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IMPROVED PRODUCTION OF PENICILLIN

DP/CPR/89/021

THE PEOPLE'S REPUBLIC OF CHINA

Terminal Report

Prepared for the Government of the People's Republic of China
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of F.R. Batchelor

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* Mention of firm names and commercial products does not imply the endorsement of the United Nations Industrial Development Organization (UNIDO). This document has not been edited.

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REPORT OBJECTIVE

The objective of this report is to present a critical review of the project dealing with both the successes and failures, and to make constructive proposals which hopefully will benefit any future projects.

THE PROJECT DOCUMENT

The original project document drawn up by Maria Quintero (UNIDO) was an excellent document clearly identifying key issues both technical and economic. It set sound and achievable targets together with a realistic timetable. There was a clear statement as to the value of the project as it was represented to her and the original rationale cannot be faulted. While there is a good case for appointing a CTA before the Project Document is finalised, in the present case it is likely the only significant comments would have been with regard to equipment, particularly if a visit to the site could have been made before finalising the document.

IMMEDIATE OBJECTIVE

The immediate objective was to develop production and isolation technologies for the manufacture of penicillin V and 6APA. With the help of the other technical advisers this main objective was met and titre averaging over 32,000 u/ml and with extraction yields over 70%.

For some reason not apparent to the CTA the production of 6APA and the downstream products was taken out of the project unilaterally by the Chinese authorities. This was after the CTA and Dr Barley had spent some time introducing the technology for the recovery of 6APA from enzymation liquor and introduced manufacturing processes for ampicillin and amoxycillin. In addition some of the equipment purchased by UNDP was specifically for 6APA production.

Without downstream processing it is the CTA's view that a substantial aspect of the rationale for the project was removed since the main object for making penicillin V was to use it for downstream production. With this caveat however the main objectives of the project were achieved. The Guangzhou Pharmaceutical Factory was left with a fully functional new microbiology laboratory and pilot plant. The staff were well trained in modern techniques of production and instrumental analysis and with ability to ferment and recover penicillin V to the efficiency set. Overall therefore the project can be considered successful in meeting the original objectives. Whether the original objectives were valid in the particular Chinese context will be discussed below.

DISCUSSION OF MAJOR INPUTS

A. GOVERNMENT INPUTS

i) New Microbiology Laboratory.

The delays in constructing this new building were the major cause of the overall delay in the project. The footings of the first structure collapsed in bad weather. Later the building was held up through overspending. The overall result was that the building was not completed until August '92 (month 27) rather than November '90 (month 6) as originally scheduled. This obviously had profound effects on the running of the project since some equipment could not be installed at all until the building was ready (eg mini-fermenters). Fortunately the technical advisers which the CTA had assembled were prepared to work and made a great deal of progress in the quite unsatisfactory old buildings so that the project was not held up entirely and the project was completed only 12 months late.

ii) Language Training

This was carried out as agreed though with varying degrees of success. Many of the younger staff were able to communicate well. As perhaps might be expected many of the more senior staff found it more difficult to speak even though their understanding was adequate. This can pose a problem in study tours, it is very frustrating for the staff at companies and institutions who receive people for training, not to have adequate feed back and be able to know whether those on the study tour have a real understanding of what has been said. It is essential that every group should contain at least one person fluent in English to ensure this feedback, unfortunately this was not always the case. The presence of a T A - C discussed below would help.

iii) Equipment

This was provided as listed, it should be noted however that the fermenters and other main equipment were rather old, though they generally worked satisfactorily. What was disappointing was the unavailability of many pieces of equipment that one would expect to find available at an antibiotic factory. There were for example no facilities for drying product, nor any simple liquid/liquid separators for use on a pilot-scale. The lack of these two made it rather more difficult to obtain good recoveries of high purity penicillin V than it should have. The recovery of penicillin V was achievable only by the introduction of a less than optional precipitation method. In fairness to the local management they had expected whole broth extraction to be used. Such

a piece of equipment was listed amongst that to be provided by UNDP and the reason it was not will be dealt with below.

iv) Personnel

Enthusiastic staff were provided. It was unfortunate that for various reasons we had no less than 3 National Project Directors. The advisability of appointing the overall Factory Director as NPD should be carefully weighed in future. For a large project such as this one it should be a full time job. On the other hand the person must also be sufficiently senior to be able to get the necessary things done. In the latter stages of this project it was apparent that the third factory director (the only one who was not also the NPD) was not fully supportive. In fairness to him he had other priorities because of the depressed market situation for lincomycin, the factories one profitable product.

