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Technical report: Transfer of technology*

Prepared for Member Countries of
Arab Company for Drug Industries and Medical Appliances
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SUMMARY

(i) It is desirable that ACDIMA should establish and sponsor a Regional Centre for Drug Research,Development and Control in one of the Arab capitals such as Amman, Baghdad or Riyadh. The centre will have 8 main units as follows:

- Industrial Pharmacy
- Chemical unit including fermentation and synthetic drugs
- Medicinal plants and natural products
- New drug development
- Formulation and packaging
- Quality control
- Engineering design
- Training

(ii) A medium sized quality control laboratory should be established as a model laboratory attached to any of ACDIMA dependent companies. Such a laboratory has the following sectional laboratories:

- Specifications and analytical development
- Chemical and physical testing
- Biological testing
- Central release department
- Inspection and checking department
- Instrumentation

The existing quality control laboratories of the Gulf Pharmaceutical Industries at Ras Al-Khaimah will serve as a model laboratory attached to a modern pharmaceutical formulation unit.

(iii) The possibility of using products from the Arab Petrochemical industry as raw materials in the Pharmaceutical industry in the member countries of ACDIMA has been investigated. It is observed that 39 bulk synthetic pharmaceutical chemicals can be synthesized in the Arab World including ACDIMA member countries. Starting materials of all these pharmaceutical chemicals are commercially available as petrochemical products in these countries and they are produced in abundant quantities. These 39 chemicals cover a wide range of medical and pharmaceutical uses. Some of them can also be used as solvents, reagents and in perfumery industry. Some petrochemical products can also be used as starting materials for the production of containers for pharmaceuticals and a disposable syringes.

It is desirable to assess the market demand for the above pharmaceutical chemicals with a view to group 10-15 of these for production in a multi purpose plant. Such a plant is ideally suited to produce a group of pharmaceutical chemicals, the individual requirements of which are not large enough to render the establishment of a separate plant for each pharmaceutical chemical economically viable. Such a multi-purpose plant is ideally suited to the ACDIMA member countries[1].

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1. Multi-purpose plant for production of UNIDO essential drugs based on raw materials and intermediates UNIDO/ID/WG.393/18.

REGIONAL CENTRE FOR DRUG RESEARCH, DEVELOPMENT AND CONTROL

INTRODUCTION:

Pharmaceutical industries depend heavily and to a great extent on research. It is very important that every pharmaceutical industry in a country should be backed by research facilities so that national pharmaceutical industries can grow properly.

Research must not be considered a luxury which some developing countries cannot afford. In the Arab World, ACDIMA could play a very important role in promoting such activity because research is considered the insurance against future backwardness and underdevelopment as well as the insurance for the advancement of nations. It is a basic obligation for every pharmaceutical industry to set aside a certain percentage of its turnover for research.

Research could be in the company's own laboratories in case of large establishments, or could be through agreements and projects with research institutes and universities in case of small ones. The role of ACDIMA is very important in both cases.

Activities of research should be directed towards specific goals and objectives reflecting national or regional needs. In this case, it is very important to define the priorities, objectives and goals and to identify the problems carefully.

In order to achieve these goals, both basic and applied research are needed. Because of the scarcity of the requisite manpower and sometimes facilities, in some pharmaceutical companies in the region, it is very important to co-ordinate the entire research activities in this field through the efforts of ACDIMA. Such co-ordination would have many benefits and great advantages as it would stimulate the academic community and make it aware of the regions' pharmaceutical problems

and needs, which will enable it to direct and initiate research according to these areas.

From the experience in developing countries in general and the Arab World in particular, usually the majority of problems and needs are not clearly specified as well as not perfectly identified, which lead the academics and university professors to prefer to direct their research according to their own particular interests. In the context of co-ordination, when a problem has to be presented to them, they have to contribute their best to solve it. Their direct involvement in such problems will make them aware of the special needs of education and training of personnel in the area.

As a consequence of the wide-spread area of the Arab World, research becomes more oriented towards social goals. It serves to bring the pharmaceutical, medical, chemical and engineering academic community of the region on one hand and pharmaceutical industries community on the other, together and so contribute very closely to the formation, expansion, promotion of national pharmaceutical production to support and improve the economics of health in the region.

ACDIMA should start, as soon as possible, to think seriously about establishing and sponsoring a Regional Centre for Drug Research, Development and Control.

The Centre should be initiated in one of the Arab capitals in a suitable geographical location based on the social, economical and environmental conditions in relation to the natural available raw materials and manpower. The three best choices for ACDIMA to/choose such a location are either Amman, Baghdad or Riyad. The Centre must be located beside a university, research centre or technical institute in order to co-ordinate mutual assistance and knowledge transfer. These institutes, in addition to their contribution in all phases of the industry, will with agreement of the Centre, offer advanced courses in industrial pharmacy, pharmaceutical analysis and control, cultivation and collection of medicinal plants

and technology for their industrialization, medicinal chemistry, microbiology, fermentation, pharmacology, clinical pharmacy, economics, public relation, acccunting, also training courses related to the activities of the Centre.

Objectives

The Centre will play a very important role as follows:-

(1) It will recommend the criteria for selecting drugs for local production in the region within the list of the essential 26 drugs reccmmended by WHO/UNIDO.

(2) One of the tasks of the Centre will be in helping, by agreement with developed pharmaceutical industries, of technology transfer depending on the condition of every country after studying the advantage/disadvantage in relation to the success of the project.

(3) It will help in the establishment and development of pharmaceutical industries and overcome the difficulties which usually face developing countries of the region. It is a known fact that the complexity of drug industry is far more sophosticated than any other industry.

(4) As a part of its activities, the Centre will help introducing the up-to-date technological requirements to participating countries at a suitable level and to adopt such technologies to the conditions of each country of the region in order to help in manufacturing competitive drugs both in price and quality as well (e.g) sophisticated "know how", extraction, compounding and formulation, sterilization, filling, packaging, modern advanced techniques of quality control facilities.....etc.

(5) An important function of this Centre is to screen all the drugs available in the Arab market and give recommendations to abandon some of them taking into consideration the most recent recommendations of developed organizations, agencies or administrations such as WHO, FDA in USA, Scandinavian Drug Control Authority and Committee on Safety of Medicines in U.K.

(6) It will develop the human resources required by the national pharmaceutical industries in the region.

(7) It will promote the co-operation between the countries of the region to harmonize their policies towards establishing a complementing pharmaceutical industry among each other which would lead to Pan Arab pharmaceutical common market as a part of a future Pan Arab common market.

(8) The Centre will be of great help in planning the strategy of pharmaceutical industry in the region and it is of utmost importance to mention that the activities of this Centre will not eliminate similar activities in ACDIMA dependant companies, but on the contrary its activities will support and potentiate the already existing similar activities, if any, amongst its companies. Naturally, any duplication of activities should be avoided.

The Centre will help promotion in the major fields of pharmaceutical industry and constitutes 8 main units which are:-

I. Industrial Pharmacy Unit.

II. Chemical Unit and includes:-

a. Fermentation Unit.

b. Synthetic Drug Unit.

III. Medicinal Plants and Natural Products Unit.

IV. New Drug Development Unit.

V. Formulation and Packaging Unit.

VI. Quality Control Unit.

VII. Engineering Design Unit.

VIII. Training Unit.

I Industrial pharmacy unit:

The unit should be responsible for the involvement in setting up manufacturing operations from the beginning, and in fact should act as a consultant to the infant pharmaceutical companies in the region in general and to ACDIMA dependant companies in particular.

One of its main tasks is to assimilate and improve technology acquired by pharmaceutical industries in the region.

From the experience in such cases, this Centre when it will act to design and plan the pharmaceutical technology amongst ACDIMA dependant companies, as well as others and give consultancy services in this field, will be able to stimulate and promote to a great extent the growth and advancement of the pharmaceutical industry especially in small companies in the region. This is very important for developing countries such as the Arab World as it generates specialized employment and manpower, as well as generates production to a great extent which is greatly needed in the most underdeveloped Arab countries.

Research priorities for this unit would be determined by the needs of industry, in terms of its immediate production programme, and also the region's long term needs. As an example, research in the field of biopharmaceuticals is very important as it will reveal the dosage form most suitable for each country in the region in light of climatic conditions and other special requirements. Another good example, is that in most Arab countries of the region in which a large part of the population live in remote areas where the doctor/patient ratio is low, and as a result the doctor is not able to supervise the administration of drugs to his patients, therefore sustained-release forms or long-acting dosage forms of known drugs on a weekly, monthly or longer periods will be of great help.

This unit will be provided with a semi-industrial pilot plant for development and applied research in relation to synthetic drugs and bulk raw materials.

II Chemical Unit:

a. Fermentation Unit:

As the progress of fermentation is continuing at an ever-increasing pace, it is important for ACDIMA to participate in this important field of pharmaceutical production. It is observed that each year, new products are added to the list of naturally produced pharmaceutical compounds derived from fermentation (e.g.) antibiotics, vitamins, enzymes, vaccines and some organic chemicals such as citric acid, essential amino-acids and ethanol.

Processes for production of such compounds should be evaluated in this unit in order to adopt the most adequate economical ones which suit the local conditions.

Contamination problems should be studied. Research should be carried out in the advancement of sterile techniques and sterilty of the equipment and the fermentation medium, also the most suitable methods to pass the inoculum into the fermenter without contaminating it.

The unit should try to improve methods for removing samples and adding materials aseptically to the fermentation vessel and to design air-compression and delivery systems and efficient methods for agitating and aerating the fermentation.

Research of this unit should be directed to solve the numerous problems in product recovery in order to increase the yield. Also, to discover new strains from the region's soil and advance desirable interactions between microorganisms and their environment, control these interactions and translate laboratory results to production-scale

operation in an economic manner. It must continue to develop, design, and scale-up, if possible, new fermentation processes.

The unit should advise dependant companies of ACDIMA having similar activities on how to operate fermentation safely and efficiently, and how to produce products which meet the quality requirements and standards set for them.

The importation of fermentation technology should be carefully screened by the unit. Preferably, it should be the most recent which offers the highest yielding strains and backed by guarantees.

At the same time, the unit will play an important role in discovering, improving and evaluating the culture strains used in different fermentation processes used in ACDIMA dependant companies.

The research of this unit will help in setting up the production of essential fermentation products such as antibiotics which can be of great benefit to the developing countries of the region.

b. Synthetic Drug Unit:

Synthetic /drugs represent the largest group of compounds used in pharmaceutical industry.

One of the activities of this unit is to plan for the manufacture of chemical intermediates and if not possible, research should be directed to make synthetic drugs from imported intermediates on an economical basis.

The programme of the unit should be devoted to synthesize the most needed essential drugs consumed in the region and preferably using the available local raw and starting materials (e.g.) petrochemical products.

Usually, individual small or medium sizedpharmaceutical companies such as ACDIMA dependant companies cannot afford to produce bulk synthetic drugs on economical basis.

Production of such compounds on an industrial scale involves, in majority of cases, sophisticated technology. Therefore, the main function of this unit is to carry out the necessary research to help in modifying or simplifying this complex technology in order to adopt what suits the conditions of the pharmaceutical industries in the region.

At the same time, not all synthetic drugs require complex technology for their synthesis. Some of the essential drugs can be easily synthesized by simple methods and can be produced in some ACDIMA dependant companies with a reasonable technical capability. When using imported intermediates, some drugs can be synthesized in one or two steps with a satisfactory yield. These kinds of processes or operations should be evaluated, modified or improved by the unit before their application on an industrial scale.

The unit can help in designing and planning multi-purpose plants for the production of drugs which have similar routes of reaction, or having reactions of the same type. To reach this goal, the unit has to carry out extensive research to reach an economical goal which then will be applied on a large scale in the interested dependant companies of ACDIMA.

III Medicinal Plants and Natural Products Unit:

It is certainly clear that the medicinal plants market shows a tendency to expand worldwide in general and especially in the Arab World. There is an increase in value and volume, and so it can help to establish and develop a medicinal plants industry based on exploring the flora of the region which will be of great value to the most underdeveloped countries of the region.

Indigenous folk medicines provide a very rich source of material for research into potential new drugs and should

be thoroughly investigated. For this purpose, a comprehensive programme should be established in order to screen the more usable medicinal plants in the region which as mentioned before extends through different climatic conditions and different kinds of soils.

The programme of the unit should involve chemical, microbiological, pharmacological and toxicological studies of plants which grow only in sizable quantities.

Each country in the region should collect and document the necessary information available about its medicinal plants, their biological activities and clinical efficacies, The unit with the collaborations of highly specialized academics will carefully evaluate the data and accordingly will decide the priorities for research.

Initially, research may be carried out on the used part or organ of the plant (e.g.) leaf, root, flower, seed, fruit....etc. Once the biological activity is confirmed on a scientific basis, this part of the medicinal plant concerned can be investigated in depth in order to isolate, purify, characterize the pure active ingredients of such part of the medicinal plant and investigate their biological and clinical actions.

The introduction of new techniques and instruments facilitate separation techniques such as TLC, GLC and HPLC especially in the early stages of investigation. This will be complemented with a semi-industrial pilot plant for isolation, extraction and purification of the active materials from medicinal plants.

