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PHILIPPINES PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

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PHILIPPINES

Technical report: Fermentation Processes, Manpower Training, and Suggestions for New Biotechnology in the Republic of the Philippines*

Prepared for the Government of the Philippines
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Prgramme

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SUMMARY

A fermentation factory purchased from abroad does not appear to be the best investment for the limited financial resources of the Republic of the Philippines. There are, however, some highly interesting opportunities for domestic manufacture of pharmaceutical ingredients, for equipment designed and built here to suit local conditions, and for improving the infrastructure for an expanding pharmaceutical industry. A section is provided with suggestions for new business, mostly for small companies.

The university system here is very good and could train the scientists and engineers needed for a major thrust in biotechnology. There is too much turnover of professors and instructors because salaries are much higher in the private sector. One way to improve the income of the faculty is to increase fees for consulting. This could arise by letting them know what others charge and by suggesting that a high fee implies that the advice is better than that of consultants with low fees. Throughout this visit, 100 computer programs for teaching were demonstrated and donated to various institutions. Books explaining the teaching programs were given to key professors, and several of them expressed a strong desire to use the programs for teaching biochemical engineering and environmental engineering.

PREAMBLE

This report is based on a one-month visit during the summer of 1988. Because of the makeup of the team of experts, I focussed on fermentation and on manpower. My interviews and visits were with government agencies, a few private companies, and with major universities. This report covers fermentation opportunities in general, education and training especially with computers, and suggestions for new businesses. These suggestions are heavily slanted toward small companies because other members of our team are particularly well-qualified to address larger companies.

INTRODUCTION

The Republic of the Philippines, as do most of the developing nations, has a debt problem and has a desperate need for the supply of health care to an expanding population. Safe and effective pharmaceuticals deserve high priority but their expense when imported is a drain on the economy. Our team was invited to investigate conditions in the pharmaceutical industry and to make recommendations on ways to increase domestic manufacturing. I found many opportunites for small new companies with only modest investments. They could suppply feedstocks to the pharmaceutical industry, manufacture equipment, and sell some final products.

A new antibiotics industry based on equipment and technology that is almost entirely imported does not apppear to be the most attractive investment opportunity, and some of the reasons are presented. Nevertheless, the logical outcome of more and more domestic manufacture of ingredients, equipment, and products would be expansions of these businesses and eventually a rather large pharmaceutical industry using mostly equipment made here. There is also a suggestion related to quality control because this is the key to export sales. Over and over I was impressed by the friendliness of Filipinos. They are so highly likable that they need only excellent products to become business leaders in Asia. The islands have excellent natural resources, a large pool of labor, and plenty of intelligent people. The conditions are ripe for exploiting biotechnology, and this report even if insensitive to some local attitudes may stimulate consideration of some new business opportunities.

ANTIBIOTICS

Let's address the problem of constructing an antibiotics plant in the Philippines. One way would be to purchase the cultures, the technology, and most of the equipment abroad. This is the route taken recently in Algeria. Such a plant is unlikely to be profitable, but such issues as national pride, independence from foreign companies, and savings of hard currencies may be more important than profit. We must appreciate however, that purchases of

equipment and technology instead of purchasing drugs is just taking money from a different pocket, and the savings in hard currencies may be long delayed.

Although fairly good microbial cultures that produce antibiotics can be purchased, the very outstanding cultures that enable a few companies to produce bulk antibiotics at a profit despite cutthroat competition are carefully guarded. Without these superb cultures, other companies can have modest profits at best. The processes have been fine-tuned over many years to maximize yields and profits. A new factory, even with good instructions and advice, can take several years to implement the very best process technology, especially because local variables such as water, feedstocks, and climate are often important. While the new factory is struggling to catch up, the competitors continue to improve and probably at a rapid rate.

Antibiotic processes vary widely in their difficulty and state of development. Old war horses such as penicillin seem straightforward, but only a few companies find this process profitable. The strains of organisms that can be purchased can produce roughly 30,000 units per ml while the secret strains of the best companies produce over 50,000 units per ml. A highly expert genetics group can improve productivity by about 5 per cent per year, so the developing nation is unlikely to gain in terms of relative yield even if they have a world-class genetics group. With a genetics group that is not world-class, a company would be certain to fall further behind each year. The marked difference in yield means that for the same cost of raw materials and labor, the company with the superior strain gets nearly twice as much penicillin per batch.

An antibiotics factory in a developing country should survey the various possible products to uncover the best investment opportunities. Although sales volume in their nation is very important, this can be misleading. Producing penicillin inefficiently in an expensive factory is unlikely to be the best of all the investment opportunities. Antibiotics used against tropical diseases but with non-optimum processes because of low sales and insufficient attention in developed countries should get special

consideration. Selecting the best options is a heavy responsibility, and this report does not offer specific suggestions for antibiotics.

Technology Fermentations can be easy or difficult depending on the protection afforded by the product. Penicillin has a broad spectrum that discourages many contaminants. A narrow spectrum of a product such as erythromycin offers much less protection. Other factors of importance are cost of raw materials and operating temperature. A US company would be horrified if their normal cooling water could not control a fermentation. My former company used river water at one of their factories and encountered serious problems in controlling the temperature of fermenters during the very hot summer periods. When surface or well water cannot be used, the alternative is refrigeration. This is ruled out in the US because the factory can be located in a more northern state. The new antibiotics plant in Algeria requires refrigeration that is highly expensive. A factory in the Philippines would be well advised to select an antibiotic fermentation that operates at a relatively nigh temperature and to avoid penicillin that requires temperatures in the range of 28 degrees that is too close to the temperature of available cooling water.

Product recovery costs for some antibiotics are roughly equal to fermentation costs, but in some cases recovery costs 10 times as much as fermentation. The nature of the product is the major factor. A number of antibiotics are readily extracted into immiscible organic solvents. This is quite affordable and is highly effective as the first step in both concentration and purification. Other antibiotics have functional groups that can impart electrostatic charge that permits purification by ion exchange. Again this is reasonable in cost and accomplishes both purification and concentration. Both solvent extraction and ion exchange scale up to large sizes very well. When neither is suitable for a given fermentation product, recovery costs can soar. The new protein products produced by recombinant DNA technology tend to require very costly recovery processes that may work in the laboratory but do not scale up at all well.

