tests.

(C) Load test data of Funda Filter for OQ Slurry in DPO:

1. Quantity of crude OQ Slurry in DPO - 900 kg.
2. Time required for filtration including prefiltration, heal volume filtration - 1 hour 25 minutes.
3. Time required for Benzene wash (3 times) - 2 hours.
4. Cascading with Alkali - 20 minutes.
5. Removal of the washed Cake with Alkali Solution to the next reactor - 10 minutes.

Basic object of the introduction of this filtration system is to avoid human contact (manual handling), separation of the Cake, washing of the Cake and discharge of the Cake into the next reactor in a single filtration system. The performance has been found satisfactory except a problem of accumulation of small portion of cake near the Central Shaft of the Sercens. This will not hamper the process when the Plant will be in full operation.

Annex D

Utilisation of Analytical instruments supplied by UNIDO for inprocess control studies and analysis of the final product related to CHLROQUINE PHOSPHATE.

1. Ultaviolet-visible Recording Spectrophotometer:

This instrument has been utilised for determining the purity (Assay) of Chloroquine Phosphate (both crude and final product) (Xerox copy of UV curve annexed).

2. Karl-Fischer Aquameter

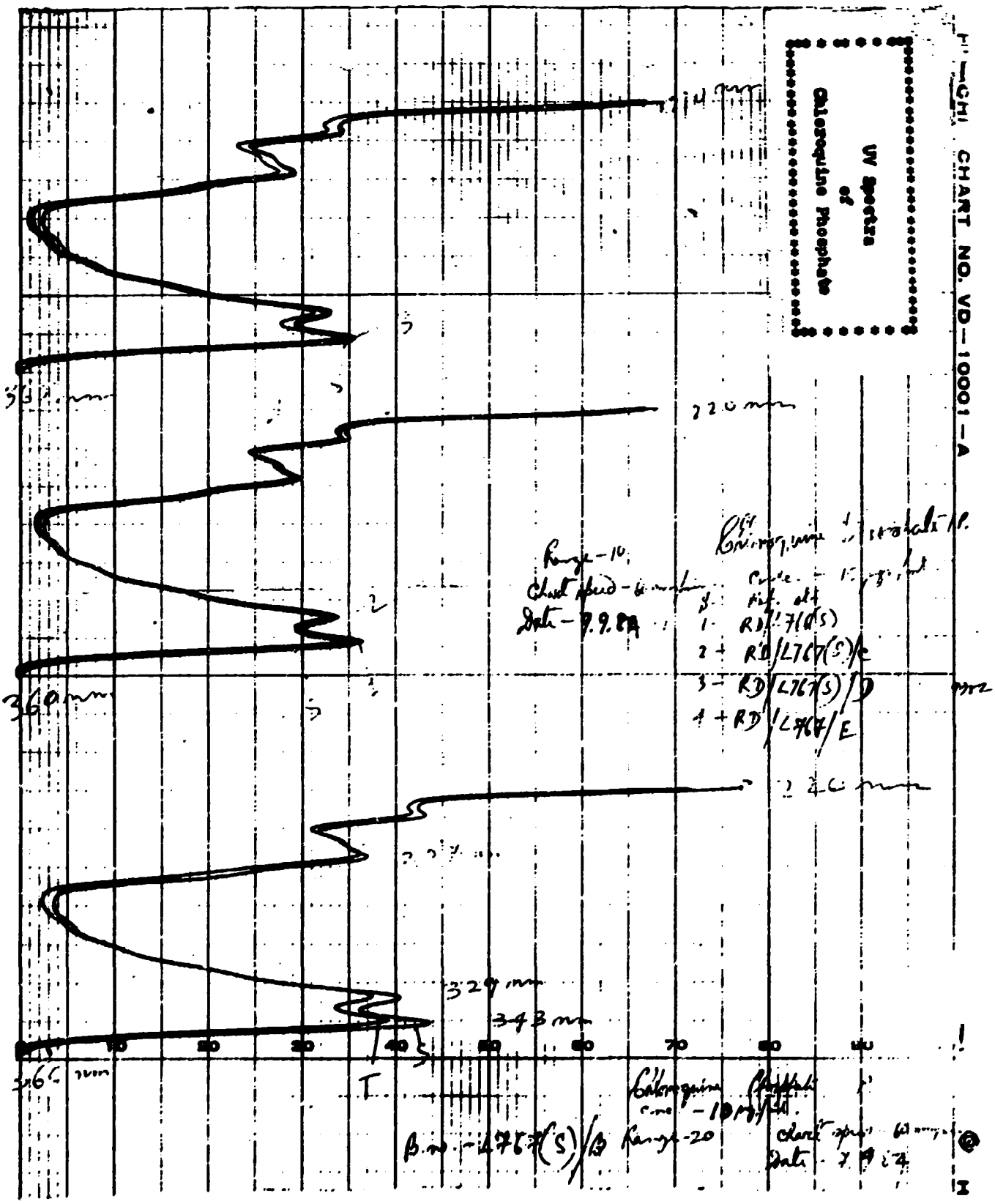
This instrument is used to determine the water content of various raw materials like methanol, phenol, diphenyl oxide, meta chloroaniline, etc.. used in the manufacture of Chloroquine Phosphate.