Usually, derivatives of these active ingredients are needed to be synthesized with the co-operation of the synthetic drug unit in order to compare biological , clinical activities in relation to their toxicity. In most cases, results reported of pure active ingredients are more reliable and more effective than the mother medicinal plant organ.

At the same time, their identified active ingredients are more accurately standardized for quality control compared to the medicinal plant organ as a whole.

In some cases, the unit can recommend, after thorough investigation to pack some of these medicinal plants as herbal tea.

An estimated 25 - 30 pure active constituents covering a wide range of pharmaceutical, medical and therapeutical interest could be isolated, on an economical basis, in this unit.

Through well planned efforts of the unit, the Arab World can realize an old dream of establishing medicinal plants and a natural products industry with possible future expansion to include the perfumery and cosmetic industry as the basis of this latter industry is the volatile oil which constitutes an integral component of such preparations. Needless to mention the direct relationship between the perfumery and cosmetic industry and man's health.

This unit will be very useful to any specialized company to be established in the future and having activities in the region, in the field of medicinal plants and natural products. Its advice will cover all processes starting from cultivation, collection, extraction, isolation, purification, characterization, derivation.....etc of active constituents.

The advice and consultation will also be extended to any drug industry in the region concerned in the preparation of extracts, tinctures or infusions used in the manufacture of pharmaceutical preparations.

IV New Drug Development Unit

There is no doubt that to get involved in the area of research of new drug development is a sophisticated practice, time consuming and expensive. Through co-ordination and proper calculated priorities in research, it could serve a very useful purpose.

The new drug development unit will make the whole region aware of all problems connected with new drugs. Research in this field can be carried out parallel both into the development of new drugs and into the process technology for manufacturing pharmaceutical dosage forms with the co-operation of formulation and packaging unit.

Priority research areas in this unit should be devoted and directed to the following:-

1- Biological (microbiological and pharmacological)screening of folklore and traditional medicine.

2. Biological screening of terrestrial plants, marine flora and fauna of the region.

These two previous priorities are carried out in co-operation with medicinal plants and natural products unit.

3. Biological screening of synthetic chemicals of pharmaceutical or medicinal interest either synthesized locally or elswhere.

This unit, can be a focal unit for co-ordinating research activities in the priority fields. Faculties of Medicine, with their huge facilities and their specialized knowledgeable staff can play a very important role in co-ordinating research with the unit when it comes to the problem of diseases, their pathogenesis and host/parasite relationship; also in the field of immunology and therapy which can be best investigated in their different departments and their clinics and hospitals. Clinical pharmacy and pharmacology research could be well co-ordinated with departments of the different specialized clinical medical departments.

One of the most important and valuable results of this kind of co-ordination is that the new drugs discovered in the research laboratories of this unit should be clinically investigated, tried and evaluated under local conditions. This is very important in order to detect any variations on account of genetic, nutritional or environmental factors, before manufacturing, distributing and marketing them. Needless to mention that Arab World represents 1/10 of the surface of the globe having various genetic, nutritional and environmental conditions.

V Formulation and Packaging Unit:

In recent times, emphasis is given to the biological availability of drugs and focussed great attention on the equivalence, on differences that may exist between apparently similar, if not, identical formulations and on the relationships that prevail between a drug substance and its formulation environment.

The activities of this unit in the field of formulation are to prepare adequate formulas, or modify already existing ones to reach maximum safe biological effect. Research should be devoted to optimize the bioavailability of compounds and drugs synthesized or isolated in other units of the Centre. It is very often necessary to carefully select the chemical derivative of the drug substance, its particle size, its physical form and to combine it with excipients and compounding or manufacturing aids that will not significantly alter the properties of the drug. The unit should carry out experiments to select the most suitable dosage form, and to consider numerous other questions of formulation, manufacture, packaging and storage. To develop an optimum formulation is not an easy task as many factors readily influence formulation properties.

As drug substances are seldom administered as pure chemical compounds, it is the task of this unit to search for the proper kind of formulation. These may vary from a simple solution to a very complex drug delivery system. This complexity is not intentional, but is determined by the properties that are expected from or built into the dosage form.

The unit must be involved in advising and selecting the best packaging materials for all the preparations produced by ACDIMA dependant companies which suit the climatic, economical and other conditions of the region. It is vital that the package selected adequately preserves the integrity of the product.

When selecting a package, for a new product, the unit should examine its physical and chemical characteristics, its protective needs, and its marketing requirements.

Since, almost, no container or closure available is completely nonreactive, it is necessary, for the unit, to test them both in conjunction with the preparations under investigation which are produced by ACDIMA dependant companies and which they will enclose in order to ensure that there is no physical or chemical interaction which will affect established drug standards for purity, identity, strength and quality.

The materials selected by the unit should have the following characteristics:-

1. Protect the preparation from environmental conditions.
2. Does not change product's physical, chemical and biological properties.
3. Inert with the product.
4. Adaptable to commonly employed high-speed packaging equipment.

At the same time, the determination of the optimum container and closure for a specific product is primarily a function of the unit. Tests should be conducted to

measure:-

1. Physical and chemical changes which occur in the container and closure under various conditions (e.g.) extreme heat, moisture and light.
2. Moisture and gas permeability.
3. Reactions and interactions between the drug and the container/closure at elevated temperature and moisture.
4. Physical protection provided by the container and closure against impact, motion, pressure and other stress.

It is very important for the unit to recommend the selection of the container/closure assembly of each product and the suitable package for every dosage form which provides suitable protection against the loss of chemical and pharmaceutical integrity, while meeting cost factors.

VI Quality Control Unit

The quality control unit is one of the most important units of the Regional Centre as it can be considered central quality control laboratories or a department for all ACDIMA dependant companies. It will participate in planning, establishing and monitoring the quality aspects of manufacturing operations to ACDIMA dependant companies.

The role of this unit as the central quality control laboratories will work hand in hand and side by side with the local quality control laboratories of ACDIMA dependant companies. The activities of this unit will provide an impetus for the activities of these local laboratories. It will be the main advisor and consultant to these local laboratories by keeping them always well informed about the most recent advanced techniques and the latest developments in the modern methods of instrumental analysis in the field of quality control. Also, its activities will be of great importance and help to the different national governmental quality control laboratories in the region. There must be a sort of co-operation and co-ordination between both of

them. As a matter of fact, the data and results obtained by this unit could be of great help to the national governmental quality control laboratories. After establishing a good reputation as competent, and after establishing confidence in both the medical profession and consumers, its activities together with the national quality control laboratories will be complementary.

The unit will carry out, all tests and assays required to establish whether or not drugs under investigation conform to the specifications claimed for them, also investigations on new or improved analytical methods. Developing new methods of control is of great importance especially under local conditions such as drugs used in the treatment of communicable and parasitic diseases indigenous and commonly spread in the region. Its activities will cover the whole region and not limited to one country contrary to the activities of the local quality control laboratories attached to each company. The activities will be directed to all kinds of test assays (e.g.) chemical, physical, biological (microbiological and pharmacological).

A major task for this unit is to develop common standards and specifications for the drugs commonly used in the region. The data or information obtained will be of great value in preparing a future Regional Pan Arab Pharmacopoeia or an official Formulary.

It is very important, through the efforts and activities of this unit, to work towards unification of standards and specifications of drugs either locally manufactured or imported. It is more convenient and safe for the pharmaceutical industries as well as the medical and pharmaceutical professions to follow unified standards and specifications of all existing drugs in the region.

Future programme of the unit will include the production and supply of chemical reference standards to any

interested drug company, enterprise or institute, in addition to ACDIMA dependant companies.

The unit will play a very important role as a training centre for any staff member of any of ACDIMA dependant companies as well as others.

Future plans will be expanded to include international trainee and supply of chemical reference substances not only within the region but also outside it as well.

VII Engineering Design Unit

Production of either pharmaceutical chemicals or pharmaceutical preparations is a type of industrial enterprise which requires a high degree of technical skill for sucess.

This unit carries out the process design work which starts from a sketch of process flowsheet which forms the basis for carrying out the development of the exact plant flowsheet. At the same time a certain amount of design work on equipment is carried out. The process engineer must take into account the subsequent activities of mechanical design, layout, construction...etc. This must be done at least to the extent of ensuring that the process is practical and economical.

It is the function of the engineering design unit to work out the details of the equipment, types of instruments and their specifications to be used. It has to design and develop the layout of the plant and the pipework needed to interconnect vesseles and equipment. It is the responsibility of the unit to prepare accurate engineering drawing, flowsheets, line diagrams, electrical diagrams, and layout drawings and piping diagrams. These drawings are simply the "Blueprints" of the pharmaceutical plant.

Advice and recommendations are given by the unit for the determination of the site requirements, the design

criteria, and the environmental control criteria. In the selection of the site, the soil conditions are to be considered and the seismic state of the area, the reliability of the water and electricity sources, the effect of the prevailing air and water pollutants on plant processes, and the effect of plant operations on the ecology of the community. Auxiliary sources of water and electricity sufficient to assure safety of personnel, community, equipment, processes, and products should be planned, by the unit, in case of the failure of community supplies.

VIII TRAINING UNIT

Pharmaceutical production needs a wide range of expertise. For this reason, in order to set up and adequately operate a well profitable commercial scale pharmaceutical manufacturing enterprise, it is important for the training unit to pay close attention to the professional training of the following kind of manpower:-

1. Management experts.
2. Pharmacists, chemists, biologists, pharmacognosists, phytochemists, biochemists, physical pharmacists, engineers and bioengineers.
3. Pharmaceutical analysts and quality control personnel.
4. Pharmaceutical, chemical technologists and biotechnologists.
5. Technicians.

The unit should help in the creation of training facilities and the development of manpower resources as this is very important for developing countries as the case of the Arab World. Some Arab countries where ACDIMA is active, have a scarcity or, in some cases, no qualified professional experts in such important areas as synthetic chemistry, phytochemistry and natural products, industrial pharmacy, quality control and bioengineering.

It is the major function of this unit to co-ordinate between these countries and these qualified professional experts. Also, the unit is responsible for the arrangement of training programmes offered within other developing countries outside the region which will be more relevant and appropriate to the scientific and technical environment in which the persons so trained will have to operate than training in developed countries.

The unit should make an estimate of each of ACDIMA dependant companies for its requirements of trained manpower needed for its pharmaceutical industry plan and then draw up a training programme related to the existing local facilities. Co-operation in this field can take the form of:-

1. Short visits of experts from developed countries with reputed pharmaceutical industry to assist in setting up and running the new manufacturing and quality control departments according to WHO/GMPguidelines of 1975; also for training manpower.
2. Tours by the junior staff and personnel of ACDIMA dependant companies to developed countries to study for higher specialized academic degrees or to recieve instructions in specific occupations and professional training.
3. Recommending that opportunities for updating knowledge through-short visits to big reputed pharmaceutical companies in developed countries should be made available to all specialists of ACDIMA dependant companies from time to time through out their careers. They should be encouraged to attend local and international meetings of scientific socities at which lectures are given and/or topics of interests are discussed.

To conclude, the most important thing to mention with great emphasis is that once this Centre will be inaugurated

as an important scientific institution in the Arab World, through continuity of stable steady policy, the proposed Regional Centre for Drug Research, Development and Control will be most effective and most productive.

MODEL FOR A MEDIUM SIZED QUALITY CONTROL LABORATORY ATTACHED TO ANY OF ACDIMA DEPENDENT COMPANIES, ITS ORGANIZING WORK AND STRUCTURE.

INTRODUCTION:

The quality control laboratory plays a very important role in any industry or establishment concerned with quality. This role is more significant in the field of pharmaceutical industries.

Every manufacturer should maintain a quality control department of appropriate capacity. It controls all starting materials, the quality and stability of pharmaceutical products according to the official requirements or established specifications.

The quality control laboratory carries out tests and assays required to establish whether drugs conform to the specifications claimed for them, and also carries out investigations on new or improved analytical methods. Its type and size will be determined by a number of factors (e.g.) location, facilities, nature of pharmaceutical industry and number of its products. For example, some of ACDIMA projects such as :-

1. Arab Company for Antibiotics Industries and Medical Appliances, Baghdad, Iraq, is specialized in Antibiotics production.

   The quality control department of such a project has special laboratories to carry out microbiological testing and assay for all antibiotics produced, also for testing pyrogenicity, sterility and microbial contamination.

2. Pharmaceutical Solution Industries Limitid, Jeddah, Saudi Arabia, is specialized in parenteral solutions.

The quality central department of such a project has special laboratories for chemical quality control of the products, laboratories for testing pyrogenicity, sterility and microbial contamination.

3. Gulf Pharmaceutical Company, Ras Al-Khaimah, United Arab Emirates, which produces a reasonable number of different pharmaceutical preparations covering a wide range of different dosage forms including a limited number of antibiotic preparations.

The quality control department of such a project has chemical, physical, microbiological laboratories, also laboratories for testing pyrogenicity, sterility and microbial contamination.

(A visit to this company and its quality control department will be discussed in details at the end of PART-II).

Priniciples that should determine the structure and management of a quality control laboratory in industry such as in any of ACDIMA dependant companies are :-

1. The size and structure of the laboratory, the available sources, extent and pattern of drugs manufactured.
2. Personnel requirements, in term of both trained and supporting staff.
3. The equipment necessary for the required scope of activities and the need to ensure that facilities for its maintenance are available.
4. The reagents, calibration and maintenance of instruments, and general stock keeping.
5. Methods for obtaining representative samples and the standard operational procedures to be followed for testing, record keeping and sample retention.