Recommendation A prudent plan would be improvement of the infrastructure of an antibiotics industry in the Philippines. Long range but major rewards would come from heavy emphasis on local manufacture of equipment. There would be new industry and jobs for the Philippines if devices, the piping, electric components, and other equipment were manufactured here. Another item is a pilot plant. Dr. W. Padolina at UP Los Banos had some of his fermenters constructed at a company that makes Jeepneys, and his designs and experience would be highly valuable when the pilot plant tries for mostly Phillipine manufacture.

A good multi-product pilot plant needs about ten small fermenters for each product. Discussions with Dr. Padolina, Dr. W. Jose, and Dr. L. Joson covered the merits of different sizes of fermenters. Very small fermenters save on ingredients but provide insufficient liquid for frequent sampling and are much less reliable in terms of reproducibility and scale up. Large fermenters can be far too costly to operate especially when the ingredients are expensive. Although a size from 60 to 100 L is considered ideal in the US, we decided that a 10 L pilot plant fermenter is about right for the Philippines.

Ideas to be tested in small fermenters should get their initial evaluation in shake flasks. Each battery of 10 small fermenters should be supported by 50 to 100 slots on a shaker for flasks. Good results from the 10 L fermenters must be scaled up to full production, usually by tests in a 4000 L fermenter. One or two of these is needed for each battery of small fermenters.

In addition to an analytical laboratory there must be a culture laboratory. Its responsibilities are preservation of cultures and the mutation and selection to find improved cultures. The same labs could be used for both the pilot plant and the production plant, but US companies tend to have separate labs. One reason for this is that the production group has grave responsibilities to avoid contamination (almost totally) and to insure that there are always good cultures available for upcoming runs.

An estimate of the time to establish a really good pilot plant in the Philippines is 8 years. If after 5 years from its construction the pilot plant is progressing well, design and construction of the production plant could start.

Some pilot plants in the US are being reconfigured for bioprocesses that use plant or animal cells. This is very costly because these cells grow very slowly in rich media and are easily overrun by contaminants. To prepare for future R and D, a new pilot plant in the Philippines should have one or two small fermenters than can perform well with cell cultures.

Any large new pharmaceutical installations in the Philippines should follow closely the experiences in Algeria. Their antibiotics plant is entering the start-up phase but with some of the technical leadership not yet in place and without sufficient trained workers. They have not proved that the raw materials are satisfactory. A frank discussion of the problems is in UNIDO ESTABLISHMENT OF A DEVELOPMENT PLAN FOR THE PHARMACEUTICAL INDUSTRY, ALGERIA, Technical Report: The Medea Antibiotic Complex, 1 Aug. 1988.

CHEMICALS AND INGREDIENTS FOR PHARMACEUTICALS

A great deal of relevant material to our project for the Philippines can be found in an earlier report for Algeria, UNIDO/IO/R.213 30 December 1985 Establishment of a Development Plan for the Pharmaceutical Industry UC/ALG/85/062 Technical Report: Transfer of technology for the production of pharmaceutical chemicals in a multi-purpose plant. This UNIDO report lists many active ingredients with market demands and with brief descriptions of some of the processes for their manufacture. It is particularly interesting that the feedstocks for many of these ingredients are themselves biochemicals that are not available commercially in the Philippines. Descriptions and designs for the pharmaceutical plant are in this UNIDO report and in an accompanying report ID/WG.393/14/Rev.1 20 December 1985 Technical Profiles for Production of Pharmaceutical Dosage Forms. While there may be some very attractive investment opportunities based on these UNIDO reports, some

consideration should be given to producing the feedstocks for such a factory and for producing other biochemicals here. Whereas other countries have definite advantages for a petrochemical industry, the Phillipine Islands would be ideal in many respects for new industry based on biotechnology. There is already an excellent sugar industry, corn and casava are readily available, and a wide variety of plants grow here.

The Department of Science and Technology, particularly in the laboratories of Dr. Lydia Joson, has demonstrated pilot plant production of several organic solvents and biochemicals. Instead of diverting much of the attention to antibiotic fermentations, there is strong justification to continuing to develop these fermentations for solvents and chemicals in support of existing and new industries.

One type of new industry based on feedstocks from agriculture seems not to have been considered. By the early 1930's, Henry Ford and others had explored processes for pyrolysis of wood. This is also known as destructive distillation. Among the many products are acetone, acetic acid, formic acid, and charcoal. The organic compounds are first encountered as a very crude mixture that is costly to purify. At least one factory was built, but it failed because cheap petrochemicals were introduced at about that time and were too competitive. Since then the price of petroleum has escalated and purification technology has improved. It seems timely to reinvestigate pyrolysis of wood and of agricultural wastes in the economic context of the Philippines. There is already a good market for charcoal from coconut, and modifying the process to collect other products should not be difficult.

A few years ago, I heard at a meeting in Gatlinburg, Tennesse a paper by scientists at Battelle Memorial Institute about alkaline pyrolysis of sugars or polysaccharides to get a mixture of products including the sodium or calcium salts of acetic, lactic, glycollic and formic acid. It was particularly interesting that the proportions of products depends on which sugar is the starting material. Some research with Phillipine caustic and with local lime that tends to be different depending on where it is found

might be quite interesting. A typical reference is J.M. Krochta, J.S. Hudson, and C.W. Drake, "Alkaline Thermochemical Degradation of Cellulose to Organic Acids", Biotechnol. Bioengr. Symp. 14 (1984), pp. 37-54.

HUMAN RESOURCES AND MANPOWER

This overview is based on five contacts with the University of the Philippines (Diliman, Quezon City), four visits (including one overnight) to University of the Philippines (Los Banos), and two visits to De la Salle University. Most of the contacts were with chemists and chemical engineers, but some biologists were interviewed. Dr. A. Nazarea at UP Diliman told us about an inovative program with practical training for graduate students in molecular biology. One seminar was presented at the Diliman campus, and two were presented at Los Banos. Two members of our team presented seminars at the Department of Science and Technology (Bicutan), and education and training were discussed with some staff members.

The Phillipine educational system has many strengths and some weaknesses. Salaries for professors are low by international standards, and there are not many Ph. D.'s in engineering. Good professors have heavy work loads and get attractive offers to leave the university to enter private industry. Most of the young instructors and professors accept the teaching positions as stepping stones to better jobs, and some immigrate.