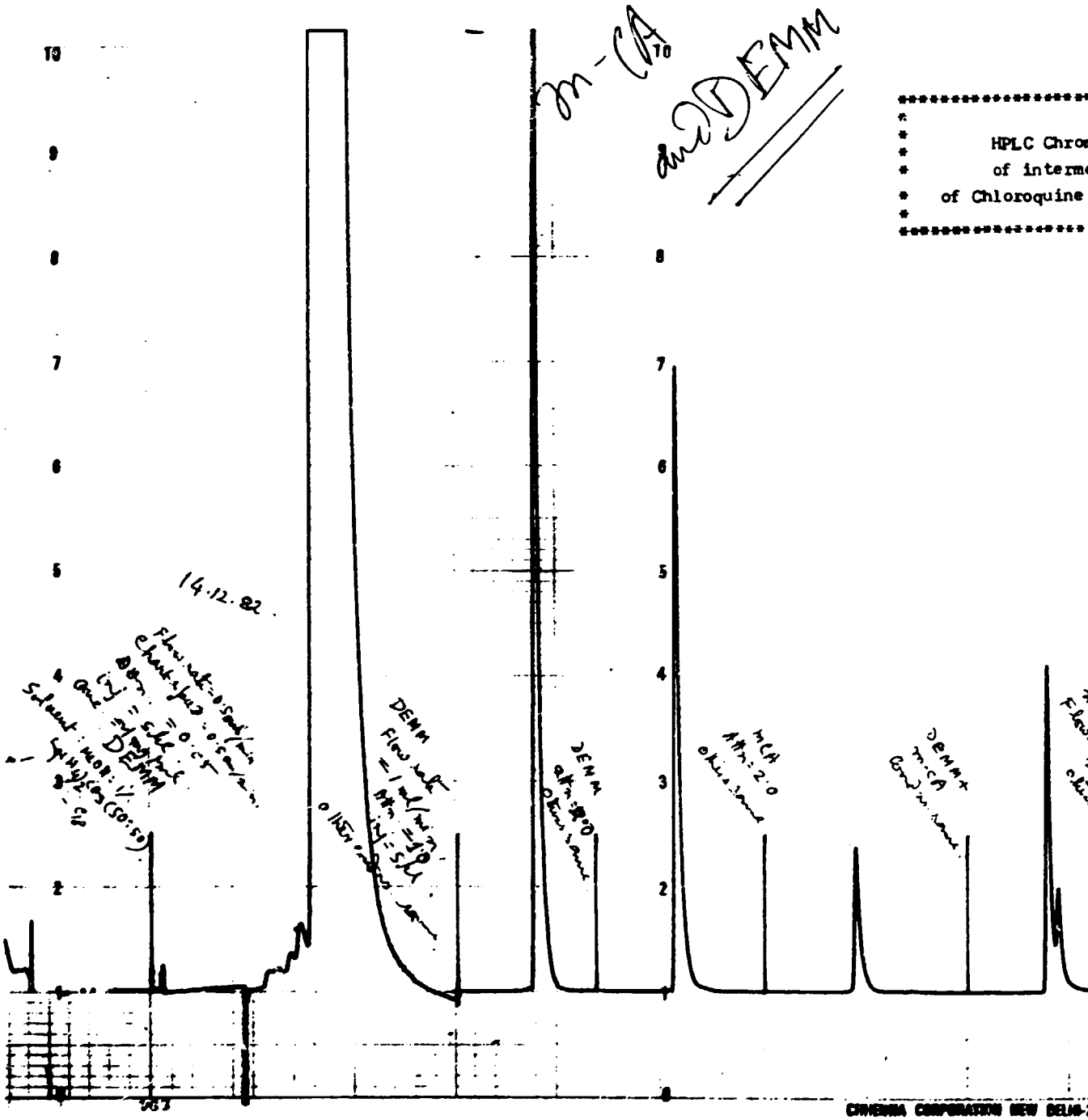
3. High Pressure Liquid Chromatograph (HPLC)