B. UNDP INPUTS

i) Experts

The CTA was fortunate in being able to gather together a group of experts with considerable knowledge of the antibiotic industry. They, with one exception, had all worked for one of the major multinational companies (Beecham) and were used to working together as a team which I hoped showed the benefit of teamwork to the Guangzhou staff. The only adviser who was not known to the CTA and was appointed largely because of requests from the Chinese side proved something of a disappointment, he was not really part of the team and his input was properly co-ordinated with that of the rest of the team. With a large project of this nature I feel it is essential the CTA meet all candidates before they are appointed. Industrial projects of this nature depend so much on good teamwork.

One problem which arose was the feeling on the Chinese side that the experts should spend longer on each visit. From the point of view of the international experts they felt they were already spending the maximum useful time on each visit. Furthermore it also has to be remembered that the best international experts will have other demands on their time. The problem was to a large extent solved by finding a more "hands on" fermentation technologist who was used to day-to-day work with mini-fermenters. Even so there is a limit to both the time experts are prepared to be away from home and perhaps more important the amount they can achieve on any one visit. This was particularly apparent in the present project where each fermentation takes a week to run for extraction work therefore broth was available only once per week. One cannot spend days waiting for the next result.

In addition to the specific help with the project many of the experts held seminars on scientific matters of direct relevance to the project, for example Assay Methods for B.lactams, a paper which explained the chemistry behind each of the methods and the consequent limitations on specificity etc. This was particularly important in this present project because without valid methods of analysis little progress would have been possible.

ii) Fellowships and Study Tour

These could and should be an important part of the overall programme of technology transfer but are becoming increasingly difficult to organise. In highly competitive industries such as the antibiotic industry multinational companies find it difficult to accept candidates for training who will ultimately be helping the competition. The concern is undoubtedly exacerbated by the value of the cultures which have been developed to produce the antibiotics. Such cultures have a market value of a million dollars and can easily be stolen by anyone who has access to them. In consequence companies do not risk anyone other than their own employees handling them. Add to this the current recession and it can be seen how difficult it is too gain access to commercial companies. Usually this can only be done by personal contact.

The situation with non-commercial organisations is also becoming difficult, partly because of the recession but also due to the behaviour of other visitors in the past. The Director of the British Pharmacopoeia told me he would not be prepared to have any fellowship visitors from China because of past experience. It is thus very important that a good impression is made and this must be impressed on all future visitors. Unfortunately the incident in Germany when the Guangzhou group left Braun before their training was complete and made arrangements to visit Westfalia Centrifuges (without the knowledge of the CTA) and then got lost in Hamburg, did not exactly impress either the Braun or the Westfalia management, and can only make similar visits more difficult in future.

A different problem occurred during the US visit. While the microbiologists at least had the experience of working in a US laboratory, the course bore no relation to the project or what had been requested or was understood to have been arranged. In part this was supposed to have been arranged with the TA who was a Departmental Head at the American Type Culture Collection but the visitors were not able to make contact with him during the visit.

In the view of the CTA part of the problem arises from the bureaucratic procedures within UNIDO Vienna, visits have to be arranged by the backstopping office through an entirely separate unit. This unit then deals with a 'government' agency in the country of the visit who then contact potential recipients often using channels that don't get to the senior executive with whom the CTA has perhaps obtained agreement for the visits. During this project the process sometimes took so long that the window of opportunity was lost. It was made the more difficult by the delays in getting local (Provincial) permission for trips out of China followed by delays in getting first passports and then visas.

It would help expedite communications and the setting up of visits if it were clearly the responsibility of the backstopping officer and, providing the visits were properly budgeted for in the original Project Document, could be arranged directly by liaison between the CTA and backstopping officer.

Although it would add a little to the expense I also believe it desirable that the CTA or the relevant TA accompany each group. This would ensure that everything is properly co-ordinated with the aims of the project. He or she could ensure the right things are targeted. It should be remembered that those going on the study tour often do not know what training they ought to be receiving and even when they do, are not in the position of doing other than accept what is offered.