I studied the curricula at University of the Philippines at Diliman, University of the Philippines at Los Banos, and at De la Salle Univerwsity, a private institution. The courses were much the same as at universities in the US but with some minor differences. For example, a few US universities still start engineering students in mathematics at the level of algebra and offer calculus as a sophomore course. The top US engineering universities, however, insist on calculus as the first course for freshmen. In the Philippines, university students take a year of math before calculus. They then take enough math to reach the level required of US undergraduate students but may not have to take an additional mathematics elective. Another shortcoming is

the lack of sufficient computers for effective training of all students. Each department has a few personal computers that serve mainly as word processors, and there is a need for rooms full of computers so that all students have access. All things considered, the B.S. engineering degree in the Philippines seems quite good. Photocopies of relevant materials from the catalog of the University of the Philippines (Diliman)and a description of the program in biochemical engineering are in the appendix.

When there is significant expansion of the production of pharmaceuticals and fine chemicals in the Philippines, the universities will not encounter much difficulty in increasing the numbers of trained persons. They will need more computers, more laboratory equipment, and supplies. They have sufficient faculty and classrooms. However, there may be additional duties for these professors as consultants or as partners for new enterprises. Also, there is not much backup to allow for sabbatic leaves, overseas training, and quick replacements if key persons leave the universities.

In one respect, talent in the Philippines is underdeveloped. The best preparatory schools are in or near Manila. Students from other islands and districts tend to score lower on the entrance exams and are underrepresented at the top universities. Although this may be corrected gradually as district schools improve, it seems wiser to provide coaching or special preparatory schools that would have an immediate impact on increasing the numbers of students from other islands who succeed at the best universities.

Recommendation One way of increasing faculty salaries immediately would be to raise fees for consulting. In the US, professors know the approximate consulting fees of their colleagues and set their own fees accordingly. They do not want to be accused of being a low-cost, less-desired consultant. If the professors here pass the word around that expensive advice gets more respect than cheap advice and if they command consulting fees that are worthwhile, there is a strong possibility of supplemental income that is greater than their salaries. Quite a few US professors make more from consulting than they earn from their universities.

TEACHING WITH COMPUTERS

I have been a pioneer in developing simple but effective teaching programs for personal computers and have published three books that integrate with personal computers. My programs are in the Public Domain to encourage distribution, use, tailoring to the needs of specific groups, and improvement. I have demonstrated the programs on nearly a dozen occasions during this assignment. There seems to be a good match of these programs with the needs for technical training and refresher courses in the Philippines.

I have more than 100 teaching programs written by me or by my students. With so many to choose from, a teacher is certain to find some that are suitable for courses in engineering or in sciences. Free copies of my programs were provided to many of the scientists and engineers that I met here. Professors at three universities plan to evaluate the programs and have said that they are likely to use several of them quite soon. Programs fall into the following categories:

- Simulation exercises
- Tutorials
- Animations of figures
- Games.

Games that include winning or losing can be wonderful teaching tools because humans play instinctively. Tutorials substitute for lectures. Poor tutorials just present text on the computer screen and differ little from reading a book, but good tutorials involve tutorials are much more effective than is a poor professor but not as good as a masterful teacher. Nevertheless, tutorials that compete with professors today will lead to future tutorials that are better than any professor. An analogy is the evolution of programs for playing chess that started at the duffer level and now challenge international chess masters.

While I strongly oppose full substitution of computers for professors, I believe that a course with the computer 30 to 40 per cent of the time can provide excellent education. This frees the professor for more office hours or recitation sections to interact with the students and to explain rather than to lecture. Another important point is cost of teaching. Good computer programs, especially those provided to the Public Domain, at no cost, are bargains. My floppy disks with about 75 programs each cost me about $1 US to purchase and to copy. The tutorial programs are longer than the others, and a disk with only tutorials would hold about 10 programs. This is only 10 cents per program versus anywhere in the range of $20 to $1000 per lecture by a human being. (The larger number is typical for travel costs and honorarium for a professor from another university.)

With some practice and experience, a tutorial can be programmed in about 20 hours. I very seldom write tutorials anymore because my students enjoy this task. Past practice was assignment of term papers, but now I offer the option of writing a computer program instead. Students report that this is interesting and instructive because they improve their programming skills while delving deeply enough into a topic to explain it well. Several professors here say that they intend to offer the computer project as an option to a term paper. The project could be adapting or improving one of my programs or it could be a totally new program. Over a period of time there will be an enormous collection of good programs throughout the world for good teaching. There are already computer clubs and individuals that maintain collections of programs. In many cases, there is an electronic bulletin board that is accessed with a computer, a modem, and a telephone. Programs can be downloaded at no cost except for the telephone bill.

My books explain and expand on the computer programs. The flyer describing one book follows this section; another book for Biochemical Engineering will go to the printer for publication by early Fall 1988. Free copies of the Environmental Engineering book were given to Dr. Padolina (UP Los Banos) and Dr. Jose (UP Diliman).

Some programs stand alone quite well while others are much more effective when aided by the books. Although my books are copyrighted (US Library of Congress), I expect that copying will be common. I have offered my books to the Philippines at just the production cost and shipping (no profit for me). Prof. Jose has a relative who is an importer and can ship at a price well below that of mailing. To encourage teaching with computers in less developed countries, I am considering including text files right on the floppy disks with the instructions and explanations of some programs. These files could be printed out and given to the students. This would set an example for other authors of programs to provide free instructions. There is also the possibility of puting book manuscripts on floppy disks. It is much easier to duplicate a floppy disk than to put an entire book through a photocopier page-by-page.

In summary, public domain programs written in BASIC offer low cost, effective instruction that is easily modified to meet a specific need. My programs for the MS/DOS system (IBM and clones) are easily translated to other operating systems. The advantages of teaching with computers are excellent pacing for each user, easy repetion of material that was not comprehended, immediate interaction and reinforcement that aid learning, better graphics than a book because of color and animation, and potential for adding sound. Disadvantages are that a human should still be available for explanations and problems with the software or hardware can be deadly frustrations. In some cases it is easier to take a book from the shelve to find information than to power up the computer and to search computer files. Finally, the computer is beautifully suited to some material and offers a fresh approach to education.

SUGGESTIONS FOR PRODUCTS AND TECHNOLOGY

Product Blood containers

Recomendation A new design of blood containers should be developed and manufactured in the Philippines.

Background In a meeting with C.T. Narcisco, M.D. at the Heart Center, Ivanov, Walker, and Bungay were shown a 4-pack of containers used at the blood bank. This 4-pack costs P/ 419 from a foreign company, and this is a painful price for the Philippines.