In process control procedure for analysis of the intermediates "Acrylate" and "Chloroquine base" has been established with this instrument (Xerox copies of the HPLC curves enclosed).

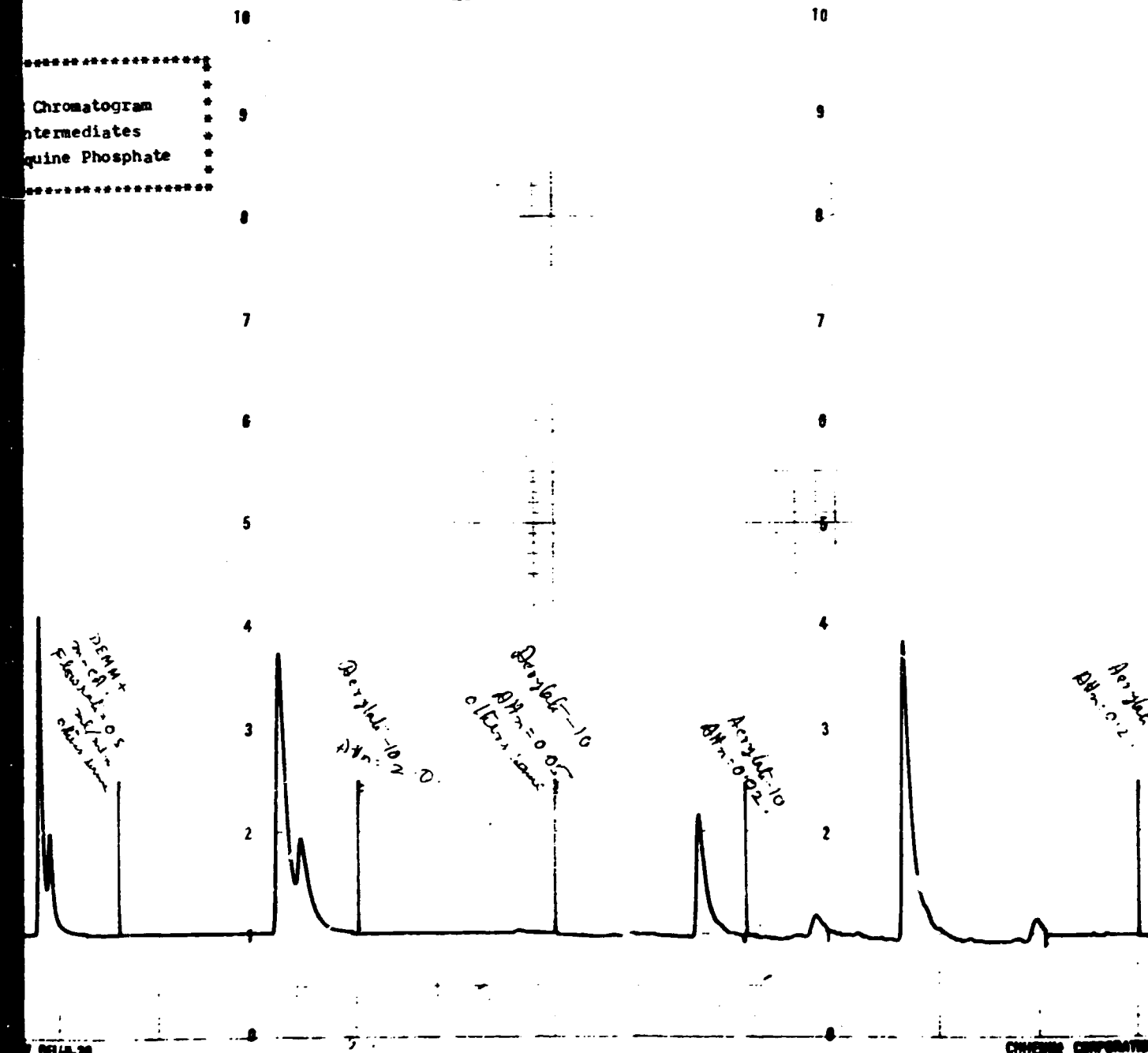
Analysis of 4,7 - Dichloroquinoline is under study.