The CTA did accompany the first study tour on the Swedish part of their visit but unfortunately other engagements prevented him being with the group in Italy. Feed-back from the group indicated a much greater value from the Swedish part of the visit, than from the Italian part which seemed to concentrate on marketing rather than technology.

iii) Equipment Purchases

It has already been mentioned above that it would be useful for the CTA to be involved in the finalisation of the equipment list. It is only then that the full details of the necessary equipment can be confirmed. In the present case there were two unfortunate problems, first to be useful for experimental work a control fermentation is always necessary so at least two mini-fermenters were required rather than the single one envisaged (two were adequate for training and to demonstrate how these fermenters can be used to optimise parameters for scale-up to larger fermenters but in reality several are required to run such a project efficiently).

The cost of the solid-liquid separator for whole broth extractions was seriously underestimated, its true cost would have more than taken up

the entire budget. Fortunately it was inappropriate to purchase this item because the smallest scale pilot plant model was of too great a capacity to have operated on the 1m3 pilot fermenters available to the project. Also at the time of starting the project this system was still largely experimental with only one company operating it successfully so that in the opinion of the CTA more conventional isolation procedures should be learned first.

The above two items fortunately to some extent cancelled one another out though the project was left without any conventional liquid/liquid separators.

The purchasing system was also not without its problems. The Guandong Provincial staff repeatedly claimed that they could have purchased some items more cheaply than did the UNIDO buying group. This is in fact often true and I am sure many supplying companies regarded UNIDO as a 'deep pocket". It is also well known that many items can be bought more cheaply outside Europe. The other problem is that the UNIDO purchasing group rely on tenders. While I accept the need for some controls to ensure proper competitive purchasing, it is equally important to take the views of the technical advisers into account and obtain what they know to be the best equipment even if it costs marginally more. This has been amply demonstrated in the present case when Braun won the tender from Biolafitte. The Biolafitte fermenters are the accepted standard in the industry and are small pilot plant units rather than large laboratory models. While the Braun equipment is satisfactory for bacterial and streptomyces fermentation it is not ideal for penicillin fermentation as has been confirmed once again by the problems experienced in Guangzhou.

In industry there is also the need to ensure the best prices for equipment but this does not necessarily mean accepting the lowest tender the tender is taken only as a guide. Furthermore the cost of training and service also need to be taken into account. In many cases experienced technical advisers could negotiate a better overall deal than the UNIDO Buyer, they have often done just that during their industrial experience. The UNIDO purchasing group should also remember that sophisticated scientific equipment varies in many ways that is not necessarily readily apparent from a general buying specifications. The CTA spent some personal time and effort in negotiating with both Braun and Millipore over equipment problems and in both cases was able to get the repairs and replacements of quite significant value carried out free of charge.

REVISION OF THE PROJECT

The original project document clearly sets out the uses of penicillin G & V indicating its main use was as a raw material for conversion to 6APA & 7ADCA and ultimately the semi-synthetics penicillin and cephalsporins. Of the total world production of both penicillin G and V some 80% of each is converted to semi-synthetic antibiotics. The paper clearly identified the need for the downstream production within China. At the time of writing that paper no 6APA or 7ADCA was being manufactured. It was stated 150 tonnes of ampicillin were made locally. Actually 150 tonnes of sodium ampicillin was being made locally but from imported ampicillin trihydrate. At the time no semi-synthetic penicillins were being manufactured with China. There was thus a clear need and business opportunity which the Guangzhou factory should have been able to fulfil. Data or Chinese and world production of penicillin G & V is appended (Appendix I). There was and is no Chinese production of penicillin V or amoxycillin. While in the rest of the world 80% of all penicillin is converted to downstream products none of the 20% of world production in China is converted. (except when it was exported outside China).

As the project document clearly identifies there was an obvious need to convert the penicillin in China. While some penicillins V could be used as an oral antibiotic for upper respiratory tract infections most should be converted for local use.