Plan A totally new design of blood container aimed at very low cost is needed. An entrapeneur should be found to work with suppliers of components and with blood bank people to develop this design. It should be solely a Phillipian venture with no input from foreign experts. This report has no design suggestions for fear of diluting the pride and satisfaction that will come from a Phillipine design. However, the following points should be considered:

1. What features of the present container are expensive but not really essential?
2. What containers and tubing presently available of Phillipine manufacture might be incorporated or modified for use with blood?
3. Would hospitals and blood banks prefer to assemble and sterilize the blood containers themselves to save money?
4. Would adding some low-cost features help sales in the Philippines and in other countries?

Product Reference serum for calibration and control of blood testing.

Recommendation Vials of reference serum should be manufactured locally.

Background Serum is sold in vials throught the world for convenient calibration of blood testing. A dozen or so of the most commonly assayed blood factors are specified for the reference serum. Concentrations at the high end of the range for normal blood or slightly elevated levels are preferred. To achieve these levels, serum may be spiked with enzymes. Some companies spike with plant, microbial, or animal enzymes, but sera with only human enzymes are considered to have the highest quality. At least one US company obtained blood from undertakers because enzymes are released into the blood after death.

Plan Obtaining sera, pooling to get large lots, assaying the components and dispensing into vials are very easy. Developing an effective means for preservation with reasonable shelf life is not so easy, and short shelf life (refrigerated) greatly lowers the value. Freeze drying is used, but a production-size lyophilizer costs over $ 300,000 US. It would be best to purchase a protocol giving the exact conditions for freeze drying because it would cripple a company to work out their own protocols for freeze drying over a period of weeks or months with no salable output from the large units.

Comments Imported reference sera are well into their expiration period because of time lost in shipping. Material manufactured locally avoids this delay and may have remaining shelf life comparable to that of the imported sera. As the manufacturing techniques improve, the Phillipine sera may attain long shelf life that will be an important sales advantage. An initial product with inferior shelf life can still be desirable if priced competitively and used quickly.

For this suggestion and for others, large lyophilizers (freeze dryers) are required. In discussions with another expert (Cameron), we think that these could be manufactured in the Philippines. The general principles are well known, and the basic designs are so old that patents present no problems.

There is considerable maintenance on these units so there is a great advantage for local manufacture and repair. Downtime on expensive machinery while awaiting parts from abroad plagues companies here, and continuous service from a less elegant machine is much better than intermittent service of an imported machine.

Resources required A new company would require an analytical laboratory in addition to the production facilities. Sales, marketing, and administration are beyond the scope of this brief discussion. For the control sera alone, filling machines and a freeze dryer would cost about $100,000 for moderate capacities. Only five or six production workers and analysts would be needed.

Product Diagnostic Reagent Kits

Recommendation Small companies in the Philippines should manufacture simple kits using dry filling technology.

Background I was formerly Vice President/Technical Director of a company that made diagnostic reagent kits for medical laboratories. This was a highly profitable business until the advent of automatic analyzers that consumed very small quantities of reagents. Although the largest hospitals here have some of these expensive analyzers, small laboratories will continue to use kits for many years because there will be insufficient capital for major new equipment. When labor costs are low, there is less justification for purchasing labor-saving devices.

Our US company was using freeze drying exclusively for the final processing step until I had several products switched to dry filling. Some kits were significantly better and costs were reduced for the dry filled versions versus the lyophilized versions. Whereas very expensive free dryers were essential for the old versions, dry filling of powders by hand competes in speed with the freeze drying step. Machines for automatic dry filling are far more productive and are less expensive than freeze dryers. A company with four or five employees could offer a few products with hand filling and could reinvest profits for automation as the business grew.

Technology Most diagnostic reagent kits are used with body fluids such as blood and urine. Coronary infarction, for example, causes release of enzymes to the blood from damaged heart muscles. Finding elevated levels of certain enzymes in the blood aids the physician in diagnosing this disorder. Some test kits contain the substrates for enzymes and another reagent that couples with the enzymatic reaction to change its electromagnetic radiation absorption as the reaction procedes. Other kits are based on a series of reactions leading to a change in adsorption of one of the ingredients. Whereas the kits based on one reaction may need no auxillary enzymes, those kits based on a sequence of reactions usually contains enzymes. Kits without enzymes are

excellent canditates for dry filling while kits with enzymes are usually best with lyophilization.

When kits are prepared for lyophilization, ingredients are dissolved and dispensed into vials. Freeze drying takes from one to five days. Dry filling requires blending of powders and dispensing by volume. Research and development may be required to get a blend of powder that packs well and gives reproducible weights when dispensed by volume. Powders with low bulky density (fluffy powders) do not dispense well. We developed a simple trick that greatly increased shelf life of vials filled with powder - anyhdrous calcium chloride was added as a internal dessicant. We built a room that was held at very low humidity to minimize pick up of moisture by our powders. This worked well, but I would now recommend puting the equipment in a box at low humidity with gloves mounted in the walls at critical locations so that operators could make adjustments. We found that there was an abrupt rise in humidity each time our dry room was entered, and a dry box with no humans inside should be easier to operate. For large volumes of air to a room, chilling to condense moisture is effective. For a dry box, passing air over columns filled with dessicants should be relatively inexpensive. The dessicants change color when approaching exhaustion and must be regenerated.

Typical Product LDH: If memory serves, our kit for assaying the concentration of lactate dehydrogenase in blood contained lithium lactate, NAD, and calcium chloride. It might be possible to get the exact recipe. The powder was filled into ampoules and was a very reliable kit that was activated by adding water and blood serum. There were start up problems in educating the suppliers of chemicals to furnish products free of lint and dust because these appear in the vials when the powder dissolves in water.

Filling equipment Filling by hand requires a device that is gripped and moved through a resevoir of powder. The adjustable cavity is blocked by a screen that is too fine for the powder to pass. Vacuum draws the powder into the cavity, excess is tapped off, and air pressure discharges the powder into a container. One person can fill hundreds of vials per hour. A filling

machine uses the same principle but with eight or ten chambers in parallel on a drum that rotates below a hopper of powder and above the containers. Thousands of vials can be filled per hour. Reaching into a glove box to operate a hand filler is not an uncomfortable task.