Code of Good Practices in the Manufacture and Quality Control of Drugs (GMP).

The quality of pharmaceutical products depends on the correct performance of all manufacturing operations and

must be built into the product during all the research, development and manufacturing process.

The quality of pharmaceutical products is dependent just as much on the conditions under which they are manufactured. The development within the pharmaceutical industry over many years of practices designed to ensure reliability and safety in manufacture and quality control has resulted in the establishment of guidlines to WHC/GMP of 1975.

Responsibilities and Duties of Quality Controller

Quality control is the responsibility of a specifically designated quality controller appointed by the management. His independence and authority are critical to the success of any policy of GMP. He must be completely free of all responsibility for actual production processes, so that objective criticism of production methods can be made should this be necessary.

The quality controller should also be equally independent of other divisions of the firm, so that all decisions on matters of quality and safety may be reached on their merit without pressure or the threat of being overruled on grounds of commercial expediency.

Satisfactory laboratory facilities must be provided under the responsibility and supervision of the quality controller to permit such testing that he may deem necessary to decide on the acceptance or rejection of raw material, materials in-process, finished products and packaging materials.

Raw materials may only be released for use in manufacture when the batch has been passed as satisfactory by the quality controller. Where in-process control is in effect, material at each stage must have the approval of the quality controller before being passed to the next

stage of the process. Similarly, the release or the rejection of each batch of finished products for packaging and for distribution must have the agreement of quality controller.

The duties of the quality controller must also include the compilation and approval of specifications for all active ingredients and excipients used in the process, for in-process controls, and for finished products. Duties also extend to examination and evaluation of the stability of each product, the retention of representative samples from production batches and the determination of shelf-life and expiry dates.

The director of quality control or quality control manager should report directly to the president or vice-president of the company, and should be on the same organizational level as the production manager. His discussions on quality should be subject to review only by the highest level of management.

In order to ensure true independence of control, samples for analysis should be taken by the quality control staff using approved sampling methods. The only allowable exception to this rule is in respect of samples for in-process control, which may be taken by the production staff, provided that sampling procedures are to be followed.

The Control Organizing Work And Structure.

Each pharmaceutical company has a control organizational structure and defined control functions which differ somewhat from one to another, yet they have one and the same objective and goal which is to assure the quality of the drug. There are basic control concepts inherent in all pharmaceutical firms. At the same time, basic control functions remain quite similar, as they are needed to fulfil the assigned responsibilities of the quality control department.

The quality control organization is usually subdivided into several departments or laboratories as follows:-

1. Specifications And Analytical Development Laboratory.

Since the quality of a finished medicament may often depend on the quality of raw materials used in manufacturing operations, the establishment of specifications for raw materials is an important function. Such specifications should be developed jointly by staff involved in research, product development and quality control. It is necessary to develop and improve specifications for the quality characteristics of the final products being manufactured.

In addition to the usual criteria such as description, identification, moisture content, pH, specific gravity, surface tension, alcohol content, hardness, disintegration, weight variation, sterility, pyrogenicity, safety and assay .....etc, special consideration should be given to the advisability of additional critical features such as dissolution rate, uniformity of individual unit content, related foreign substances, irritation, microbial content and stability.

Since many pharmaceutical products contain more than one active ingredient and since many of the inactive ingredients in a formulation may be tested qualitatively and quantitatively, it is essential that an active group of qualified scientists constantly engage in the development of new assay methods.

2. Chemical And Physical Testing Laboratories.

Every lot of every shipment of raw material and every lot of finished products which can be controlled by chemical and physical tests, should be tested in either laboratory of quality control organization. This requires a well-equipped chemical laboratory, properly staffed for the performance of a great number of chemical analyses.

It should be located in an accessible area and protected from the noise and vibration common to manufacturing operations. These laboratories personnel should be skilled in the special instrumentation of UV and IR

spectrophotometry, atomic absorption spectrophotometry, spectrophotofluorimetry, non-aqueous titrimetry, chromatography (column, gas, paper, TLC & HPLC), polorography and potentiometry.

3. Biological Testing Laboratories.

(Microbiological and Biological)

A number of finished products require biological assays, even though chemical tests, may be required for other components of the formulation. A great number of pharmaceutical products, such as parenterals, for example, require sterile and pyrogen tests before release to the market. The adequate biological testing laboratories must provide facilities for a variety of microbiological and pharmacological testing procedures.

The staff of the biological laboratories should be well trained and experienced since many of the procedures used are complex. A high degree of skill and judgement are required to perform and evaluate microbiological and pharmacological assays, as well as sterilty, pyrogenicity, bactereological, irritation, safety and acute toxicity tests.

4. Central Release Department.

It is the responsibility of the quality control organization to examine all the records resulting from the excercise of qua ity control functions throughout all steps of manufacturing and packaging operations, and for the determination of their completeness and accuracy, as well as for their maintenance and storage, for they are of great value. They provide a complete history of each lot of each product manufactured and therefore, make it possible to reconstruct the features of any package distributed in the market. This fact gives these records scientific and leagal status.

Complete and accurate records are maintained of the reciept and distribution of every lot of raw material and finished product. Further, in order to permit additional analysis, if necessary, retention samples of these products are held in local areas, under conditions of storage comparable to those to which the finished products are subjected in the market. These retention samples must be examined at regular intervals to check the physical appearance of the lots that have been distributed in the market. Additionally, another collection of rentention samples should be held for periodical chemical, physical or biological testing for stability of the active components of the preparations under study.

5. Inspection and Checking Department.

The resonsibility for inspection and sampling of every shipment of raw materials recieved, and every lot of finished products for distribution falls within the duties of quality control department. The selection of samples of raw materials and finished products is an important aspect of the quality control function. The department is also responsible for examining and checking all manufacturing, filling, packaging and labelling operation, as well as maintaining periodic examinations or the quality of inventories throughout all phases of storage, shipping and distribution. It is very important to emphasize that these responsibilities are independent of the responsibilities of production and packaging personnel.

Duties of the Quality Control Department

The quality control department should have the following principal duties as recommended by the WHO/GMP of 1975 :-

1. To prepare detailed instructions, in writing, for carrying out each test and analysis.
2. To release or reject each batch of starting material.

3. To release or reject "half-finished" products, if necessary.
4. To release or reject packaging and labelling materials and the final containers in which drugs are to be placed.
5. To release or reject each batch of finished drug that is ready for distribution.
6. To evaluate the adequacy of the conditions under which starting materials, "half-finished" products, and finished drug are stored.
7. To evaluate the quality and stability of finished drug and, when necessary, of starting materials and " half-finished" products.
8. To establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
9. To establish, and when necessary revise, control procedures and specifications, and
10. To be responsible for the examination of returned drugs to determine whether such drugs should be released, reprocessed, or destroyed. Adequate records of the disposition of such drugs should be maintained.

Model for Medium-Sized Quality Control Laboratory

Such laboratory could be a model to any of ACDIMA dependent companies.

The laboratory deals with some 1500 ± 10% full analyses per year and is equipped to provide almost all types of tests for drug identity and purity, assays for content and strength based on chemical, physical, instrumental, microbiological and pharmacological techniques, and various performance tests for dosage forms.

The laboratory has several separate components including a chemical unit, physical unit, instrumental unit, microbiological unit(e.g.)inoculation/incubation ,

biological safety tests unit (e.g.)pyrogen testing , pharmacognosy (medicinal plants and natural products)unit, and special dosage-form unit in some cases. In addition there must be special rooms for chromatography, balances, also for distillation, washing, drying and include ovens, water baths, rotatory evaporators.....etc.

Adequate offices for the director or manager, staff, and for documentation, store for samples, and for chemicals and glassware should be available.

There should be a library of reference books, manuals, and professional and scientific journals. The department should be air-conditioned with adjustable rate of humidity.

Premises.

A floor area of about 600 - 800 m^2 is required. All laboratory rooms should be supplied with running water and drainage, electrial power and gas. Climatic conditions will determine the need for air-conditioning and heating systems. The supply of water should be of adequate pressure for the use of vacuum aspirators, otherwise suitable vacuum pumps should be installed.

The building should be constructed of fire-resistent material, connecting corridors should be determined not only by working efficiency but also by safety considerations, particularly in areas where inflammable liquids or compressed gases are used or stored. Items like inflammable solvents or reagents should be stored in specially constructed stores in accordance with local fire regulations.

Each unit should be provided with rooms equipped with its specific requirements (e.g.) hooded benches in chemical unit,electrical outlets and voltage-stabilizers in balance rooms, physical and instrumental laboratories, laminar airflow equipment in microbiological unit. Rooms or labcratories for chromatographic determination mainly

for TLC should be thermostatically controlled and protected from draughts and direct sunlight. All rooms should be provided with storage cabinets for reagents, glassware, and samples, wall shelving and writing desks.

Rabbits used for pyrogen testing should be kept in a room apart from other areas of the laboratory. Both the animal house and the animal experimentation rooms should be thermostatically controlled within $\pm$ 2°C. In warmer climates, as in the case of the Arab World, the temperature is usually maintained within the range 23 - 25°C.

Technical facilities are required for microbiological unit. Such a unit should be designed and constructed of such materials that the highest standards of cleanliness and sanitation can be maintained and freedom of dust, insects and vermin is ensured.

Adequate precautions should be taken to avoid contamination of the drainage system with dangerous effluents and also to avoid airborne dissemination of pathogenic microbes and viruses.

All laboratories and units should be clean and sanitary at all times.

Animal Quarters

Quarters for animals should be designed in a manner and constructed of materials that permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care should include isolation units for quarantine of incoming animals and vermin-free food storage. Provisions should be made for animal inoculation rooms which shall be separate from the post-mortem rooms.

There should be a provision for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

Animal Care

Animals used for test purposes should show no signs of communicable disease, and shall be adequately housed at all times. They must be provided with a well balanced diet, and be kept clean and saintary.

Animals interded for use in tests should be observed daily during a quarantine period of not less than one week. In some instances it is desirable to maintain the animal rooms constantly at the optimum temperature for the particular species and test, and it may also be necessary to maintain pure strains of test animals.

It is desirable to use specific pathogen-free (SPF) animals for testing of certain biological substances.

Animals or animal carcasses should not be removed from the establishment if capable of transmitting disease. Animals that die from infection should be destroyed, preferably in an incinerator.

Staffing Manpower:

The staffing complement comprises about 35 persons including the director of the department, 6 - 8 analysts, lo - 12 laboratory technicians, 5 - 6 supporting and housekeeping staff, one storekeeper, one librarian, one bilingual typist, one arabic typist, one documentation assistant, one secetary/clerk and two messengers.

It is the recommendation of WHO/GMP of 1975 that those who are responsible for supervising the manufacture and quality control of drugs should possess the qualifications of scientific education and practical experience. Their education should include the study of an appropriate combination of :-

1. Pharmaceutical chemistry, analytical chemistry,biochemistry....etc.
2. Chemical engineering
3. Microbiology

4. Pharmacology and toxicology
5. Pharmaceutical sciences and technology.
6. Physiology and histology.
7. Other related sciences.

They should also have the adequate practical experience in the quality control of drugs. In order to gain such experience, a preparatory period may be required, during which they should excercise their duties under professional guidance. Their scientific education and practical experience should be such as to enable them to excercise independent professional judgement, based on the application of scientific principles and understanding of the practical problems encountered in the quality control of drugs.

They should preferably not have any interests outside the manufacturer's organization that :-

1. Prevent or restrict their devoting the necessary time to their assigned responsibilities.
2. May be considered to entail a conflict of financial interest.
3. They should be given full authority and the facilities necessary to carryout their duties effectively.

All personnel should be motivated towards the establishment and maintenance of high-quality standard.

The director of the laboratory should be a pharmacy graduate preferably with graduate advanced studies in pharmaceutical analysis or related subjects. Analysts are preferably to be also pharmacy graduates specialized in analytical chemistry and instrumentation, physical pharmacy, biochemistry, microbiology and pharmacology, as appropriate to their assigned responsibilities.

However, in many laboratories, pharmacological testing is restricted to routine tests for pyrogens and acute toxicity which would not be rewarding to a graduate pharmacologist. A degree in biological sciences might be appropriate for an analyst with responsibility for both microbiology and pharmacology.

In selecting personnel for the biological units of the laboratory, it must be recognized that quantitative aspects are of fundamental importance. An appreciation of mathematical and statistical principles is essential.

Trained technicians are desirable, otherwise provision must be made for in-service training in the laboratory.

Professional high ethical standards are mandatory for the director of the laboratory and the analysts.

Equipment:

The general laboratory equipment, together with items required in the chemical and physical units are listed.

Major items of equipment required for the instrumental laboratory and for testing of dosage forms, as well as the equipment required for microbiological and pharmacological units are also listed.

Water demineralizers and distillation stills are always needed.

LIST OF EQUIPMENT, INSTRUMENTS AND APPARATUS.