These procedures are being constantly followed for monitoring the different stages of the process of manufacture of chloroquine Phosphate.

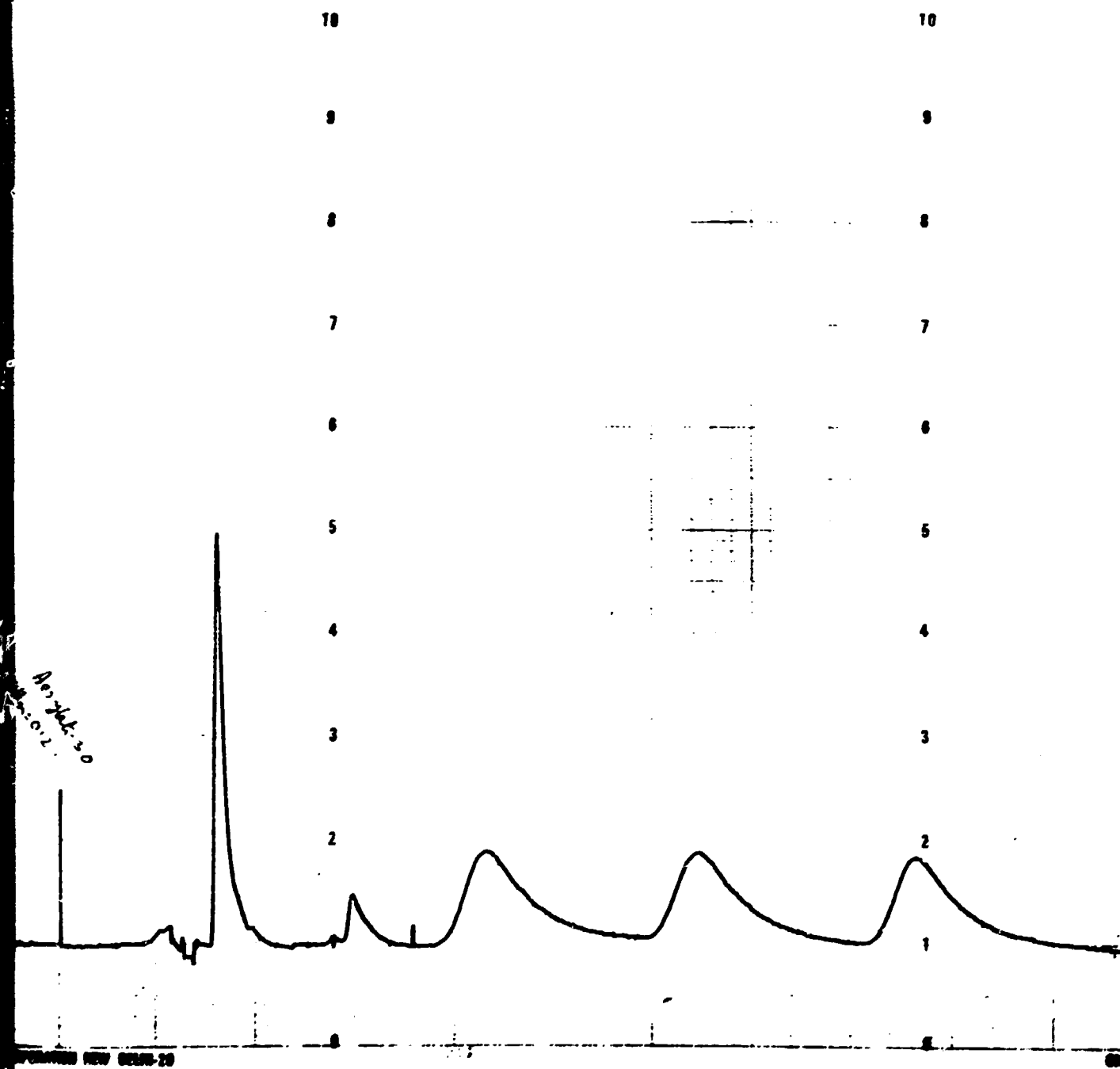

UV Spectra of Chloroquine Phosphate
CHART NO. VD-10001-A
214 mm
220 mm
240 mm
329 mm
343 mm
Range-10
Chart speed-6
Date-7.9.84
1- RD/L767(S)
2+ RD/L767(S)/C
3- RD/L767(S)/D
4+ RD/L767/E
Range-20
Chart speed 6
Date 7.9.84