Comments With LDH kits as the test case, economics and technology of hand filling could be evaluated here. In addition to diagnostic reagent kits, there are opportunities for dry filling various pharmaceuticals. When employed at a major US pharmaceutical company, I often observed sterile dry filling. Specifications are more rigorous for drugs than for analytical kits. The weight must equal or excede the dosage on the label, and this requires a slight overfill so that vials that deviate below the mean value of the dose will still be above the value on the label. Poor control of bulk density means lost profits because the overfill must be increased. Perhaps sterile dry filling is already practiced here, but I saw none during my visit. The problems of dry filling are straightforward. It would be an interesting challenge for biochemical engineers to produce crystals with good bulk density, for pharmacists and analytical chemists to devise processes, and for plant engineers to develop acceptable manufacturing.

Resources required A hand gun for filling costs only a few hundred dollars. A glove box for low humidity based on dessicants could be built for a similar cost. Two operators and one analyst could handle the work load for small lot sizes to evaluate whether the products were marketable.

Product Water for Injection

Recommendation The amount of water for very high quality pharmaceuticals should be increased by creating new facilities that are almost entirely composed of equipment manufactured in the Philippines.

Background A recent UNIDO Report* points out the very great need for electrolyte and other fluids in developing countries because of the prevalence of diseases that dehydrate and upset the balances of body fluids. We saw a small unit for preparing distilled, pyrogen-free water at Pascual Laboratories so there is good precedent for local manufacture of high quality water. In the US, injection water and solutions tend not to be very profitable except for a few companies such as Abbott Laboratories that have specialized in these products and have lowered manufacturing costs by handling large batches. This suggests that too small an operation is not an attractive opportunity here. Furthermore, importing elegant, expensive equipment is unlikely to lead to a profitable factory when small cost factors are crucial.

The components of a water plant are pumps, columns with deionizing resin, boilers, condensers, and resevoirs. Usually there are three resevoirs - one is filling, one is providing product water, and the other is full and is being tested. The tests are conductivity (an extremely simple test) and pyrogenicity. The presence of pyrogens (fever producers) is checked by injection into rabbits and seeing if their body temperature rises. A newer test that many companies use alone or with the animal test is based on turbidity of serum from the horseshoe crab when pyrogen material is added. This is called the Limulus lysate test. Materials of construction are important because metal containers can impart ions to the water and glass

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* UNIDO/IO/R.210, 10 December 1985, Establishment of a Development Plan for the Pharmaceutical Industry, UC/ALG/85/062, ALGERIA Technical report: Establishment of facilities and Transfer of Technology for the Production of Intravenous Fluids

containers of low quality can dissolve to add silicates. Although most plastics are essentially insoluble in water, plasticizers or unreacted monomers can leach into the water. Plastic resevoirs could be quite satisfactory after extraction for many days with water. Dust and dirt can be serious problems, but the initial batches of good water will flush them from the system. All openings to the atmosphere should be blocked with filters such as fine-pore membranes to prevent the entry of dust and contaminants.

Comments Design and construction of new facilities built of locally available materials presents challenges but these can be conquered fairly quickly. The UNIDO report discusses materials. The resevoirs should be as large as possible because there is no serious penalty for overcapacity and quality control costs are minimized if the batches are large. The UNIDO report suggests resevoirs of 4000 L. This water is itself a salable product and is the basis for other products such as isotonic saline, various concentrations of dextrose for injection, electrolyte solutions, and pharmaceuticals sold as solutions. Furthermore, excellent water can be used in the final recrystallization steps for many of the ingredients needed for manufacture of pharmaceuticals. For example, dextrose (glucose) is presently imported. A superb grade of dextrose could be manufactured locally using the excellent water or water of no cost from batches of injection water that do not quite meet specifications.

Resources required The investment in stills, deionizers, and resevoirs would be roughly $100,000. Two or three operators and two analysts should be sufficient. The animal testing for pyrogenicity could be a significant cost but is outside of my expertise.

Product Small Fermenters

Recommendation Small fermenter for the laboratory or pilot plant should be designed and manufactured in the Philippines for both domestic and foreign sales. These should be sold in kit form and as individual parts in addition to fully assembled models.

Background Prices are exorbitant, delivery is slow, and service is delayed for equipment purchased abroad. There are many companies manufacturing small fermenters, and only a few unessential features are patented. Basic designs would have no patent problems. Availability of these units would extend Phillipine purchasing power and provide more research power throughout any inititiative in biotechnology.

Plan There are already experts on bioreactor design at Phillipine universities (e.g. W. Jose at UP Diliman and W. Padolina at UP Los Banos). They could assist manufacturers to provide basic, low-cost, small fermenters. It is proposed that fermenters be sold either completely assembled or in kit form. Selling kits and parts would be a novel approach to rock-bottom costs, and many groups throughout the world could lower import duties on finished goods by buying kits and parts. Furthermore, countries that have suitable motors, piping, and the like could reduce costs even more by mixing in their local components.

Comments Several professors considering the manufacture of small fermenters have mentioned several alternatives such as purchasing the reactor vessels from foreign companies and building the rest of the equipment here. UNIDO should consider supporting this R and D and may wish to get input from other developing countries.

Technology Enzymatic Hydrolysis of Starch

Recommendation Perform R and D to find a new process.

Background About 20 years ago the starch companies throughout the world switched from hydrolysis with acid to enzymatic hydrolysis. This was part of the corn wet milling industry that traditionally has invested very little money in research. The enzymatic technology requires amylases that do not inactivate quickly at elevated temperatures that are used for liquefaction of starch. Such enzymes come from thermophilic microorganisms and are discarded after processing. Very soon after the expensive conversion to the new processes, even better technology based on immobilization of the enzymes for repeated use was reported. The starch companies showed no interest because the expensive retrofitting for simple enzymatic hydrolysis had not been amortized.

There is a small corn wet milling industry in the Philippines that employs the obsolete method of hydrolysis with acid. The Department of Science and Technology performs research and development of batch enzymatic hydrolysis of starch. A continuous process with immobilized enzymes should be considered. This would be an interesting opportuinity to leapfrog the technology of developed countries by going directly to hydrolysis with immobilized enzymes. The basic technology can be found in the research literature, but there are some recent developments concerning immobilization of enzymes that should not be expensive to implement.

Product Mannose

Recommendation Produce mannose from copra waste.

Background Many people met during this assignment expressed interest in copra waste, the material after expressing coconut oil. It is rich in protein that is not available nutritionally because of trapping by a network of sugar polymers called mannans that have the monomer mannose. Research by Dr. Padolina, Dr. Josan, and others concerns producing the enzyme mannanase to destroy the mannan polymer to convert copra waste to digestible animal feed. One product of this treatment is mannose, and this sugar is used as a filler in several pharmaceutical dosage forms.