Chemical and Physical Unit

No.	General	Price US $
1	Microbalance	1500
3	Analytical balance	500
3	Laboratory balance	300
1	Refrigerator (with freezer compartment)	1500
1	Water distillation still	3000
1	Water deionizing equipment	10000
1	Drying oven	500
1	Vacuum oven	1000
1	Oil vacuum pump	300
10	Water vacuum pump	200
1	Muffle furnace	2500
6	Heating plates with magnetic stirrers	1000
3	Mechanical stirrers	300
3	Vacuum rotary evaporator	2000
10	Drying piston	100
6	Water bath (electrical)	1000
3	Automatic titrimeter	1000
1	Kjeldahl apparatus and micro	200
1	Mechanical shaker with adjustable rate of shaking	300
1	Centrifuge (table model)	1000
1	Electric melting point apparatus	100
1	Electric freezing point apparatus	100
1	Equipment for TLC including	
	-spreader	
	-spotting equipment	
	-developing chambers	
	-spraying bottles	
	-UV viewing lamps	
	-densitometer	20000
1	Equipment for paper chromatography	500

No.	General	Price US $
6	Columns for chromatography	100
1	Ultrasonic cleaner	500
1	Vortex mixers	500
5	Heating mantles for flasks	1000
6	Variable transformers	500
1	Micrometer calipers	250
1	Glove box	100
1	Sieves with shaker (set)	700
1	Microscope	500
3	Blender	500
12	Apparatus for limit test for arsenic (B.P. & U.S.P.)	150
1	Platinum crucible and dish	1500
3	Vibrospatula	200
	Total:	55400

No.	Major	Price US $
1	IR spectrophotometer(Recording, grating, and acessories)	30000
1	UV/visible recording spectrophotometer, computer controlled	30000
1	UV/visible spectrophotometer	5000
1	Visible spectrophotometer (spectronic type)	1000
1	Gas chromatograph	6000
1	HPLC chromatograph	10000
1	Polarimeter (manual)	300
1	Photoelectric polarimeter	500
1	Refractometer	150
1	pH-meter with electrodes	1000
1	Anionic and cationic selective electrodes (set)	2000
1	Disintegration test equipment	2000
1	Dissolution test equipment	2000
1	Karl-Fisher titrator	1000
6	Azeotropic distillation set	500
3	Oxygen flask combustion apparatus	1500
2	Hydrometer	200
1	Viscometer	500
1	Ice machine	500
1	Solvent recovery apparatus	250
1	Atomic Absorption spectrophotometer	7000
1	Flame photometer	2000
1	Osmometer	5000
1	Fluorometer (filter)	1000
1	Hardness tester	1000
1	Dehumidifier	500
1	Electrophoresis apparatus	5000
1	Friability tester	500
	Total:	116400

Microbiology Unit

No		Price US $
1	Autoclave	1000
1	Bacteriological microscope	1000
2	Incubator	3000
1	Centrifuge with refrigeration	10000
1	Membrane filter assembly for sterility tests	700
1	Colony counter with magnifier	200
1	Laminar flow bench	4000
1	Hot-air sterilizer	500
1	Spectrophotometer, visible (simple model)	1000
1	Nephelometer and turbidimeter	800
1	Refrigerator	2000
1	Deep freezer	2000
1	Large-plate microbiological assay equipment, including zone reader and recorder	5000
1	pH-meter with electrodes	1000
3	Blender	500
5	Zone magnifier for petri dishes	100
1	Zone projector for large plates	500
1	Cleaning machines for glassware, especially one for cleaning pipettes	200
2	Water bath (thermostatically controlled)	1000
1	Mechanical shaker with adjustable rate of shaking	300
6	Anaerobic jar	300
	Total:	35100

Pharmacology Unit

No		Price
1	Isolated organ bath	800
1	Polygraph	5000
1	Artificial respiratory pump (large and small animals)	600
1	Physiograph with strain guage transducer	10000
3	Mercury manometers (large and small)	100
1	Operation table (large animals)	4000
1	Operation table (small animals)	1000
1	Slow infusion pump	600
1	Electric balance	1000
1	Centrifuge-small bench	1000
1	Mechanical shaker with adjustable rate of shaking	200
1	Photoelectric colorimeter	1000
1	Hot air oven	10
1	Incubator	1500
1	Temperature recording apparatus for pyrogen testing for rabbits	3000
1	Microscope	500
3	Stop watch	200
3	Anaesthetic boxes for cats and rabbits	300
1	Small animal weighing cages	100
1	Balance	100
1	Refrigerator	2000
1	Guillotine	100
	Syringes	100
	Polyethylene tubes	100
	Total:	34400

Pharmacognosy Unit

Medicinal Plants and Natural Products

No		Price US $
1	Balance	100
1	Hammer mill with sieving arrangments	3000
3	Percolator (glass)	400
3	Percolator (Stainless steel)	1500
1	Circulation pump	300
1	Vacuum pump	300
1	pH-meter with electrodes	1000
1	Centrifuge table model	1000
6	Continuous extraction apparatus (Soxhlet apparatus)	2000
1	Vacuum oven	1000
1	Muffle furnace	2500
1	Microscope	500
1	Nuclear magnetic resonance (NMR)	40000
		53600

Total price for all equipment, instruments and apparatus:-

55400
116400
35100
34400
53600

Total : 294900 US $

Visit to Gulf Pharmaceutical Industries "JULPHAR" Ras Al-Khaimah, United Arab Emirates

The visit was completed on Saturday 27th and Sunday 28th, October 1984. The Company is one of ACDIMA dependent companies having a medium sizedquality control department. It can be taken as a good representative model example.

Staff met:-

1. Dr.Saad F. Khayat	Managing director
2. Dr.Mostafa Hassanein	Quality control manager
3. Dr.Magdy Salama	Deputy production manager
4. Dr.Fayez Haroon	Store and quarantine officer
5. Dr. O. Larsson	Development manager
6. Dr.S. Black	Technical director
7. Dr.Miss Wagdiah	Packaging manager

The factory is located in Ras Al-khaimah on a fairly large area and consists of 2 main buildings. They are:-

I A. Administration office which includes managing director, marketing, financial, public relations....etc(1st floor)

B. The 2nd floor includes the main library and modern laboratories for quality control. They are

1. Chemical laboratory
2. Physical laboratory
3. Microbiological laboratory
4. Instrumental laboratory
5. Chromatography laboratory (TLC & HPLC)
6. Balance room
7. Store for already analyzed raw materials, final pharmaceutical preparations and reference samples.

The other wing of the 2nd floor includes laboratories for development of the different dosage forms.

II. It includes production, packaging, quarantine and store.

Everyone was very helpful and supplied all the necessary information. There is real harmony and co-ordination between departments from one side and top administration from other side

Observations

1. Personnel

Those responsible for supervising the manufacture and quality control, and also for development possess the qualifications of scientific education and practical experience (pharmacists, chemists, chemical engineers, technicians.....etc). There is an adequate number of trained professionals, also an adequate number of technically trained personnel available to carry out the manufacturing and quality control operations in accordance with established procedures and specifications. Every manager is given full authority and the facilities necessary to cary out his duties effectively.

2. Premises

Premises are suitable regarding to:-

a- Compatibility of other manufacturing operations that may be carried out in the same or adjacent premises.

b- Buildings are designed and constructed to prevent the entry of animals and insects and permit easy cleaning or disinfection.

C- Lighting and air conditioning are satisfactory and controlled in order to avoid any adverse effect during the process of manufacture and storage, also to assure the accuracy/and functioning of laboratory instruments.

d- Working spaces are adequate minimizing the risk of confusion between different drugs or their components, the risk of the possibility of cross-contamination by other drugs or substances, omission of any manufacturing or control step.

e- Storage areas have adequate space, suitable lighting, and equipped to allow dry, clean and orderly placement of stored materials and products under controlled temperature and humidity. They are provided with modern shelves and electrical doors.

f- Quarantine is suitably separated from the store.

3. Equipment

Manufacturing equipment is new, ultra modern, designed, placed and suitably maintained for their intended use.

4. Sanitation

Manufacturing premises are maintained in accordance with the sanitary standards. There/is enough personnel assigned to and responsible for cleaning operations.

Eating, smoking and unhygienic practices are strictly prohibited and not permitted by all means in manufacturing areas.

Well-ventilated toilet facilities, also facilities for hand washing and rooms for changing clothes are available near working areas for use of manufacturing personnel.

5. Starting Materials

Records of the starting materials concerning the supplies, date of receipt, date of analysis, date of release by the quality control department are followed.

6. Manufacturing Operations

Operations are carried out under the supervision of qualified professionals. Contents of vessels and containers used in the manufacture and storage between manufacturing stages are identified by clear labels.

Documents relating to manufacturing procedures contain all the necessary informations including the detailed instructions and precautions to be taken in manufacture

and storage, also the description of all necessary quality control tests and analysis to be carried out during each stage of manufacture.

Batch manufacturing records provide a complete account of the manufacturing history of each batch and show all the necessary informations.

7. Labelling and Packaging.

A modern system of labelling and packaging is observed. All the labelling and packaging materials, including leaflets are stored and handled in order to ensure that labels, packaging materials and leaflets relating to the different products do not become intermixed.

8. The Quality Control System .

The quality control department is supervised by a suitably qualified pharmacist directly responsible to the management and independent of other departments. The department controls all starting materials, monitors the quality aspects of manufacturing operations, and controls the quality and stability of the produced dosage forms.

The department takes samples of starting materials and finished products according to the established procedures and maintains adequate analytical records concerning the examination of all samples taken.

All laboratories are equipped with ultra modern equipments and instruments necessary for the analysis of all raw materials, finished drugs, stability tests.....etc.

9. Self-inspection.

In order to maintain strict adherence to all manufacturing procedures and prescribed controls, the company applies the system of self-inspection through the quality control department.

10. Distribution Records.

Adequate records of the distributed finished batches are maintained in order to facilitate prompt and complete recall of the batch if necessary.

11. Conclusion

From observations during these two complete days of visiting the company, and discussions with all the managers and other professionals and personnel, and from experience of what had been observed in international drug companies in Western and Eastern Europe, USA and others in Arab World, "JULPHAR" stands and is considered as a modern drug company in the region.

The quality control laboratories of this company can play an important role as a training Centre for a limited number of two or three junior trainees.

The company certainly adheres to all the rules, applies and follows the WHO/Good Practices in the Manufacture and Quality Control of Drugs (GMP) of 1975.

It is hoped that this company would be encouraged by all possible means especially as it is established in an area of the world where the pharmaceutical industry did not exist before. At the same time, such an infant company like "JULPHAR" with such good performance deserves a great deal of admiration, encouragement and congratulations.

POSSIBILITY OF USING PRODUCTS FROM THE PETROCHEMICAL INDUSTRY AS RAW MATERIALS IN THE PHARMACEUTICAL INDUSTRY IN THE MEMBER COUNTRIES OF THE ARAB COMPANY FOR DRUG INDUSTRIES AND MEDICAL APPLIANCES (ACDIMA).

INTRODUCTION:

Petrochemical industry is considered to be one of the most important modern industries and the base for industrial development. This is clear as there is a direct relationship between this kind of industry and the other sectors of national economy. There are many petrochemical products used in agriculture such as fertilzers and insecticides; in textiles and synthetic fibers; in plastic, rubber, packaging and construction industry. None of the Arab countries where ACDIMA is active is using any petrochemical products in their pharmaceutical industries.

Importance of Petrochemical Industry and its Characteristics

The Arab countries have realized the importance of the petrochemical industry in developing other industries and also their economy. They started since the last decade in planning and establishing a good number of petrochemical projects which are considered some of the largest in the world. The reason for these important decisions are as follows:-

1. High revenues of investment in the field of petrochemical industry (e.g.) one kilogram of crude oil is sold at about 15 US cents, while one kilogram of petrochemicals is sold at about 50 to 135 US cents (prices of 1984). Some studies reveal that the revenues for the total capital in this industry can reach easily up to 28% (prices of 1984).
2. To develop this kind of industry for the purpose of export, in addition to local consumption, is to

diversify the foreign commerce policy of Arab countries which produce oil in excess quantities. For example, Western Europe is the main market for the Arab crude oil, but will not be the main market for petrochemicals as most of Western European countries manufacture their own. These Arab countries have to look for other markets in Asia and Africa to sell the excess of their products. This diversity in export policy and foreign commerce is very important as it will not make the economy of these Arab countries totally dependent on the Western European market for selling their crude. The economy of these Arab countries and the rest of the region would thus stand to benefit.

3. The capacities of Arab petrochemical projects are presently exceeding the demands of Arab market to a great extent and very soon, within a few months, only Saudi Arabia, a member country of ACDIMA, will become one of the World's leading exporters of petrochemical products.

Two gleaming industrial cities, one at the Gulf port of Jubail will begin large-scale production in early 1985, and the other complex at Yanbu on the Red Sea will begin production in early Spring of 1985. When they will reach full capacity by the end of 1985, Saudi Arabia expects to have between 4 and 7% of the world market of petrochemicals. This share may grow larger as the Saudis have an unbeatable advantage which is that their petrochemicals are made from natural gas that used to be flared as a waste product. Therefore, they may make chemicals for roughly 1/7 of the cost of other rivals such as the United States or Western Europe.