It seemed to the CTA that the objective was to make semi-synthetic antibiotics to fulfil the need for these antibiotics in China. The total world production of ampicillin and amoxycillin for example is around 12,000 tonnes of which less than 200 tonnes is used in China despite its high percentage of the world's population. This production of semi-synthetic could have been set up in advance of penicillin V being available since penicillin G was readily available in China and in any case penicillin V or 6APA could have been obtained readily. It would have been quite logical and good economic sense to have integrated backwards.

To remove the downstream production from the project would seem to take away the prime reason for the project, ie to supply the Chinese people with semi-synthetic antibiotics. It would if the project were taken through to full scale manufacture of penicillin V simply have added another supply of bulk penicillin to the world market which surely was not the aim of the project.

It would seem probable that no proper business plan was drawn up by the Guangzhou Pharmaceutical Plant other than that it seemed a good idea because there was no penicillin fermentation in Guandong Province or even in the Southern half of China. They were also already in the fermentation business making lincomycin, so had some fermentation experience.

Appendix 2 illustrates some of the points which should have been taken into account and these may have made significant changes to the Chinese views on the project. Whether similar consideration should be taken into account by UNIDO in deciding whether to support future projects is a matter for consideration.

Tripartite Meeting

The Final Tripartite Meeting held on 15th November 1993 was an excellent and constructive meeting. The National Project Director Liang Zhuohuai presented a final report which showed the main aims of the project, to make penicillin V on a pilot plant scale had been achieved. The main discussions centred on what to do now particularly as only one seminar to achieve horizontal transfer to other factories in China had been held, and that at an early stage of the project.

It was agreed that now the Guangzhou Pharmaceutical Company was well trained in the appropriate technologies it would be appropriate for them to operate as an Institute offering training to other throughout China. This would perhaps enable penicillin V to be manufactured at a more suitable site, preferably one where there was already penicillin fermentation capacity. Many companies in the West alternate between penicillin G & V. The fermentation is essentially the same. The same organism can be used with only small changes to the fermentation and extraction and of course a different precursor.

From the point of view of the technical advisers this seems an excellent idea. Although all were naturally disappointed not to see progression to a full scale plant they all had great satisfaction in feeling they had left some motivated staff well trained in modern fermentation technology.

APPENDIX 5

MICHAEL BARBER AND ASSOCIATES

WORLD PENICILLIN GK PRODUCTION 1988 - 1993 (TU) TABLE 2

MAJOR PRODUCING COMPANIES (LOCATION)	YEAR TO DECEMBER 31ST 19"					
	88	89	90	91	92	EST 93
ANTIBIOTICOS LEON, E	3200	3300	3400	3500	3600	3600
BEECHAM IRVINE, GB	3500	3700	3700	3600	3200	3000
FERSINSA/CIBIOSA COAH, MEXICO	900	1000	900	1000	1000	1100
GIST BROCADES DELFT, NL; OPORTO, P	5200	6200	5800	6200	6600	6600
SYNPAC CAMBOIS, GB	1900	1900	1900	2000	2400	2500
HOECHST FRANKFURT, D	1800	1800	1900	2100	2200	2300
N CHINA PHARMACEUTICAL WORKS HUABEI, HEBEI PROV., CHINA	1600	1800	2000	2200	2300	2500
PFIZER GROTON, CT, USA (Disc Jun 1991)	1500	1500	1200	700	-	-
RHONE POULENC ELBEUF, F (Closed 1990)	1200	1100	800	-	-	-
SUBTOTAL MAJOR PRODUCERS	20800	22300	21600	21300	21300	21600
SUBTOTAL MINOR PRODUCERS (SEE TABLE 2)	6500	6900	7300	7600	8400	8200
WORLD TOTAL	**27300**	**29200**	**28900**	**28900**	**29700**	**29800**
World Total in Tonnes (rounded)	17300	18500	18300	18300	18800	18900

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The above total represents the estimated World production of penicillin GK in TU (trillions of International units, million megaunits) These totals have been revised from earlier years to take account of new data, incorporated into Table 2 Consolidating Tables 1 and 3

WORLD TOTAL Pen GK (TU)	27300	29200	28900	28900	29700	29800
WORLD TOTAL Pen VK (TU)	10600	12000	12500	12000	12500	12100
WORLD TOTAL Penicillin (TU)	37900	41200	41400	40900	42200	41900
World Total Pen GK (Tonnes)	17300	18500	18300	18300	18800	18900
World Total Pen VK (Tonnes)	6700	7600	7900	7600	7900	7700
World Total Penicillin (Tonnes)	24000	26100	26200	25900	26700	26600

