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PROGRAMME ON ENVIRONMENTALLY SOUND AND SUSTAINABLE MANAGEMENT OF PHARMACEUTICAL INDUSTRIES*

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FOREWORD

In the spirit of The Declaration of Rio (UNCED 1992), following the call of Agenda 21 for a high quality environment and healthy economy for all peoples of the world, organizations of all kinds - from the government level to industrial enterprises- are increasingly concerned to improve and demonstrate their environmental performance.

Industries, dealing with chemicals are in the front line of interest concerning environmental protection.

The present study has been prepared to assist both authorities (governments, local municipalities, NGOs) and companies (producers, importers, distributors) in the implementation and maintaining of environmentally sound and sustainable management in the pharmaceutical industries.

The study is consisting of three parts:

Part I PROGRAMME. (LEGISLATION, CHEMICAL SAFETY)

Part II GUIDELINES FOR THE PRODUCERS OF ACTIVE SUBSTANCES

Part III GUIDELINES FOR THE PRODUCERS OF PHARMACEUTICAL PREPARATIONS

Part I of the study is dealing with the environmental issues of the pharmaceutical industry focussing to environmental legislation, chemical safety, waste management, and has been intended primarily for use by government officials and directors of enterprises and relevant institutes.

In Part II and III the practical aspects of production of active substances (medicinal chemicals) and formulation of finished products (dosage forms) are summarized. For the better understanding case studies are also attached.

During the preparation of the study a Conference on International Trade in Dangerous Chemicals has been organized by the European Commission (Brussels, 5 to 7 July 1995). The proceedings of the conference has also been used to provide up to date information.

Although the imminent publication of ISO 14000 Standard Series of Environmental Management has not been taken place yet, the spirit and philosophy of it is supposed to be reflected in the study.

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List of Annexes and Attachments

ABBREVIATIONS

BOD	Biological oxygen demand
CEC	Commission of the European Communities
COD	Chemical oxygen demand
EC	European Community
EEC	European Eonomic Committée
EMS	Environmental management systems
EPA	United States Environmental Protection Agency
EU	European Union
FAO	United Nations Food and Agricultural Organization
GMP	Good Manufacture Practice
ILO	Untied Nations International Labor Organization
IOMC	International Organization on Programme on Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
LD_{50}	is the (single)dose of the material which causes the death of 50% of a group of test animals
LC_{50}	is the concentration of a material in air which causes the death of 50% a group of test animals when given over a set period of time, usually 1 to 4 hours
LEL	Lower Explosive Limit
ODP	Ozone depletion potential
ODS	Ozone depleting substances
OECD	Organization for Economical Cooperation and Development
PAH	Polycyclic aromatic hydrocarbons
PCB	Polychlorinated biphenyls
POP	Persistant organic pollutants
SSI	Small scale industry
TSS	Total suspended solid
UEL	Upper Explosion Limit
UNCED	United Nations Conference on Environment and Development (1992)
UNEP	United Nations Environmental Programme
USEPA	United States Environmental Protection Agency
VOC	Volatile organic compounds
VOS	Volatile organic solvents
WHO	United Nations World Health Organization
WWTP	Waste water treatment plant

DEFINITIONS

Active substance

(Bulk Pharmaceutical Chemical)

Chemical hazard
A hazard involving chemicals or processes which may realize its potential through fire, explosion, toxic or corrosive effects.

Damage
The loss of inherent quality suffered by an entity (physical or biological.

Environmental management
Those aspects of the overall management function (including planning) that determine and implement the environmental policy.

Environmental management system
The organizational structure, responsibilities, practice, procedures, processes and resources for implementing environmental management.

Environmental policy
A public statement of the intentions and principles of action of the organization regarding its environmental effects, giving rise to its objectives and targets.

Harm
Loss to a human being consequent on damage

Hazard
The situation that in particular circumstances could lead to harm.

Risk
The possibility of suffering harm from a hazard.

OBJECTIVES

BACKGROUND

In the spirit of The Declaration of Rio (UNCED 1992), following the call of Agenda 21 for a high quality environment and healthy economy for all peoples of the world, organizations of all kinds - from the government level to industrial enterprises- are increasingly concerned to improve and demonstrate their environmental performance.

The movement to protect the environment started from countries in which the industry has been the most developed, consequently the damages in environment caused by the industry appeared quickly.

The situation of the developing countries is different.
For them, industrialization seems to be one of the ways out of poverty.
Since their industrial development started later they may utilize the experiences of the industrialized countries.
Unfortunately lack of financial resources, know-how, standards and information together with inadequate environmental legislation often lead to widespread use of environmentally unsound production processes that waste raw materials and energy and unnecessarily cause pollution.

The global tendency for heavily polluting and/or highly resource/energy intensive industries to be relocated in developing countries increases the environmental risks.

ROLE OF UNIDO

In developing countries

Environmental protection is an integral part of UNIDO's fundamental mandate:
"to encourage and extend assistance to the developing countries for the development, expansion and modernization of their industries", "to provide a forum and act as an instrument to serve the developing and industrialized countries in their contacts, consultations and negotiations", "to coordinate all activities of the United Nations system regarding to industrial development".

UNIDO wants to play a leading role in the implementation of these objectives, also in the area of environment protection and continue co-operation with UNEP, WHO, and other international organizations to support them in carrying out programmes and projects derived from their mandate.

In East European transitional economies

The above quoted mandate of UNIDO has been extended to the Eastern European transitional economies. These countries with their historical, political and industrial traditions have similar and different elements in comparison with both developing and industrialized countries. Their experience may be useful for planning and/or improving industrial sectors in developing countries and have high level scientific and industrial knowledge on one hand but they need assistance in elaborating industrial policies and know-how in environmental protection on the other.

UNIDO, is one of the few international agencies specialized in government services such as assistance in the formulation and assessment of industrial policies and strategies relating to subsectoral investment promotion, formulation of subsectoral programmes, as well as technology development and transfer.

OBJECTIVES

The present programme is trying to collect and summarize all necessary information on the environmental aspects of the production and formulation of pesticides.
The aim is to yield assistance to all involved in the pharmaceutical industry in the developing countries:
governmental and local municipal authorities,
non governmental organizations,
companies producing, formulating or distributing pharmaceutical products.
Annexes, attachments and list of relevant publications will help to get more detailed information.

PART I

CHEMICAL MANAGEMENT PROBLEMS OF SMALL SCALE INDUSTRIES

Evidence from a number of countries shows that the growth of industrial activity is closely related to the progress of small industrial enterprises. Governments in most countries promote small scale industries (SSI) through fiscal and policy incentives. In India, for example, it is estimated that proliferation of SSI units is at a rate of 20% compounded annually with employment exceeding 11,000,000.
Many countries have established specific government organizations to promote and oversee the development of the SSI sector.

In the pharmaceutical industry the occurrence and role of SSI may give rise to special advantages, but also to problems.
Pharmaceutical companies in most cases may be originated from small workshops, usually those of pharmacies. The majority of the big multinational companies have been developed from small family owned pharmacies. The other route has been that of the chemical manufacturers, who increasing both the volume of production and also the spectrum of their chemical products, gradually invaded into or rather created the pharmaceutical *industry*.

In developing countries both model may exist but differs significantly from the "traditional" way of development, due to peculiar character of these countries.
The small private enterprises start usually as agents of foreign companies doing marketing, sales, and distribution activities. Later they begin to import the bulk product and carry out the packaging. Formulation from imported active substance is the next step. In certain cases, following the principle of "backward integration" the production of the active substance itself is going to be implemented, usually starting with the last process step (in most cases purification of the imported "technical material" from contaminants and producing the active substance complying with the required quality requirements). Continuing the backward integration gradually more steps of the process may be introduced and finally the so called "total synthesis" of the material is implemented. The whole above mentioned procedure may be in frame of a transfer of technology from a donor, or done by the industrial venturer on its own independently from foreign companies.

The other way of creating new pharmaceutical plants is the practice of establishing a production unit of a foreign company.

It is obvious that in case of transfer of technology or establishing a daughter company, the *donor or owner resp. bears responsibility relating to environmental and occupational safety.* They have to provide all data and procedures both to the manufacturer and also to authorities in order ensure chemical

safety relating to the whole production.

SSI profile

In case of independent enterprises the situation is more complex. The small industry manufacturing establishments having less than 50 employees, comprise some 60-75% of chemicals manufacturing establishments in many rapidly industrializing countries, but provide only 15-20% of output. In many cases these enterprises were established prior to requirements for environmental impact assessments. Estimates of their inputs into the total national annual exposure burden vary widely. Based on Indian experience, for example, their contribution may be as high as 40% of total annual generation. A survey of the Asian Development Bank has indicated that the generation of hazardous wastes by SSIs is disproportionately high compared to their share in total industrial output.

SSIs suffer from a number of serious constraints in attempting compliance with new regulations. Economically they are characterized by *low capital investment, fierce competition, lack of the necessary skills and managerial resources.*
In order for a SSI enterprise to survive, it must utilize the cheapest means of production with small or no overhead costs. This type or administration normally leads to aggravated occupational safety and health problems, public health detriment in adjacent communities and environmental degradation.

Proper managerial skill and practice

Most small scale businesses, including many family enterprises, are managed by the owners themselves who may have proper education and expertise in pharmaceutical or medical sciences and practice, however lack adequate (if any) industrial managerial practice, are unfamiliar with knowledge of modern technic particularly with waste pre-treatment and disposal technologies. Examples of inappropriate management include the use of domestic *sewage systems for inadequately treated waste discharges, the use of surface drains, creeks and other water bodies for effluent discharge and both on and off-site surface disposal of sludge and toxic residues.*

Governmental support, assistance

Not all constraints on small industries are directly attributable to pure and sole economic factors.

Many of the industries are located in urban housing areas or have been illegally developed on government land over a period of many years. Little if any place is available for the treatment and

disposal of wastes.
Establishing of "industrial parks" i.e. areas dedicated towards industrial purposes located away from residential areas may provide with the advantages of necessary infrastructure, i.a.:

- proper energy supply
- central storage
- centralized collection and processing of wastes and expended waste treatment facility
- well organized, trained and equipped emergency crew

The cost sharing of certain services, first of all those relating to waste minimisation and management can assist SSI enterprises to comply with recent regulations which they could not afford alone.

Information, education especially in environmental management issues may also be useful and necessary inputs to improve the standard of management of SSI enterprises.

Communal transportation, handling, storage and waste pre-treatment facilities have many advantages in addition to the cost sharing effect, some of which are as follows:

- utilization of wastes, by products
- regeneration of solvents or by-products
- technologies for large scale systems can be used
- technically specialist operators, independent from enterprises, subject to on-site supervision by the responsible authorities.

ENVIRONMENTAL MANAGEMENT SYSTEMS

The aim of an EMS is to enable its user to establish procedures to set an environmental policy and/or objectives, achieve compliance with them, and to demonstrate such compliance to others.
The user can be any organization dealing with the legislation, control, use, production or distribution of pharmaceutical products.
As the present study is dealing with the pharmaceutical *industry*, users of medicines (i.e. hospitals, other health institutions etc.) are not discussed.
Recently, pharmaceutical companies started to undertake environmental "audits" in order to prove to authorities, or commercial partners their environmental performance.
However, such audits can assess only the present status, but can not give the assurance that the company will continue to meet legislative requirements.

ENVIRONMENTAL POLICY

Environmental policy is consisting of the intentions and principles of action of the organization regarding its environmental effects.
The organization may be the government or its institution; regional or local municipality; enterprise or its production unit.
It must be public, objectives and targets must be clearly formulated avoiding ambiguity.
The policy shall contain the targets and consequent tasks of all nt levels of hierarchy within the organization.

Internationally accepted and /or used prescriptions and guidelines are worth to be complied with, or followed.
The number of publications relating to various aspects of environmental protection is abundant. Principles are laid down in form of prohibitions in most of them. Practical measurements remain to the executers.The aim of the present study is to draw the attention to laws, rules, prescriptions, guidelines shortly all available publications relevant for the legislation and operation of the pharmaceutical industry.
Practice of the industrialized countries (US, Canada, the European Union, Japan) are the best to follow, always bearing in mind the local specialties and possibilities.
A list of documents can be found among the references of the present study, but the *EPA Guides to Pollution Prevention (esp. the volume: The Pharmaceutical Industry)* and the *Technical and Economical Study on Reduction of Industrial Emissions from the Pharmaceutical and Cosmetics Industry prepared by ECE and the British Standard BS 7750 Specification for Environmental Systems*

seem to be the best guidelines for the elaboration of the environmental policy.

The policy shall also take into consideration the operational and business requirements of the organization.
Finally, but not least the financial resources should not left out of regard either.

Operational requirements,
especially the technical ones are key items. Processes of the production of *bulk pharmaceutical chemicals* (synthetic, fermentation, extraction) generate by-products: effluents and wastes. The safe handling (source reduction, material substitution, recirculation, regeneration, utilization, elimination etc.) of them is the core of the ELMS. The *formulation* of pharmaceutical products seem to be more harmless for the environment, but the character of certain products may also need due precaution in order to avoid contamination, especially certain chemotherapeutics, antineoplasmatics, allergizing substances, products having hormone-like effects etc.

Governmental level
The task of the government is to enforce the realization of its environmental policy by legislation and control.
During efforts to follow foreign prescriptions, real possibilities are always borne in mind. Impracticable orders are counterproductive by urging to prepare false or ambiguous assessments thus leading to temporarily hidden consequently uncontrollable damages in the environment.

The development of national, regional, local or site specific "cradle to grave" management plans for chemicals must take into the range, quantities and locations of the substances of concern. The plans need to impose responsibilities on all who have a role in the import, transport,production, packaging, storage, distribution of pharmaceutical chemicals and their finished forms.

Legislation is important per se, but also as an interface between chemical safety and other special regulations (e.g. employment, industrial relations, trading standards etc.)

Planning new facilities
Beside general principles it is important to pay attention to certain special characteristics of the pharmaceutical industry.

Distance from residential areas has to be taken into consideration. Especially when new facility is going to be planned, future plans of the municipality for the extension of residential quarters must have first priority. Properly chosen distance from the factory may

avoid daily harassment of the neighboring population and decrease the probability of possible accidents.It has to be stressed that the *remoteness of an industrial plant in itself does not replace the necessary working,- and environmentally safety measurements, because nature and environment must be protected even in remote areas.*
However, since the planned operation of machinery is relating to normal working conditions, in case of a breakdown the damage (first of all pollution) may be reduced by distance. Especially casualities of the population can be decreased.
Odor and noise are the most sophisticated nuisances first of all due to individual sensitiveness to them, but also because of the difficult and complex way of protection.
Distance from residence area is certainly not a drawback.

Distance from natural waters (rivers, lakes etc.)may also yield similar considerations: breakdown in the waste water treatment facilities can also not absolutely excluded.
Proper space for secondary safety equipments (e.g.valves), additional treatment (chemical or biological) together with the self cleaning possibility during the residence time of the waste water in the ducts or containers (artificial ponds) may result in decreasing or eliminating the damage.
An additional advantage may be the dilution effect of communal sewage as well.
It is obvious, that the proper distance from inhabited areas yields the safest, most cost effective i.e. optimal protection of the population and environment.

Interrelations, conflicts of interests
The policy should not only commit the organization to set up and or meet relevant regulatory and legislative requirements, but also define how it will seek to meet, exceed or develop the requirements of some, or all, of the other interested parties and secure continual improvement in environmental performance.

Format
The environmental policy should be public and available in a readily understood format to interested parties (e.g. in annual report, booklet or display)

Enterprise level
Duty of the management of a company in this respect is first of all to abide law. Since legislation on environmental issues is far from complete even in some industrialized countries and is in an initial phase in
in the majority of the developing regions, the proper way of environmental management is the responsibility of the enterprise. The present study is intended to help in finding reliable references to elaborate and implement suitable measurements.

Part II and III resp. are dealing with special issues and problems of enterprises producing and or handling pharmaceutical products.

ENVIRONMENT MANAGEMENT SYSTEM REQUIREMENTS

A brief summary of the requirements based on BS 7750 is the following:

- Organization and personnel
  - responsibility, authority of key personnel
    - inc. authorized management representative
  - interrelations within general management
  - training of personnel
- Resources
  - technical
  - financial
- Environmental effects
  - register of legislative, regulatory and other policy requirements
  - communications
    - for and from interested parties
    - internal and external
  - evaluation
  - objectives and targets
  - environmental management programme
- Documentation
  - manual
  - documentation
- Operational control
  - work instruction
  - procurement and contracted activities
  - monitoring and control of relevant processes
    - criteria for performance (in written form)
  - verification of compliance with specified requirements
  - acceptance criteria when results are unsatisfactory
  - non-compliance and corrective action
- Audits
  - audit plan
  - environment management reviews

Detailed specification or the above mentioned elements - intended to apply to all types and sizes of organizations - can be found in BS 7750 and its application for industrial and commercial enterpriseswill be discussed in Parts I and II resp.

The philosophy of the approach to set up and operate such an EMS is shown schematically in flow chart form in Figure 1.

Application of BS 7750 for industrial and commercial enterprises will be discussed in detail in Parts I and II resp.

Governments and local municipalities
may find essential support in the mentioned standard, especially if they are at the initial phase of setting up proper organizations and introduce measurements to control the protection of their environment.
As a first step, a preparatory review may be prepared in order to collect all aspects of the organization, to identify strength, weaknesses, risks and opportunities as a basis for establishing the EMS.
This review should cover the following areas:

- evaluation of significant environmental effects
- legislative and regulatory aspects
  - environmental objectives and targets beyond regulatory requirements
  - expected changes in regulations and legislation
  - views of relevant interested parties
- examination of all existing environmental management practices and procedures
- assessment of feedback from previous incidents
- use of hazardous processes
  - disposal or use of hazardous materials
- environment hazard and risk assessment of potential emergency situations
- environmental aspects of emergency planning
- environmental effects of investment policies
- nature conservation
- visual impact, noise and odors
- complaints and their recording and follow-up

The resulting report should highlight:

- the nature and extent of problems and deficiencies
- an improvement programme designed to ensure that the personnel and material resources required are identified and available.

Improvement programme
should focus first of all, but not exclusively to

- reduce waste and the consumption of resources
- reduce or eliminate the production of polluting releases to the environment
- control the environmental effects of raw material sourcing (e.g. on habitats, on species diversity and on natural beauty)
- minimize the detrimental environmental effects of new developments through strategic planning
- management of risks
- chemical accident prevention, preparedness, response
- emergency situations

Appropriate levels of municipality should, where necessary, define specialized and/or more detailed environmental targets, consistent

specialized and/or more detailed environmental targets, consistent with the government policy, in addition to the overall objectives.

It is essential that the newly set up system should lay emphasis on the *prevention* of adverse environmental effects, rather than on *detection and amelioration* after occurrence.
Real, feasible and practical prescriptions must be a first priority.
Attention is to be paid to certain limit values, concentrations of in effluents, wastes. These should be measured. Proper instruments together with validated methods and trained personnel must be available.

plants in order to avoid contamination of medicines and to protect the environment on one hand; but also limits the possibilities of the recycling of materials on the other .

Liquid effluents

The primary waste water source is the washwater of equipment and floors, which may contain medicinal chemicals, inorganic salts, sugars, and typically has low BOD, COD, and TSS, with near neutral pH.

Air emissions

in addition to the dusts may result from the use of volatile solvents.

Propellants used in aerosol flasks may be dangerous for the environment not at the site of production but at the application. Prescriptions for ODSs are to be followed.

Waste sources

The pharmaceutical industry produces a wide range of gaseous, liquid and solid waste types.

Atmospheric emissions may be
- gaseous
- volatile (incl. VOC = volatile organic compounds and ODS = ozone depleting substances)
- particulates, in form of aerosols, i.e. suspensions of fine solid particles or liquid droplets, such as dust, smoke, fog, or mist, or
- combination of them.

From synthesis plants:
- losses during filling, emptying tanks, drums
- storage and transport of mother liquors and wet cake
- off-gases and vapor losses from reactors, dryers
- milling, sieving, packing of solid materials
- relief valve, bursting disc discharge
- building ventilation
- incineration

from fermentation plants:
- as for synthetic plants plus:
- organisms in fermenter off gases
- odors in fermenter off gases
- vapor losses from extraction plants

from extraction plants:
- as for synthetic and fermentation plants plus:
- solvent losses in extracted residues
- vapors from desolventiser exhaust

from formulation plants:
- solvent vapor losses from tablet coating
- vapor losses from solvent tanks
- milling, sieving, packing of products
- wet and dry granulation
- manipulations with dried materials
- active ingredients in ventilation exhaust

Coarser particles (larger than 10 microns) settle out of the air quickly. They are, therefore, most troublesome near their source. Smaller ones travel farther. The most problematic are those less than 1 micron (generally referred to as aerosols) because they remain suspended in the air and move easily away causing pollution far from its source.
The "fine", or "superfine" powders and their hazards will be discussed in the section dealing with formulation plants, while volatile exhausts are generated frequently by organic synthesis.

Simplified reactions in the atmosphere
The following formulas are a set of simplified reactions that generate the various atmospheric problems related to air pollution:

NO_2 + Sunlight= NO + O
$O + O_2 = O_3$
$O_3 + NO = NO_2 + O_2$
$HO + RH (+ O_2) = RO_2 + H_2O$
$RO_2 + NO = RO + NO_2$
$RO + O_2 = HO_2$ + Aldehydes, ketones and other hydrocarbons
$HO_2 + NO = HO + NO_2$
$O + SO_2 = SO_3$
$SO_3 + H_2O = H_2SO_4$

List of odor threshold values, classification of airborne carcinogenic compounds and photochemical ozone creation potentials of certain substances can be found in the annexes.

Liquid effluents

and runoff water from pharmaceutical production plants may be toxic and polluting consequently need proper management.
Even surface runoff waters in production areas are likely to contain residues, so they also requirement some sort of treatment. The segregation of clean uncontaminated rainwater via dedicated, sealed drains may significantly reduce quantities of effluent requiring treatment.
Cooling waters are normally recycled in close-loop systems and remain uncontaminated. However, a proper surveillance is needed in order to avoid leakage. Undetected leakage may result in long term, chronic pollution and the identification of the source is not always easy, especially in large industrial sites.

From synthetic plants:
- seal losses from liquid ring vacuum pumps
- wash water from various equipment
- scrubber liquor
- leaks from storage tanks
- contaminated storm water
- fire water run-off

from fermentation plants:
- as for synthetic plants plus:
- waste water from fermentation, fermenter broth
- organic solvents in waste water from extraction

from extraction plants:
- as for synthetic plants plus:
- waste water from extractors containing animal organs and parts of medicinal herbs
- wash water from extractors containing the same

from formulation plants:
active ingredients in wash waters of equipment
active ingredients in wash water of rooms
contaminated storm water
fire water run-off

Solvents most commonly used in pharmaceutical manufacturing are listed in Table 1:

Table 1.
Solvents Commonly Used in Pharmaceutical Manufacturing [1]

Acetone
Cyclohexane
Methylene Chloride
Ethyl Acetate
Butyl Acetate
Methanol
Ethanol
Isopropanol
Butanol
Pyridine
Methyl Ethyl Ketone
Methyl Isobutyl Ketone
Tetrahydrofuran

Toxic effects of common pollutants in aquatic and terrestrial environment are summarized in Annex VIII.