4. A clear advantage in petrochemical industries is that each stage of production is easily characterized, although it is difficult to apply a method which includes all petrochemical products. However, it is possible to classify

this industry into 3 important classes.

a- Basic Products.

b- Intermediate products.

c- Final products.

Basic products include olefines (ethylene, propylene and butadiene), aromatics(benzene, toluene and p-xylene) and methanol.

The chain of production which starts from the basic products to the final products include ethylene, propylene as basic materials in the plastic industry, the aromatics in synthetic fibers, the butadiene in the rubber industry, and finally the methanol after converting it to formaldehyde in the resin industry.

These processes in the petrochemical industries lead directly to the increase of value of crude oil.

Development of Petrochemical Industries in the Arab World

Petrochemical industries started in the Arab World in the sixties when Egypt started production of ammonia. Then Kuwait started establishing a petrochemical complex in 1966. But the real petrochemical industries started in the Arab World since the mid seventies when some Arab countries started planning and establishing a large number of petrochemical projects.

The number of projects that already exist, nowadays, or under construction in Arab World including member countries of ACDIMA, for the production of basic olefinic, aromatics and methanol are 21 projects having a total production capacity of 5610 (thousand tons) yearly devided as follows:-

Ethylene	2670	thousand tons	48%
Propylene	165	" "	3%
Butadiene	65	" "	1%
Methanol	2330	" "	41%
Aromatics(benzene, toluene and p-xylene)	400	" "	7%

From the above data, it is clear that production of basic petrochemicals/in the Arab World is concentrated on ethylene and methanol which represent 89% of total production capacity. Propylene, butadiene and aromatics represent only 11%. This shows that Arab projects did not give enough priority to basic petrochemicals which are used mainly and on large scale in synthetic fibers industries, rubber and plastic industries, in addition to pharmaceutical industries.

The number of projects that already exist and those under construction in Arab World including member countries of ACDIMA for the production of intermediate petrochemicals are 17 projects with total production capacity of 1882 (thousand tons) yearly and include the following intermediate petrochemicals :-

Ethylene dichloride, vinyl chloride, ethylene glycol, formaldehyde, melamin, styrene and dimethyl triphthalate.

The production capacity for the intermediate petrochemicals (e.g.) ethylene dichloride, vinyl chloride, ethylene glycol and styrene is about 93% of the total production capacity for the intermediate petrochemicals as seen from the following:-(*)

Ethylene glycol	550	(thousand tons)	29%
Styrene	470	" "	25%
Ethylene dichloride	454	" "	24%
Vinyl chloride	287	" "	15%
Other materials	121	" "	7%

The number of projects which exist and those under construction in the Arab World including member countries of ACDIMA for the production of final petrochemicals are 34 projects with total production capacity of 1785 (thousand tons) yearly and include:-

a- Final petrochemicals used in plastic industry which represents 87% of total production capacity.

b- Final petrochemicals used in synthetic fibers which represent 2% of total production capacity.
c. Final petrochemicals used in detergent industry which represent 5% of total production capacity.
d. Final petrochemicals used in paint industry which represent 1% of total production capacity.
e. Final petrochemicals used in rubber industry which represent 5% of total production capacity.

The following table shows the production of Arab World including member countries of ACDIMA of petrochemicals in 1981 and the expected production in 1985, 1990 and 2000. The data were presented from companies operating in the Arab World and also from different Arab authorities. All agree on one assumption that production between 1990 and 2000 will be more or less the same.

Arab Petrochemical Production In 1981 And Expected Production In 1985,1990 And 2000

(in 1000 tons)

Petrochemical Products	Production 1981	Expected Production 1985	1990	2000
Ethylene (b)	185.6	1343	2600	2600
Propylene (b)	-	n.a	165	165
Butadiene (b)	-	n.a	45	45
Methanol (b)	39	1650	2330	2330
p-xylene (b)	-	30	38	38
Toluene (i)	-	4	5	5
Ethylene dichloride (i)	-	118	454	454
Vinyl chloride (i)	n.a	190	283	283
Ethylene glycol (i)	-	400-500	550	550
Formaldehyde (i)	n.a	16.5	16.5	16.5
Melamine (f)	n.a	15	25	25
Dimethyl terephthalate (i)	-	n.a	60	60
Polyethylene (L.density)(f)	185.6	753-830	1038	1043
Polyethylene(H.density)(f)	-	85-121	161	161
Polyvinyl chloride (f)	27	173	257	260
Polypropylene(f)	-	n.a	50	50
Styrene (i)	-	37	470	470
Polystyrene (f)	-	-	-	-
Polyurethane(soft sponge)(f)	-	n.a	10	10
Toleune diisocyanate(f)	-	-	-	-
Polyester resins (f)	12	14	14	14
Polyethylene terephthalate(f) (polyester fibers)	n.a	26.5	26.5	26.5
Polycabroamide(f)(Nylon Fibers)	n.a	4	4	4
Polyacrylonitrile (f) (acrylic Fibers)	-	-	-	-
Alkylbenzene (f)	-	n.a	90	90
Polyvinyl acetate (f)	8.3	14	14	14
Polybutadiene (f)	-	n.a	30	30
Polystyrene butadiene (f)	-	n.a	60	60

(b) basic (i) intermediate (f) Final (n.a) not available

Arab World including member countries of ACDIMA

Source:
Arab Industrial Development Organization, basic study submitted to the 6th Conference of Industrial Development of Arab Countries, Damascus, October 20-25, 1984.

At the same time, the previous study reveals the expected excess in the production of petrochemical products in the Arab World, and also projects under construction in relation to basic and intermediate petrochemicals. It is as follows[1]:-

Petrochemical Products	Thousand tons		
	1985	1990	2000
Polyethylene (L.density)	510	562	123
Ethylene dichloride	118	454	454
Ethylene glycol	490	540	540
Propylene	-	99	99
Styrene	-	445	445
Benzene (C_6H_6)	72	90	90
Xylene (mixture)	197	247	247
Methanol	1150	2330	2330
Ethylene	305	305	365

[1] Same previous source

Inorganic Chemicals Available in Arab World, including member countries of ACDIMA, from petrochemical operations.

Chlorine, bromine, sodium hypochlorite, ammonia, ammonium sulphate, caustic soda, potassium salts, sulfur, sulfuric acid, hydrochloric acid, nitric acid, oleum (So_3 and H_2So_4).

Besides there are ammonia operating projects in some countries namely Iraq, Jordan, Kuwait, Libya, Saudi Arabia, Syria and United Arab Emirates.

P.S. At the same time urea and guanidine, two organic compounds are available in abundant quantities in the Arab World including member countries of ACDIMA, from petrochemical operations.

Problems facing petrochemical industries in the Arab World including member countries of ACDIMA

Most petrochemical industries in the Arab World are still in the early stages either in planning, establishment or production. Some of these projects are still in the early stages of production. Many difficulties and problems are facing this kind of industry. Some of them are daily problems and need quick action, and some need basic or radical solutions. The most important problems facing the petrochemical industries in the Arab World, nowadays and in the near future are summarized as follows:-

A- Research and Development

Petrochemical industries are one of the few modern sophisticated industries in which its development depends to a large extent on scientific research and advanced development which aims to:-

(1) Reduce the cost of production through

a- Production of petrochemicals from available cheap raw or starting materials.

b- Use of new catalysts in order to avoid or lessen any formation of undesirable by-products during production.

c- Production of petrochemicals at low temperature and pressure in order to save energy and costs.

d- Completion of reactions in shorter time in order to increase production capacity.

e- Establish larger production units in order to cut expenses.

f- Apply advanced automation in production in order to reduce labor expenses.

(2) Improve products qualities and manufacturing various petrochemical products through reaction with additives.

It is a fact that until now, this kind of research and development is not available in the sector of

petrochemical industries in the Arab World including member countries of ACDIMA. They will certainly depend for good many years to come on American, European and Japanese advanced technology.

B- Quality of labor production

The Arab World, in general, suffers from a scarcity of skilled labor capable to operate the huge petrochemical complexes. Quality of workmanship needs to be improved. The most important result of this could be the production of substandard products which limit competition with other foreign products. Recruiting expatriate labor, personnel, technicians or experts will increase the cost of production.

C- Pollution

There is always a strong fear that petrochemical industries can cause environmental pollution especially if they are in urban areas or populated areas.

D- Maintenance

Maintenance for such complicated equipment as the case of petrochemical equipment needs highly skilled experts and the continuous availability of the necessary spare parts as well. These are two serious problems usually facing developing countries in the case of Arab World.

E- Market Capacity

The market capacity of the Arab World is very limited to consume all their production of the petrochemical industries. They must be marketed in the international markets such as Africa and Asia on a competitive basis.

Petrochemical Products Available in Large Quantities in the Arab World including member countries of ACDIMA

A. Methanol

The uses of methanol for example to produce:-

1- Acetic Acid

2- Petroproteins to a lesser extent

3- Gasoline substitute

This should cause a significant increase in its consumption. The possibility of producing large quantities of methanol at low cost in Arab producing oil countries is through natural gas. This certainly will cause major changes in the volume of trade towards consuming areas. It is estimated that future expected production in the Arab World will reach 2330 (thousand tons) from 1990 untill the end of this century. This figure may become greater if policies to substitute methanol for motor fuels are implemented sooner than expected. With the large amount of methanol available in the Arab World, it may be preferable to diversify outlets rather than to limit them to the export of methanol only. Furthermore, during the next decade, different uses and local demand for methanol should certainly emerge, thus bringing about different industrial production. One of these industrial productions will be in the field of fine pharmaceutical chemicals.

1- Acetic Acid.

Production of acetic acid will be mainly geared towards satisfying the regional demand. It plays a very important role in synthesis of analgesics mainly acetyl salicylic acid.

2- Single Cell Protein "SCP"

Most economic evaluations show that, until now, it is more economically feasible to import soya beans and

even fish meal than to set up a "SCP" plant.

However, in case of a local market for the protein-short Arab countries, this would represent considerable foreign currency savings.

The production of hydrogen-based single cell proteins, although this industry is still in its infancy, is considered one of the most promising routes for achieving these aims. Until now, they have been confined to uses such as milk substitutes in Europe, also in livestock industries in many countries.

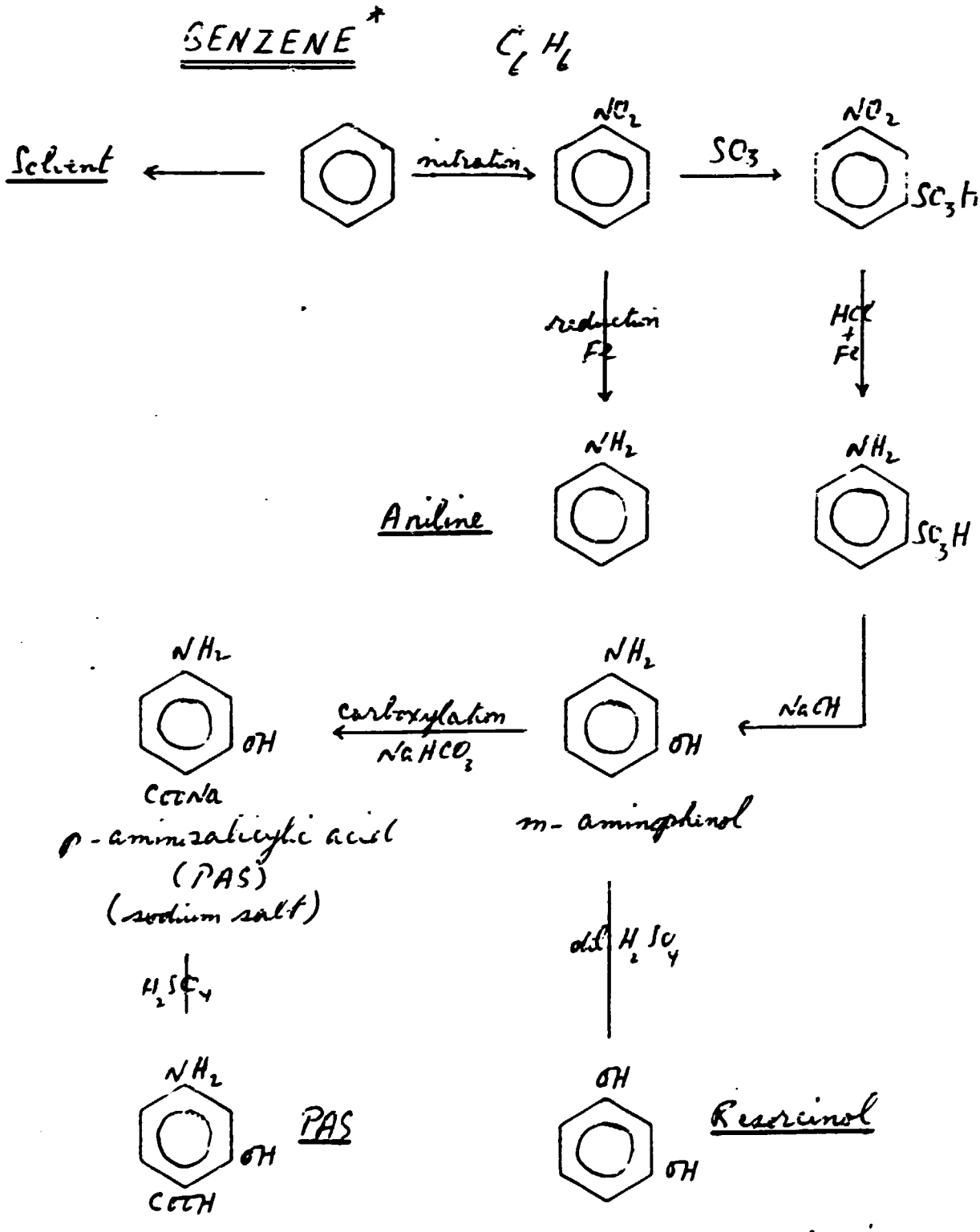
The feasibility of establishing an indigenous synthetic protein industry is at present actively studied in the Arab World as has been seen from various OPEC Synthetic Protein Expert Group meetings held since the beginning of this decade.