MICHAEL BARBER AND ASSOCIATES

MINOR PRODUCERS OF PENICILLIN GK 1988 - 1993 (TU) TABLE 3

COMPANY/COUNTRY (LOCATION)	YEAR TO DECEMBER 31ST 19**					
	88	89	90	91	92	EST 93
BRISTOL MYERS SQUIBB ANAGNI, I; (CLOSED 1993); SAO PAULO, BRA, (CLOSED 1990)	900	1000	800	600	600	100
MEIJI SEIKA GIFU, JAP	800	800	900	800	600	600
CHINA (Excl NCPC)						
Harbin Pharm Factory	600	700	800	1000	1100	1200
Jinan Antibiotic Factory	300	300	400	500	700	750
Jiangxi Dong Feng Pharm Co.	100	100	100	100	200	300
Sichuan Pharm Plant	100	100	100	100	200	250
Zhangjiakou Pharm Factory	-	-	-	-	200	300
Tangshan Pharm Factory	-	-	-	-	-	50
Puzan Samen Pharm Factory	-	-	-	-	50	-
Shijiazhuang Vet Medicine Factory	-	-	-	100	200	250
Huaxing Pharm Factory	-	-	-	-	50	100
Others # and discontinued	100	100	-	-	-	-
Total Other China (rounded)	1200	1300	1500	2000	2900	3300
INDIA						
Hindustan Antibiotics	300	400	450	500	600	700
Indian Drug & Pharmaceutical (IDPL)	300	300	350	400	400	400
Alembic	-	-	-	-	-	-
Total	600	700	800	900	1000	1100
EASTERN EUROPE						
Antibiotice, Iasi, (Rom)	100	100	100	100	100	100
Biogal, Debrecen, (H)	200	200	200	200	200	200
Biotika, Slovenska Lubca, (CZ)	300	300	300	300	300	300
Pharmakhim, Raszgrad, (Bul)	400	500	500	600	600	600
Polfa, Tarchomin, (PL)	600	600	700	700	800	800
Others ## and discontinued	300	200	200	100	100	-
Totals	1900	1900	2000	2000	2100	2000
RUSSIA and CIS						
Biochimik, Saransk	150	200	200	200	150	150
Biosyntez, Penza	250	250	250	300	250	250
Krasnoyarsk M/F, Krasn.	350	350	400	400	400	350
Syntez, Kurgan	150	150	200	150	150	150
Kiev M/F, Kiev (Ukr)	100	150	150	150	150	100
Totals	1000	1100	1200	1200	1100	1000
OTHERS ###	100	100	100	100	100	100
TOTAL ALL MINOR PRODUCERS	6500	6900	7300	7600	8400	8200

\# Plants have been identified in Changchun, Dalian, Dandong, Shanghai (No 3) and Suzhou. These may produce sterile salts but are reported not to be fermenting penicillin G during 1993

Includes Jenapharm and Neubrafarm (GDR), ICN Galenika (Serbia)

Includes Algeria, Brazil, Pakistan etc.

MICHAEL BARBER AND ASSOCIATES

WORLD PENICILLIN VK PRODUCTION 1988 - 1993 (TU) TABLE 4

COMPANY (LOCATION)	YEAR TO DECEMBER 31ST 19"					
	88	89	90	91	92	EST 93
BIOCHEMIE KUNDL, A	3600	3900	3600	3600	3800	4000
BRISTOL SYRACUSE, NY	2500	2600	3200	3300	3400	3500
FERMENTA (GIST BROCADES) STRANGNAS, S	700	900	1300	1400	1600	1600
FERMTEC CARONNO PERTUSELLA, I (Closed 90) WESTCHESTER, PA (Closed early 91)	1200	1400	1300	300	-	-
LILLY LAFAYETTE, IND	1200	1400	1400	1400	1500	1600
NOVO# KALUNDBORG, DK	600	800	1000	1300	1500	700
MINOR PRODUCERS¶	800	800	700	700	700	700
TOTALS	10600	12000	12500	12000	12500	12100

NOTE NOVO CEASED PRODUCTION AT KALUNDBORG MID 1993

¶ NOTE: THIS INCLUDES GLAXO (GB), BIOTIKA (CZ) AND BIOGAL (H) AS WELL AS OCCASIONAL CAMPAIGN BATCHES BY COMPANIES SUCH AS GIST BROCADES AND HOECHST AND IN EASTERN EUROPE.