Solid wastes

A range of non-recoverable waste types arises from the manufacture of pharmaceutical products. These include process and effluent sludge, spent catalysts, residues of animal organs and medicinal plants, contaminated containers and package waste.
All concentrated wastes containing significant contamination should where possible be routed for disposal by high temperature incineration.

Lightly contaminated residues, such as package materials and unusable containers, can make up large volumes of low-density waste.

from synthesis plants:
residues from incinerators
sludge from WWTP
contaminated packing
still bottom residues from solvent recovery plants
reject pharmaceutical materials
from fermentation plants:
as for synthesis plants plus:
spent biomass

from extraction plants:
as for synthesis plants plus:
plant or animal residues from extraction process
from formulation plants:
active ingredients in dust collection systems
reject pharmaceutical products
contaminated packaging
contaminated clothing (gowns, gloves, etc.)

Waste minimization

Wastes from the pharmaceutical plants are in most cases be environmentally sensitive and may involve high costs for disposal. Pharmaceutical manufacture is a diverse and highly competitive industry. Because of the highly specific and often confidential nature of each company's specific operations, only very general discussions of material substitution and process modification can be given.

Methods of waste minimization are manifold corresponding to the nature of the material(s) in question and will be discussed in the respective sections of the present study.
A comprehensive summary of the possible methods is as follows:

Source reduction
of hazardous wastes can be achieved in industry through changes in
- products
- raw materials
- process technologies
- organizational practices.

Material substitution
is a change in one or more of the raw materials used in production in order to reduce the volume or toxicity of waste generated.
Replacement of solvent-based solutions by aqueous-based ones, or chlorinated solvents by non-chlorinated media are the most common examples.
In order to avoid unnecessary nuisances in the technology or in the re-registration, involvement of R&D activity is inevitable.

Process modification
or modernization may also result in reducing volume or toxicity of wastes. In most cases the product/waste ratio is determined by the product yield. Consequently improving yield means simultaneous increase in product volume and decrease in waste generating. Better controlling of reaction parameters, introducing improved process control, prevention of fouling deposit in order to improve heat and mass transfer in the reactor are the most common measures to be taken into consideration.

Good Operating Practices
can help to reduce hazardous or other waste generation by

- management incentives
- employee training
- closer supervision
- production scheduling
- additional documentation
- materials tracking and inventory control
- spill prevention
- material handling and storage procedures
- maintenance programmes
- waste stream segregation

Other aspects of the interrelations between environmental management systems and quality assurance activities inc. GMP are discussed in the respective chapter of the present study.

Recovery and recycle
includes direct reuse of waste material, recovering used materials for a separate use, and removing impurities from waste to obtain relatively pure substances. The strict quality control requirements of the pharmaceutical industry often restrict reuse opportunities, though some exist.
Recycling can be performed either on-site or off-site, depending on the capital investment, operating costs, and expertise needed.
Recycling of solvents either directly or recovered from wastes is widely used in the pharmaceutical industry. Processes for solvent recovery from concentrated waste streams include distillation, evaporation, liquid-liquid extraction, sedimentation, decantation, filtration.

Waste exchanges
are recently developed in industrialized countries. They can be grouped as follows:

- information exchanges are clearing houses for information on supply and demand, and typically publish newsletters catalogues
- material exchanges take temporary possession of a waste for transfer to a third party
- waste brokers charge a fee to identify buyers or sellers, but do not take possession of the waste

On-site waste treatment

Due to the extremely big number of compounds having wide variety of physical and chemical character, generally usable method for the treatment is not available. The responsibility of the producer in developing the proper process for treatment is paramount.

The main aspects of waste management are:

- survey
- inventory
- transport
- storage
- treatment
- utilization
- disposal (incl. site selection)
- risk assessment

In industrialized countries the *hazardous waste service sector* has expanded rapidly to cover (nearly) all above mentioned aspects of hazardous waste management.
Without such an industry, each waste generator must acquire the skills and equipment to deal with its own hazardous chemicals.

The following considerations deal with those *pre-treatment procedures which are necessary to be carried out on-site, "statu nascendi" of the waste. These processes should be regarded as inherent parts of the technology. New technologies should be introduced only in case if they contain them, ongoing ones are to be completed by them.*

Atmospheric emissions

In order to prevent discharge of hazardous materials into the air gases and vapors are to be treated depending on their physico-chemical properties:

- *condensers* may collect vapors into liquid form
- *adsorbers* can bind gaseous substances onto solid surface
- *scrubbers* can absorb gases, vapours or facilitate reaction (if necessary) by the aid of some process liquid (water in most cases)
- solid state particles can be separated from the air flow by *filters and dust precipitators*. Solid particles, especially those "superfines" may be charged electrostatically, thus represent powder-explosion hazard. Precaution, including checking pyrotechnical properties of the material in question is strongly recommended.

Needless to mention, that the above mentioned treatment methods also generate new wastes by transforming gaseous substances into liquid or solid forms.

Liquid effluents

Most cases the first step of the treatment is
sedimentation, and/or
filtration in order to separate solid particles.

Sticky, paste like components, or viscous liquids may cause problems and need sophisticated methods.

Solved substances depending on their chemical properties may be separated from the waste liquid or transformed into less harmful materials by suitable

chemical reactions, most frequently
neutralization (by acids or bases)
precipitation and *sedimentation* or *filtration*
wet air oxidation.

Organic solvent wastes may be incinerated "in situ". In some cases it is the most economic and also environmental friendly solution of waste treatment, especially when discharge of VOSs, POPs, ODSs, can be eliminated. There are a number of various "small, but beautiful" devices on the market. Temperature and residence time of combustion are to be considered carefully. Quality, particularly construction material is worth for proper consideration, especially when halogenated compounds will be incinerated.

Solid wastes

At present, solid wastes are in most cases transported from the manufacturing plant without any pre-treatment to either incineration or disposal as landfill, or further utilization. However, in order to reduce dependence on land disposal through waste prevention, minimization and other technical possibilities represent the first choice in the hierarchy of hazardous waste management options. Chapter 20 of UNCED Agenda 21 stipulates that prevention of the generation of hazardous wastes and the rehabilitation of contaminated sites are the key elements for environmentally sound management.

Measures for control & reduction of emissions

Measures for control and reduction of emissions are inherently joined to the technologies where they originate from; consequently they will be discussed in Part II and III of the present study.

Dedicated waste treatment facilities

As mentioned previously, each waste generator must acquire the skills and equipment to deal with its own hazardous chemicals. The principle may be evident, but to comply with it is another question. The complete procedure of the waste treatment in many

cases may be more sophisticated or more expensive than to be executed as a "do it yourself" activity by the manufacturer, particularly if it is a SSI enterprise. It is unlikely that all waste generators will gain the necessary competence. *The minimum request towards producers is the proper pre-treatment which enables wastes for transport and/or further treatment.*

Establishing of local service enterprises specialized for waste treatment is essential, particularly for SSI enterprises.
Governments can foster the growth of a local service industry by providing contracts for handling hazardous chemicals.
Local engineering firms can also form joint ventures with foreign firms until they develop the proper level of expertise.
Regulations can be set up to encourage the collection and centralized treatment of hazardous chemicals, the construction of centralized incinerators and the siting of secure landfills.
Economic measures like free land for site, tax holiday, exemption from import duty for equipment etc., may enhance the development of such enterprises.

The central/communal transportation, handling, storage and waste treatment facilities have many advantages, some of which are as follows:

- central facilities resolve the problems associated with small scale operations esp. lack of capital investment and operational costs
- presently available technologies for large scale systems can be used
- the management of central facilities can be by technically specialist, independent operators subject to on-site supervision by responsible authorities.

Landfill

is the placement of wastes into or onto the ground and, in many cases because of the nature of the materials involved, equates to long-term storage. It is far the most commonly practiced waste disposal method in the majority of countries.
As a result of serious environmental and health problems experienced with historic and abandoned dump sites and the very high costs associated with cleanup measures at contaminated sites, many countries have introduced the "specially engineered landfill concept", the wastes for which are only consigned to site selected for their containment properties, these being natural, augmented by or provided directly by liners. The overall engineering being such as to ensures far as possible the isolation of wastes from the environment. Such landfills are considered a final resort option only to be used after every effort has been made to reduce, mitigate or eliminate the hazards posed by such wastes.

In a number of countries, landfill disposal is likely to be the only method available for the disposal of significant quantities of hazardous wastes.

Existing and ongoing landfills, where a significant proportion of biodegradable or bioconvertible materials is contained in the wastes deposited, will benefit from improved controls over the moisture content, pH, compaction/density. This will allow for improvement in the chemical and biochemical degradation of wastes leading to a more stabilization of the mass. Useful pre-treatment technologies are solidification and chemical fixation.

Guidelines of the Basel Convention on the control of transboundary movements of hazardous wastes and their disposal are to be followed during planning, establishing new landfills, and also for controlling, monitoring of existing or abandoned landfill sites.

Incinerators

Incineration has been used, particularly in Europe and the USA to treat hazardous wastes for many years. Its main advantage is that it permanently destroys many of the hazardous characteristics of the waste. Organic compounds burn over a broad range of temperatures, forming carbon dioxide, water and products of incomplete combustion, some of which may be more toxic than the original waste but there would be a much smaller quantity of such compounds. (It should be noted, that in some countries, both municipal and hazardous waste incinerators have been identified as significant sources of such pollutants as dioxins and furans. However, when applying best available technology, such environmental effects could be minimized.)

Some organic compounds, including some found in certain hazardous wastes, combust less readily and must be subjected to higher temperature before they before they are fully combusted. As a consequence, to ensure maximum destruction of the organic compounds in the wastes, hazardous waste incinerators must maintain extremely high temperatures (typically ranging from 850°C to 1300°C) and have adequate residence time.
Consequently, a high level of technical competence is required in designing, operating and monitoring an incineration facility.
A condensed summary of incineration subsystems and typical process component options may be found on Fig.7.

Incinerators may used for the burning of
- municipal, or
- industrial wastes, or
- combination of them.

Since properties of municipal and industrial wastes differ

significantly a careful selection of equipment and incineration technology is needed.

Types of incinerators

- inclined moving grate type
  is used for the burning of municipal wastes, while
- cyclonic units (the simpler and cheaper), and
- rotating kilns, with after burner chamber (the more effective and expensive) represent the types of industrial incinerators.

Typical incinerator processes of a rotary kiln are illustrated on Fig.8.

Incinerators, though not as efficient in terms of heat recovery as steam-raising boilers, are often used as heat generators to produce warm water or steam for heating or generating electric energy.

CHEMICAL SAFETY

Chemicals, their residues and wastes need to be handled safely to avoid deleterious effects on public and occupational health and environmental quality. Many of them occur as pollutants and contaminants in air, soil, water and food. In some countries historical gross chemical contamination has resulted in a need for restoration which will require major capital investment and the development of new technologies.

Chemical releases, let it be large scale accidental or small but ongoing may cause loss of lives, health impairment, both acute and chronic, and environmental degradation as well as material damage and loss of natural productivity. Global importance of these effects is now becoming more widely recognized.

The issue is not just serious but also extremely complex, because chemicals, their combinations or mixtures with biological agents which, through their additive and synergistic interactions, have human and ecological toxicities near impossible to access scientifically.

Hazards associated with chemicals are still frequently perceived as a problem of developed and rapidly developing economies, however, nearly all countries of the world manufacture, formulate and import chemicals. Problems of chemical safety are exacerbated in developing countries where production technology may be inadequate, legislation and enforcement lacking, hazardous waste dumped carelessly and a population unaware of the dangers of misuse of chemicals.

Governments often have expressed a need for more effective programmes at the national level to identify in advance those hazardous technologies and systems which are likely to give rise to problems.

In the absence of an effective national registration process and of a government infrastructure for controlling the manufacture, formulation, availability, storage and disposal of chemicals, some importing countries lack the ability to assure safe in-country use.

INTERNATIONAL ORGANIZATIONS' EFFORTS ON CHEMICAL SAFETY

Although local problems need local solutions, chemicals are frequently "transboundary pollutants or contaminants" and need international cooperation to mitigate their effects through more

To a limited degree the international agencies particularly the United Nations Industrial Development Organization (UNIDO), the World Bank and the Regional Development Banks already provide guidance for chemical safety activities as part of development assistance, in particular for industrial and agricultural development and transfer of environmentally sound technologies.
The agencies (particularly ILO, UNEP, and WHO) also provide guidance on prevention of chemical accidents, and on preparedness and response to chemical emergencies and to develop mechanisms for international intervention at the request of countries in response to major chemical disasters.
The following list of organizations and publications is intended to give assistance in the legislation and management of chemical safety.

The International Programme on Chemical Safety (IPCS),
a joint activity of WHO, ILO and UNEP, administered by WHO, was established in 1980.

Agenda 21
The *United Nations Conference on Environment and Development, Chapter 19, Agenda 21 (UNCED 1992)* reiterates these concerns and markedly adverse impacts of chemical misuse on the economies of developing countries, recognized that environmentally sound management of chemicals was an important component of sustainable development set up an international strategy for action on chemical safety into the twenty-first century.
The conference called for strengthening of IPCS as the nucleus for coordination and cooperation among international safety activities and for the establishment of an intergovernmental mechanism for chemical risk assessment and management.

Commission on Sustainable Development
The United Nations General Assembly adopted the report of UNCED and established a Commission on Sustainable Development to oversee the implementation of the recommendations.

Intergovernmental Forum on Chemical Safety
To follow up the UNCED recommendation, an international conference on chemical safety was convened and hosted by the Swedish Government in Stockholm in 1994, whereby an Intergovernmental Forum on Chemical Safety was established. It is a non institutional arrangement to consider and provide advice and, where appropriate, make recommendations to governments, international organizations, intergovernmental bodies and non governmental organizations involved in chemical safety on aspects of risk assessment and management. It will provide policy guidance with emphasis on regional and subregional cooperation, develop strategies in a coordinated and integrated manner, foster understanding of issues, and promote the required policy support.

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Interorganizational Coordinating Committee
The establishment of the expanded IPCS, codified by a memorandum of understanding among FAO, ILO, UNEP, UNIDO AND WHO will provide a mechanism to build up *collaborative international programmes on chemical safety. It will also enable long-term planning and implementation of activities.* Coordination between international organizations is ensured through regular meetings of the Interorganizational Coordinating Committee.

Steering Committee on Chemical Safety
is a mechanism, within WHO, for coordination of related chemical safety activities. Policy advice to the executive heads of the international organizations is provided through meetings of the **IPCS Advisory Committee.**

Following the endorsement of the WHO global strategy for health and environment, the implementation of the IPCS currently falls into the following four broad areas corresponding to priority programme areas in chapter 19 of Agenda 21:

- chemical risk assessment
- chemical risk communication (incl. harmonization of classification and labelling of chemicals, and information exchange on toxic chemicals and chemical risks
- action on chemical emergencies
- strengthening of national capabilities and capacities for management of chemicals

ELEMENTS OF CHEMICAL SAFETY

In order to improve chemical safety the following issues are to be taken into consideration during planning or operation of a plant dealing with the production, transport, storage, distribution of pharmaceutical products.
The following sections will summarize general information on chemical safety; focussing to duties of authorities (governments, municipalities) such as: regulatory, controlling, prevention activities related to communities and environment.
Tasks of the enterprise level will be detailed in Part II an III of the present study.

Problems of chemicals and their identification

Information on chemical substances is primarily required for three purposes:

- risk assessment (characterization, management)
- medical and public health response to acute and chronic exposures
- timely provision of appropriate health and environmental responses during incidents, accidents, and emergencies.

Information on chemicals and their formulations manufactured, imported, exported, transported, used and disposed of in the country is necessary.

The development of a centralized national information programme on chemical safety for the collection of data on all chemical products, and for the dissemination of objectively evaluated information should be considered of the highest management priority for chemicals. Access to comprehensive chemical toxicity data is a fundamental component of any national management programme.

Annex I and II provide model formats for developing National Status Profiles for chemicals Information.

A *toxicological information service* is needed to provide up-to-date information on the potential health and environmental effects of chemicals and their products.

Most of the information currently available pertaining hazardous chemicals has been established under developed country conditions.

The situation in *developing countries* is rather different.

Climate conditions in tropical regions, where most developing countries are situated, may have a sizeable impact on the dispersion of hazardous chemicals in ground water, the atmosphere, in the food chain, and on the potential for occupational exposures as well.

Information sources on chemical safety

As mentioned before, there is no globally accepted consolidated directory data bases and regulations relevant to chemical safety. There are, however, many information sources.

The *London Guidelines for the Exchange of Information on Chemicals in International Trade* are a set of guidelines widely adopted by Governments. The export to developing countries of chemicals that have been banned in producing countries or whose use has been severely restricted in some industrialized countries has been the subject of concern, as some importing countries lack the ability to ensure safe use, owing to inadequate infrastructure for controlling the importation, distribution, storage, formulation and disposal of chemicals. All countries which export chemicals subject to the *Prior Informed Consent (PIC)* procedures should have the necessary mechanism in place to ensure that export does not take place contrary to importing countries' decisions.

Further sources of information are the following:

Environmental Health Criteria (IPCS)

- Health and Safety Guides (IPCS)
- International Safety Cards (IPCS)
- INFOTERRA (environmental data base) (UNEP)
- International Register on Potentially Toxic Chemicals (UNEP)
- RISKLINE a bibliographic database on toxicology and ecotoxicology (KEMI National Chemicals Inspectorate Sweden)

Risk assessment
identifies, characterizes and qualifies the potential adverse effects on human health or ecosystems, of defined exposures to a chemical substance or mixture, or to a chemically hazardous process or situation.
It consists of the following interrelated elements:

- *hazard identification* i.e. identifying the adverse effects which a special chemical or process has an inherent capacity to cause.
- *dose-response assessment*
- *exposure assessment* (dose/level/duration)
- *risk characterization* (incidence and severity of adverse effects due to actual or predicted exposure).
- *priority setting*
  identifying pollutants of greatest concern in air, water and soil
  "multiproblem chemicals" (candidates for risk reduction)
  persistent organic pollutants (POP)
  ozone depleting substances
  establishing priorities for evaluation health and environmental effects
  list of priority chemicals for testing

- *need for international cooperation*
  technical
  financial
  information (reciprocal, with neighboring regions)

Risk management
of chemicals includes the full range of activities required to prevent and assess their intrinsic hazards, and to ensure their safe production, transportation, storage, use, and ultimate disposal, so that health and the environment are protected. Environmentally sound management of chemicals and the mechanisms developed for implementing chemical safety must be through an integrated approach including both risk assessment and management.

Principles of risk management:
main objective: prevention should be preferred to clean-up
preparedness for response to chemical emergencies
poison control programme providing toxicovigilance,

prevention and response to poisoning
- integration: it is total exposure that matters; all significant sources and pathways and the full life-cycle of a chemical "from cradle to grave" should be taken into consideration
- sound infrastructure is needed
- chemical safety information should be available to all
- intersectoral (national) coordination is essential
- responsibility of central, regional and local authorities
- legislation
  on chemicals, pollution, etc.
  registration,
  license to sell, use, store, manufacture (for enterprises)
  certificate of competence (for individuals)
- economic option (incentives, subsidies, selective taxation, economic instruments based on the "polluter pays" principle
- monitoring and surveillance
- "industry response care programmes" for prevention and emergency measurements

Risk assessment and management system introduced in the European Community is displayed in Fig.6.

Chemical emergencies

Details are discussed in Section "Prevention and Response in Chemical Accidents".

More detailed and specified information and data can be found in the IPCS Guidelines for the Strengthening of National Capabilities in Chemical Safety, and in the international reference manual: Chemical Safety by Mervyn Richardson.

PREVENTION AND RESPONSE IN CHEMICAL ACCIDENTS

Most people in industry provide assurances that industrial plants are designed and maintained in accordance with high industrial safey standards.However, proper design, maintenance and procedures in operation does not mean that accidents will not occur.
The unfortunate reality is that such risks, may be minimal, remain and the hazards posed can never totally eliminated.

Some of the chemical accidents have become historical milestones: the dioxin release in Seveso, Italy in 1976, the release of methylisocynate at Bhopal, India in 1984, the fire at a chemical warehouse in Basel, Switzerland and th e discharge of contaminated waters into the Rhine in 1986.

Chronic adverse impacts of chemicals have also been reported in a number of cases, producing, carcinogenic, mutagenic, and teratogenic effects on exposed people. Fish contaminated by organic mercury in Minamata Bay, cadmium-contaminated rice in Toyama Prefecture and rice oil polluted by poly-chlorinated biphenyls (PCB) in Japan have become classic cases of tragic chemical accidents.

Pharmaceutical industry being user, producer of hazardous chemicals is not an exception either. Prevention and response to chemical accidents must have a first priority in the design and operation of pharmaceutical plants.

Human error
Having accepted that some accidents cannot be totally prevented, the elaboration of clear guidelines and emergency plans for potental chemical accidents are necessary.
Most investigations conclude that accidents were often due to human error either during operation, in maintenance, and even in response to emergencies arising out of industrial accidents.
The man in the field must not only know his job well, but also be vigilant at all times and trained how to react in case of accident. The proper, calm reaction can be ensured only by due education and training. The knowledge of all materials involved, icluding results of possible unwanted chemical reactions should be the basis.
Responsible, mature and well trained people are needed in cherge at all levels.

Planning, design
The major problems relating to preparedness and response to chemical emergencies have been recognised as:

- inadequate planning, particularly at the early development stage for new industries

PART II

INDUSTRY PROFILE

The following sections of the present chapter yield a comprehensive summary of the manufacturing of active substances in the pharmaceutical industry.

The principal processes employed in the manufacturing of pharmaceutical active substances are:

chemical synthesis
fermentation and
extraction
storage, transport

Formulation into various dosage forms and packaging of finished drugs, research and development will be discussed in Part III of the present study.

Processes, raw materials and wastes of these activities are discussed from the point of view of possible environmental hazards.

CHEMICAL SYNTHESIS

Vast majority of drugs today are produced by chemical synthesis. Production in the pharmaceutical industry is differing from that of the chemical industry in many respects:
Active substances have in most cases *complicated molecular structure* produced by multi step *sophisticated chemical reactions* on a batch basis in relatively *small scale* and *high purity* under *particularly controlled procedures* to assure the standard quality of the product.