HPLC Chro
of interm
of Chloroquine
14.12.82
DEMM
m-CA
MCA
DEMM
CINDIA CORPORATION NEW DELHI

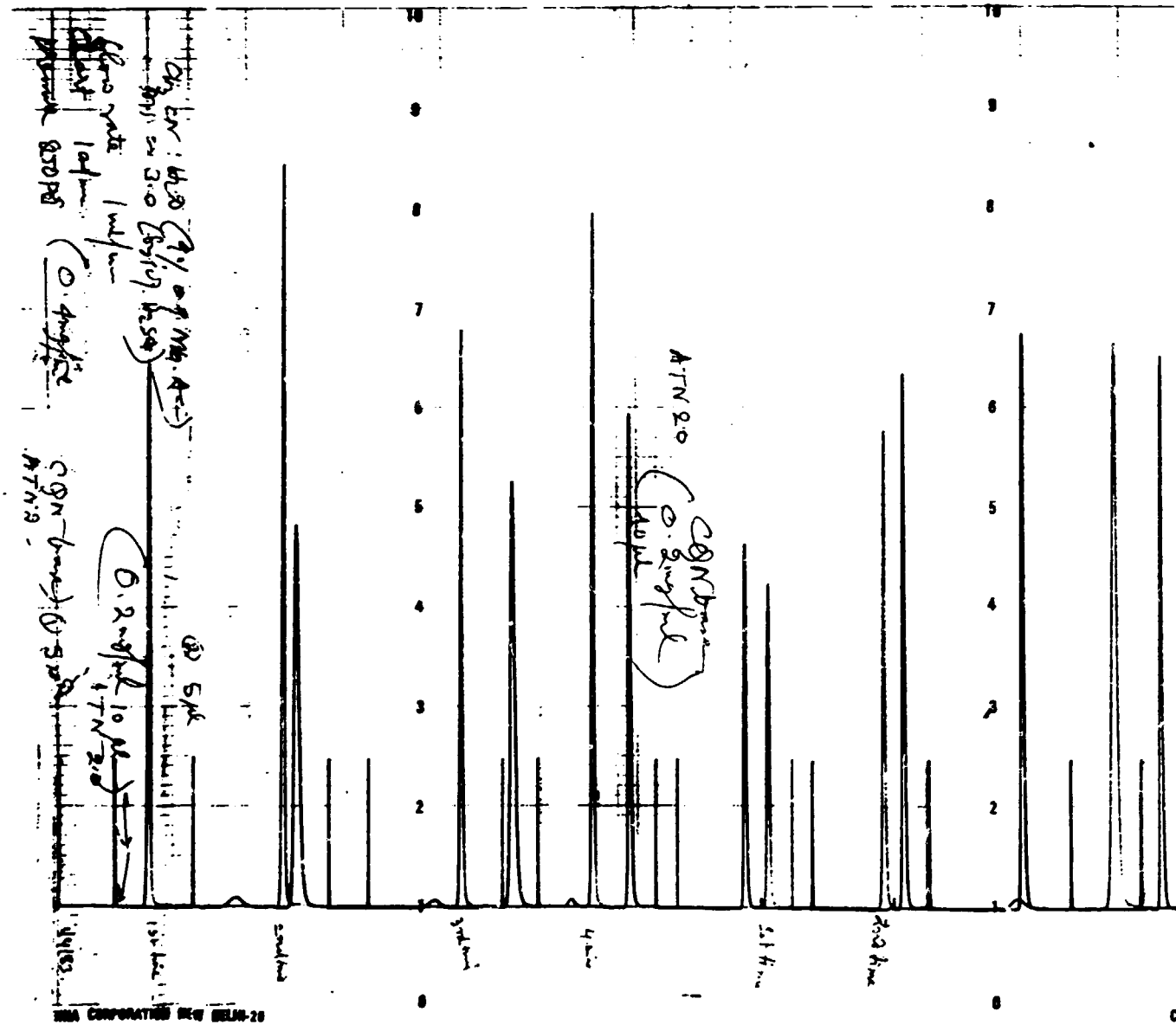
SECTION 1


Chromatogram
ntermediates
quine Phosphate
10
9
8
7
6
5
4
3
2
1
0
DELHI-20
CHEMIRAM CORPORATION