An Arab -based "SCP" plant from methanol industry, and sponsored by ACDIMA could be competitive with plants located in industrialized developed countries due to the availability of methanol at cheaper prices in the Arab World.

B. Formaldehyde

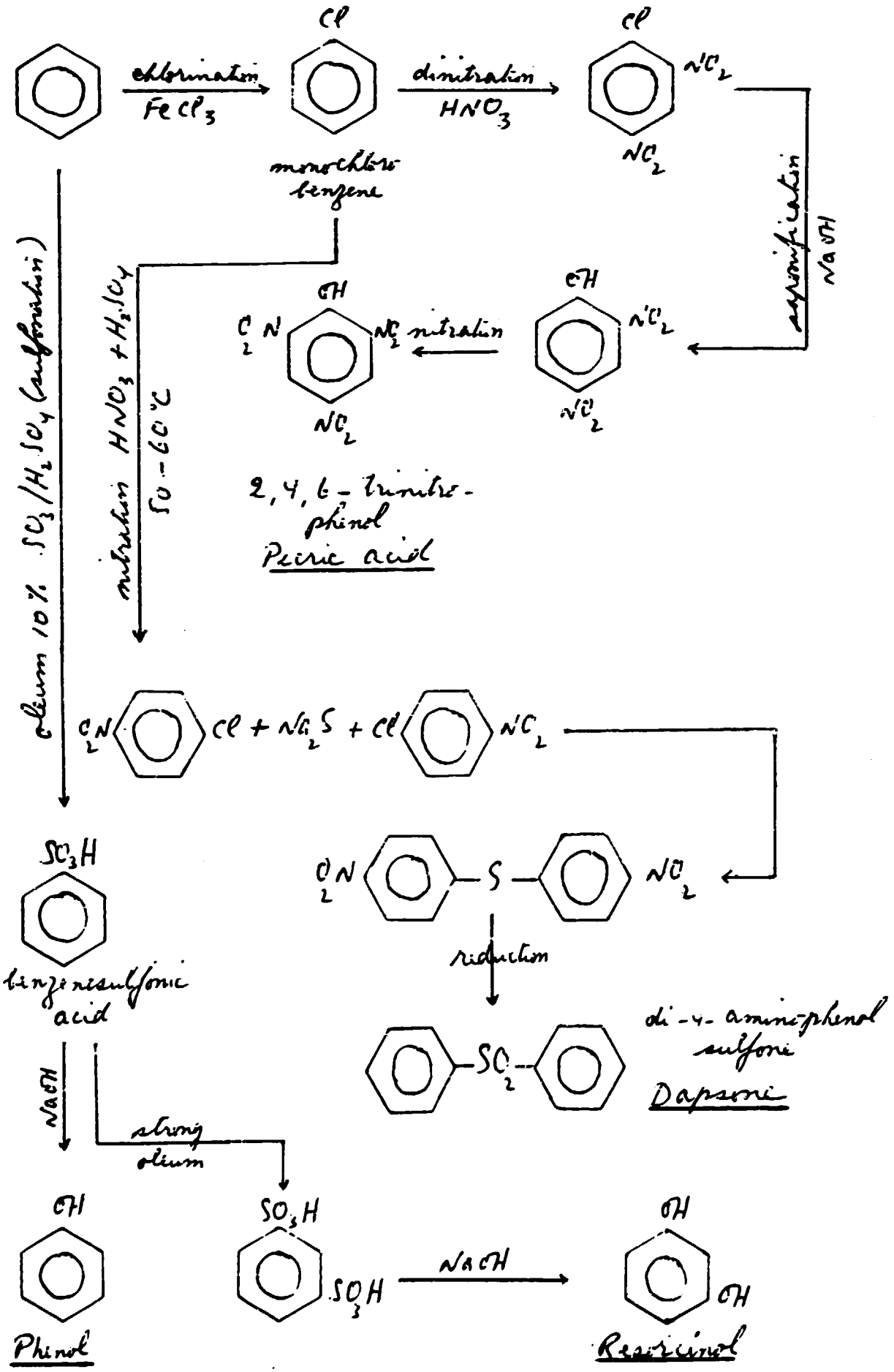
Formaldehyde is the most commonly produced and consumed methanol derivative. Its development is closely connected with the building industry, in addition it has a wide use in pharmaceutical industries.

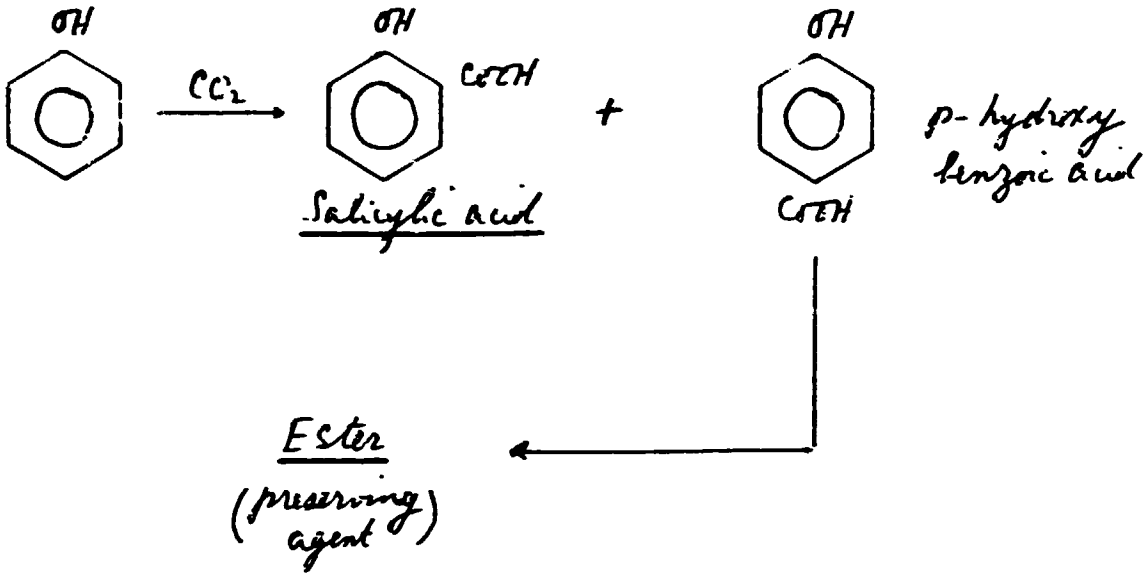
Possible Routes for Production of Pharmaceutical Chemicals

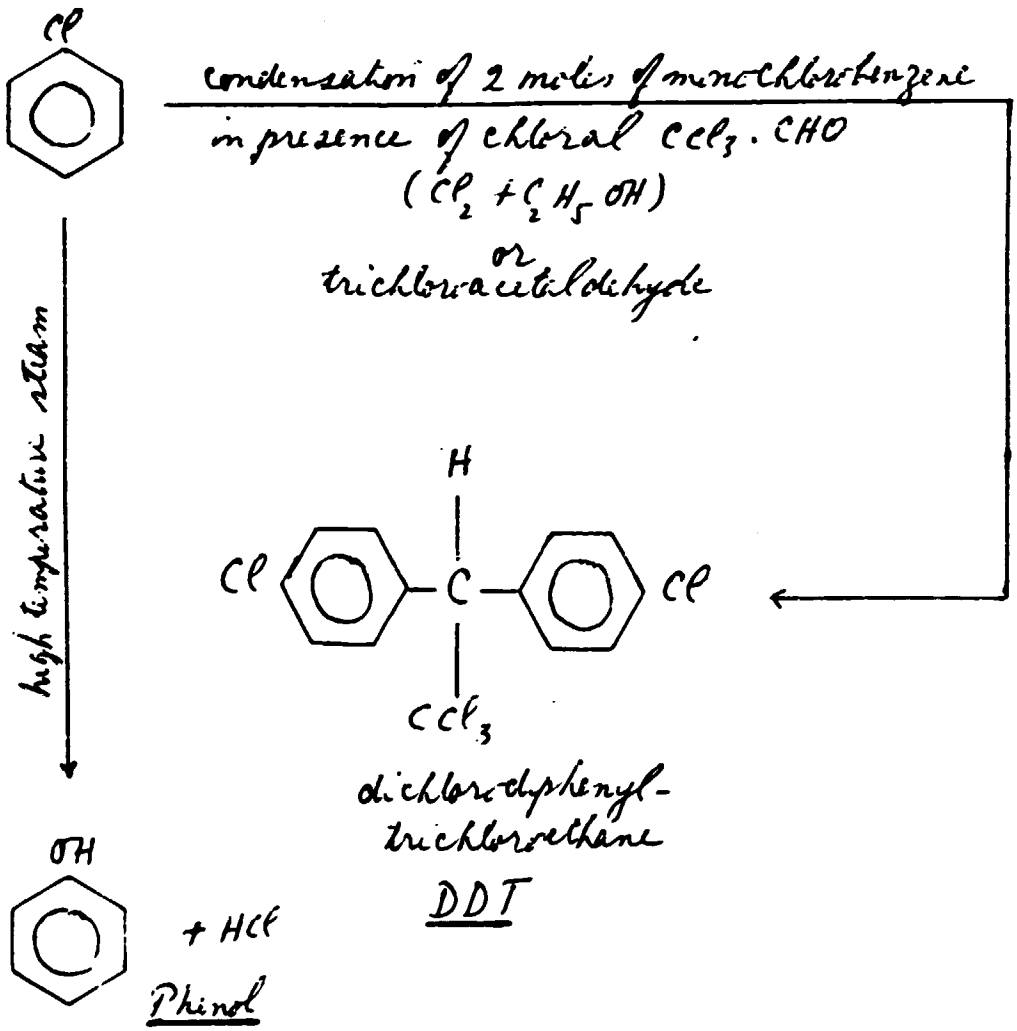


* excess of Benzene production as mentioned previously in the report is as follows (in thousand tons)

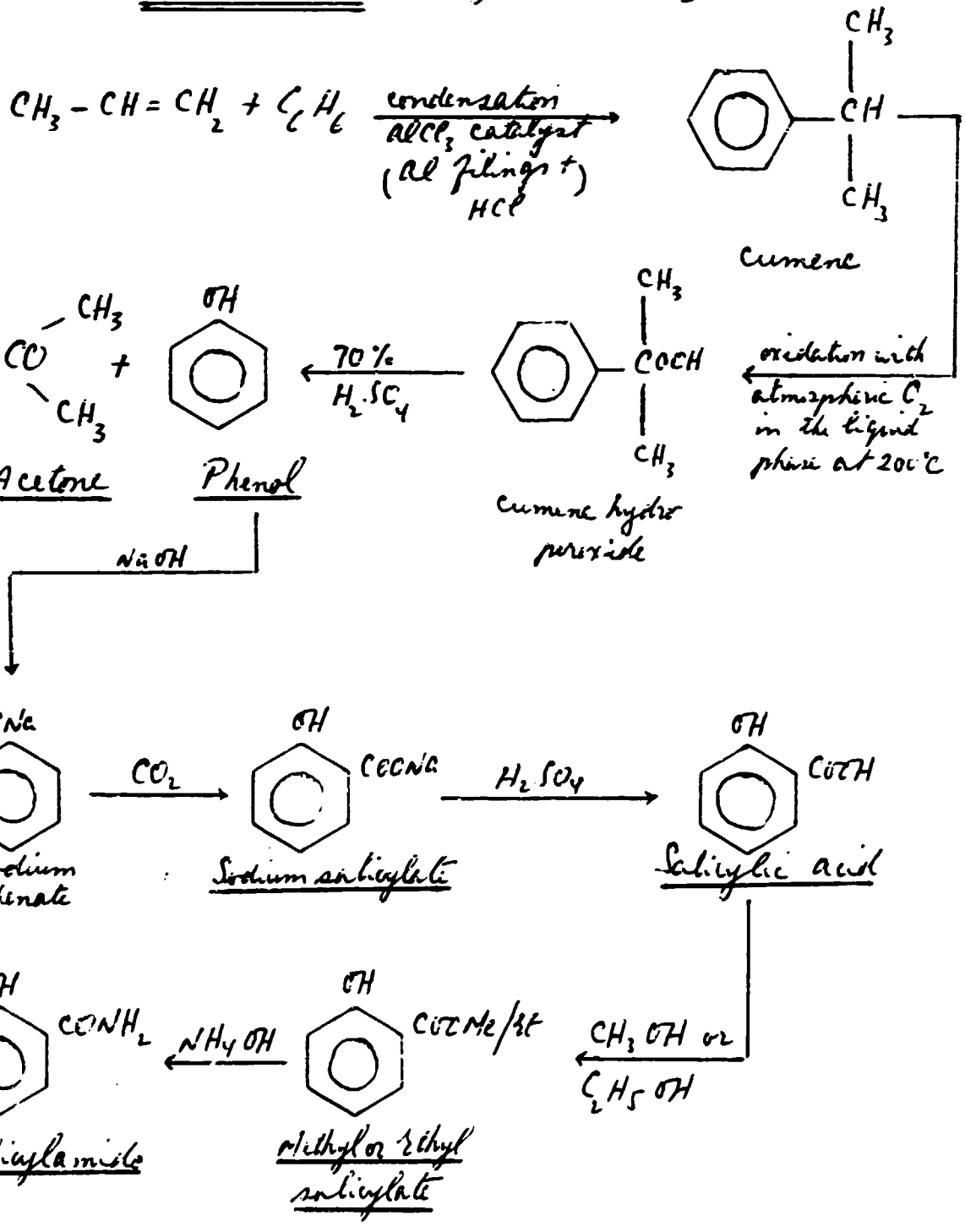
72 in 1985, 90 in 1990 and in 2000.