Raw materials and intermediates are usually supplied by the chemical industry where the production is carried out in dedicated plants, suitable sizes, consequently cheaper compared to the pharmaceutical plants, where the priorities are different.
General practice of the pharmaceutical companies is to buy starting materials as "near" (in chemical sense) as possible to the end product and execute only the most delicate steps in their own plant.
If the material of the end product is available on the market in a low quality, or "technical grade", the best solution is to prepare the product by - in some cases relative simple - purification.
It is obvious, that the conditions, priorities in a pharmaceutical plant differ significantly from those of the chemical industry.

The following sections of the present chapter deal with the special features of the production of active substances in the pharmaceutical industry, particularly from the point of view of

environmental hazards.

A typical synthesis plant will consist of:

- production
  - reactor and separation system
  - separation, purification
  - materials handling (finishing) - raw material storage
- auxiliary activities
  - raw material storage
    - solid materials
    - liquids
      - bulk solvent storage in tanks
      - drum, container storage
    - industrial gases
  - storage of intermediates and products
  - transfer systems, piping, transport within plant
  - waste treatment and recovery
  - maintenance, energy supply

Production

Reactor

In synthesis plants usually *batch reactor vessels* (stirred tank reactors with heat transfer jacket) with size ranging from some hundred liters to ten cubic meters are the basic items of equipment which determine the size of the production.
A typical synthesis reactor arrangement is illustrated in Fig.1.
All parts of the reactor which are, or can be in contact with the chemical materials must be resistant to corrosion, consequently they may be: glass, glass lined steel, stainless steel, or special alloys.

Process control is key element of the system, due to the many remote organs (valves, switches, measure and control instruments) and the demand for the regulation of different parameters (temperature, pressure, concentration).
Manual operation is going to be obsolete.
The computer aided control systems have the additional advantage of uniformity of the batch processes, a prerequisite of the standard quality of the product.
Within a drug manufacturing plant, reaction vessels and ancillary equipment are often arranged into separate, dedicated process units being used for the production of one single, or a family of products.
In this case an integrated process control of the whole unit is necessary.

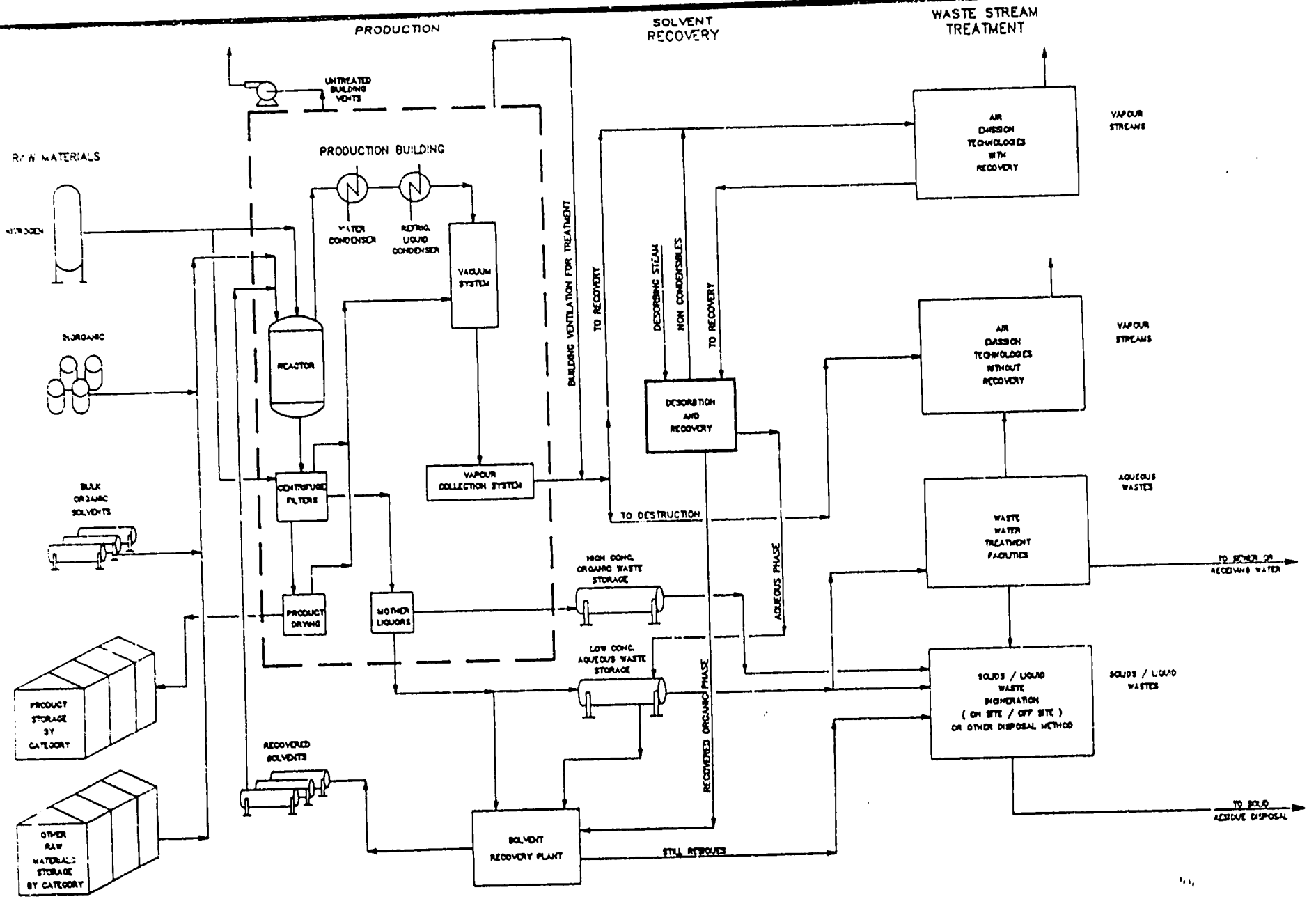
The batch type processes together with the technological flexibility of the stirred tank reactors yield the possibility of producing more than one product with the same equipment.
(Multi-product-, or multi-purpose-, or flexible plants). It has to be noted, however, that this flexibility has its own technological

and economical limitations, especially the time and labor requirements of the changing of products.
If the aim of the plant is to serve as a training basis for the personnel, or scale up/develop new process, or justify technological parameters, or validate process elements, the multi *purpose* plant will perform its duty.
A multi *product* plant may produce with good economy only a properly selected range of products.
Flexibility and change of products raise additional tasks to avoid unnecessary harms in environment. Some pharmaceutical products are manufactured in single product "campaigns", which may last a few days, weeks, or months depending upon the market. At the end of the campaign, process equipment is thoroughly cleaned - which results in huge amount of liquid wastes. Proper handling of such waste water is often neglected because of time constraint of tight campaign schedules.

Separation
Multi-step chemical reactions need certain procedures between the particular reactions in order to separate the product from remaining raw materials or by-products and to produce it in the purity required by the next reaction step.
The most typical separation procedures are: crystallization, filtration, sedimentation. If the solvent is to be removed, drying is also used.
Air ducts of centrifuges and dryers are the main sources of the volatile solvent emissions.
The rotating drum of the centrifuges work as a rotor of ventilator resulting in blowing out significant amount of air with high solvent content. The situation is much more favorable if the system is working under inert gas (usually Nitrogen).
Fluid bed dryers use air flow to lift, move the wet material and mix and contact intimately the particles with the hot air. The drying process is quick,
The dryer may be combined or closely connected to the filter (in many cases a centrifuge). Such more or less closed systems reduce the possibility of contamination of the product, but also the transportation losses and minimize the volatile solvent emission losses.

Purification
Due to the high requirements on the quality - first of all the chemical purity - of the pharmaceutical substances,the various separation procedures are the most frequently used processes in order to get rid of impurities and contaminants.
These are the suitable combinations of the following unit operations: (multiple) crystallization, filtration, adsorption, extraction, chromatography, drying).

In most cases the details of the purification are delicate know-how elements of the process and the best kept secrets of producers.
They - together with the *materials handling* procedures which result in the appropriate physical properties - ensure to meet the quality



GENERALISED MODEL – SYNTHESIS PLANTS

requirements of the product.
A simplified model of a synthesis plant may be found in Fig. 2.

Materials Handling
Milling, sieving, blending, and packaging of powder products or intermediates gives rise to *particulate emissions* which must be controlled using dust filters. The primary reason is the protection of the personnel but properly designed filter systems may also prevent dust entering the external environment.
Disposal of contaminated filters requires care and they are frequently incinerated.

Auxiliary activities

Storage, transfer of solid, liquid and gaseous raw materials, solvents, intermediates, (together with the recovery and/or treatment of wastes and facilities management may be regarded sometimes as "only" auxiliary processes, notwithstanding should merit due consideration, concerning working safety and environmental protection.
For example warehousing has been highlighted as a potential source of water pollution in the event of fire if proper precautions have not been taken to collect the run off water. Following a fire in a pesticides warehouse which caused major pollution to the river Rhine, many chemical manufacturers, especially located near major rivers, installed catch basins to collect run off water during a fire.
Concerning the hazards of warehousing, there is no difference between the pharmaceutical and chemical plants. In consequence of this, all regulations and guidelines elaborated by international organizations for the safe handling of dangerous chemicals (discussed in detail in following chapters of the present study) are also valid and be borne in mind.

Raw materials

Chemicals used in synthesis operations range widely and may include
- organic and inorganic reactants (solid, liquid, or gaseous)
- catalysts and
- liquids as solvents or reaction media.

Solid raw materials may be stored in containers or bags, outdoor or indoor. Segregation of different materials is essential. Due attention has to be paid to the chemical properties of the stored materials. Incompatible substances (those which have inclination to react)have to be stored in segregated compartments equipped with proper fire fighting and safety system.

Liquid materials are stored in tanks or drums.
Tank farms must be designed to store a complete range of fresh and recovered solvents. In order to reduce the potential of fire hazard, solvent tanks may be located underground. To avoid the risk

of ground contamination great care is needed to prevent leakage. (Double containment, leak monitors etc.)
It is common to have separate tankage for fresh solvents and mother liquor (or solvents for recovery) and recovered solvents.
In order to avoid mistakes and facilitate the transport of solvents, departments or buildings or product lines may have their own tankage.
In order to save place (especially in densely built urban areas) solvent tanks are located in the basement of production buildings. Even in case of appropriate fire precautions this solution can not be recommended.

Drums are used for the storage of quantities which are too small for tank system. Inflammable, explosive, toxic or corrosive liquids must be properly segregated even in external in storage.

All solvent storage areas (tank farms, drums; indoor or external) should be equipped with fire run-off systems in order to avoid pollution of the environment.

Transfer systems
Piping is commonly used to connect storage tanks with the receiving vessels. Pumps, valves, instruments, connections are emission sources.
Piping and air ducts are to be designed and operated with care in order to avoid cross contamination or accident caused by inadvertent contacting of non-compatible chemicals.

It is generally accepted practice that all raw materials entering a manufacturing site are accepted only when full ecotoxicological data has been provided by the supplier.

Emission sources

Waste streams from chemical synthesis operations are complex due to the variety of operations and reactions employed.

Solid wastes
Most common source of solid wastes are the various filters:
- process filters (including centrifuges)
- dust filters of the air ducts

Residues from reactors, still bottom tars are difficult to handle because of sticky behavior due to their moisture content.
Cleaning of equipment, working areas and warehouses also result in solid wastes of different nature.
In most cases these wastes will be incinerated.
Some sorts of used packaging materials can be reused or recovered, but care should be taken to avoid misuse of them.

Liquid wastes
Virtually every step of an organic synthesis generates a "mother liquor"(liquid medium in which certain operations take place e.g.: heating, cooling, mixing, crystallization, or chemical reaction)

Inoculum is prepared from the working seed (population of a microbiological strain maintained carefully in laboratory). A few cells from this culture are matured into a dense suspension through a series of test tubes and shaker flasks. All transfers are carried out in aseptic conditions aimed to grow sufficient cell mass (microorganisms or animal cells) in appropriate state to inoculate the production fermenter.
For further propagation, the cells are then transferred from the laboratory to seed-tanks which operate like full scale fermenters, but are designed not to produce the product, but for maximum cell culture growth. The final seed tank volume equals to 1 to 15 percent of that of the full scale fermenter.

Preparation of the fermentation media

The nutrients of the microorganisms must contain the necessary materials for the metabolism. Generally the main components are: carbohydrates, proteins, lipids and minerals.
The preparation steps may consist of cleaning, washing the raw material (in most cases agricultural products, or by products, in some cases wastes) mechanical treatment in order to ensure the suitable particle size distribution, and sterilization by steam at 120°C.

Production

Fermentation
starts with sterilization of the fermenter, a vessel equipped with mechanical stirrer, heater/cooler jacket, instruments, inlet/outlet pipe connections. Then the cell culture is charged from the seed tanks into the fermenter. Nutrients of the microorganisms are also fed into the fermenter. For both inputs sterilized pipes and valves are used. If the fermentation is aerobic (which it is most frequently), the content of the vessel is aerated with sterile air or oxygen. Agitation may be carried out either by the aeration system or by mechanical stirrer usually equipped with baffles. Control of the process is carried out by monitoring i.a. dissolved oxygen and CO_2 concentration, pH, temperature.
Size of the fermenters vary widely from 1-2 liters to 10.000 m^3.
Residence time may be in the range of 10 to 200 hours.
A simplified scheme of a production fermenter can be seen in Fig.3.
(Continuous fermentation in the pharmaceutical industry has recently been introduced in routine production of special, high value products such as monoclonal antibodies.)

Crude product recovery
At the end of the fermentation, the fermenter ''broth'' is usually filtered to separate solid biomass (mycelium) from the liquid phase. In most cases the product is in the filtrate. If not, it has to be gained from the filtercake.

Concentration, Purification

disintegrating, milling (which their ancillary processes such as screening, sedimentation, drying) are the most common procedures.

Extraction

may be carried out continuously, using specially designed equipment. One of them - dedicated for the extraction of alkaloids - is demonstrated in Fig. 6.

In continuous extractors the direction of flow of the two media, - the raw material and the solvent - may be parallel or counter current. Due to economy, counter current extractors are used widely.

A continuous counter current extractor takes in fresh raw material and solvent at opposite ends and transports them in opposite directions, so the nearly saturated solvent is met with the fresh raw material and the nearly fully extracted raw material meets the fresh solvent before leaving the extractor, consequently the difference of concentration of the active ingredient between the two phases is always at maximum resulting in high efficiency.

The solvent may be water, ethyl alcohol, some ketone, alkane, or a number of other solvents.

The active substance is leaving the equipment dissolved in the liquid phase.

Extraction may also carried out by batch operation, or semi continuously in multi stage (cascade of stirred) extractors.

Concentration-purification

A series of concentration and purification steps such as liquid-liquid extractions, precipitation, filtration, sedimentation, distillation etc., may be required to isolate the desired product. Once the final product has reached the desired purity, it is recovered by processes such as crystallization, filtration, and drying. For heat sensitive products thin film evaporators, ultrafiltration, freeze-drying or recently extraction by ultracritical CO_2 are used to remove the solvent.

Emission sources

Solid wastes

of natural product extraction include spent raw materials such as leaves, roots, animal tissues. The treatment of spent material is a major problem because of its bulk in relation to the quantities of product. Concerning landfill - the most usual, cheapest, however in some cases rather questionable method, as seen in other parts of the present study - some authorities set a limit of 3% by weight of the organic solvent content of wastes. Minimization of residual organic solvent content is of first priority.

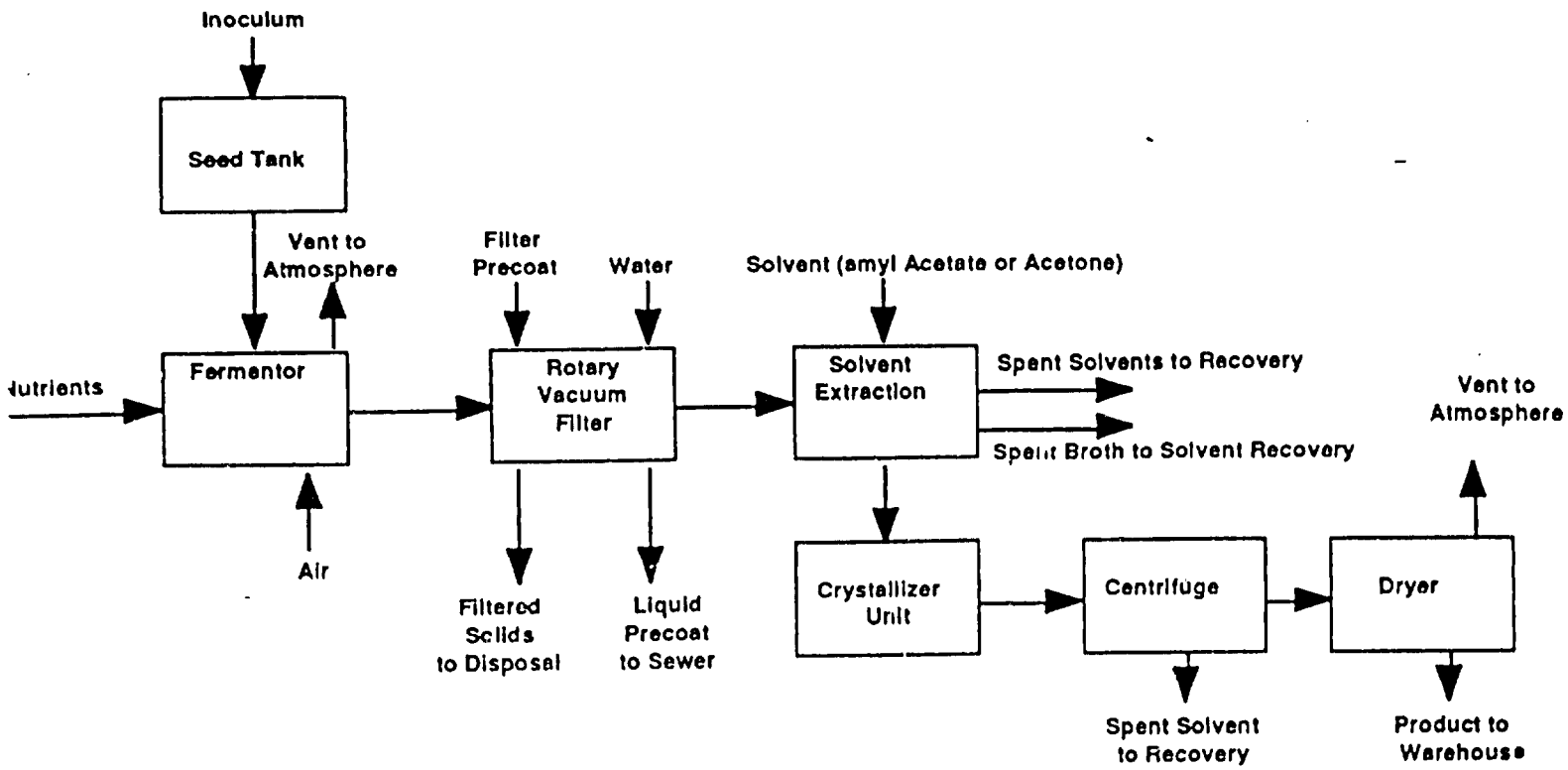
Alternative disposal method may be incineration whereby organic solvent-, and spent activated carbon content is a plus.

Liquid wastes

The extraction plants usually give rise to problems of control of liquid effluents very similar to those of synthesis plants.

Extraction waste waters have typically low BOD, COD and TSS levels and a pH in the range of 6 to 8.

Air emissions
The use of volatile solvents need condensers, scrubbers and ad-, or absorbers. Examples will be given in Part III of this study.


Inoculum
Seed Tank
Vent to Atmosphere
Filter Precoat
Water
Solvent (amyl Acetate or Acetone)
Nutrients
Fermentor
Rotary Vacuum Filter
Solvent Extraction
Spent Solvents to Recovery
Spent Broth to Solvent Recovery
Vent to Atmosphere
Air
Filtered Solids to Disposal
Liquid Precoat to Sewer
Crystallizer Unit
Centrifuge
Dryer
Spent Solvent to Recovery
Product to Warehouse

The product can be obtained from the liquid phase and purified by a combination of various separation processes. In most cases: solvent extraction, precipitation, ion exchange, adsorption, chromatography, ultrafiltration, centrifugal sedimentation.
By solvent extraction, the aqueous filtrate is contacted with the suitable organic solvent, typically methylene chloride or butyl acetate, to transfer the product into the solvent phase.
Downstream processes of the production of most commonly produced pharmaceutical substances and product groups are summarized in Fig.4., and a process flow diagram of a typical fermentation plant may be seen in Fig 5.

Emission sources

The fermentation process usually generates large volumes of wastes such as the spent aqueous fermentation medium and solid cell debris. The aqueous medium is very impure, containing unconsumed raw materials (corn steep liquor, fish meal, molasses). Filtration processes result in large quantities of solids in form of spent filter cake which incudes the solid remains of the cells, filter aid (anorganic minerals), and also small amount of the final product.

Solid wastes

As raw materials of the fermentation are usually of natural origin (agricultural sources, such as corn steep liquor, fish meal, molasses), unconsumed raw materials are frequently utilized as additives to animal food. Residues of the final product in the mycelium may be useful, especially in case of vitamins, amino acids or pharmaceutical substances.
If the utilization for animal feed is not possible, incineration may also be considered. Organic solvent content or spent active carbon prove to be useful.
Solid wastes thus can be used to produce heat energy, but this can also be achieved through biogas generation as well.
Anorganic filter aids are inert and incombustible, so landfill as ultima ratio may be taken into consideration, but only in case if the waste material meets environmental requirements.
In all above cases solid wastes -due to their moisture content - are sticky, which makes their manipulation difficult.
The odor of biomasses has also be taken into consideration especially in the neighborhood of populated districts.

Liquid wastes

After product recovery, spent filtrate, spent solvent from extraction are discharged as waste liquids augmented by waste water from equipment cleaning and fermenter vent gas scrubbing.
Waste waters from fermentation operations typically have high BOD, COD, and TSS levels with a pH range of 4 to 9: while those from solvent extraction have low BOD, COD, and TSS levels, with pH=6-8.

Air emissions

Volatile solvents used in product recovery operations may release vapors to air, so exhaust treatment is necessary.

The usually large volume of the air flow, combined with low concentration values make the recovery of organic solvents difficult. Practical methods and equipment will be shown in other parts of the present study.

NATURAL PRODUCT EXTRACTION

Natural product extraction is the production of pharmaceutical materials (be it [a mixture of] identified compounds, or traditional substances as ''essential oils'') from natural sources such as roots, leaves of plants; animal organs tissues. These pharmaceutical, which exhibit certain pharmacological properties, are in most case well known since centuries, however, the exact identification of their active ingredients is not always simple. Separation and analysis of them need expertise and high level instrumentation. The effect of the drug is attributed to ''lead'' components (alkaloids, such as morphine, vincamine etc.) or synergism of - in some cases unidentified - active substances. Anyhow, their therapeutic and preventive efficiency has been proved since generations and confirmed by up to date methods.