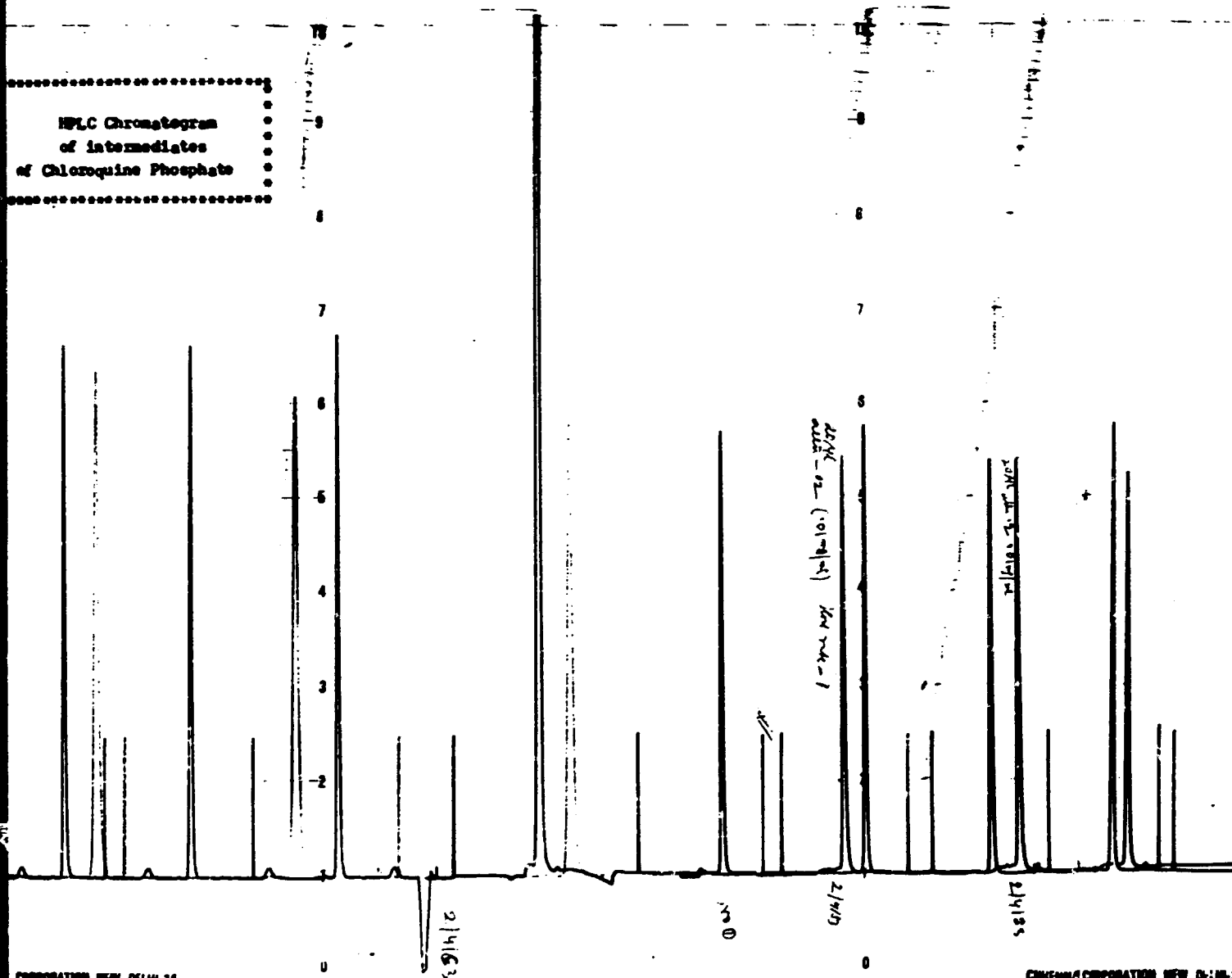
SECTION 2



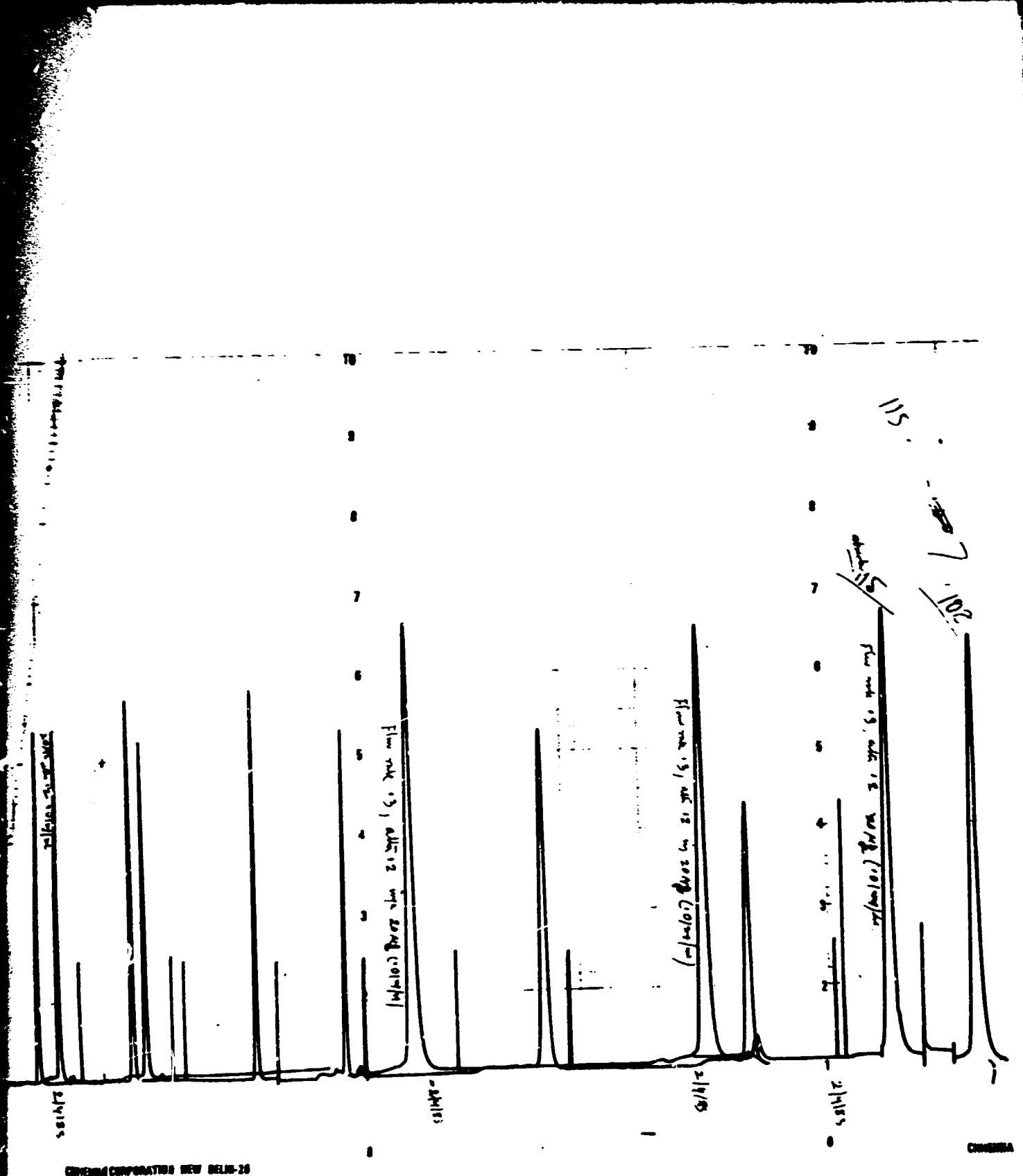
SECTION 3



SECTION 1


HPLC Chromatogram
of intermediates
of Chloroquine Phosphate
CORPORATION NEW DELHI-26

SECTION 2



SECTION 3