With only slight changes in methodology, the processes now proposed for converting copra waste to cattle feed could result in an aqueous solution of mannose. Treatment with activated carbon produced from coconut shells should remove color and permit the cyrstallization of pure mannose.

Technology Unsterilized fermentation equipment

Recommendation Research and development already underway in the Philippines for ethanol fermentation without sterilization should be extended to other products.

Background I have published several articles about low technology for bioengineering and have mentioned it it some of my other publications. The general idea is to omit sterilization to save fuel costs and to avoid pressure vessels that are expensive. The ethanol fermentation is the classic case of no sterilization because contamination is uncommon with vigorous yeast that lower the pH to a range that discourages most other organisms and they elaborate ethanol that impairs or kills organisms. When the concentration of alcohol approaches 10 per cent, the yeast themselves function poorly.

Large scale manufacturing of ethanol has been successful in Brazil and was tried briefly in the Philippines. Fuel alcohol produced in equipment suitable for pharmaceuticals is unlikely to be profitable, and technology more akin to agrobusiness makes more sense. This same commercial strategy should be considered for fermentations other than ethanol. Although low technolgy would seem to imply crude engineering, the converse is so. It may take very good sophisticated engineering to develop reliable low technology. The problem is exacerbated for the Philippines where fermentation plants might have to be constructed mostly of imported materials and equipment. The rewards of effective low technology would be great if domestic materials were used.

Technology Cooling water for various processes.

Recommendation Perform engineering and cost analysis on the feasibility of using ocean water for cooling a fermentation plant.

Background An atomic power plant was constructed in the Philippines adjacent to the sea shore so that ocean water could be used for cooling. Streams and wells here range from 24 to 42 degrees Celsius, and maintaining industrial bioprocesses at their proper temperatures is a serious problem. The penicillin fermentation usually is operated at 28 degrees, and this could not be controlled with available water. The ethanol process is operated at higher temperature in warm countries but should not get too hot because more ethanol is lost when swept away with the carbon dioxide that is evolved. A costly solution is to use refrigeration. Sea water is fairly corrosive and presents a host of problems. Nevertheless, its use by the atomic power plant proves that in some case, cooling with sea water is feasible. It is my understanding that atomic power here, as in the US, is opposed by politically powerful groups. If the plant with sea water for cooling cannot be operated, it might be economically attractive to divert its cooling equipment to a fermentation plant. Alternatively, the technology of the atomic plant can serve as a guide for design of a unit for biotechnology.

Comments New technology for cooling with sea water would be an interesting research project here. Materials made in the Philippines should be used in the heat exchangers, lines, and pumps. A two-stage system in which the sea water cools the plant cooling water would allow the use of customary materials of construction throughout most of the plant.

Technology Quality control.

Suggestion Establish procedures that could insure that Phillipine goods have the very highest quality.

Background One of the most difficult problems that a developing nation faces in selling on world markets is convincing customers that the quality of their products is high. However, the most usual form of quality control is attempting to meet minimum specifications. With just a little more effort and education, it is possible to instill and enforce an attitude of achieving very high quality.

Good quality control should not be just the responsibility of the analytical laboratory but of all persons in research and development laboratories and in production. They should not blindly accept analytical results but should continually be challenging the analysts. Some methods are:

1. Resubmit samples to see if the analysts get the same answers.
2. Send duplicates but with different labels.
3. When materials are stable with time, resubmit every so often with different labels.
4. Send a sample accompanied by the same material diluted to various concentrations. When corrected, the results should agree.

Exactly the same procedures should be carried out by the director of the quality control laboratories and by the agencies that supervise them. Poor tests or poor performance can be identified and corrected. When everyone trusts the QC people, there will be pride that spreads throughout the entire company and leads to a feeling that they can perform equally well in research and in production to make products of the highest quality.

FRAGMENTARY IDEAS [not fully thought out]

1. Chlorochemicals The chlorine/caustic industry exists in the Philippines and has the same key problem as other factories throughout the world. Chlorine markets are not as large and as flexible as those for sodium hydroxide. The coproduct nature of the reaction means that 1.1 ton of caustic soda is produced for each ton of chlorine, but the markets react differently. At present the demand for caustic soda is increasing while markets for chlorine are holding steady or showing a decrease because environmental regulations discourage introducing chlorinated chemicals into the environment. An imbalance in markets is causing prices of caustic soda to rise steeply (Chemical and Engineering News, Aug. 8, 1988, page 20). Chlorine is not used very much in the Philippines because swimming pools, the plastics industry, and water treatment are not big markets. Excess chlorine is available at relatively low prices and could be used for chemical synthesis. Among compounds that should be considered are: $SOCl_2$, $POCl_3$, $FeCl_3$, $AlCl_3$, and chlorobenzene. If a biomass industry develops, there will also be excess lignin, a polymerized aromatic phenolic compound. Reactions of lignin with chlorine have not been studied very much and might be an opportunity for new commercial processes leading to chlorinated aromatic compounds. Low cost could also inspire more use of chlorine for treating industrial wastes in such processes as removal of cyanide from metal plating wastes by oxidation with chlorine.

2. Ship-borne chemical plant Some chemical plants have been constructed on ships or barges and sent intact to areas that need them. When water and electricity are connected, the plants are ready to operate. We were told that the approximate shipping cost between islands in the Philippines is $25 per ton, and goods are often brought for less from foreign countries. To develop chemical industry on various islands, it is unwise to build factories that are too small to be economic. It is costly to ship raw materials to another island and to ship back finished products. A floating factory could eliminate

shipping by mooring at various islands long enough to satisfy local markets for chemical products and then repeating this act at another island.

3. Fodder yeast from wastes We were told that one-half of the distilleries in the Philippines were closed because of pollution problems. The wastes contain fermentable materials left over from ethanol production and constitute a high BOD (biochemical oxidation demand). In the Soviet Union, factories that produce ethanol from wood also have unfermented sugars (mostly pentoses) in the effluent. These are used to grow fodder yeast. Some factories make no ethanol and go directly for fodder yeast. Research in the Philippines and elsewhere has focussed on biogas instead of fodder yeast from various effluents. Since protein is by far the more valuable product, some research is justified to solve pollution problems while producing microbial protein.