One of the characteristics of natural product extraction is that the amount of finished product is small compared to the amount of raw material used. During each process step, the volume of material being worked can greatly diminish to the point where final purification may occur on volumes less than one thousandth of the initial volume. Another characteristic is the various and irregular form of the raw material:
fiber-like materials from various parts of plants; or formless, sticky consistence of animal organs. Handling of such materials is one of the most sophisticated problem of the process.
Because of these properties of the materials, conventional batch-, or continuous processes and equipments used in other fields of the chemical or pharmaceutical industry are not suitable for natural extraction processes.

Typical steps of processes in an extraction plant are:

- preparation
- extraction
- concentration - purification

Preparation

Raw materials are generally easily degradable. Animal organs must be kept cool and need to be immediately processed, some herbs may be stored only in dried state, however, materials of natural origin tend to loose content of active substance with time.
Storage of solvents and other auxiliary activities are similar to those already discussed in the section of synthesis plants.

The first step in the process is to prepare the raw material for extraction. This step is determined by the purity and physical form of the incoming raw material. Cleaning, washing, drying and usually

disintegrating, milling (which their ancillary processes such as screening, sedimentation, drying) are the most common procedures.

Extraction
may be carried out continuously, using specially designed equipment. One of them - dedicated for the extraction of alkaloids - is demonstrated in Fig. 6.
In continuous extractors the direction of flow of the two media, - the raw material and the solvent - may be parallel or counter current. Due to economy, counter current extractors are used widely.
A continuous counter current extractor takes in fresh raw material and solvent at opposite ends and transports them in opposite directions, so the nearly saturated solvent is met with the fresh raw material and the nearly fully extracted raw material meets the fresh solvent before leaving the extractor, consequently the difference of concentration of the active ingredient between the two phases is always at maximum resulting in high efficiency.
The solvent may be water, ethyl alcohol, some ketone, alkane, or a number of other solvents.
The active substance is leaving the equipment dissolved in the liquid phase.
Extraction may also carried out by batch operation, or semi continuously in multi stage (cascade of stirred) extractors.

Concentration-purification
A series of concentration and purification steps such as liquid-liquid extractions, precipitation, filtration, sedimentation, distillation etc., may be required to isolate the desired product. Once the final product has reached the desired purity, it is recovered by processes such as crystallization, filtration, and drying. For heat sensitive products thin film evaporators, ultrafiltration, freeze-drying or recently extraction by ultracritical CO_2 are used to remove the solvent.

Emission sources

Solid wastes
of natural product extraction include spent raw materials such as leaves, roots, animal tissues. The treatment of spent material is a major problem because of its bulk in relation to the quantities of product. Concerning landfill - the most usual, cheapest, however in some cases rather questionable method, as seen in other parts of the present study - some authorities set a limit of 3% by weight of the organic solvent content of wastes. Minimization of residual organic solvent content is of first priority.
Alternative disposal method may be incineration whereby organic solvent-, and spent activated carbon content is a plus.

Liquid wastes
The extraction plants usually give rise to problems of control of liquid effluents very similar to those of synthesis plants.
Extraction waste waters have typically low BOD, COD and TSS levels and a pH in the range of 6 to 8.

Air emissions
The use of volatile solvents need condensers, scrubbers and ad-, or absorbers. Examples will be given in Part III of this study.

REDUCTION OF EMISSIONS
COST EFFECTIVE POLLUTION CONTROL

END OF PIPE WASTE TREATMENT

Industrial pollution control in general - and also in the pharmaceutical industry - traditionally has been carried out essentially on an end-of-pipe basis.
Such *end-of-pipe waste treatment* is in most cases a destructive system, i.e. they provide no return for the company in terms of process efficiency.

The size (and cost) of waste treatment equipment bears a direct relationship to the volume to be treated and also to the concentration of pollutant.
For example most physical and chemical treatment (neutralizing, oxidation, reduction, flocculation, sedimentation etc) parameters and sizes of equipment are determined by hydraulic factors such as surface loading rate and retention time; or biological treatment is similarly depending on pollution load, such as COD (chemical oxygen demand).

It is evident therefore that the reduction of waste quantities have a significant impact on the size and cost of an end-of-pipe system. Increased environmental pressure, on the other hand, require industry to meet tighter regulations which in increasing number of cases can not be met by conventional end-of-pipe solutions without seriously impacting the economical viability of the individual process.
Accordingly, new approaches have emerged in recent times, such as -

- *source management* defined as ''the development of full understanding of the nature of all waste streams, (liquid, gaseous, or solid) and the exact circumstances by which they are generated in order to eliminate or minimize pollution before it arises.''
- *waste prevention and reduction* posing the questions: how can the generation prevented, or the volume reduced, or the reuse, or recovery of the waste be realized.

This progressive shift from waste treatment towards waste prevention has the following benefits:
- waste quantities are reduced
- raw material consumption and therefore resp. costs are reduced
- waste treatment costs are reduced
- pollution potential is reduced
- working conditions may be improved
- process efficiency can also be improved

WASTE AUDIT

In order to prevent, reduce waste generation or to consider recycle or reuse it the process itself is to be examined thoroughly to identify the origins of wastes, the operational problems and those areas where improvements can be made.

A waste audit is the starting point therefore to approach problem identification and solving.

A properly organized and executed waste audit enables to take a comprehensive look at the site or process to facilitate the understanding of material flows and focus the attention on areas where waste reduction and cost saving is possible.

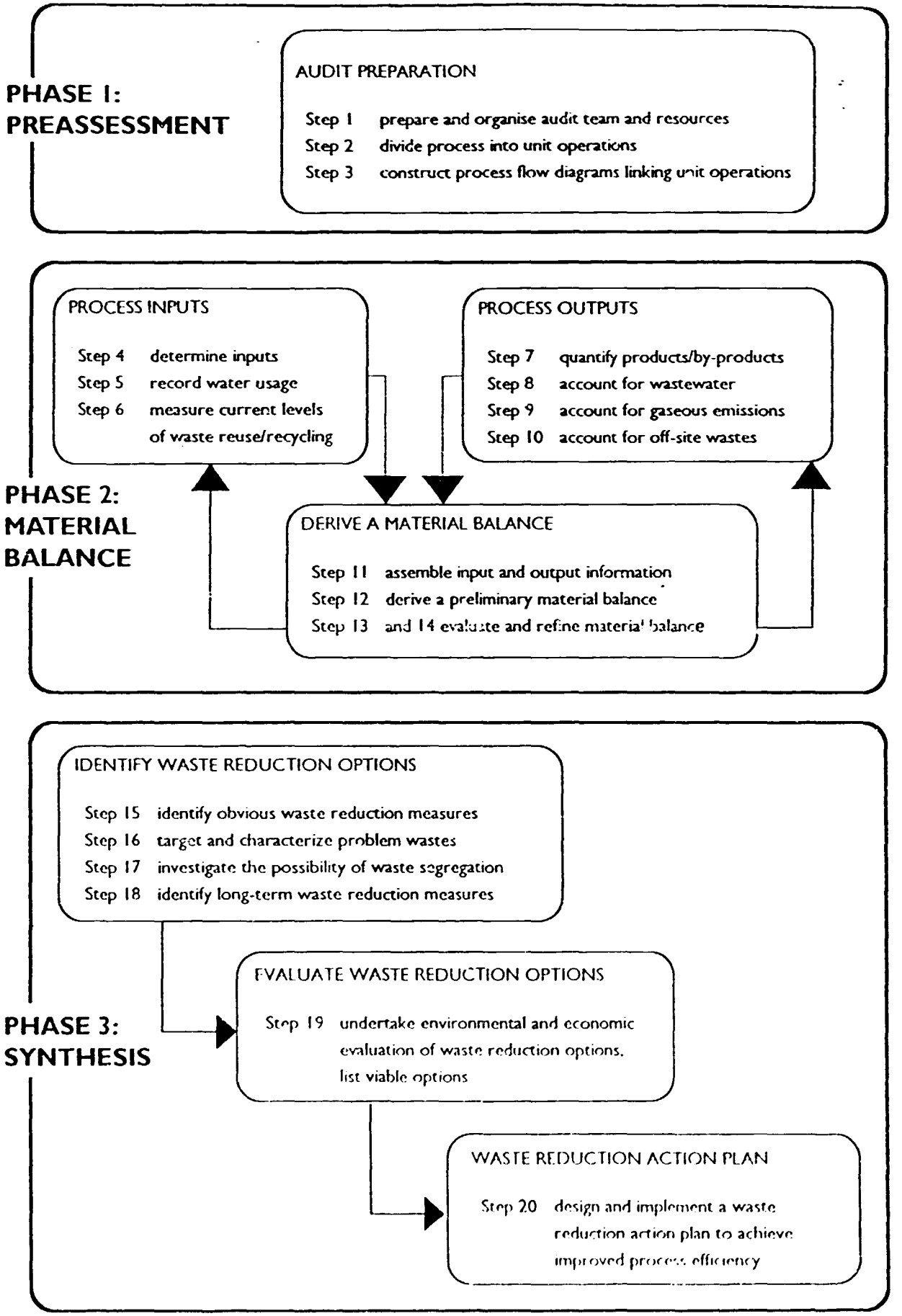
Undertaking a waste audit involves observing, measuring, recording data, collecting and analyzing waste samples. To be effective it must be done methodically and with full management and operator support.

A good waste audit

- defines sources, quantities and types of waste being generated
- collates information on unit operations, raw materials, products, water usage and wastes
- highlights process inefficiencies and areas of poor management
- helps set targets for waste reduction
- increase knowledge of the process
- helps to improve process efficiency

The waste audit procedure can be applied on various scales. At plant level, wastes can be traced to particular processes allowing allocation of treatment charges where necessary; and at the process level the exact origins of wastes can be identified enabling waste reduction measures to be established.

A waste audit approach leading to the implementation of a waste reduction action plan has been elaborated by UNDO/UNEP [29] is illustrated in the form of a flow diagram in Fig. 7.


PHASE 1:
PREASSESSMENT
AUDIT PREPARATION
Step 1 prepare and organise audit team and resources
Step 2 divide process into unit operations
Step 3 construct process flow diagrams linking unit operations
PHASE 2:
MATERIAL
BALANCE
PROCESS INPUTS
Step 4 determine inputs
Step 5 record water usage
Step 6 measure current levels of waste reuse/recycling
PROCESS OUTPUTS
Step 7 quantify products/by-products
Step 8 account for wastewater
Step 9 account for gaseous emissions
Step 10 account for off-site wastes
DERIVE A MATERIAL BALANCE
Step 11 assemble input and output information
Step 12 derive a preliminary material balance
Step 13 and 14 evaluate and refine material balance
PHASE 3:
SYNTHESIS
IDENTIFY WASTE REDUCTION OPTIONS
Step 15 identify obvious waste reduction measures
Step 16 target and characterize problem wastes
Step 17 investigate the possibility of waste segregation
Step 18 identify long-term waste reduction measures
EVALUATE WASTE REDUCTION OPTIONS
Step 19 undertake environmental and economic evaluation of waste reduction options, list viable options
WASTE REDUCTION ACTION PLAN
Step 20 design and implement a waste reduction action plan to achieve improved process efficiency

COST EFFECTIIVE POLLUTION CONTROL

Based on a properly executed waste audit the optimal solution can be selected in two steps, by integrated source control followed by optimized end-of-pipe waste treatment.

Integrated source control
embrace a number of key technical, management and operational initiatives:

- application of cleaner processes
- enhanced housekeeping practices
- water conservation, incl. reuse and recycle
- waste avoidance or minimization
- materials recovery and,or reuse
- disciplined monitoring of performance

Needless to say is that the management of the company has definitive role: its initiative is a precondition of the success. This include awareness, commitment, training at all levels of the hierarchy and also a management struccure that positively links production, pollution control and environmental management.

Optimized end-of-pipe control
Integrated source control in isolation is not sufficient to achieve the overall objective of cost effective pollution control or cost effective environmental management. This requires detailed consideration of optimized end-of-pipe treatment of wastes, reduced to minimum by integrated source control.

Key technical issues concerning optimized end-of-pipe treatment could include provision of the following:

- effective segregation of waste-water streams for optimized pre-treatment, energy recovery, etc.
- effective flow and load pre-balancing
- control systems to prevent the overdosing of reagents
- upgrading of existing facilities

Management and operational initiatives are the same as identified for integrated source control(i.e. commitment at all levels, better training to ensure efficient operation and performance monitoring of end-of-pipe systems).

An overall summary of the principal components of cost effective pollution control and benefits are illustrated in Fig.8.

CASE STUDY I
SOURCES OF EMISSIONS AT THE SYNTHESIS OF NALIDIXIC ACID

Nalidixic acid is a generic anti-infective quinoline derivate, developed about 30 years ago (first publication: USP 3 149 104 [Sterlig Drug; granted 15.09.1964; priority:03.01.1961]).

There are various synthesis options for the synthesis, one of the most frequently used will be summarized.

The aim of the present summary is not to give a description of the process for direct use for production, but to demonstrate the places where by products, waste are generated; identify the wastes and give recommendation for their treatment.

Consequently the process description does not contain know-how elements of the production. These can be obtained from process donors or from UNIDO.

PROCESS DESCRIPTION

Step I. Condensation of 2-amino-6-picoline (2-amino-6-methylpyridine)with diethylmalonate and trietoxy-methane (ortho-formic-acid triethylester) at 110°C. Product: Intermediate I = PAMM (Picolylamino-methylene-malonate).

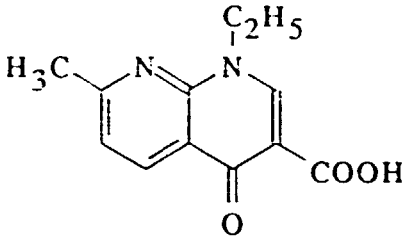
Step II. Cyclisation of the open chain PAMM obtained in the first step in Diphyl (Diphenyl-ether) at 250°C, isolation of Intermediate II= Naphtiridinester (4-hydroxi-7-methyl-1,8-naphtiridine-carboxylicacid-ethylester).

Step III. Intermediate II is ethylated by triethylphosphate in petrolether at 70-80°C, hydrolysed at 100°C for 3-4 hours, dissolved in water and acidified to obtain nalidixic acid. This is purified with activated carbon in acetic acid, concentrated, centrifuged and dried.

The following description will contain:

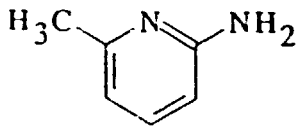
- Data on Nalidixic acid USP XXII
- Flow charts
- Flow sheets

NALIDIXIC ACID USP XXII



Molecular Weight:		232.23
Formula:		$C_{12}H_{12}N_2O_3$
CA-Number:		389-08-2
Names:	CA:	1,8-Naphthyirdene-3-carboxylic acid, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-
	INN:	Nalidixic Acid
	Other names:	1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphtyridine-3-carboxylic acid
Indication:		Anti-infective, quinolin-derivative