APPENDIX 2

SOME THOUGHTS ON PENICILLIN BUSINESS STRATEGY

The Market

The total world production of penicillin G is around 18,000 tonnes of which only 2,000 is used directly the rest is converted to downstream products. For penicillin V the production is 7,500 tonnes of which only about 1,500 is used directly.

Traditionally the price is in $US even though penicillin G is no longer produced there. Over the last 20 years the price has fluctuated considerably in response to supply/demand. The effects of demand imbalance even over the last 3 years has been such that the price for long term contracts has ranged from as low as $12.5 per BOU to as high as $24 per BOU. In real terms when inflation is taken into account the price has fallen dramatically. It is unlikely to rise in the medium term as some three factories each capable of making 1,000 tonnes per annum come on stream in India in the next year. Also all the factories in China and the former Soviet Bloc are capable of producing more than double the amount of penicillin per fermenter per year if modern technology and management is adopted.

Production

Cost of Factory

Before building a new factory some thought should be given to the economics in relation to potential sales.

Let us take a plant producing say 1,000 tonnes per annum (probably the smallest economic size). This would cost a minimum of $100 million for a greenfield site. Amortised over ten years with no interest this is $10 million per annum. Interest is perhaps a further $5 million giving a total of $15 million per annum, or $15 per Kg.

The value of the output at present price of $30 per Kg makes value of the output $30 million. The current direct cost of making penicillin G by the most efficient producers is $12 per BOU or $20 per Kg making the total cost $35 per Kg or a LOSS of $5 on every Kg produced.

Siting of Factory

The following lists some of the desirable requirements to be considered when choosing a site for an antibiotic factory. Obviously not all have to be answered positively but it helps if the majority and certainly the more important are:

Compatible working Practices
Low Energy Cost with minimal Interruption of Supply
Temperate Climate
Plentiful Cold Water
Easy Disposal of Waste
Locally available Raw Materials
Good Transport
Local Education Infrastructure
Access to Good and Appropriate Technology

In comparison with some other parts of China Guandong Province is not the ideal site for a penicillin factory. Taking some of the above points for example it can be seen that:

Energy is not as readily available as in areas where coal is available. Several Chinese antibiotic factories generate their own electrical power thus minimising power cuts. A power failure of say 30 minutes will cause complete loss of a penicillin fermentation. Even shorter cuts will cause severe sterility problems if there is no short term emergency generator available on site.

The penicillin fermentation is a relatively cool one 24 - 26°C. It therefore needs cold water with a good temperature differential to remove heat generated by the fermentation. A 100m3 tank generates heat equivalent to 4 tonnes of coal. With a high ambient temperature cooling towers will not chill the cooling water adequately and expensive energy has to be used.

All of the required raw materials based on corn (corn steep & glucose) grown in the north of China. Transport within China is still a very substantial problem. Factories such as Huabei have their own on site plants for making corn steep and liquid glucose. At the present time the yield per m3 per fermenter per year in this factory is less than half the western world.

Overall it can be seen that sites further north particularly those already fermenting penicillin not only have the capacity to expand production without further capital investment in fermenters but are also in a much more favourable position climatically and in terms of raw material supply. It thus makes good sense to transfer the technology gained in Guangzhou to a more appropriate site. Thus the decision taken at the Tripartite meeting makes good business sense.

Marketing

In the experience of the CTA, China is an unusual market situation. To a large extent the individual provinces behave almost like individual countries undoubtedly this is partly due to distances and problems in communication and in the local context a penicillin plant in Guandong province with Guangzhou the third largest city in China would seem logical.

It was assumed in the original Project Document that penicillin V for oral use ampicillin and amoxycillin were not readily available because of lack of technology. This was undoubtedly one reason but not the only reason.