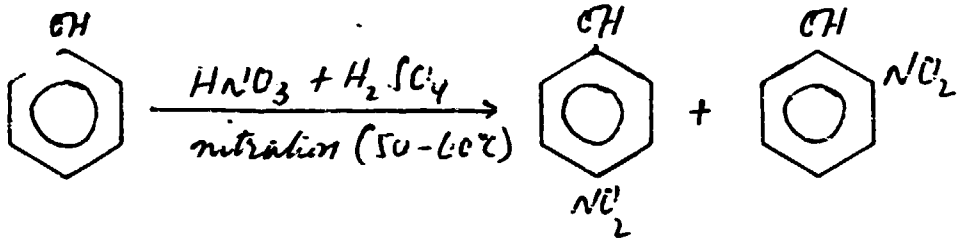

Cl
chlorination
FeCl3
dinitration
HNO3
NO2
NO2
monochloro benzene
saponification
NaOH
OH
NO2
NO2
nitration
NO2
NO2
2,4,6 - trinitro - phenol
Picric acid
nitration HNO3 + H2SO4
50 - 60°C
oleum 10% SO3/H2SO4 (sulfonation)
Cl + Na2S + Cl
NO2
SO3H
benzenesulfonic acid
reduction
di - 4 - aminophenol sulfone
Dapsone
NaOH
strong oleum
OH
SO3H
SO3H
NaOH
OH
OH
Phenol
Resorcinol

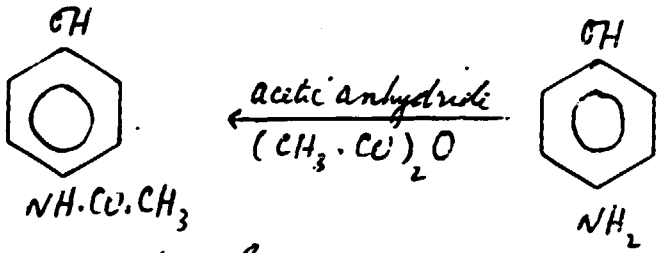

OH
CO_2
OH
COOH
Salicylic acid
+
OH
COOH
p-hydroxy benzoic acid
Ester
(preserving agent)


Cl
condensation of 2 moles of monochlorobenzene
in presence of chloral $CCl_3.CHO$
($Cl_2 + C_2H_5OH$)
or
trichloroacetaldehyde
high temperature atm
H
Cl
C
Cl
CCl_3
dichlorodiphenyl-trichloroethane
DDT
OH
+ HCl
Phinol

PROPYLENE $CH_3 - CH = CH_2$







Paracetamol

(p - acetamidophenol)

ETHYLENE $CH_2 = CH_2$

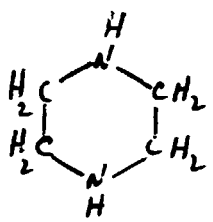
$CH_2 = CH_2$ ⟶ pure ethylene for medical use must be free from acetylene, aldehydes, hydrogen sulfide, phosphine and carbon monoxide, all traces of acids and alkalies.

Anesthetic

$CH_2 = CH_2 + Cl_2$ —(chlorides of Fe, Cu, Sb (catalyst))→ $CH_2Cl - CH_2Cl$

ethylene chloride

—(alcoholic ammonia; Hofmann amine synthesis)→



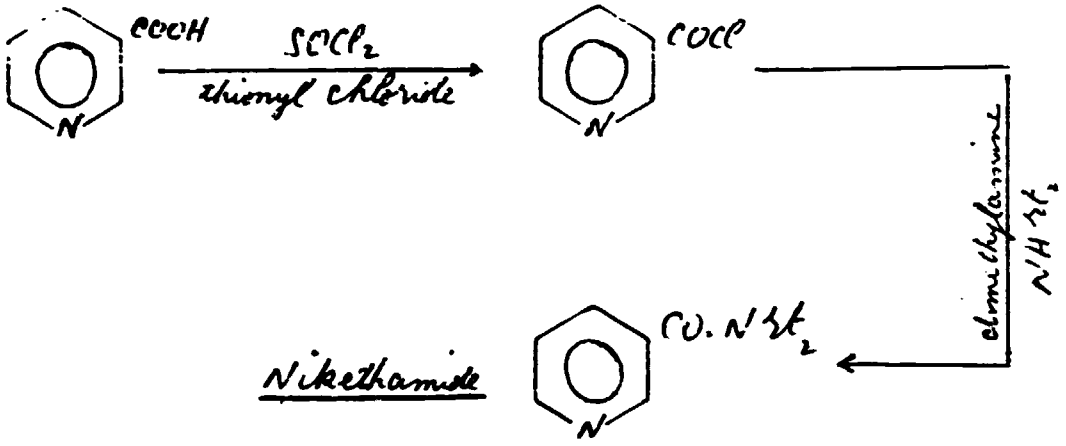
Piperazine

$CH_2 = CH_2$ —(direct oxidation; palladium copper chloride at 102 °C (catalyst))→ CH_3CHO acetaldehyde —(polymerization)→ $(C_2H_4O)_3$ paraldehyde

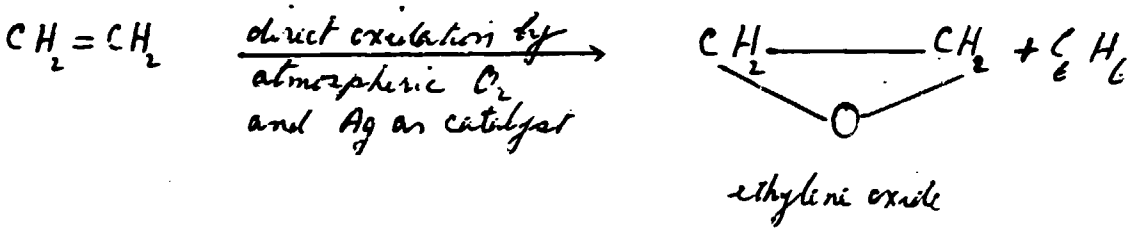
—(ammonia)→ 2-methyl 5-ethyl pyridine —(HNO_3)→

Nicotinic acid —(ammonia at 320°C)→

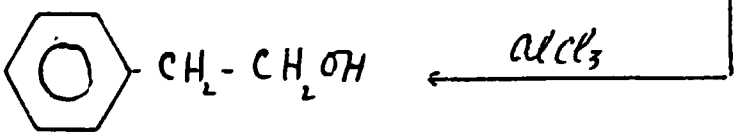
Nicotinamide



Nikethamide

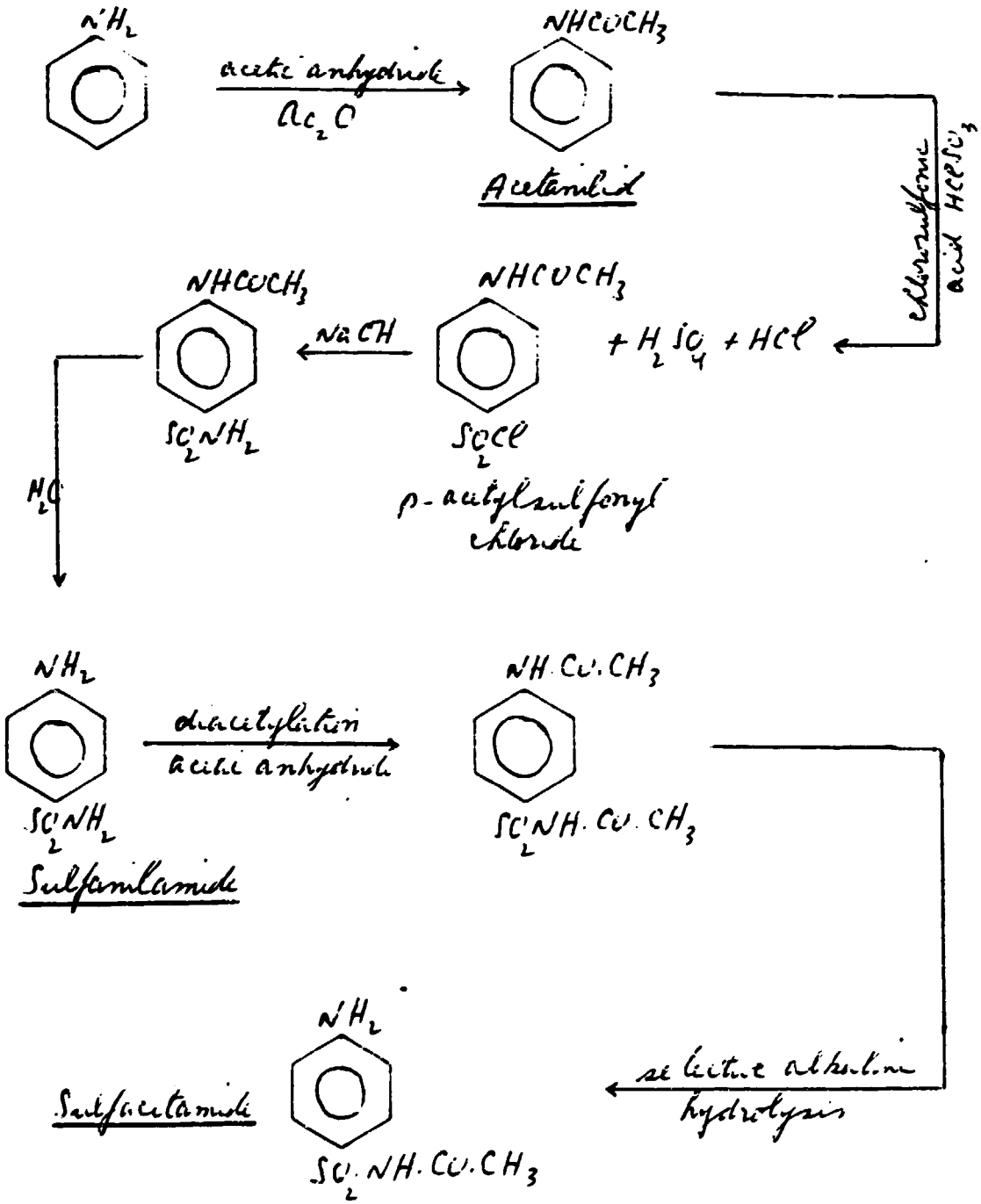


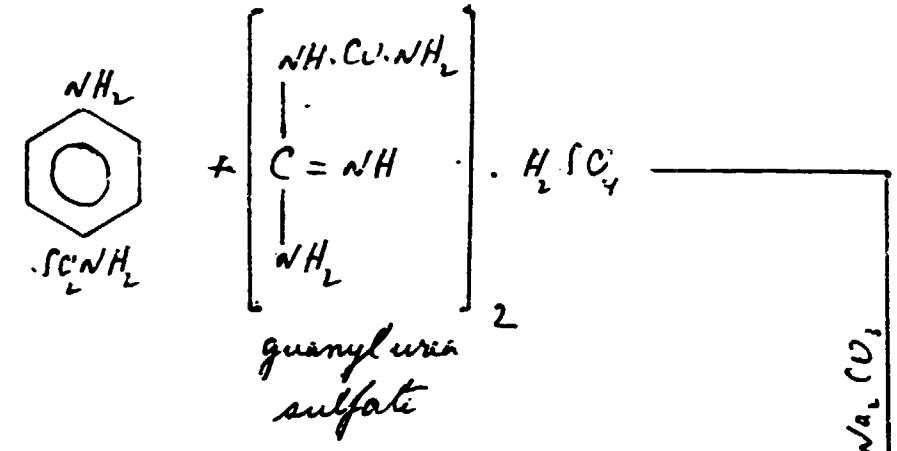
ethylene oxide

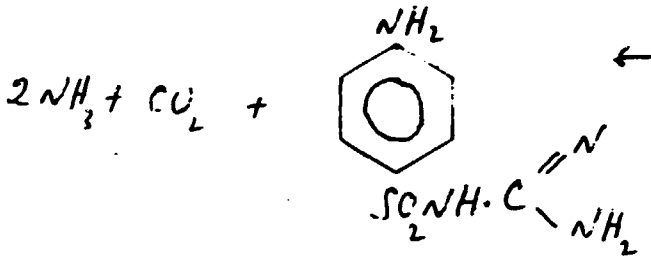


β-phenylethyl alcohol

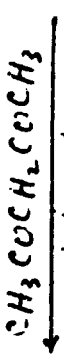
ANILINE $C_6H_5NH_2$ (From Benzene)