PREPARATION

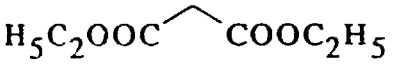


2-Amino-6-methylpyridine

MW = 108,14

$C_6H_8N_2$

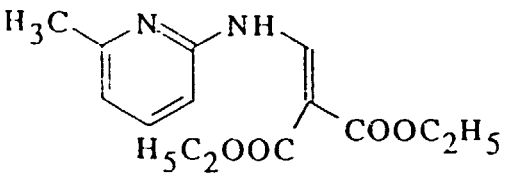
+



Diethyl malonate

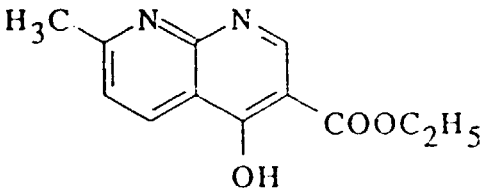
MW = 160,17

$CH(OEt)_3$



$C_{14}H_{18}N_2O_4$ MW = 278,31

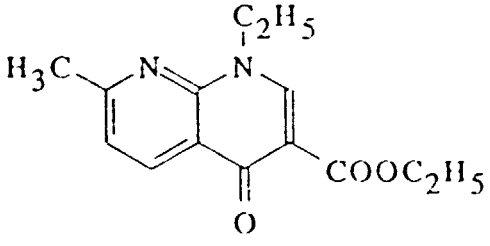
Diphenyl-ether

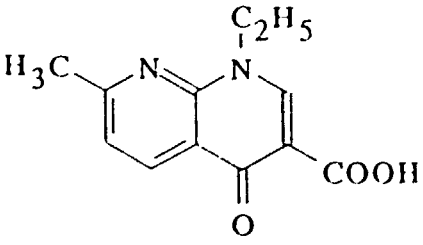


$C_{12}H_{13}N_2O_3$ MW = 233,25

Et_3PO MW = 134,16

Triethylphosphate

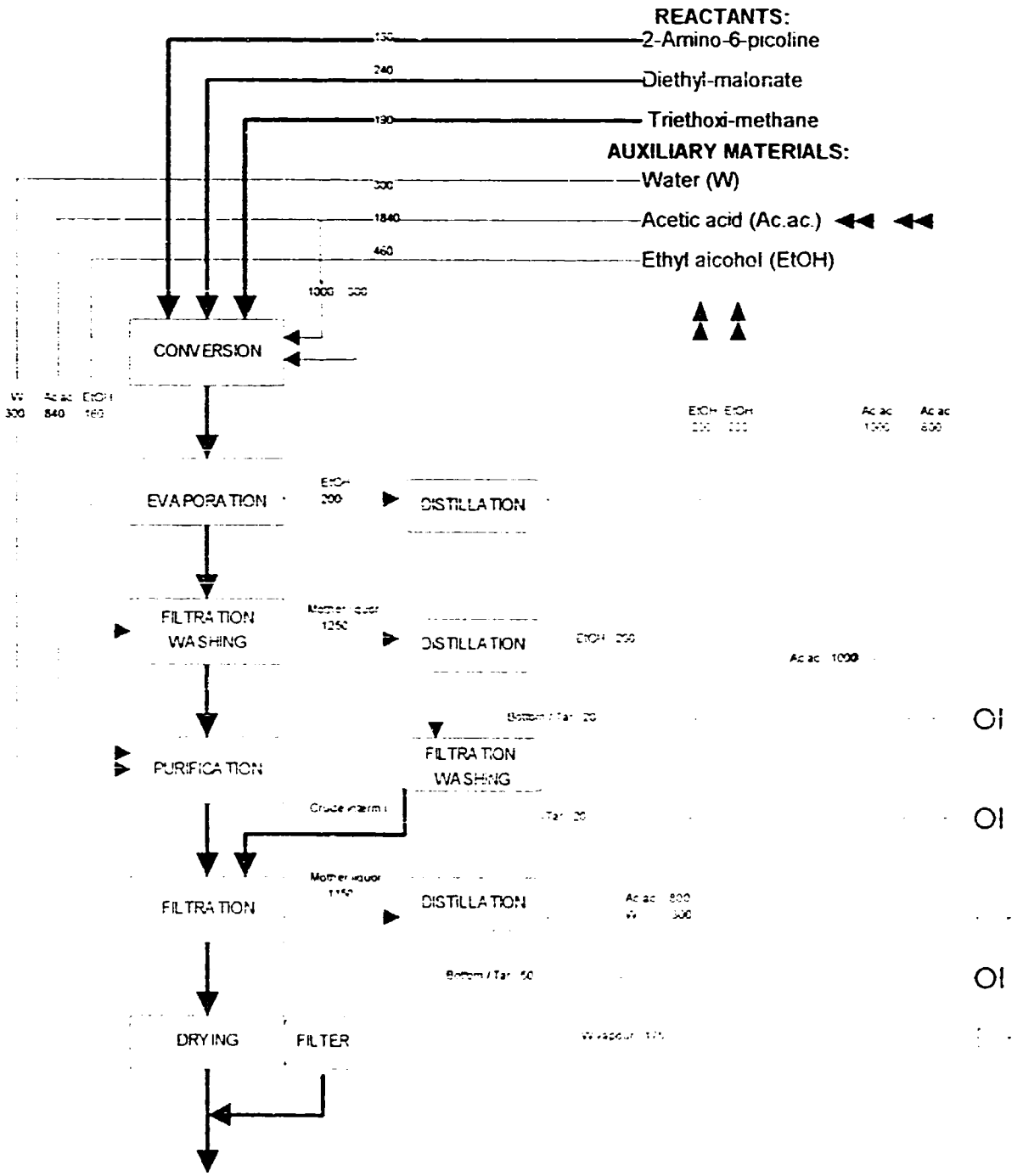




Nalidixic Acid

NALIDIXIC ACID
FLOW CHART

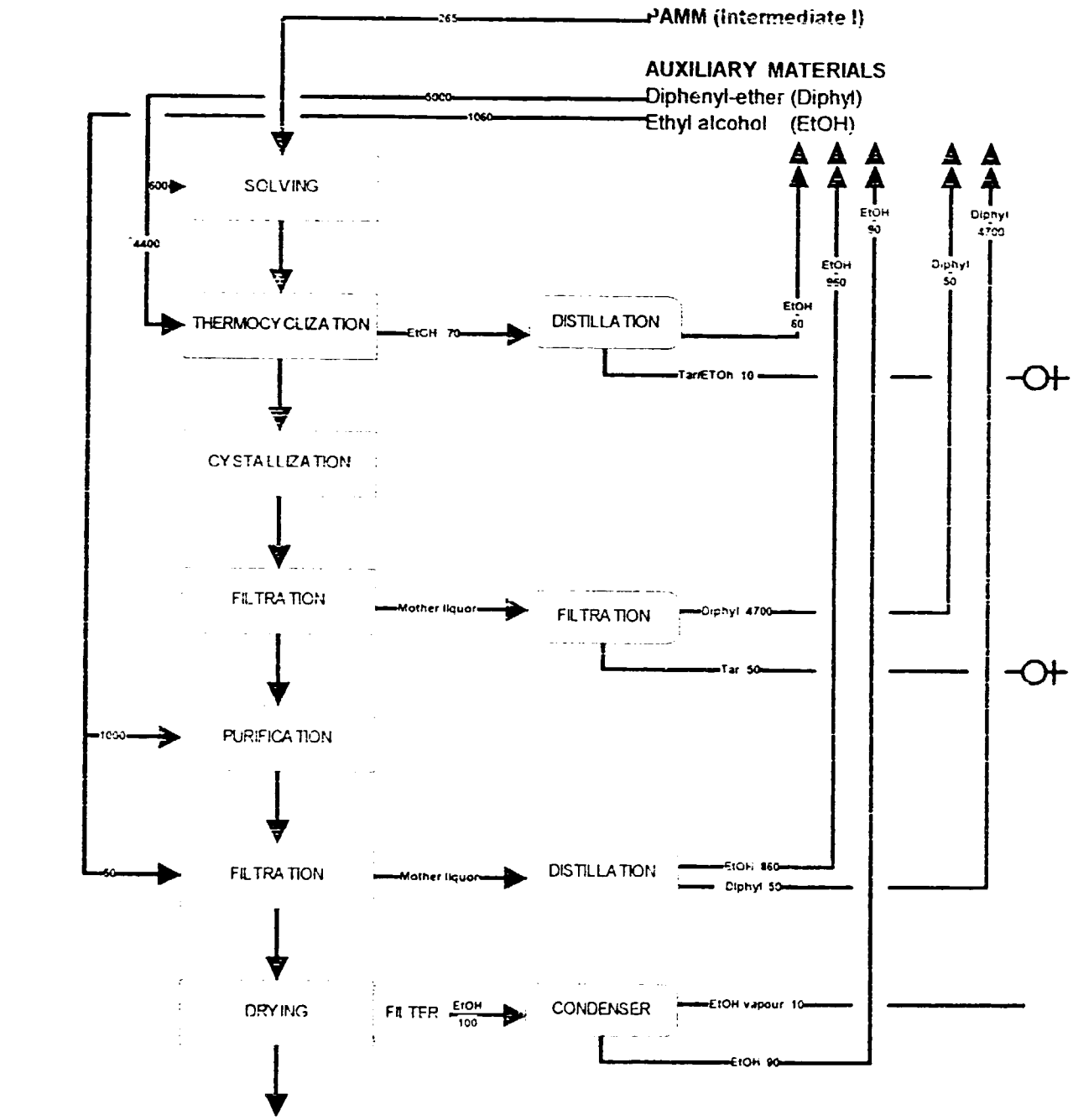
Step 1



265
Intermediate I = PAMM
(Picolylamino-methylene-malonate)

NALIDIXIC ACID
FLOW CHART

Step 2



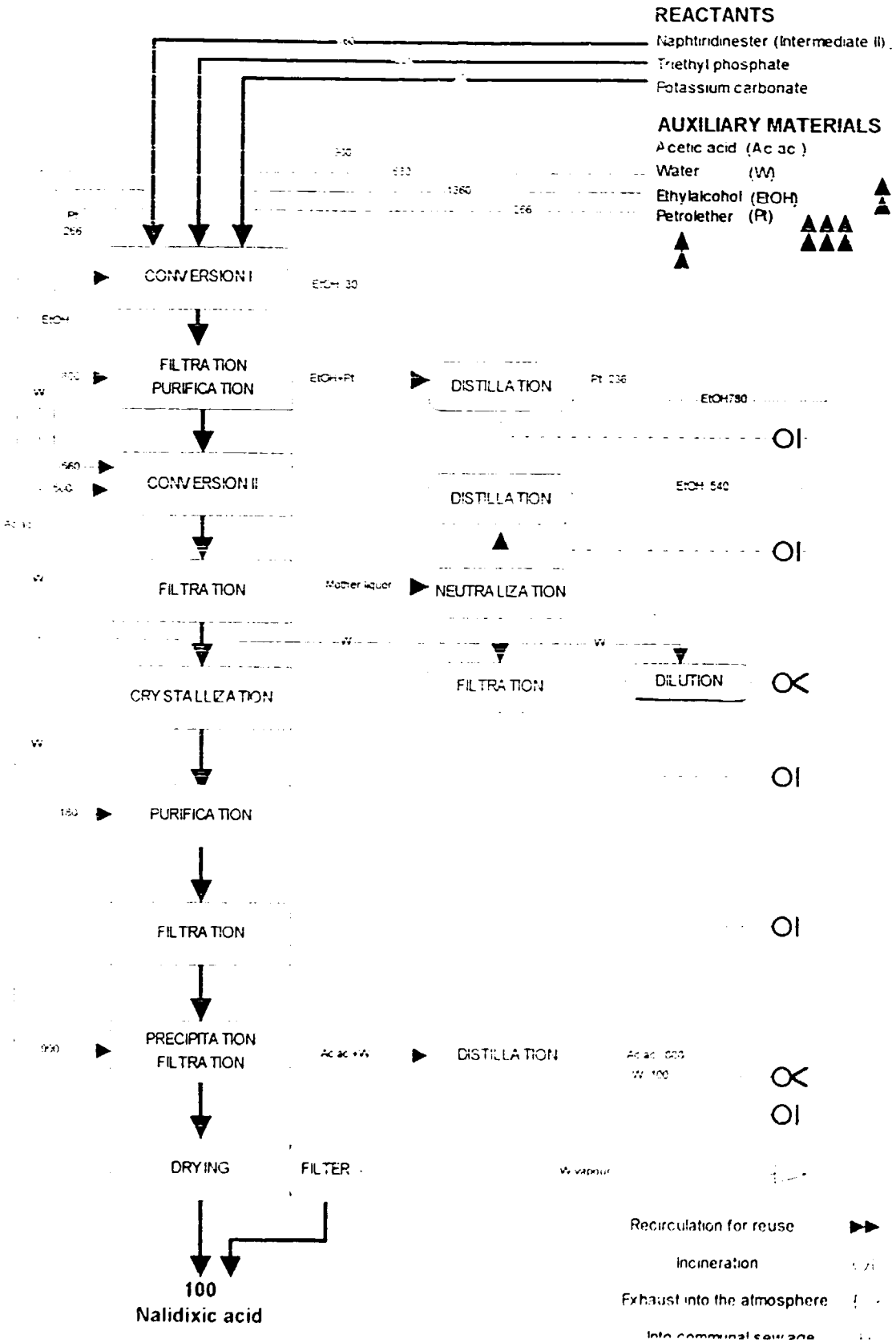
160

Intermediate II = Naphtiridin-ester

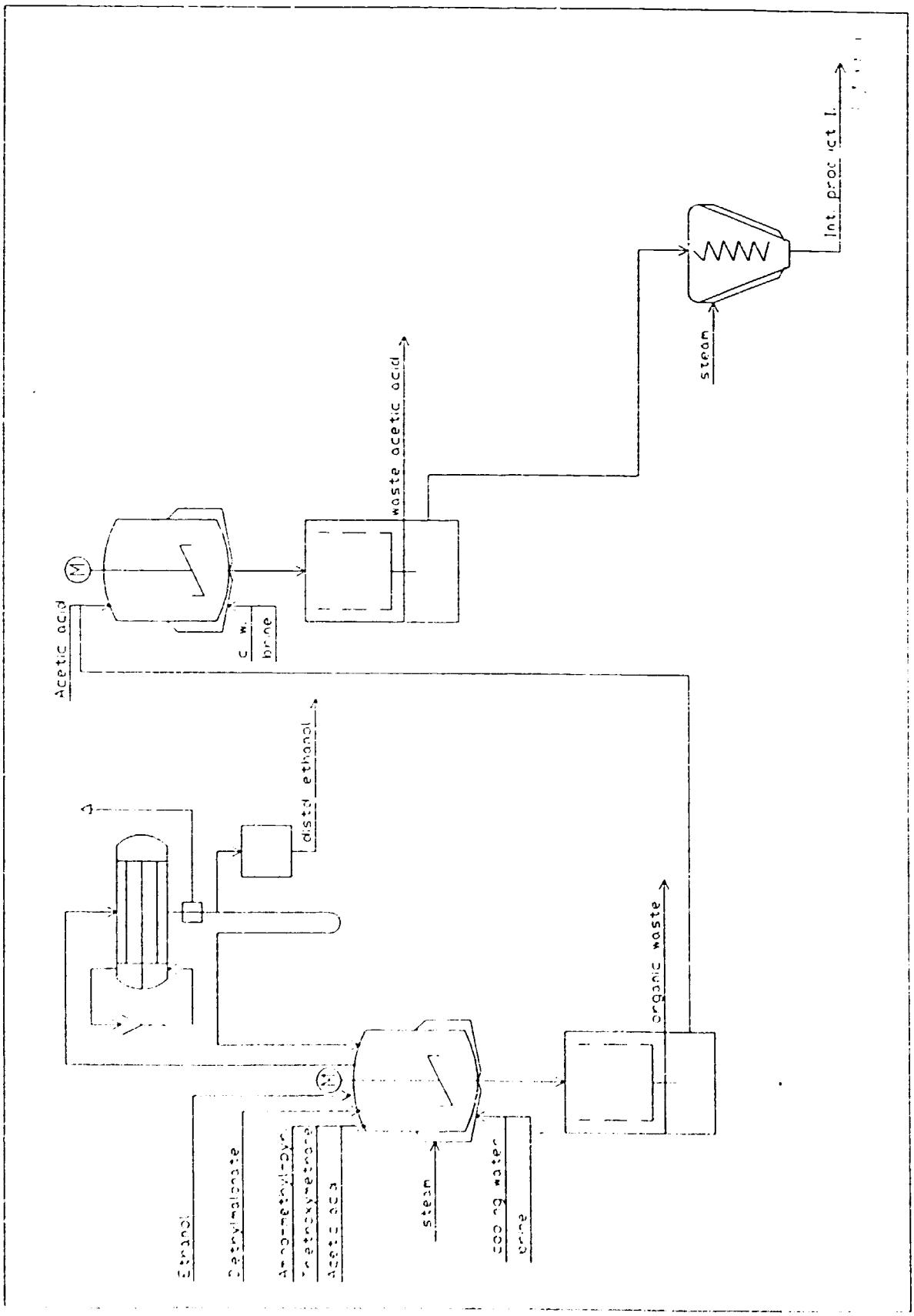
(4-hydroxi-7-methyl-1,8-naphtiridine-carboxylicacid-ethylester)

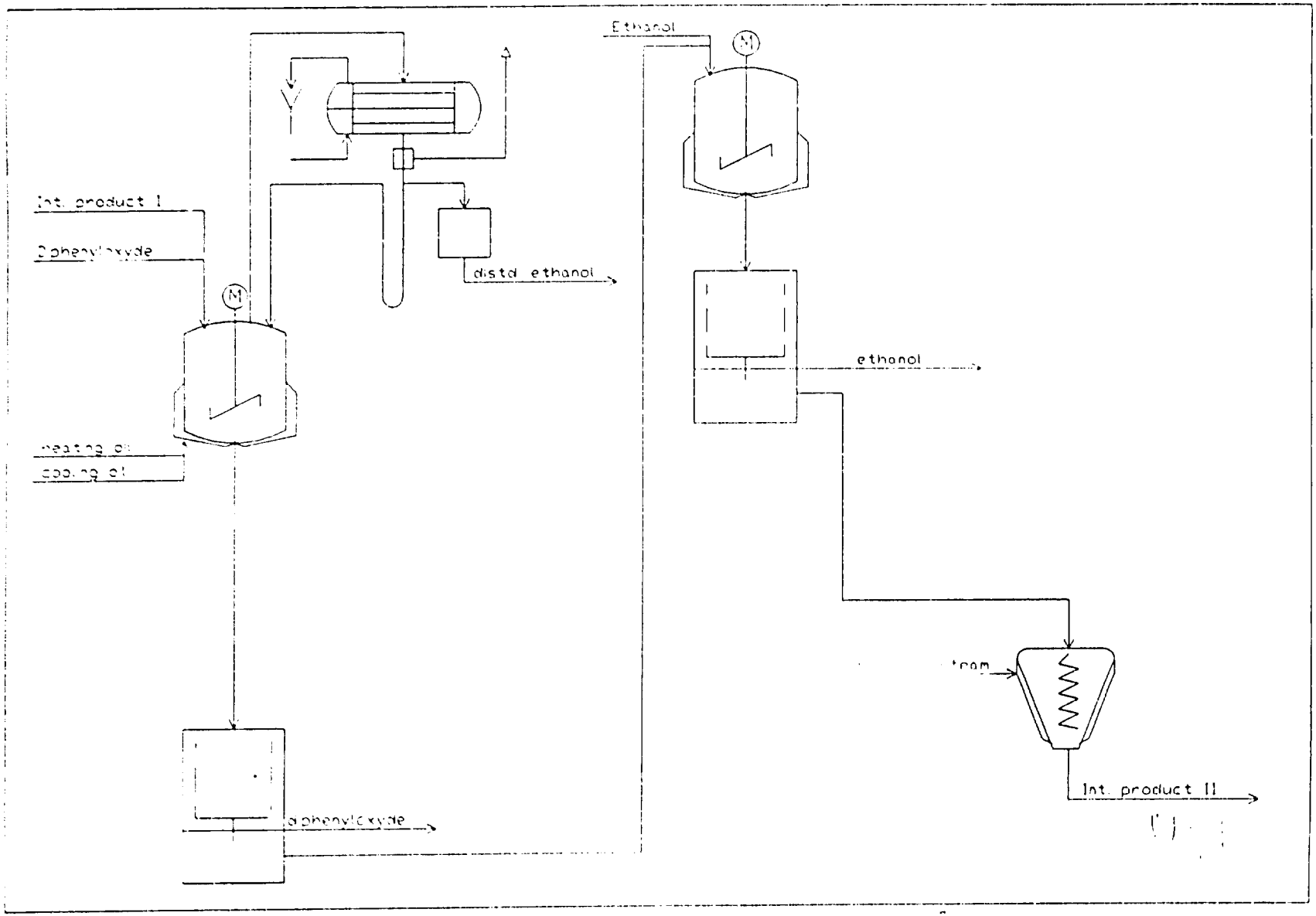
FLOW CHART

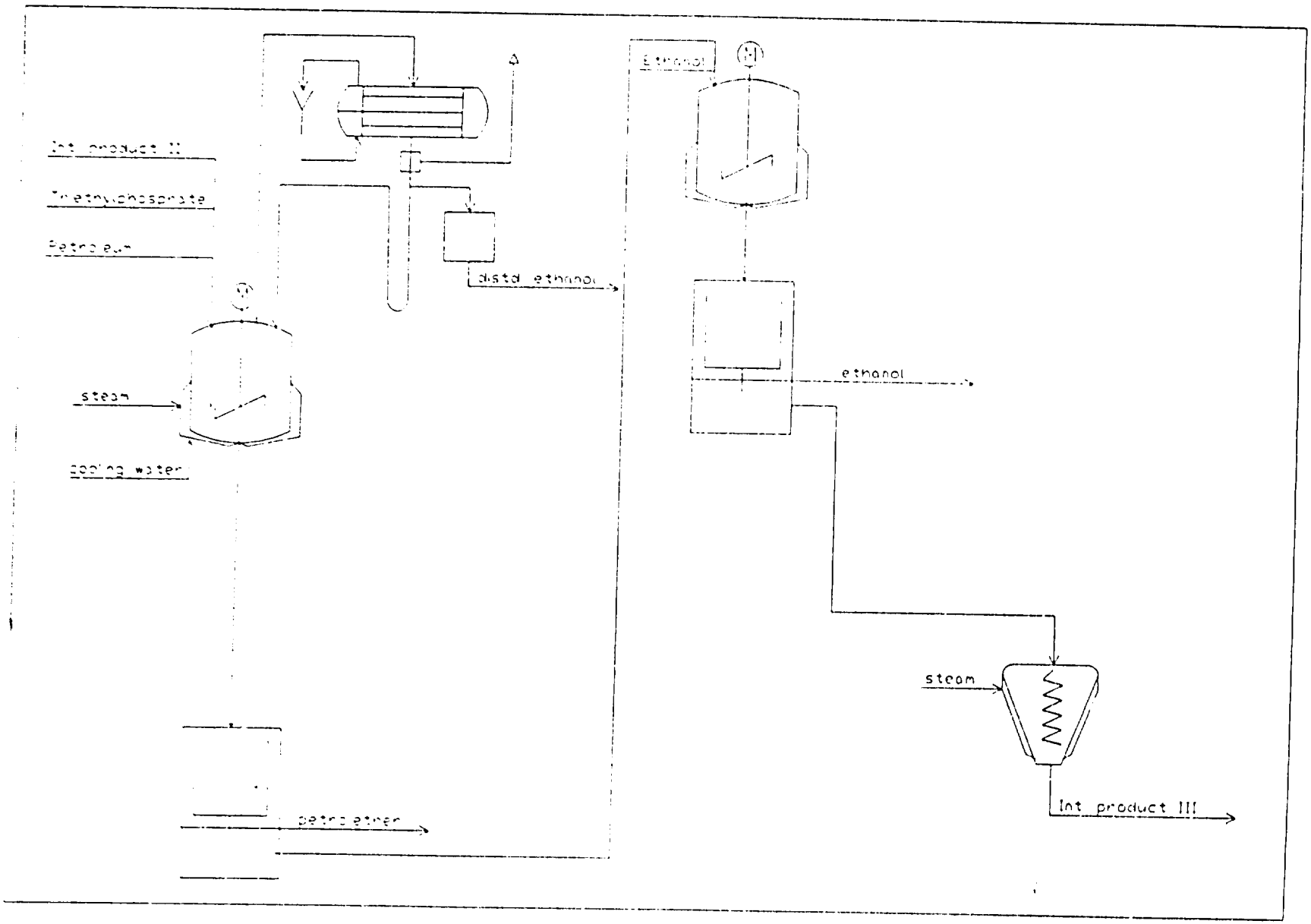
Step 3

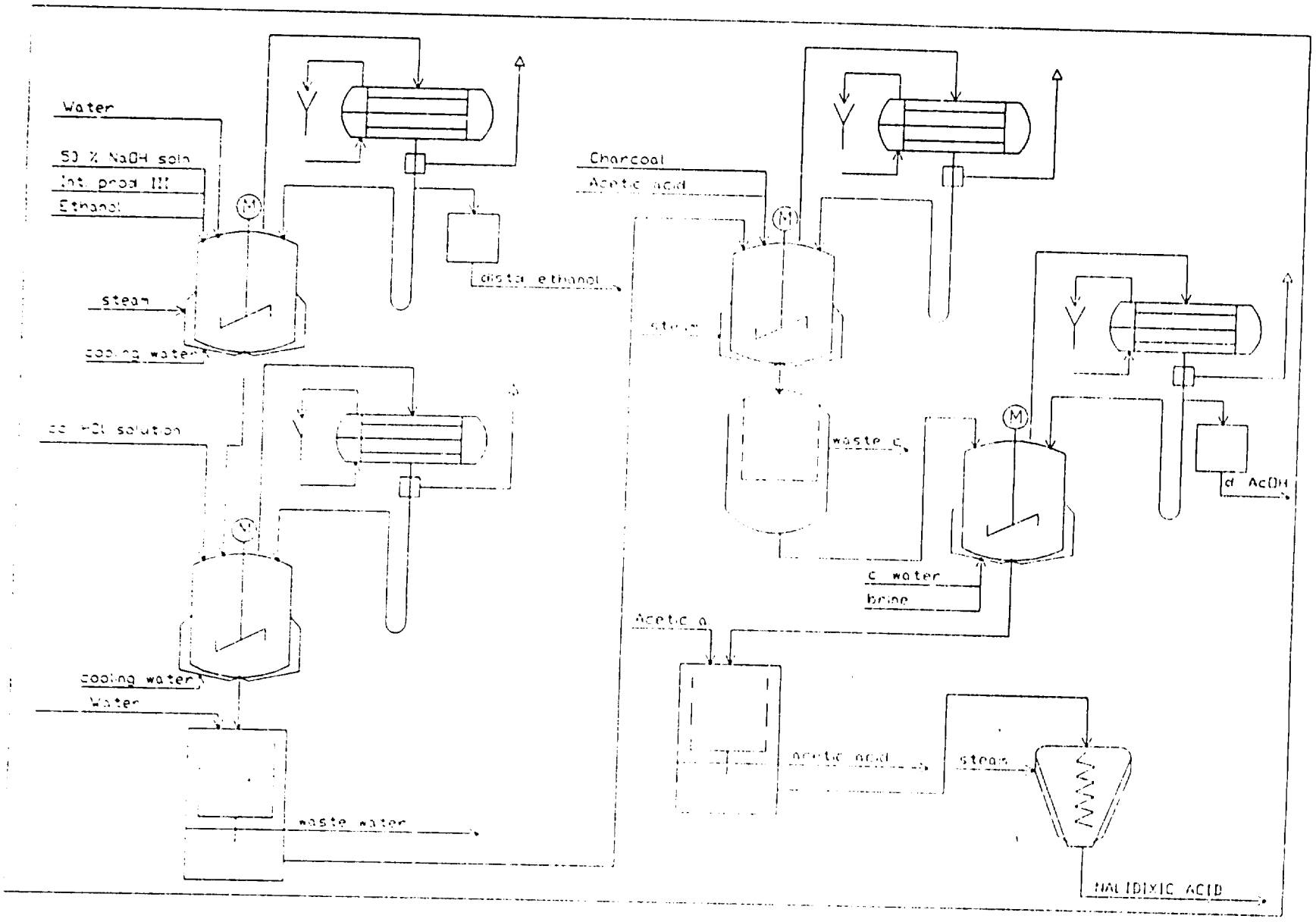


Step 1. N-alkylation




Ethanol
Int. product I
Diphenyloxyde
distd. ethanol
ethanol
heating oil
cooling oil
steam
Int. product II
diphenyloxyde


Int product II
Triethylphosphate
Petroleum
distd ethanol
Ethanol
ethanol
steam
cooling water
steam
Int product III
petroleum


Water
50 % NaOH soln
Int. prod III
Ethanol
steam
cooling water
waste ethanol
Charcoal
Acetic acid
steam
waste c
d AcOH
c water
brine
Acetic a
cooling water
Water
waste water
acetic acid
steam
NALIDIXIC ACID

CASE STUDY II

SOURCES OF EMISSIONS AT THE FERMENTATION OF PENICILLIN G

SOURCES OF EMISSIONS
AT THE FERMENTATION OF PENICILLIN G

The present case study is relating to a total volume of 760 m^3.
The volumes of the individual fermenters are 50 and 63 m^3.
Cycle of fermentation is 220 hours (10 days).
The total amount of fermentation broth for harvest, taking into account the partial harvest over the latter period of the fermentation (when some broth is withdrawn to make room for the sugar and other feeds), is thus between 50 m^3 and 65 m^3 per day.

In the fermentation sugar feed is stopped 12 hours before harvest and this will significantly reduce the unused dextrose in the medium. Typical levels of these materials at the end of the fermentation cycle might be

sugar: 2,000-4,000 mg/l
phenylacetic acid: 600-1,200 mg/l
ammoniacal-Nitrogen: 200-700 mg/l

At the end of the fermentation the mycelium (together with partial harvest) is killed with formaldehyde and flocculated with flocculating agent. The mycelium is then removed by filtration using rotary drum filters without the use of precoat. The occasional partially lysed batch may require some precoat but this is a very rare occurrence.
The recovery process is illustrated overleaf.