During the course of other work in China it has become apparent to the CTA that there is also another quite different problem. For historical reasons local medical practice has insisted on a skin test for penicillin allergy before every single dose of penicillin. The value of such a test is questionable even for injections the risk form anaphylaxis from the skin test itself is just as bad as to the dose and anyway the incidence of penicillin allergy is very low. That for some reason Chinese medicine insists on such a test for oral products - penicillin V, ampicillin and amoxycillin puts it quite out of step with the rest of the world. What is even more illogical is that though locally produced products cannot be administered without such a skin test, imported products can. Thus ampicillin or amoxycillin manufactured in say Taiwan with a Taiwanese package insert and product licence which indicates no skin test is necessary can be used in China without such a test. The locally produced cheaper product cannot.

Until this problem is sorted out, locally produced material cannot be used in the same way as it is in the rest of the world. Amoxycillin oral is of course on the WHO Essential Drug List. This is a problem which could not have foreseen by Maria Quintero when drawing up the original excellent Project Document, but which certainly affects the results of the project being used for the maximum benefit of the people of China.

COMMENTS OF THE SUBSTANTIVE BACKSTOPPING OFFICER

The CTA's terminal report is a very concise review of the project. It covers the report objective, the project document, the immediate objective, a discussion of major inputs and the revision of the project. In the annexes, he gives data on the world penicillin production 1988-1993 and his thoughts on the penicillin business strategy.

The terminal report does not present a historical narrative of the project, which was described extensively in other technical reports published earlier. While following closely the structure suggested by the Handbook for UNIDO Field Staff, IO.36 (SPEC.) 1989, the report gives a very unorthodox review of the project. The author's intention is very obvious, which is to convey in an elegant manner, a very clear message on lessons learnt through the implementation of the project. The importance of these messages are in no means exaggerated since they emerged from one of the top consultants of the pharmaceutical industry.

Dr. F. R. Batchelor made a pioneering work which can, in its extent of importance, be compared only to the discovery of penicillin. His work, which made a breakthrough and actually established the industrial scale production of semisynthetic penicillins by enzymatic conversion (deacylation) of the naturally produced penicillin G or V, was published in 1959 in Nature. He headed a very successful development team at Beecham for decades. Currently, he is consulting not only the major multinational companies producing penicillin, but also companies in developing countries and in Eastern Europe. The CTA has a lifetime experience in the forefront of a major league company, continuously developing and improving his work over a period of many years. His comments, therefore, are to be taken very seriously. This is the reason why the substantive backstopping officer decided not to change Dr. Batchelor's draft and leave it as it is, since every single words and every single sentence of his has its specific meaning which is recommendable to think about.

Dr. Batchelor's suggestion to appoint a CTA before finalizing the Project Document, is worth considering. It highlights the importance of industrial experience at all phases of development and the execution or implementation of the technical cooperation projects. His criticism was directed towards the identification and selection of equipment as was presented in the project document. We have to concur with his message that without reviewing the conditions of the manufacturing or R & D facilities at the project site in terms of human resources, equipment, and utilities, and without identifying the technology to be transferred or to be developed, an adequate and optimal list of equipment cannot be prepared. He made another comment with regard to equipment, namely that the current tendering procedures are not the best means to purchase equipment. His criticism should be accepted as it is based on actual experience. At this point, it should be mentioned that Dr. Batchelor's personal intervention to replace some damaged parts of the Braun's fermenters and Waters' filter resulted in a saving of approximately US$ 20,000 of the project's funds.

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Dr. Batchelor's "thoughts" on penicillin business strategy is not only important to the project, it can also be used in the fermentation and upstream part of the biotechnology as very pragmatic guidelines for business decisions.

The CTA is a true team player. He could put together one of the most successful and cohesive team of international experts for this technically, and politically, very difficult project. His high motivation, professionalism and honesty made him a true asset for UNIDO as well as for the management of the Guangzhou Pharmaceutical Factory. The substantive backstopping officer agrees with his conlusion that the project is left with a young, highly motivated team, who can handle the sophsiticated equipment of the new Microbiological Laboratory without difficulties. This team could be instrumental in the technology development of a new type of antibiotics that could be produced to replace lincomycin eventually. The new Microbiological Laboratory could also provide trouble-shooting services in the Guangzhou Pharmaceutical Factory, or provide R & D contract services for other companies in Southern China.