4. Fluid for kidney dialysis We were told that the price of fluid for one session at a dialysis clinic is 2000 pesos. This is so expensive that kidney transplant is a much more attractive treatment, and Number 500 was just accomplished. The surgeons have a remarkable success rate - 89 per cent when a relative donates a kidney and 78 per cent with a kidney from a cadaver (based on 30-month survival). The demand for kidneys and a long waiting time means that dialysis is needed but at a much lower cost. To serve patients other than the very rich, a dialysis system with much lower cost is needed. Research and development of a dialysis machine and of low cost fluids seem justified. Less elegant and less reliable treatment would still be a boon for people with low incomes.

APPENDIX

The Undergraduate Program for Biochemical Engineers (Based on Material supplied by Dr. Wilfredo Jose (UP Diliman)

The chemical engineering curriculum takes five years with a total of 178 units. One unit is equivalent to one hour of lecture per week (a semester lasts about 16 weeks). Each student who specializes in biochemical engineering takes a five-unit course in integrated biochemistry/microbiology followed by a three-unit biochemical engineering lecture course and a one unit biochemical engineering laboratory course. A special project and plant design relevant to biochemical engineering are required. The adviser of the student should be a biochemical engineer.

The Biochemical Engineering Option in the Masters Program in Chemical Engineering

The Masters program in biochemical engineering is shown in Table 1. A thesis is defended before a committee. A non-thesis student has to take a comprehensive examination. The major objective of the program is to provide training for faculty from other schools and chemical engineers from industry and government research institutions. The program provides traditional advanced courses in chemical engineering and mathematics while the rest are specialty courses, electives, and thesis work.

A student can elect a thesis with an original research in biochemical engineering. As a prerequisite to the biochemical engineering option, a student takes undergraduate courses that provide sufficient background in biochemistry and microbiology.

Table 1

Biochemical Engineering at UP Diliman

Master of Science (Chemical Engineering)
Biochemical Engineering Option

Course No.	Descriptive Title	Units
	(Biochemical Engineering - 9 units)	
ChE 201	Biotechnology for Engineers	3
ChE 292	Biochemical Engineering	3
ChE 294	Biochemical Engineering Plant Practice	3
	(ChE Core Subjects - 6 units)	
ChE 220	Advanced Chemical Engineering Thermodynamics	3
ChE 231	Advanced Chemical Reaction Eng II	3
ChE 241	Transport Phenomena	3
	(Applied Mathematics - 6 units)	
ES 201	Advanced Mathematical Methods in Engineering I	3
ES 204	Numerical Methods in Engineering	3
	(Thesis - 6 units)	
ChE 300	Masters Thesis	6
	TOTAL	30

For the non-thesis option 12 credits of electives can be taken in lieu of the thesis work.

Five-Year Curriculum Leading to the Degree of BACHELOR OF SCIENCE IN CHEMICAL ENGINEERING

FIRST YEAR

First Semester	*Class*	*Lab*	*Units*
English I or Pilipino 12	3	0	3
E.S. 1 (Engineering Drawing)	0	6	2
Introd. to Asian Civilizations	3	0	3
Math. 17 (Alegbra & Trigonometry)	5	0	5
Soc. Sc.*	3	0	3
CMT 11			(1.5)
P.E.			(2)
	14	6	16

Second Semester	*Class*	*Lab*	*Units*
Chem. 16 (Gen. Chemistry I)	3	0	5
English II or Pilipino 13	3	0	3
Math. 53 (Elem. Analysis I)	5	0	5
Phys. 71 (Elem. Physics I)	4	0	4
Phys. 71.1 (Elem. Phys. I Lab)	0	2	1
CMT 12			(1.5)
P.E.			(2)
	15	8	18

SECOND YEAR

Chem. 17 (Gen. Chemistry II)	3	6	5
English II Pilipino 20	3	0	3
Math. 54 (Elem. Analysis II)	5	0	5
Phys. 72 (Elem. Physics II)	4	0	4
Phys. 72.1 (Elem. Phys. II Lab.)	0	3	1
CMT 21			(1.5)
P.E.			(2)
	15	9	18

Ch.E. 31 (Intro. to Chem. Engg)	3	0	3
Chem. 28 (Quan. Inorg. Anal.)	3	0	3
Chem. 28.1 (Quan. Inorg. Anal. Lab.)	0	6	2
Math. 55 (Elem. Analysis III)	3	0	3
Phil. Hist. and Inst. I	3	0	3
Phys. 73 (Elem. Physics III)	4	0	4
Phys. 73.1 (Elem. Phys. III Lab.)	0	2	1
CMT 22			(1.5)
P.E.			(2)
	16	8	19

THIRD YEAR

Ch.E. 32 (Ind. Stoichiometry)	2	3	3
Chem. 31 (Organ. Chem. Lect.)	3	0	3
Chem. 31.1 (Organ. Chem. Lab.)	0	6	2
E.S. 11 (Stat. of Rigid Bodies)	3	0	3
E.S. 21 (Math. Methods in Engg.)	3	0	3
Nat. Sc. 3 (Found. of Biol. Sc.)	3	0	3
	14	9	17

Ch.E. 131 (Transp. Processes)	3	0	3
Ch.E. 132 (Stage Operations)	3	0	3
Chem. 180 (Physical Chemistry)	3	0	3
E.S. 12 (Dyna. of Rigid Bod.)	3	0	3
E.S. 26 (Computer Programming)	2	3	3
Speech 1 (Fund. of Speech)	3	0	3
	17	3	18

FOURTH YEAR

First Semester	*Class*	*Lab*	*Units*
Ch.E. 182 (Ch.E. Thermodyna. I)	3	0	3
Ch.E. 133 (Proc. Equipment Design I)	3	0	3
Ch.E. 134 (Proc. Equipment Design II)	3	0	3
E.E. 3 (Elem. Electrical Engg.)	3	0	3
Soc. Sc.*	3	0	3
Span. I (Elementary Spanish)	3	0	3
	18	0	18

Second Semester	*Class*	*Lab*	*Units*
Ch.E. 111 (Chem. Proc. Ind.)	3	0	3
Ch.E. 123 (Ch.E. Thermodyna. II)	3	0	3
Ch.E. 135 (Unit Oper. Lab. I)	0	6	2
E.E. 4 (Ind. Electr. & Meas.)	2	3	3
E.S. 13 (Mech. of Def. Bod.)	3	0	3
Span. II (Elementary Spanish)	3	0	3
	14	9	17