Wastewater arise from:

- spent broth
- solvent extraction (butyl acetate recovery)
- butanol distillation (azeotropic water-butanol mixture)
- crystallization blow down
- spent caustic from carbon rinsing

Solid wastes comprise:

- dewatered mycelial wastes at around 17% dry solids that are currently introduced back into the wastewater stream
- waste activated carbon containing caustic soda residues and traces of butyl acetate disposed to landfill

A summary on the environmental profile of Penicillin G can be found overleaf.

PENICILLIN G ENVIRONMENTAL PROFILE

Broth: 153m³/day
No Batches/day: 1

POLLUTION

Discharges to Water m³/day	
Waste water	517
Washing water	292
Total	809

Emissions to Air	
Air + micro-organisms	1,032 Nm³/day
Butyl acetate	132kg/day
Butanol	201kg/day
Acetone	1,438kg/day

RESOURCES

Energy	
Electric kwh/day	45,497
Thermic Gcal/day	351
Air Nm³/day	1,032

Raw Materials kg/day	
Biosynthesis	50,513
Processing	5,264
Solvents	8,594
Total	64,371

Water m³/day	
Drinking	811
Industrial	1,316

PROCESSES

BIOSYNTHESIS → FILTRATION → EXTRACTION → CRYSTAL-LIZATION → FILTRATION DRYING → REGENERATION SOLVENTS

PRODUCTS

Products	
Penicillin G	4,000 MUI/day (2,572kg/day)

OTHER PROCESS CONSEQUENCES

Recovered Solids kg/day	
Diluent	6,980

Special Waste Solids kg/day	
Waste for cremation	9,332

Solid Disposals kg/day	
Mycelium	36,950 (s.u.-16.7%)
Charcoal	1,086 (s.u.-30%)

Liquid	

Energy	

Land Contamination	

basin (12).

15. Chemical treatment I.
The treatment is carried out in stirred tank by adding of proper quantities of $Ca(OH)_2$ of any form (slaked lime, or lime water).

16. Chemical treatment II.
The second step is realized in a similar tank, also equipped with stirrer. The treatment is consisting of the addition of $Al_2[(SO)_4]_3$.
The treated was water is then pumped into the final sedimenter mixed with properly selected flocculent (in most cases a polyelectrolyte).

17. Final sedimenter.
After the final sedimentation the cleared waste water is leaving the system through a measuring (18) channel to the municipal sewage system.
The sludge is pumped into the sludge thickener.

18. Flow measuring channel

19. Sludge thickener.

20. Filter press.
The thick sludge is fed into a filter press. The dewatered filtercake is partly fed back to the adsorption process (8), the excess is transported for incineration.

CASE STUDY III

FODDER MEAL PRODUCTION FROM RESIDUE OF EXTRACTION OF ANIMAL ORGANS

Courtesy of Chemical Works of Gedeon Richter Ltd.
Hungary, 1103. Budapest. Gyömrõi-út. 19-21

Chemical Works of Gedeon Richter Ltd.

Hungary, 1103. Budapest. X. Gyömrői ut 19-21.
Tel.: 574-566/830 Technical Cooperation Department

Telex: 22-5067 richt

R D S

for Producing Fodder Meal and Pharmaceutical Raw Material

C O N T E N T S

I. Process Description

1. For Processing Soft Protein Waste to Fodder Meal

Description of Advantages

Chemical Works of Gedeon Richter Ltd. - busy since its existence, for over 80 years, with the utilization of wastes of animal provenience - have developed a new process and planned main equipment necessary for realizing the transformation of slaughterhouse wastes into fodder meal. Based on an abundance of analytical and "in vivo" resorption examinations of the products made by this process, it can be stressed that the quality of fodder meals produced by this equipment BY FAR EXCEEDS requirements of the Hungarian Standards for first class mixed meat meal of animal provenience and even those for the very best imported fish meal. Based on the essential features of the process /SHORT-TIME, INTENSIVE, CONTINUOUS HEAT TRANSFER/, advantages are given such as HIGH CONTENTS OF DIGESTIBLE PROTEIN AND USEFUL LYSIN, simultaneously with the REDUCTION IN FATS AND BACTERIA. Our product may be stored for an indefinite period, it is not objected to under the veterinary aspects and represents a protein fodder of excellent quality.

Materials to be processed

All kinds of soft internal waste arising during the processing of domestical animals, cuttings, confiscated animal organs unproper for consumption and other processing, slaughterhouse liquor residues, by-products arising during the manufacturing of edible fat, "red products" unsuitable for being put on the market, organ residues after extraction processes.

Products

- Fodder meal containing at least 70 per cent of overall protein and min. 85 per cent of digestible matter, of a quality better than the highest standardized requirements
- pharmaceutical basic material produced from hog intestines,
- industrial fat, fodder fat

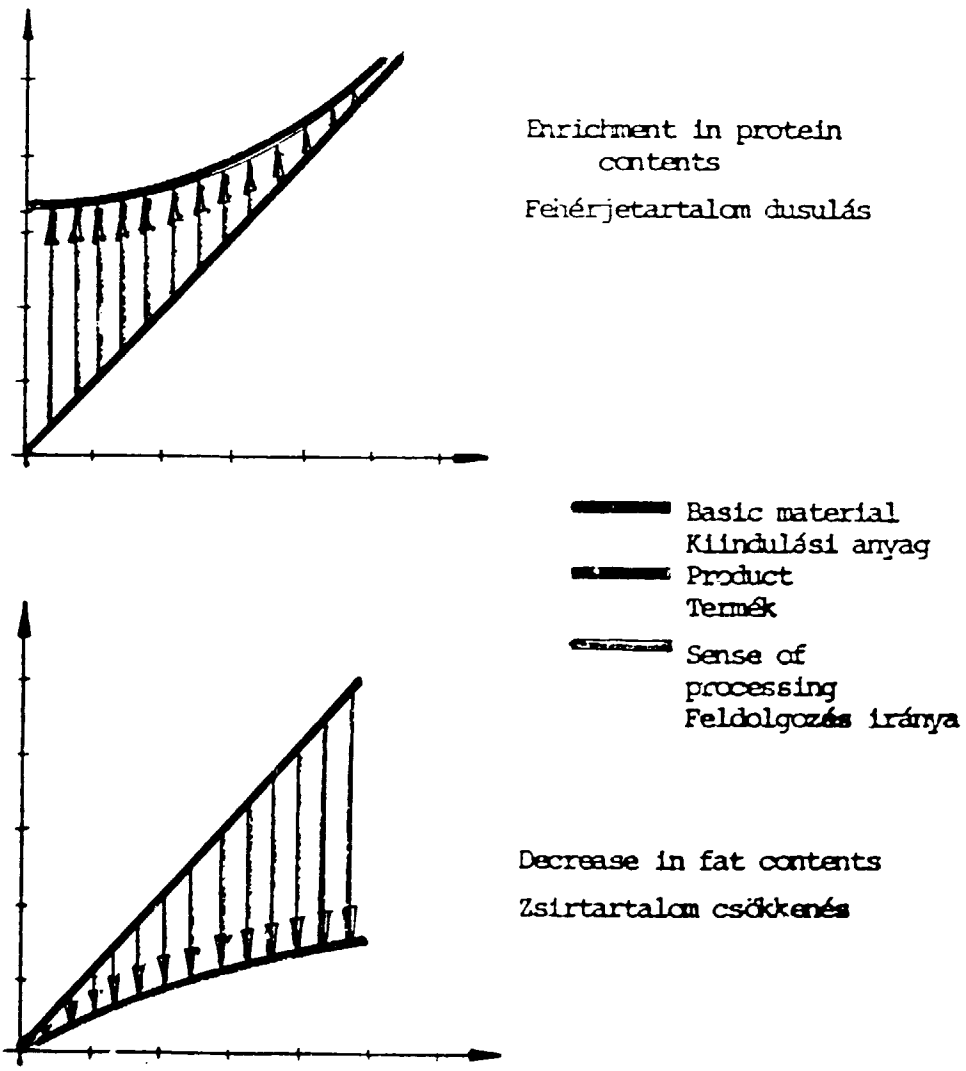


Fig. 1

Increase in overall protein contents, decrease of fat contents during processing, in % of totale dry matter

1./ Collecting tank
2./ Crusher /grinder/
3./ Conveying scren
4./ Delutung tank
5. Recirculating pump
6./ Dosing pump
7./ Instant-heater
8./ Filter
9./ Airlock
10./ Drier
11./ Airlock
12. Product storage bin
13/ Balance
14/ Dustfilter
15/ Heat-economizer
16/ Air-heater
17/ Condenser
18/ Hot water tank
19 Wasch-water pump
20/ 3 phase separator
21/ plate type cooler

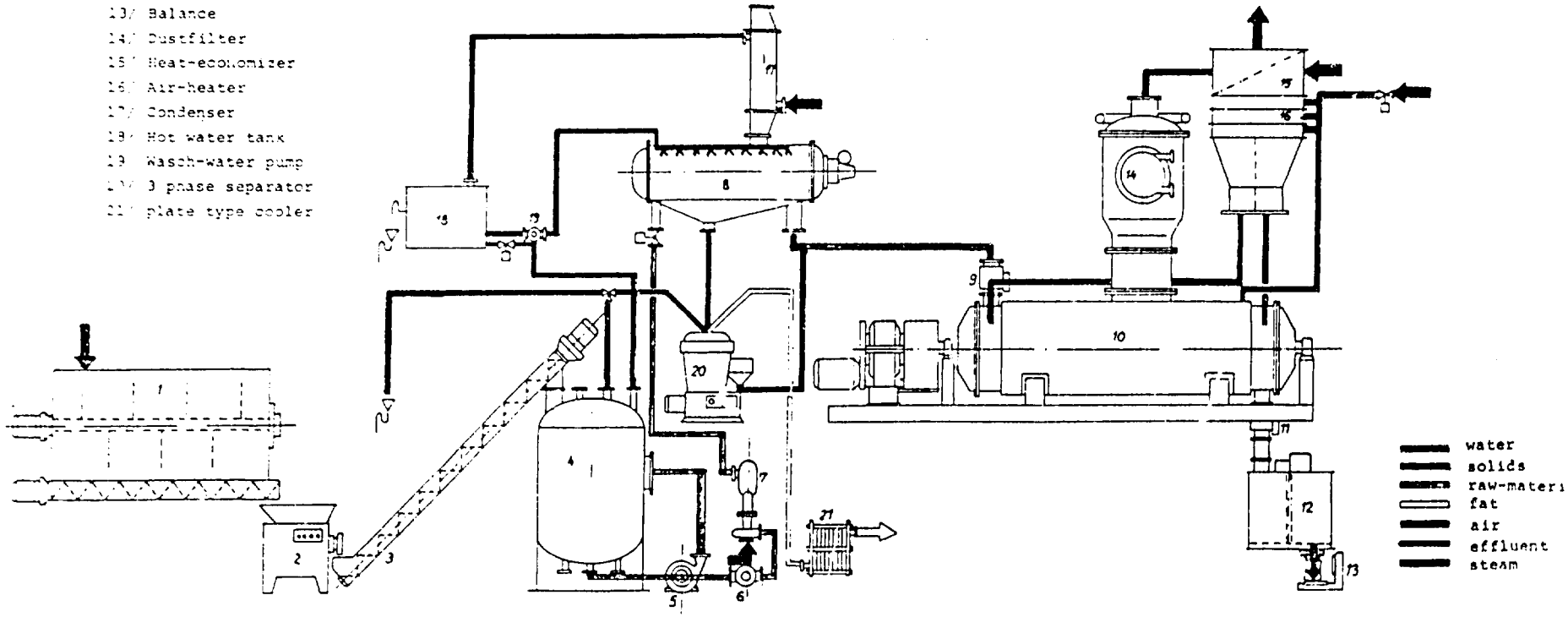


Fig .2.

Technological Description

Fig. 2 Technological Flow-Sheet For Processing Soft Residues /See next page/

In order to prepare the basic material, the residues arising on different spots and at different times in the slaughterhouses are collected by a pneumatic, pumping or container system and stored, according to the capacity of the processing line, in containers or silos.

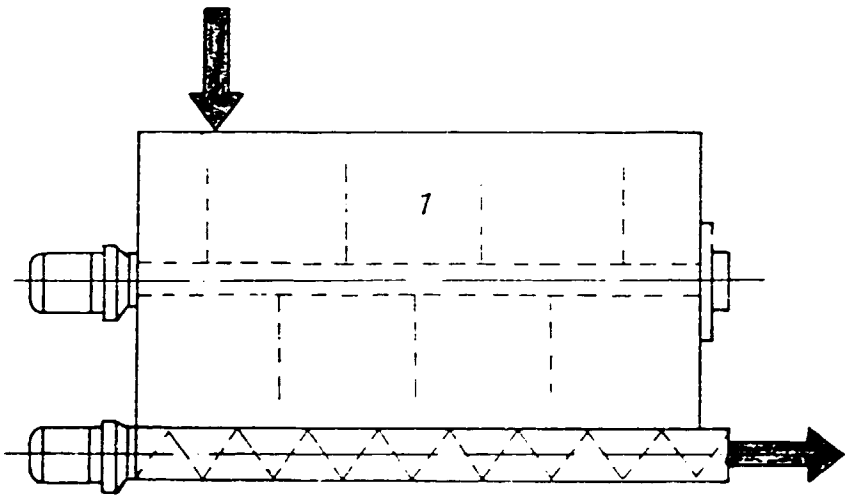


Fig. 3 Raw Material Collecting System

The preparation of the raw material aims at establishing the "particle size" and water contents which are necessary for the process and indispensable for the values guaranteed in the description of the advantages. The cutting operation is performed with an industrial meat mincer having a final screen dimension of 4 mm whereas the 2-15 per cent dry content of the diluted slurry is adjusted in an agitated tank.

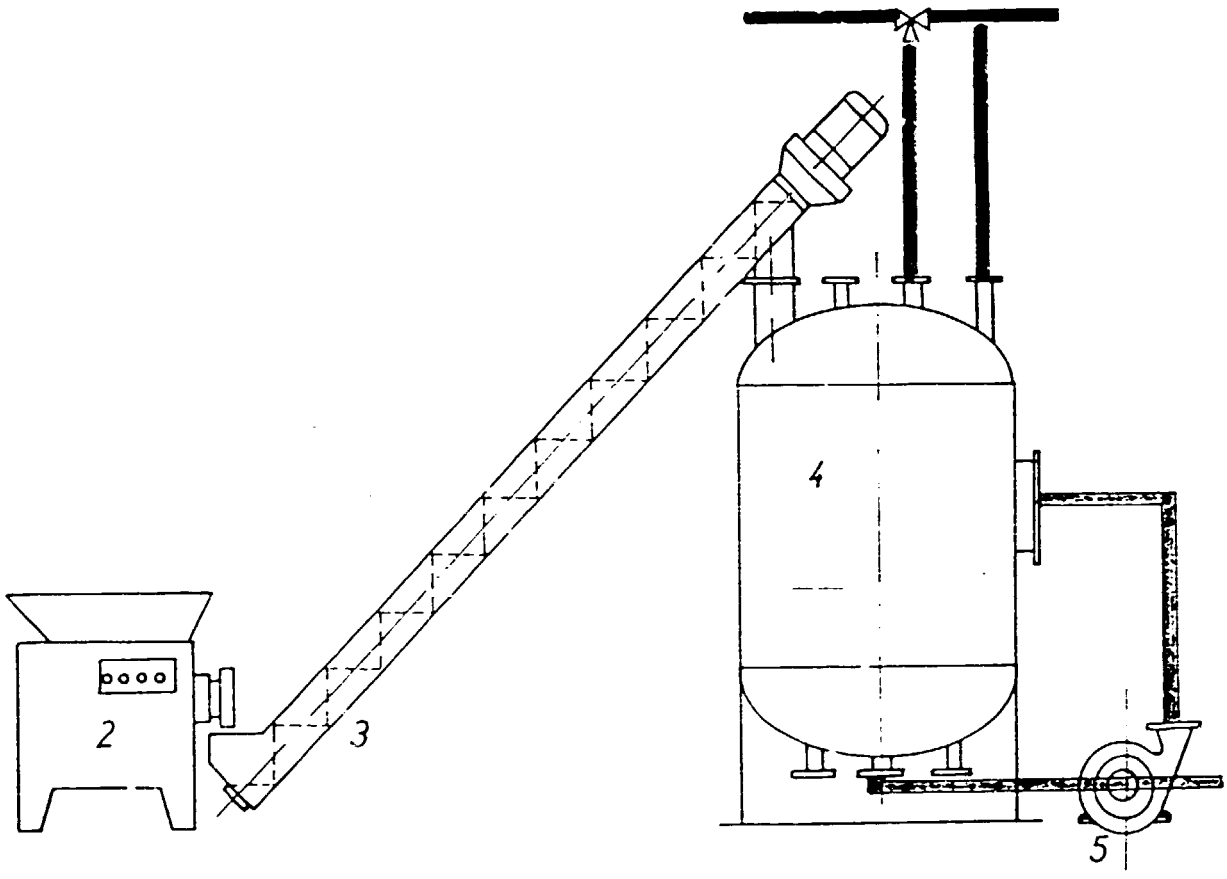


Fig. 4 Raw Material Preparing Equipment

The process forming the essence of the technolgy starts, in accordance with the slaughterhouse capacity, and with the rate of formation of raw material, depending on the processing pressure in the system, with a speed-regulated feeding pump HYPRO /high-pressure/ or JABSCO /low-pressure/; this pump forwards the prepared mixture to the instant heater denaturating unit of direct heating. After being pre-heated to the suitable temperature /incase of low-pressure to - 95°C, in case of high-pressure to 145°C/, the material goes into a pipe coil where : the particles are co agulated, and on the other hand the number of micro-organisms is reduced, during the some minutes of dwelling, to a level satisfying the official prescriptions; i.e a continuous sterilizing

process is being performed. The pipe coil ends in an expansion valve, through which the material is forwarded to the filtering unit.

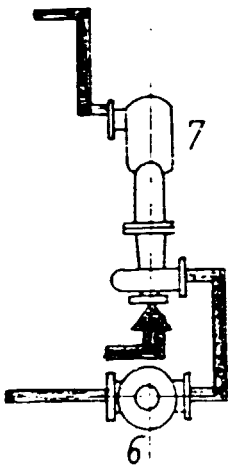


Fig. 5 Feeding, instant heater and St rilizing System

In the zig-zag filtering equipment, the denaturated and coagulated particles are /in the steam atmosphere, protected from reinfection/ continuously separated from the clear liquor and the melted fat, while they are driven towards the dryer. The separated liquid phase is forwarded to the fat line .

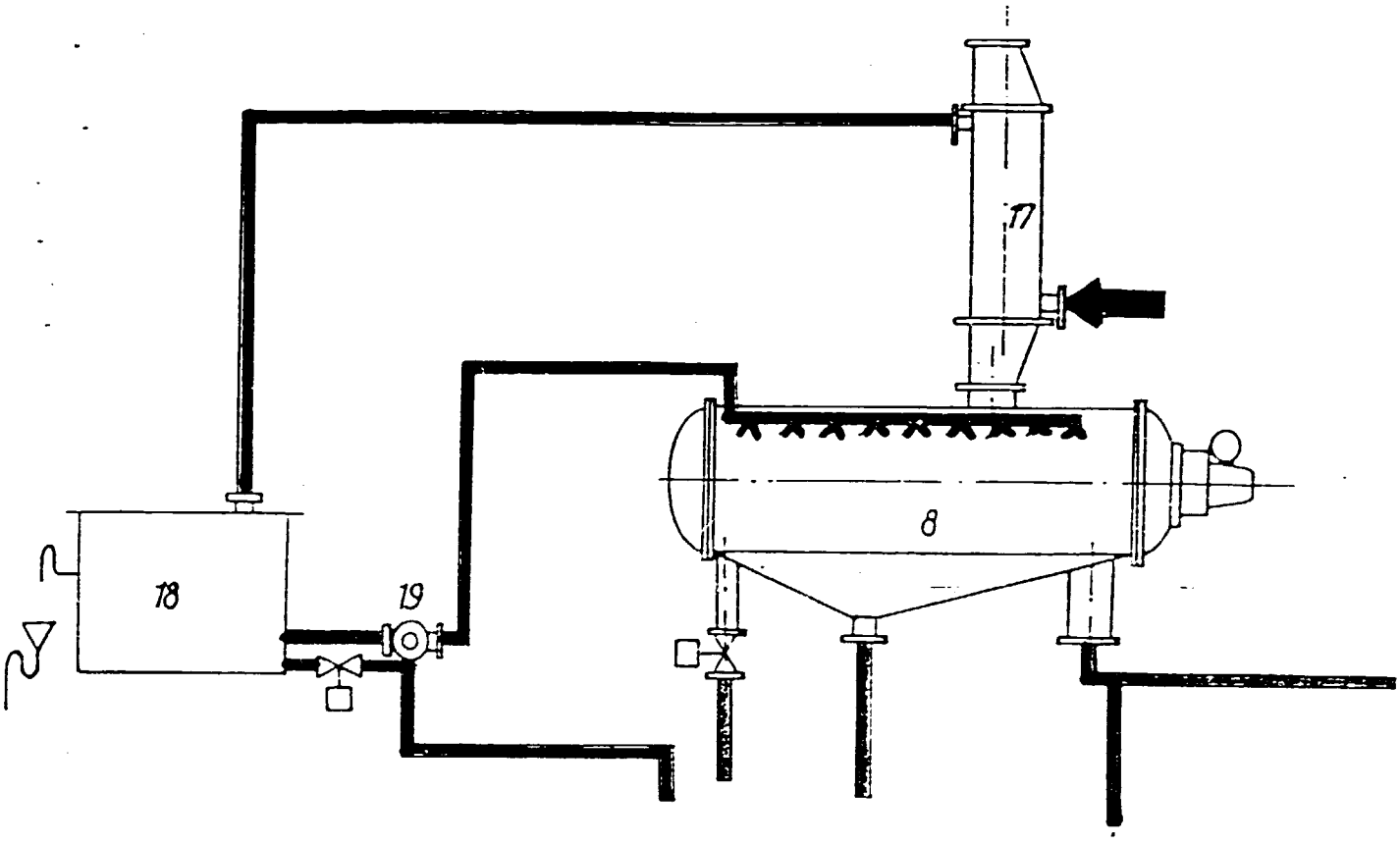


Fig. 6 Filter Equipment

The dryer is a horizontal double-wall agitated vessel heated by steam and hot-air-circulated, from which - depending on the output of the RDS systems - 15-300 kg per hour of fodder meal met the standard requirements are forwarded into the bag filling - ready-packing unit.