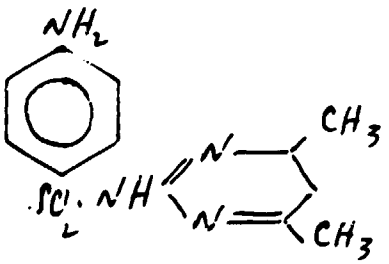






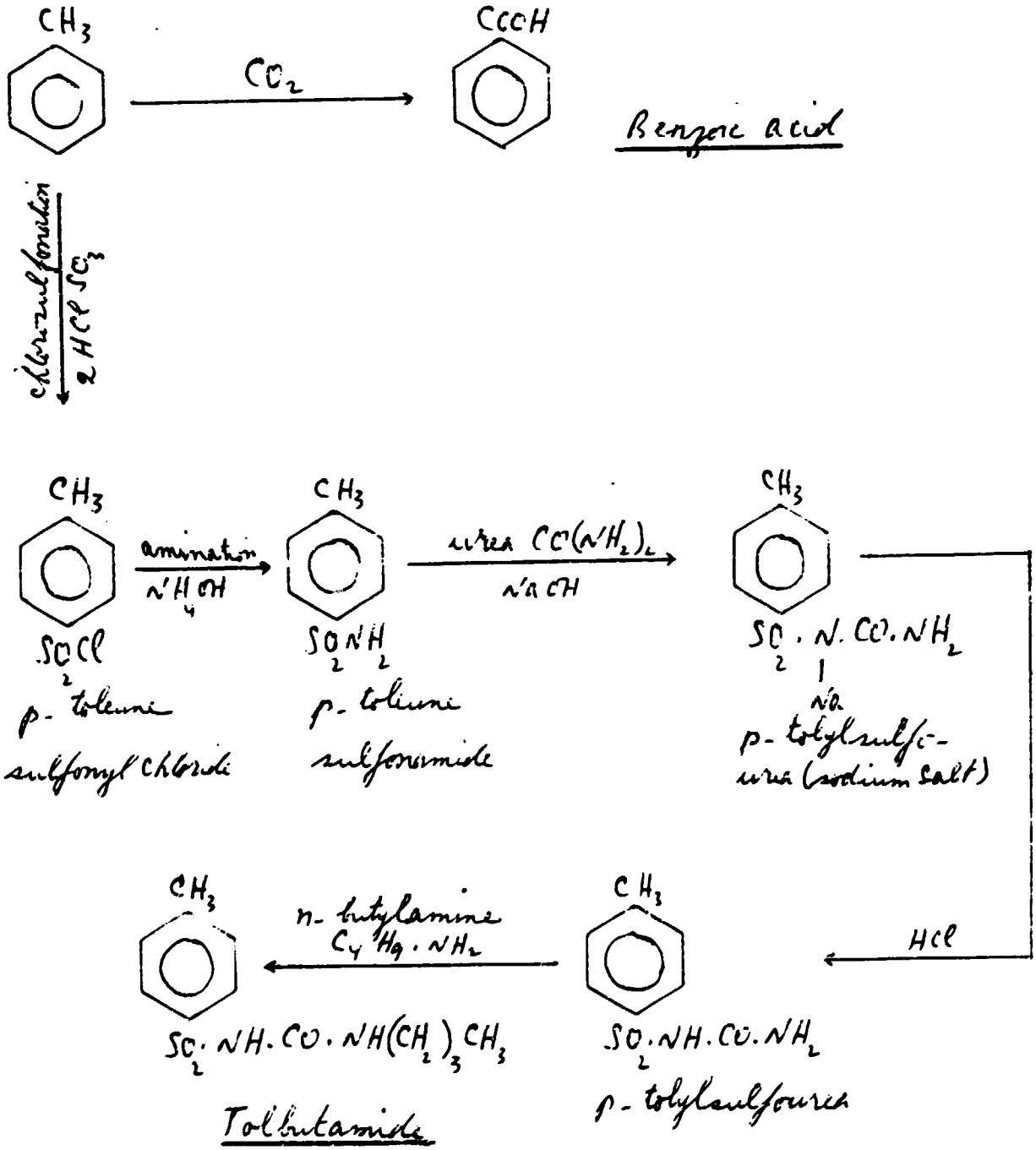
Sulfaguanidine



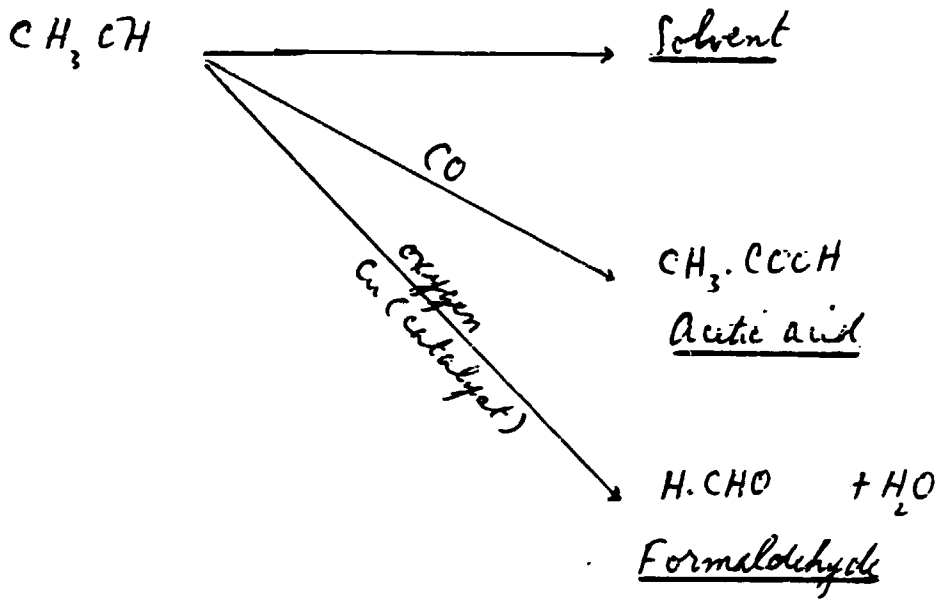


Sulfamethazine

TOLUENE $C_6H_5 \cdot CH_3$



METHYL ALCOHOL CH_3CH



ACETIC ACID $CH_3.COOH$ (from Methanol)

$CH_3.COOH$ → Cellulose acetate

$CH_3.COOH$ —(boil with alcohol, H_2SO_4)→ $CH_3.CO.CH_2.COO.C_2H_5$
acetoacetic ester
Perfumes

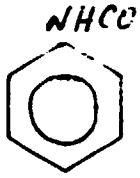
$CH_3.COOH$ —(chlorination (heat))→
$CH_2Cl.COOH$ monochloracetic acid
$CHCl_2.COOH$ dichloracetic acid
$CCl_3.COOH$ trichloracetic acid

$CH_2Cl.COOH + 3NH_4OH$ → $NH_2CH_2.COONH_4$

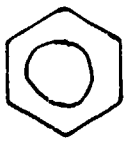
$NH_2CH_2.COONH_4$ —(acid)→ $NH_2CH_2.COOH$
aminoacetic acid
Glycine

$CCl_3.COOH + 2NaOH$ → $CHCl_3 + Na_2CO_3 + H_2O$
Chloroform

$CH_3.COOH$ —(cerium carbonate, 500°C)→ $CH_3.CO.CH_3$ Acetone

$CH_3.COOH$ —(PCl_5)→ $CH_3.CO.Cl$ acetyl chloride —(dry ammonia gas or aniline)→  Acetanilid

$CH_3.CO.Cl$ +  salicylic acid →



acetyl salicylic acid

Aspirin

$CH_3.CO.Cl$ —(anhydrous sodium acetate)→ $(CH_3.CO)_2O$ acetic anhydride

FORMALDEHYDE $H.CHO$ (From Methanol)

$H.CHO \longrightarrow$ aqueous solution

Formalin

$6H.CHO \longrightarrow C_6H_{12}N_4 + 6H_2O$

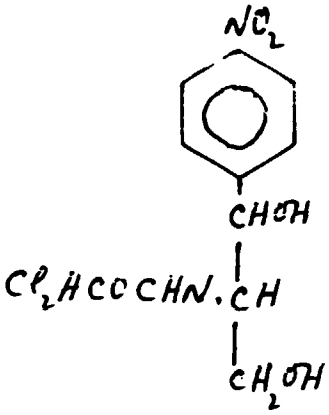
Hexamethylene tetramine

Urotropine

Hexamine

STYRENE $C_6H_5 \cdot CH = CH_2$

It is the starting material for the production of Chloramphenicol



Polyvinyl chloride "PVC"

Plastic bottles and sacs for dripping parenteral solutions and their tubes.

Polyethylene (high density) "HDPE"

Disposable injections

A Pharmaceutical Chemicals

Name	Uses
Benzene	
1. Solvent	
2. Aniline	
3. PAS	treatment of tuberculosis
4. Resorcinol	antifungal, antibacterial
5. Picric acid	treatment of burns
6. Dapsone	leprosy
7. Phenol	disinfectant, pharmaceutical necessity
8. Salicylic acid	antiseptic, keratolytic
9. Ester of hydroxy-benzoic acid	preservative
10. DDT	pediculicides
Aniline (from Benzene)	
11. Acetanilid	analgesic, antipyretic
12. Sulfanilamide	antimicrobial
13. Sulfacetamide	antimicrobial
14. Sulfaguanidine	treatment of intestinal infections
15. Sulfamethazine	antimicrobial
Propylene	
16. Acetone	solvent
Phenol	
Salicylic acid	
17. Sodium salicylate	anti-rheumatic
18. Methyl or Ethyl salicylate	local analgesic
19. Salicylamide	analgesic, antipyretic
20. Paracetamol	analgesic, antipyretic

	Ethylene	
21.	Anaesthetic	
22.	Piperazine	anthelmintic
23.	Nicotinic acid	vitamin
24.	Nicotinamide	vitamin
25.	Nikethamide	respiratory stimulant
26.	B-phenylethyl alcohol	antibacterial agent in ophthalmic solutions, perfumery
	Toleune	
27.	Benzoic acid	antiseptic, preservative
28.	Tolbutamide	oral hypoglycemic
	Methyl alcohol	
29.	Solvent	
30.	Acetic acid	pharmaceutical necessity, solvent
31.	Formaldehyde	pharmaceutical necessity, solvent
	Acetic acid (from methanol)	
32.	Cellulose acetate	enteric coating material, packaging
33.	Perfumes	
34.	Glycine	amino acid
35.	Chloroform	anesthetic
	Acetanilid	analgesic, antipyretic
36.	Aspirin	analgesic, antipyretic
	Formaldehyde (from methanol)	
37.	Formalin	disinfectant, deodorant
38.	Urotropine, Hexamine	urinary tract anti-infective
	Styrene	
39.	Chloramphenicol	wide spectrum antibiotic

B Medical Appliances

Polyvinyl chloride "PVC"	plastic bottles and sacs for dripping parenetral solutions and their tubes.
polyethylene (high density)	Disposable injections

CONCLUSION

As was shown, 39 bulk synthetic pharmaceutical chemicals can be easily synthesized in the Arab World including ACDIMA member countries. All starting materials of all these compounds are commercially available as petrochemical products. They are produced in abundant quantities, and therefore they can be purchased at cheap prices. These 39 compounds cover a wide range of medical and pharmaceutical uses, also some can be used as solvents, pharmaceutical necessity, reagents and in perfumery industry

Besides, as was mentioned before, urea and guanidine are also available in abundant quantities.

Two petrochemical products used as starting materials for the manufacture of some medical appliances are mentioned. They are available in the Arab World.

At the same time, the following are available inorganic petrochemical products, in the Arab World and of pharmaceutical interest.

1- Chlorine
2- Bromine
3- Sodium hypochlorite
4- Sodium hydroxide
5- Potassium salt
6- Sulfuric acid.
7- Hydrochloric acid
8- Nitric acid
9- Oleum
10- Ammonia
11- Sodium chloride

Ethyl alcohol and glycerol were not mentioned because ethyl alcohol is produced from sugar cane industries and glycerol from soap industries. These two industries are available in the Arab World and produce enough quantities of these two compounds.

List of Persons met

A JORDAN

1-Mr. Samer S.Fahd, B.Sc. Ch.
Intermediate Petrochemical Industries
Zerka, Jordan.

2 Mr. Ibrahim M. Kakish, Chemical Engineer
Acting Chief of Industrial Directorate
Ministry of Trade and Industry
Amman, Jordan.

3 Dr. Ibrahim Badran, Ph.D.
Director of Energy
Ministry of Trade and Industry
Amman, Jordan.

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C LIBYA

1 Dr. Ahmed Mouzughi, Ph.D.
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2 Mr. Mohamed Teyari
Manager Engineering Research
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