FIFTH YEAR

Ch.E. 121 (Ch.E. Thermodyna. Lab.)	0	6	2
Ch.E. 125 (Chem. React. Engg. I)	3	0	3
Ch.E. 141 (Plant Design I)	2	3	3
Hum. I (Introd. to the Humanities)	3	0	3
P.I. 100 (Life & Works of Rizal)	3	0	3
Span. III (Intermediate Spanish)	3	0	3
Elective	3	0	3
	17	9	20

Ch.E. 126 (Chem. React Engg. II)	3	0	3
Ch.E. 136 (Unit Oper. Lab. II)	0	6	2
Ch.E. 142 (Plant Design II)	1	6	3
Ch.E. 190 (Plant Insp. & Sem.)	1	3	2
Ch.E. Elective	3	0	3
Span. 20 (Readings in Spanish)	3	0	3
	11	15	16

Total ..... 177 units

Ch.E. 171; INTRODUCTION TO BIOCHEMICAL ENGINEERING.—Basic microbiology and biochemistry. Enzyme and fermentation kinetics. Continuous culture. Mass transfer in biological system.

Prerequisite: Ch.E. 125

3 hours a week class, credit 3 units.

Ch.E. 292; BIOCHEMICAL ENGINEERING.—Integration of the principles of chemical engineering, biochemistry and microbiology with application to the analysis of biochemical reaction sequences and related transport phenomena in fermentation operations.

Prerequisite: Ch.E. 125 or consent of instructor

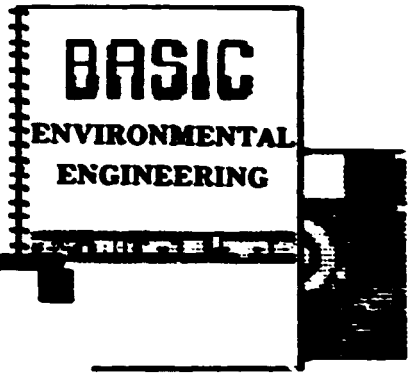
Credit 3 units

Ch.E. 293; ENZYME ENGINEERING.—Application of biochemical engineering principles to enzyme technology.

Prerequisite: Ch.E. 292

Credit 3 units.

NEW



BASIC

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Table of Contents

To: Kamen Ivanov Aug. 1, 1988

From: Henry Bungay

Re:Suggestion for more efficient organization of projects.

To follow up on our conversation about efficiency of research and development projects, I want to write out some of our ideas. The basic concept is that starting a project from scratch in any country leads to long delays that sometimes destroy any effectiveness. One attractive alternative is to start the project in a laboratory that already is a world leader in this area of research. Let's propose that duplicate facilities and equipment be established in this laboratory to be operated by persons from the country that has need of the results. After about one year, these persons would return to their country and take with them the equipment that they had mastered. Direction could continue from the parent laboratory as the project is finished in their country.

Problem 1. People may wish to immigrate.
Proposed answer: Those pursuing a Ph.D. would have a contractual obligation with the institution of the parent laboratory for part of the Ph.D. research to be carried out in their own country. No follow up research - no Ph.D. It would be unwise to immigrate without the advanced degree.

Problem 2. Money might flow to developed countries to support this research.
Proposed answer: Funds should cover only the research assistantships, duplication of equipment, and modest costs of supplies and supervisory costs. Furthermore, any qualified laboratory should be eligible, not just those in developed countries.

If you decide to promote these ideas, please let me know how I can help.

H. BUNGAY
July 11, 1988

Review of proposal: Establishment of a Fermentation Pilot Plant for Antibiotics - March 1987

Authors: National Institute of Science and Technology

The reviewer is fully in sympathy with increasing fermentation capability in the Philippines, but this proposal is unlikely to progress appreciably toward that objective. A summary of the proposal is: " buy us a facility, bring in international experts to tell us what to do, and in a few years we can be where the developed would was 10 years ago". Missing from the proposal is the number of new fermenters to be purchased. There is on p.18, one 28-L fermenters to be purchased and on p 19 a request for $260.000 for an unspecified number of additional fermenters. This would represent 4 or 5 of these 28-L fermenters. This reviewer once worked in a pilot plant with about 60 small fermenters and just a few weeks ago visited a pilot plant with about 30 very high technology fermenters at one of the world's major pharmaceutical companies. In such a pilot plant, duplicate experiment are necessary. The proposed Philippine pilot plant would be able to perform about 3 such experiments per week, so allowing for contamination and blind alleys, the objective can never be reached.

Any proposal based on outside experts will be counter productive and will stifle creativity. A true objective is to develop new attitudes. There are plenty of intelligent people in the Philippines, but they tend not to have an independent approach to science and technology. Given free reign, they have

sufficient imagination and talent to compete with other laboratories in the world. Why then ask them to focus on some of the most advanced antibiotic fermentation? This reviewer suggests that they focus on materials used in both the chemical and pharmaceutical industries and that these be produced by fermentation of indiginous resources. Some examples are citric acid, acetone/butanol, glycerol, and lactic acid. The authors of the proposal have experience with these bioprocesses, but they are spread fairly thin with too much to do and insufficient manpower and equipment. It makes sense perhaps to add one new fermentation to their work load, but they would be overwhelmed if they embark on programs for several antibiotics.

Last year in Bulgaria, this reviewer saw small fermenters of local manufacture. They were only slightly inferior to much more expensive fermenters sold in developed countries. They are made from glass, steel, bearing, motors, and components available in the Philippines. Instead of purchasing 4 or 5 elegant fermenters, the National Institute of Science and Technology could design and build their own and could work with local companies to create a new product line of small fermenters. Dr. William Padolina at UP Los Banos purchased stainless steel from abroad and took it to a local manufacturer of Jeepneys (small buses) to fabricate into fermenters. By working with this company and refining the units, he now has several reliable small fermenters for his pilot plant. The cost was much less than for

fermenters manufactured abroad. A similar program should be cost effective for the authors of this proposal. One very great advantage for local manufacture is rapid maintenance when required.

This proposal should be rejected but a new proposal with Philippine ideas should be encouraged. A work plan NOT based on taking directions from outside experts seems essential. This work plan should break each task into sub-tasks with a brief explanation of the purpose, a description of the type of experiments, and an estimate of the time required. Most funding agencies in the US demand a chart showing the approximate starting time and completion date for each group of tasks.