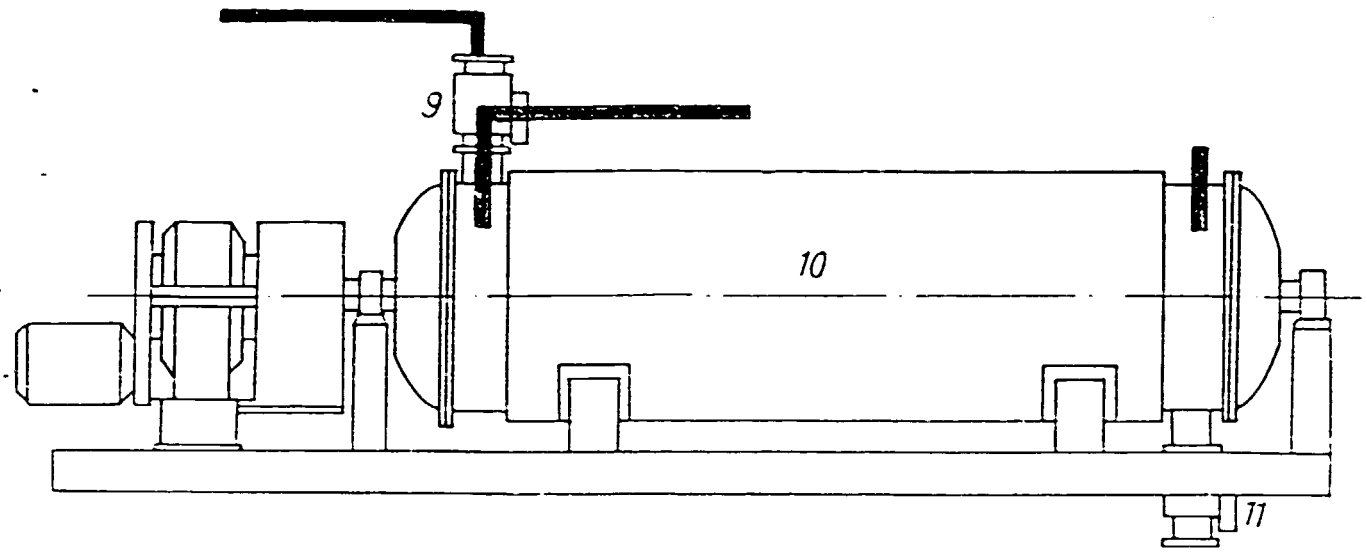


Fig. 7 Drying Unit

In the systems of higher capacity /such as RDS 1000, RDS 1500/, the dried fodder protein comes into a collecting and feeding container under which the optical balance needed for exact weighing of sacks is installed.

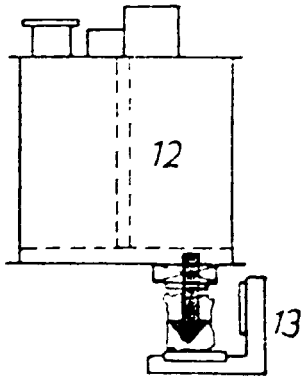


Fig. 8 Bag Filling - Ready-packing Unit

The auxiliary units for the RDS systems are:

The suspension leaving the filter is forwarded into a continuously operating, three-phase separator where the melted fat is separated. The water phase leaving the separator is being used up in part or entirely for dilution in the raw-material preparing line while the protein sludge enters the dryer.

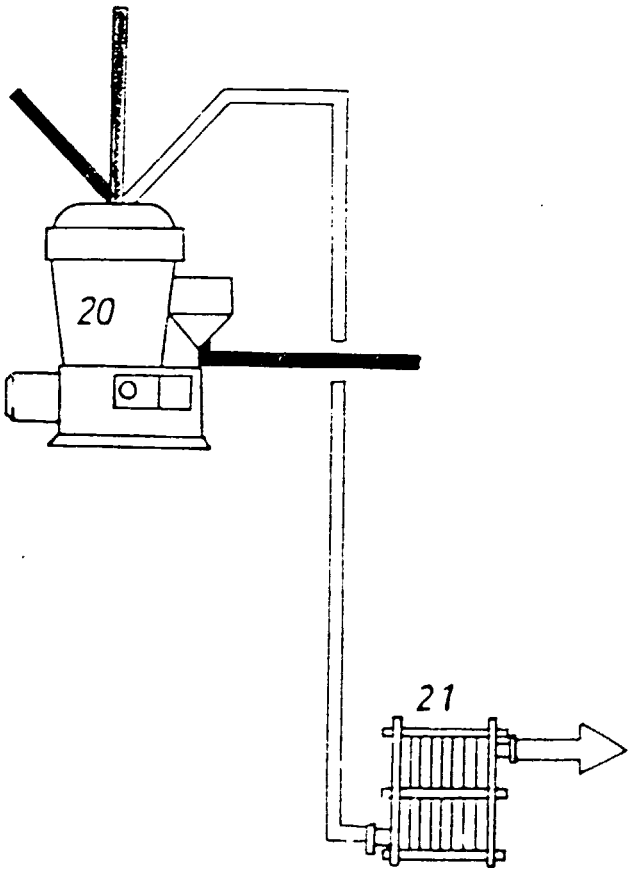


Fig. 9 Industrial Fat Line

In the higher-capacity systems /RDS 1000 and RDS 1500/, the air leaving the pneumatically cleaned dust separator goes into an economizer unit which pre-heats the fresh air entering the heat exchanger /calorifer/ heated by steam or natural gas.

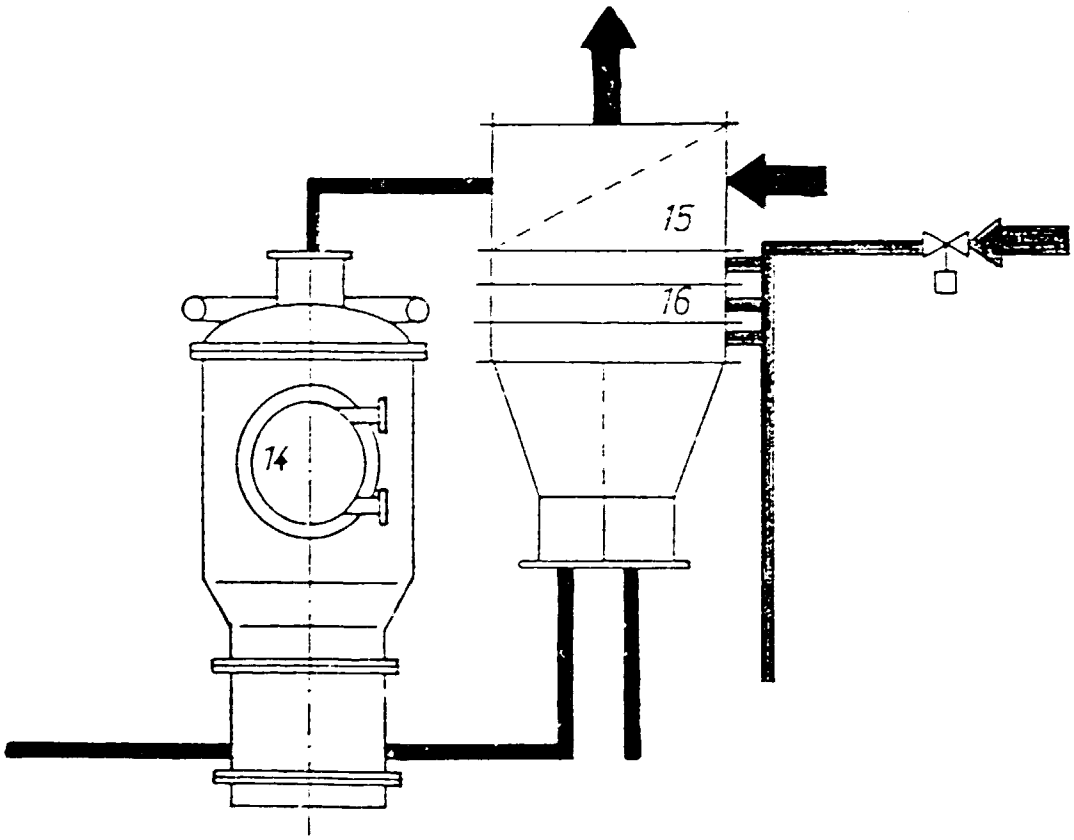


Fig. 10 Air Technique

Fig. 11 Technological Data of RDS Systems for Soft Wastes

RDS	400	600	1000	1500
Machinery Units				
Raw-material Collecting System	min. 1.5 m^3	min. 3 m^3	min. 6 m^3	min. 12 m^3
Raw-material Preparation System: mincer	150 kg/h	300 kg/h	1000 kg/h	3000 kg/h
Raw-material Preparation System: suspension tank	1 m^3	2 m^3	4 m^3	8 m^3
Feeding and Dosing System: Instant heater	100-750 l/h	200-1500 l/h	670-5000 l/h	2000-15000 l/h
Filter Capacity in Denaturated Matter	100 kg/h	300 kg/h	1500 kg/h	1500 kg/h
Drying Equipment capacity in dry matter	15 kg/h	30 kg/h	100 kg/h	250 kg/h
Storage Tank of Bag Filling/ Ready Packing System	-	-	2 m^3	2 m^3
Capacity of Fat Line	3 kg/h[X]	8 kg/h[X]	20 kg/h	60 kg/h
Capacity of Economizer System	8000 kcal/h[X]	15000 kcal/h[X]	35000 kcal/h	80000 kcal/h

[X] Technical necessity does not exist, delivered only upon special order.

2. For Processing Blood to Produce Blood Meal

Blood collected on the Slaughtering lines of Slaughterhouses may be processed after removal of plasma or together with it, in the above described RDS system. The produced blood meal shows extraordinarily high contents of total and digestible protein, meeting at the same time the veterinary aspects. As compared to the above, the process is simpler as the mincing and raw-material preparation line as well as the dilution are unnecessary and also the fat processing may also be omitted.

Fig. 12 Blood Meal Processing. Technological Flow-Sheet

/See next page/

4. Collecting tank
5. Recirculating pump
6. Dosing pump
7. Instant-heater
8. Filter
9./ Airlock
10/ Drier
11/ Airlock
12/ Product storage bin
13/ Balance
14/ Dustfilter
15/ Heat-economizer
16/ Air-heater
17/ Condenser
18/ Hot water tank
19/ Wash-water pump

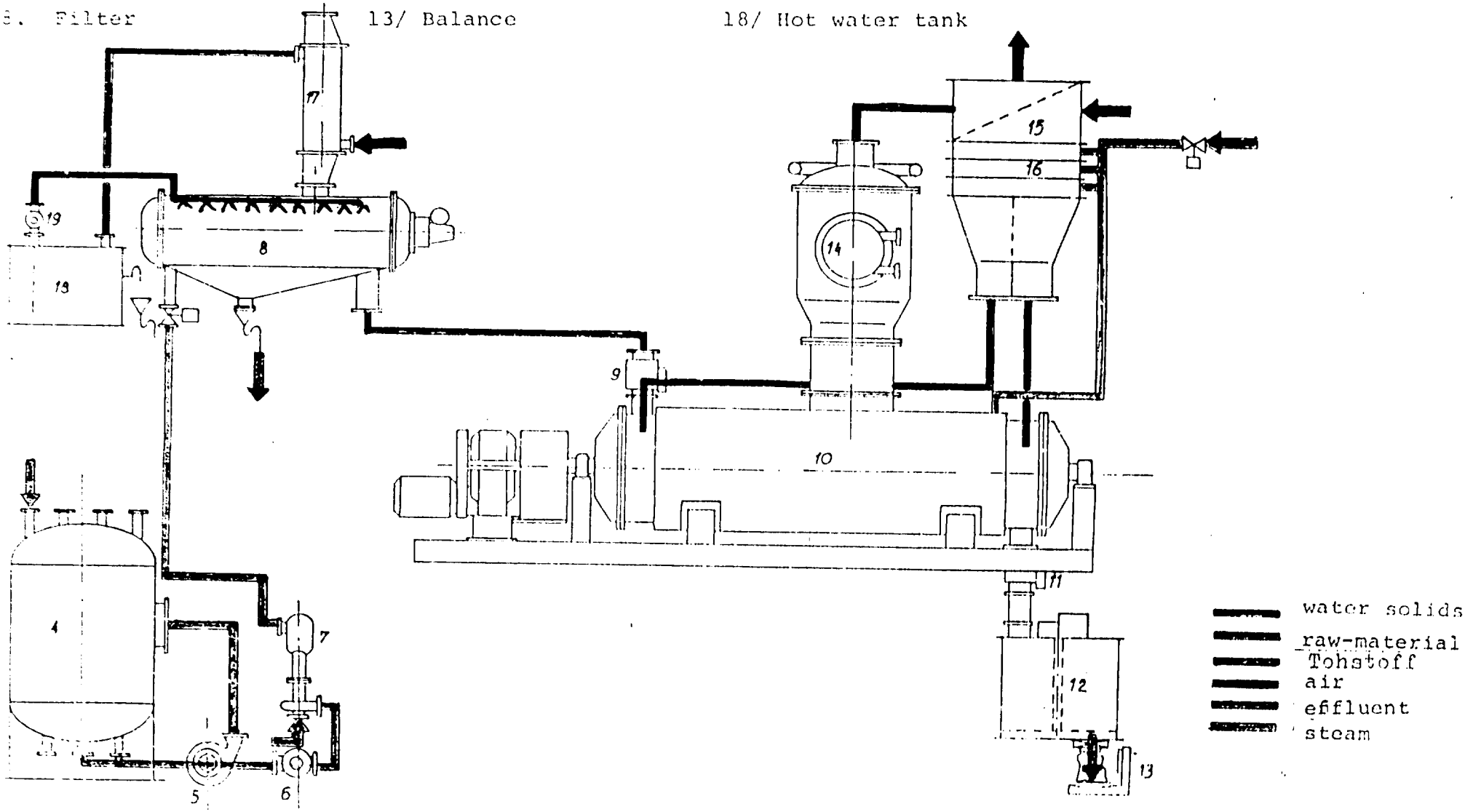


Fig. 12.

Fig. 13 Technological Data of RDS Systems for Processing Blood

RDS	400	600	1000	1500
Machinery Units				
Raw-material Collecting System	500 l	1000 l	3000 l	6000 l
Feeding and Instant heater System	60-120 l/h	150-300 l/h	400-900 l/h	1000-2700 l/h
Filter Capacity in Denaturated Matter	80 kg/h	150 kg/h	500 kg/h	1500 kg/h
Drying Equipment Capacity in dry Matter	15 kg/h	30 kg/h	100 kg/h	250 kg/h
Economizer System Capacity	8000 kcal/h*	15000 kcal/h*	35000 kcal/h	80000 kcal/h

* Due to small size delivered only upon request.

3. For Processing Bony Wastes to Fodder Meal

A great part of slaughterhouse wastes is arising as bony waste products, which may be processed by the technology described under 1, in case of an appropriate modification of the preparing lince, i.e., by substituting pre-crushing and hammer mills instead of the industrial mincers. Otherwise, the process is quite identical to the processing of soft waste materials. The total and digestible protein contents of the resulting product are lower than those of the purely soft wastes in the same proportion as bony waste is introduced but will not be lower than the value indicated for the start. The capacity of the RDS systems will be, in this case, between 20-500 kgs per hour.

4. For Processing Fermentation Liquor Residues

From the above said, the idea emerges by itself to extend the application of the system to the utilization of all sorts of protein-containing waste being denaturalized by heat to produce valuable fodder meal and also for further processing of residues arising during different fermentation processes, ensuring at the same time those advantages which are given by the continuous process instead of the batch-wise ones. Since these raw-material sources are the results of widely varying techniques, technological flow-sheets and data schemes similar to the above indicated ones can be presented only on the basis of previous experiments made for every single case.

II. Installation and Operation of RDS Systems

1. Requirements for installation of the System

According to their size, the RDS systems may be installed in two different layouts. The smaller RDS systems such as RDS 400 and RDS 600 allow a block-like layout, the system RDS 400 being even liable to be supplied and installed in a containerized layout. The various units of the technology are condensed into blocks in the following arrangement:

A : Raw-material collector and preparation
B : Quick instant heater and sterilizer
C : Air technique and economizer unit
D : Electrical and instrumental regulating and control system

This layout allows the simple installation of the systems RDS 400 and RDS 600 in existing slaughterhouses, on one level and with relatively low inner height.

For the BIGGER SYSTEMS RDS 1000 and RDS 1500, the size of the machine-units does not allow any more the installation in blocks. With such systems, there is a possibility to accommodate the equipment in independent steel structures on different levels, meeting the technological requirements, whereas for new slaughterhouses the necessary layout requirements may be considered already in the stage of preparing the projects.

The product being classified, under the aspects of inflammability, as belonging to Class "C", the requirements against the independent building must meet the prescriptions of the Hungarian Standard 595 and, under the fire-fighting aspect, to the decrees of OTSZ 4/1980 - 31.25-BM while meeting the sanitary prescriptions of the decree

EÜM 2/1981 - II.7. The social and service establishments are governed by the prescriptions of the decrees Nr. 12/1980 III.4 ÉVM and Nr. 18/1981 - VI.29 ÉVM.

Required public utilities in connection with the installation:

- water and sewage systems
- steam and/or natural gas
- electrical energy
- pneumatic auxiliary energy

Fig. 14 Technical Information on Installation of RDS Systems

Facility / RDS		400	600	1000	1500
Required building floor space		12 m^2/3mx4m/	20 m^2/4mx5m/	40 m^2/4,5mx9m/	60 m^2/5mx12m/
Required inner height of building		2,5 m	4 m	6,0 m	6,5 m
Installed machinery and equipment	total weight	3000 Kg	5000 kg	12 000 kg	18 000 kg
	loading weight	5000 kg	8000 kg	20 000 kg	27 000 kg
Electrical network to be installed /nominal current at 380 V/		3x35 A	3x63 A	3x100 A	3x 125 A
Installed electrical capacity		15 kW	25 kW	35 kW	55 kW
Steam duct to be installed NP 16		ND 25	ND 32	ND 50	ND 80
Technological water line to be installed		3/4"	1"	1 1/2"	2"
Sewers to be installed		ND 80	ND 100	ND 150	ND 150
Line for pneumatic auxiliary energy		3/4"	3/4"	3/4"	3/4"

Fig. 15 RDS Main Dimensions

RDS	400	600	1000	1500
Raw-material Collector	1.5 m^3	3 m^3	6 m^3	12 m^3
Raw-Material Preparing Tank	1 m^3	2 m^3	4 m^3	8 m^3
Instant-heater and Sterilizer	ND 40	ND 65	ND 100	ND 150
Filter Unit	Ø 450 by 1500	Ø 600 by 2000	Ø 1000 by 2500	Ø 1000 by 2500
Drying Unit	Ø 400 by 2200	Ø 600 by 3000	Ø 1000 by 5000	Ø 1500 by 6000
Dust Separator	1,5 m^2	3 m^2	10 m^2	15 m^2

Operating Data of RDS Systems

Fig. 16

RDS Size	400	600	1000	1500
Starting raw material minced	100-200 kg/h	200-400 kg/h	500-1500 kg/h	2000-4000 kg/h
Dilute suspension before sterilization	100-750 l/h	200-1500 l/h	650-5000 l/h	2-15 m^3/h
Denaturated matter after filtration	50-70 kg/h	100-140 kg/h	350-450 kg/h	800-1200 kg/h
Dry material	15 kg/h	30 kg/h	100 kg/h	250 kg/h
Fat	3 kg/h	8 kg/h	20 kg/h	60 kg/h
Electrical energy consuption	9 kWh	11 kWh	20 kWh	35 kWh
Steam /8 bar/ energy consumption max.	100 kg/h	190 kg/h	650 kg/h	2000 kg/h
Air consumption for drying p = 300 mm W.C.	1000 m^3/h	2000 m^3/h	5000 m^3/h	10 000 m^3/h
Water consumption max.	0,3 m^3/h	0,6 m^3/h	1,0 m^3/h	1,5 m^3/h
Labour requirement /persons/	0,5-1	0,5-1	1	1-1,5

4. Patent, further information

The RDS process and equipment have been patented by Chemical Works of Gedeon Richter in more than 20 countries.

The owner of the patent is ready to accept and fulfil orders on experimental and development work concerning feasibility of the RDS system, produce sample materials necessary for feeding tests, elaborate adapted projects for RDS.

Some raw-material preparing, product - handling and auxiliary equipment may be modified upon consultation with the Client, or they might be substituted by the Client's own equipments.

Further information by:

Chemical Works of Gedeon Richter Ltd.

H-1103. Budapest, Gyömrői ut 19-21

Tel: 574-566/830 Technical Cooperation Department

Telex: 22-5067 richt.h.

III Feasibility, depreciation.

Rentability of the RDS Systems producing fodder protein and pharmaceutical basic material depends on investment costs, actual interest rates, operating costs and prices, quantities of the products.

According to our existing knowledge, the Systems RDS 400 and 600 are especially suitable for producing pharmaceutical basic material, whereas the Systems RDS 1000 and 1500 are recommended for producing fodder meal, since contradictory effects prevail in the prices of products and the required amounts.

During the depreciation period, returns may be calculated by the following formula:

$$N = \sum T_i \cdot A_i - \left[\frac{B\left(1+\frac{q}{100}\right)^N}{N} + \sum T_i \left(x_{ny} \cdot k_{ny} + x_e k_e + x_g k_g + x_v k_v + x_m k_m \right) \right]$$

where N = returns, ₰ per year;
T_i = quantity of product = $K_i \cdot U$, kg/year
K = capacity, kg/year
i = number of products
A = price of product, ₰ per kg
B = investment costs, ₰
q = interest rate, %
N = depreciation period, years

x_{ny} specific raw material consumption kg/kg
x_e specific electrical power consumption kWhrs/kg
x_g specific steam energy consumption t/kg
x_v specific water consumption m^3/kg
x_m specific labour consumption h/kg
k_{ny} raw material price ₰ per kg
k_e electrical energy price ₰ per kWhr
k_g steam energy price ₰ per t
k_v water price ₰ per m^3
k_m labour price ₰ per h

Returns, which can be produced after the amortization period, may be calculated as follows:

$$N = \sum T_i \cdot A_i = \sum T_i \left(x_{ny}k_{ny} + x_e k_e + x_g k_g + x_v k_v + x_m k_m\right)$$

Specific data necessary for the calculations:

RDS		400	600	1000	1500
x_{ny}	kg/kg	—	—	—	—
x_e	kWhrs/kg	0,6	0,37	0,20	0,14
x_g	t/kg	0,0065	0,0065	0,0065	0,0065
x_v	m^3/kg	0,01	0,01	0,01	0,01
x_l	h/kg	0,05	0,025	0,01	0,005

Specific data in the above table refer to 1 kg of the total amount of the products.

CASE STUDY IV

TYPICAL WASTE WATER TREATMENT PROCESS

CASE STUDY IV
TYPICAL WASTE WATER TREATMENT PROCESS

The following description deals with a process which was planned and implemented to treat the liquid wastes of a middle size plant having facilities to produce about 10-20 active substances by synthesis and by fermentation.

The process is consisting of the following main parts:

- pre-treatment
  - mechanical
  - chemical
- biological treatment in two steps
- chemical/physico-chemical treatment
- sludge treatment

The batchwise manufacturing of the individual products is going on in form of campaigns due corresponding to market fluctuations. Consequently the load of the treatment plant is uneven; both flow rate and composition of the waste water may change abruptly.

Nominal parameters of the waste water to be treated are as follows:

capacity	= 3,200 m^3 per day, or 250 m^3 per hour
COD max.	= 12,000 x 10^{-3} kg per hour
COD/BOD ratio	= 1,6
NH_3/NH_4^- max.	= 1800 x 10^{-3} kg/m^3
fat-oil max.	= 500 x 10^{-3} kg/m^3

Process description

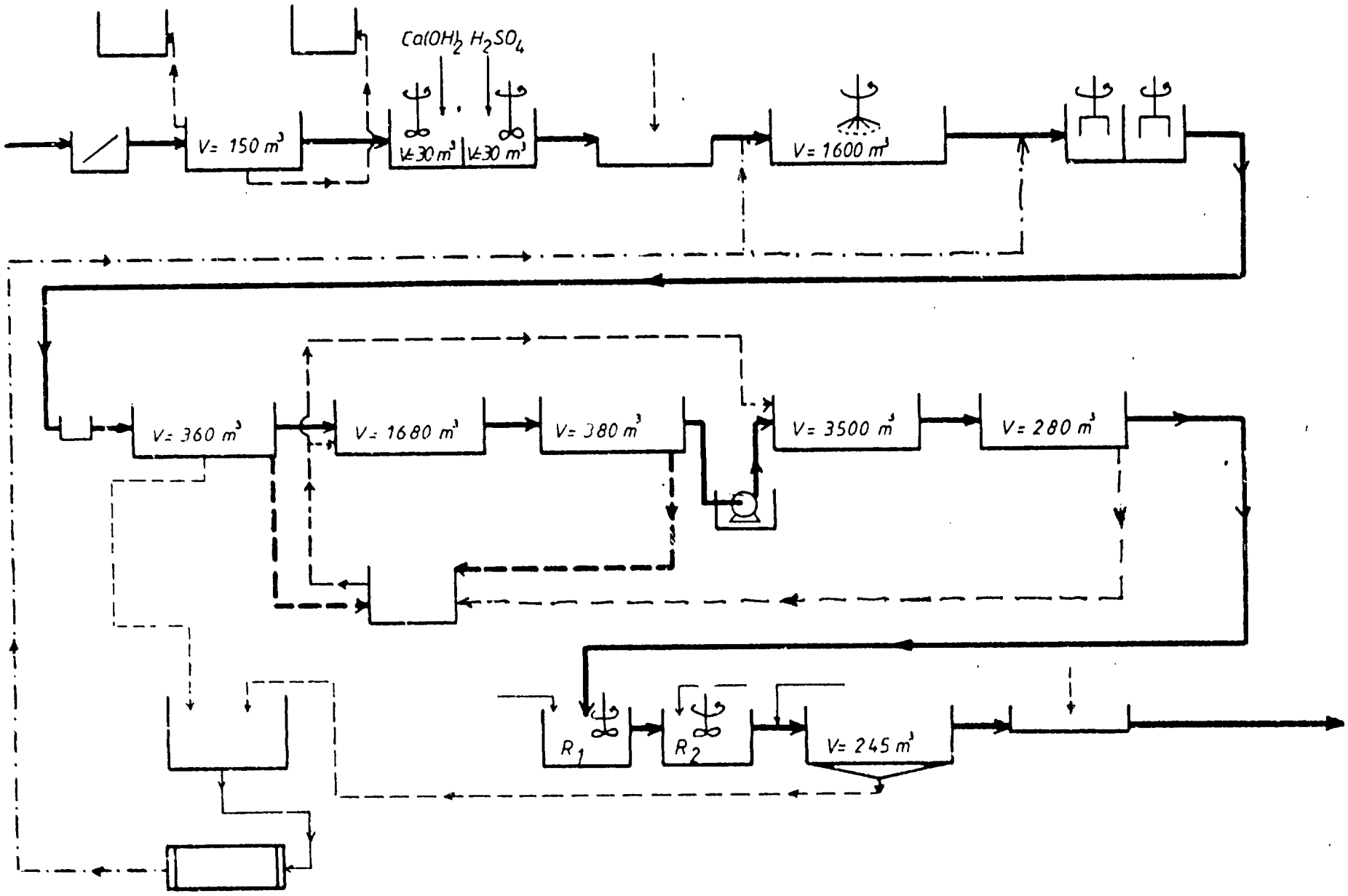
A simplified flow sheet is illustrated in the figure overleaf.
Sizes of the individual vessels are indicated.
The description is following the item numbers of the flow sheet.

1. Grate shaft.
Separation of large mechanical impurities.

2. Sand-, and solvent separator.
The separation takes place on basis of difference in specific gravity of the components.
The supernatant solvent is collected in receiver tank 3., while the sedimented sand and heavy solvents are transferred by sludge pump into receiver tank 4.

3. Receiver tank for the supernatant (light solvents) from 2.

4. Receiver tank for sand and heavy solvents from 2.


$Ca(OH)_2$ H_2SO_4
V= 150 m³
V=30 m³
V=30 m³
V= 1600 m³
V= 360 m³
V= 1680 m³
V= 380 m³
V= 3500 m³
V= 280 m³
R_1
R_2
V= 245 m³

5. Neutralizer
Neutralizing is carried out in two steps. Depending on the chemical character (first of all pH) of the waste water, adequate amounts of $Ca(OH)_2$ and H_2SO_4 can be added. The neutralizer is equipped with mechanical mixers.

6. Flow measuring channel.

7. Homogenizer.
The sedimentation of the sludge originating from the previous neutralization is prevented and a homogenous suspension is maintained by floating fans which also ensure certain pre-aeration.

8. Adsorption basins.
Sludges from the previous neutralization and from the biological treatment are used to adsorb residual solvents and potentially toxic components before the biological treatment.
The process is enhanced by low speed stirrers.

9. Sedimentation basins.
In long sedimentation channels the sludge in sedimented, collected by mechanical scrapers and pumped into the sludge thickener (19), or to the activator (12).

The sedimented waste water is fed into the first biological treatment system which is consisting of the aeration basin (10), post-sedimenter (11) and slugde activator basin (12)

10. Aeration basins.
The oxidation process is carried out by the air. The liquid/air contact is ensured by high speed aeration rotors.

11. Post-sedimentation basins.
The long channel arrangement ensures the final separation of the sludge from the liquid phase. The sludge is collected by scraper system and fed to the activator basin (12).

12. Activator basins.
The proper oxygen input and maintaining of suspension is carried out by vertically arranged agitators.
The activated sludge is fed back to the aeration basins (10,13) of the first and second biological treatment systems.

The waste water is then fed into the second biological treatment system (13,14 and 12) which is working similar to the first one:

13. Aeration basins.
The oxidation process is carried out by the air. The liquid/air contact is ensured by high speed aeration rotors.

14. Post-sedimentation basins.
The separation is carried out in a Dorr-type sedimenter.The sludge is collected by scraper system and fed to the activator

P A R T III

PRODUCTION PROFILE

The following sections of the present chapter yield a comprehensive summary of the manufacturing of pharmaceutical finished products.

Active ingredients produced by synthesis, fermentation or extraction are further processed to be able for usage. The so called "dosage forms" are elaborated to deliver the active substance to the proper site of the body and to produce the desired result with the least adverse effects. Quality of the dosage forms of the individual drugs is stricty controlled by the producer and the whole quality assurance management system is supervised and monitored by the health authorities. The number of dosage forms is rather large. They may be summarized into the following groups:

- solid dosage forms
  - tablets
  - coated tablets (dragées)
  - capsules
  - powders
- liquid forms
  - solutions, (syrups)
  - suspensions
- injections (solutions, powders, freeze-dried)
  - large volume parenterals (infusion)
- semisolid and plastic dispersions
  - creams, ointments, gels, suppositories
- aerosols

Dosage forms for veterinary use can be classified in the above categories. Sizes, content of active substance, and mode of administration are complying to the special requirements.

Tablets account for over 90 percent of all oral medicines. Tabletting in most cases consists of the following major steps:

- preparation
- granulation
- compression
- coating

Preparation

Containers, sacks of raw materials arriving from the warehouse are opened and the required quantities are weighed and fed into respective equipment. In some cases milling and /or classifying (sieving or sedimentation) are used in order to achieve the required particle size distribution of the component. The preparatory steps represent the main source of dust emission into the environment.

Granulation

As a next step, activ ingredient(s) is (are) blended with lubricants, fillers and bi. 'ers, such as lactose, starch or sugar; and other ''excipients'' (auxiliary materials). In order to get uniform mass for tablets the powder mixture has to be transformed into free flowing particles "granules". In the context of pharmaceutical formulation, granule means a free flowing conglomerate of fine particles. Granulation may be carried out using wet or dry methods. The equipment may be the classical mechanical kneading machine or the more advanced fluid bed granulator which is modern, effective, but needs proper care to prevent dust explosion or powder vent into the environment.

Compression (pressing o.' tablets)

The final form of the product is reached in the tabletting press. In order to avoid contamination of the product, tabletting presses are separately located in closed cabinets with properly designed ventillation. Fine dust of the the product is collected in the filters of the exhaust ducts. In a well controlled plant fine dusts may be present only in the washwater of the equipment and room.

Coating

Effect of the tablet may be modified by the use of coating, which process may be realized either in rotating drums or in fluid-bed by the aid of air flow. In both cases the coating substance is dfissolved or suspended in water if possible, but volatile solvents may also be used. Especially by fluidized bed granulation care must be taken to prevent the emission of organic vapors into the environment.

Liquid forms

The production of liquid forms be it injections or other (oral or topical) preparations represent much less potential danger for the environment. However ethylene chloride is worth mentioning, because of its contribution to the "greenhouse effect" to the atmosphere. In most cases the handling of cleaning liquids requires precaution.

The same applies to the semi solid and miscellaneous products.

Propellants used in aerosol flasks must meet globally accepted prescriptions for chlorofluorocarbons as ozone layer depleting substances.

The wastes generated during these various formulation processes result from the

- processes themselves
- cleaning and sterilizing processes
- chemical spills
- rejected products.
- returned goods

Dust emission

During mixing and granulation dusts can be generated which in some cases may be recycled into the formulation process, but such

procedure must comply with the qual ity assurance requirements. Extremely careful dust control is necessary to avoid contamination of pharmaceutical products by each other ("cross contamination"). Generally speaking, dust control has first priority in the handling and packaging of solid state products especially powders.
The high cost of these powders (material costs represent 30 to 70% of the manufacturing costs)provides a strong incentive to the industry to minimize any losses of such products. The introdution of Good Manufacture Practice (GMP) into the production of pharmaceuticals leads to high standards of air filtration in the plants in order to avoid contamination of medicines and to protect the environment on one hand; but also limits the possibilities of the recycling of materials on the other .

Liquid effluents
The primary waste water source is the washwater of equipment and floors, which may contain active substances, norganic salts, sugars, and typically has low BOD, COD, and TSS, with near neutral pH.

Air emissions
in addition to the dusts may result from the use of volatile solvents.
Propellants used in aerosol flasks may be dangerous for the environment not at the site of production but at the application. Prescriptions for ODSs are to be followed.

MANUFACTURING PROCESS OF THE CIBA PHARMA PLANT IN TANGI

The pharma plant in Tangi uses Pharmaceutical substances imported from abroad and manufactured by other local companies to process them into proper dosage forms. The general idea is to deliver the active ingredient of a drug to the specific body part with the least disturbance to the human system.

Essential drugs are all those listed in the WHO list by name or as a member of a therapeutic group. The drugs are classified in to two groups : commodity and specialty. Commodity drugs are multisource and they compete on price only. Specialty drugs are essentially single source and they compete on quality. The very moment a product has a feature that distinguishes it from the other similar products, the product becomes a specialty. These products once again can be categorized according to their dosage forms.

DOSAGE FORMS

ORAL DOSAGE | **PARENTERAL DOSAGE** | **EXTERNAL DOSAGE**

SOLID FORMS | **LIQUID FORMS**

TABLETS **CAPSULES** **POWDERS** **SYRUPS** **SUSPENSIONS**

Solid dosage form mainly consists of tablets and capsules with the less frequently form of powders. All these three forms together represents the most popular group of dosage forms. Since taken via the most acceptable route, the oral route, and permitting a high accuracy of dosage in a relatively small volume allowing handling ease, the solid oral dosage has gained its popularity. Also these products are not very susceptible to hydrolysis as they are usually water free which makes them more stable than other forms. These forms can be produced in large quantities regardless of the fact that the production of these drugs require rather highly specialized equipment. Appropriate formulation of the product assures the quick release of the drug after application while some ensures the controlled release of it. Solid oral dosage forms are catagorized as follows.

SOLID DOSAGE FORMS

TABLETS | **POWDERS** | **CAPSULES**

COATED **UNCOATED** **EFFERVESCENT** **MISC.** | **HARD SHELL** **SOFT SHELL**

SUGAR **FILM** **COMPRESSED**

LOZENGES **CHEWABLE TABLETS** **SOLUTION TABLETS** **BUCCAL & SUBLINGUAL** **DISPERSABLE TABLETS**

TABLETS

Tablets are defined in a WHO publication as solid, flat, or bi-convex, generally circular disks, prepared by compressing or moulding a drug or a mixture of drugs, with or without an excipient, absorbant, or adhesive, a moistioning agent, a lubricant, or a disintigrating agent. It is unanimously the most popular form for oral administration due to its stable, concentrated form. The accuracy and quick dispensing ability also contribute to the patient/user friendliness of tablets. A step by step description of a typical formulation plant producing tablets and capsules follows.

FLOW CHART FOR TABLETS AND CAPSULES IN A FORMUULATION PLANT

TRANSPORTATION OUT GOING

IN COMING

WAREHOUSE DRUGS AND EXCIPIENTS

FINISHED PRODUCTS

WEIGHING ROOM

PRETREATMENT

COMPACTION CAPSULE FILLING

TABLET COATING

QUALITY CONTROL

REWORKING

PACKING

TRANSPORTATION OF MATERIALS IN AND OUT OF THE PLANT

Since the formulation plants depend on the externally produced drugs and other additives, all the raw materials, both for manufacturing pharmaceuticals and packing, have to be brought into the plant. The finished products have to be transported out to the wholesalers as well. Definite measures are taken to minimize the risk of mishandling these materials.

WAREHOUSE KEEPING ALL THE RAW MATERIALS AND THE FINISHED PRODUCTS

This is where all the drugs and final products are stored. It is close to the loading zone and also to the production unit. Here the quality control people check whether the materials are acceptable for their operation. There are separate storing spaces for medicinal drugs, packing materials, auxiliary ingredients, and the finished products. This is done to avoid cross contamination. Even the sample taking by the quality control personnel is done in an area with laminar air flow for the same reason. Storage conditions also vary such as cold storage place, dark place etc. with the requirement of each substance being stored.

WEIGHING ROOM

After the medicinal drugs and other additives have gotten the green ticket by the quarantine, they are taken to the weighing room from the closely located warehouse. Here all the necessary chemicals are weighed to their

required portions for different products and then sent to the production unit. The weighing is done very carefully to avoid cross contamination of raw materials, in the presence of a pharmacist.

PRETREATMENT OF DRUGS AND AUXILIARIES

To be tableted, the drugs have to have certain characteristics: they have to be able to flow uniformly and quickly into the pressing dye, cohere when compressed, be ejected easily and quickly from the compressing equipment. Substances with these characteristics are rare and therefore, the drugs have to go under preliminary treatment in order to be converted into a form that is suitable for tabletting. This process is also known as granulation since all the chemicals are mixed together to make granules which are ideal for tablet pressing or capsule filling. In the terminology of pharmacy, 'granules' means free flowing conglomerate of fine particles giving uniform mass to tablets and capsules.

The wet granulation method is a process of size-enlargement, sticking particles of drugs and excipients together using an adhesive to produce a granular mix with increased flow and cohesive properties under pressure. This process involves several steps such as mixing, wetting, drying, sieving, remixing, and granulating. The following is a flow chart for the process.

WEIGHING ROOM — **DRUG + DILUENT**

MIXING

WETTING — **WATER + GRANULATING AGENT**

GRANULATION

DRYING

SIEVING/DISINTIGRATING

MIXING — **LUBRICANT + GLADIENT + DISINTEGRANTS**

COMPRESSION

The purpose of the mixing stage is to ensure homogenity of drug content thus making it an essential step in pharmaceutical formulation. In ideal situation, any sample of the mixture should have the same composition as that of the bulk material. When coloring and flavoring is used, uniform dispersion is needed to ensure flawless blending and good outlook of the product. For small dose tablets, the weight of the tablets are often too small to be handled with ease. Therefore, various diluents are used to bulk the tablet up to a convenient size. Ideal diluents are inert, harmless, cheap, and do not hinder the tabletting process. Lactose, the most commonly used diluent, is usually used in the form of alpha-lactose monohydrate due to its stability.

To be able to be granulated the mixture has to be wetted with a granulating agent which quickens the process. The granulating agents enables the particles of drug and other excipients to cohere together in granular form. They are usually known as binders and adhesives. Water can also act as a granulating agent with hydrophilic and water soluble materials. Anhydrous granulating agents are required for substances that react with water. Povidone, dissolved in isopropanol is one such agent.

Granulation improves the flow and compression properties of the mixture and also prevents the segregation of the components of the powder mixture and dust generation. The particles can be enlarged in size by the use of an adhesive. The mixture has to be soluble in the fluid and the process is directly related to the amount of the granulating fluid present. Finally, the powder particles have to form bonds among them to be able to adhere with sufficient strength to prevent breakdown.

When granulation is done, the product exists as a damp mass of granules which must be dried. The mechnism of the drying process by the application of heat is as follows: the atmosphere above the wet solid is heated so that the relative humidity falls and the solid loses water until it reaches equilibrium with the modified condition. Even when the lost water is removed and the temperatre decreased the solid doesn't regain the moisture lost. The rate of this process is inversly proportional to the depth of the powder bed.

Sieving is done to break up any aggregates of particles that might have occured after drying. Which means that the dried granules are passed through a screen to break up the large particles so that the mixture is uniform in every aspect once again. It also removes foreign materials from the powder blend.

After granulation and sieving another mix is needed to blend in the remaining ingredients such as the lubricant, disintegrant, and glidant.

Glidants are added to enable the granules to flow smoothly in the pressing die cavity. Finely divided silica is the most popular glidant in use currently.

Lubricant is an important step in every tablet formulation to overcome the friction between the formed tablet and the die wall. A lubricant makes the ejection of the tablet from the die easier and helps to weaken the ejection pressure on the tablet to prevent break down. The degree of coating the granules with lubricant is directly proportional to the mixing time.

The tablets have to be stable when stored yet they have to disintegrate fast into their component drugs when they are digested. Often disintegrants provide a hydrophilic network within the structure of the tablet so that water may diffuse through it.

Colors and flavors are also required to the mixture at this stage. Colors make the sorting process of different products easier on the personnel and the manufacturers can also use it as trademarks. Flavoring on the other hand helps disguising the taste of drugs. Only iron oxide dyes are used in this plant.

In one equipment, all the above described processes is done using a fluid bed granulator. A fluid, air in this cases, is passed into the powder bed from below with sufficient velocity to suspend the particles in air and move relative to one another giving an effective mixing. When the granulating agent is spraved over the particles, they stick to each other and adhere on collision. When the granules are formed and have reached the stage when they have to be dried, hot air is blown from below instead and each particle is, therefore, surrounded by hot air ensuring rapid drying of the mixture. The temperature of the bed can be precisely controlled and a free flowing product is obtained quickly and effeciently. The second mixing and drying effect can be achieved by the same mechanism and the particles will be ready to be compressed.

COMPACTION

The formation of almost all kind of tablets involves a compression stage when uniform amount of particles are flowed in to a pressing die and compressed to form tablets with low porosity which are then ejected from the die. The majority of the tablets are circular in cross section with different shapes. The punch faces are, therefore flat, bevelled, or cone shaped and also be embossed to provide engravings on the tablets.

The rotary press used in this plant involves the use of multiple dies and pairs of punches around a circular rotating turret. All the lower punches are passed under the powder bed which is continually being filled by a feed hopper going as low as it can and passes through a weight correction chamber where the excess powder is swept off from the punches. The upper punch is then lowered while the other one is lifted so that the powder experiences a two way compression force to form the tablets. The upper punch is then lifted to allow the lower punch to pass through the ejection chamber to eject the tablets from the punches.

COATING

Tablets are coated to improve palatibility, increase stability, disguise taste, prevent dustiness during packing, controll availability of drug, and produce an elegant drug. Not all the products are coated. There are two methods of coating in practice in Ciba pharma plant :

TABLET COATING

SUGAR COATING **FILM COATING**

Sugar Coating

A layer of sucrose is applied to the tablet core in this process. It is a very lengthy process and increases the mass of the tablets by a large degree. Some times the engravings on the tablets are toatlly obscured. Several steps are involved in this process as well. These are o ned below.

SOLUTION MAKING

SEALING

SUBCOATING

SUGAR COATING

DRYING

POLISHING

Solution Making

The coating material is usually an aqueous solution or disperston which has to be made prior to coating. As the solution can start disintegration of the tablets, a water insoluble polymer also has to be dissolved in organic solvent to prepare the sealing solution. All this solutions or dispersions are made separately before starting the actual coating process.

Sealing Stage

To prevent the tablets from water penetration, the tablets are precoated by an organic solution such as cellacephate, polyvinyl acetate phthalate, and shellac. Since they are all resistant to gastric juice, minimal amount of coating is applied at this stage.

Subcoating

This stage ensures the right shape of the product. Dusting with dry powders such as calcium carbonate, starch, sucrose, or talc is done after gum solution of gelatin or acacia is applied. It is continued until the desired shape is obtained.

Sugar Coat

Syrup is now applied to the tablet to provide the final coat of sucrose over the tablet. This step is also repeated several times until satisfaction has attained. If dyes are added at this time in the form of insoluble lakes or pigments, the product can be given colorization with the use of titanium oxide as the opacifier.

Drying

The excess liquid phase must now be removed at this stage. It is usually done by blowing hot air over the tablets. This is not a very efficient system since the inlet and outlet air travels through the same path and evaporation occurs only from the tablet surface. When dyes have been used to give color to the tablets, the evaporation has to be slow in order to prevent uneven coloration at the surface of the tablet.

Polishing

To give the tablets a nice finishing the matt tablets are transformed into another pan of poly ethylene glycol. The pan is rotated to provide uniform coat of polishing material on the tablets.

Film Coating

Since the 1950s film coating has been the more popular form of tablet coating. The three main steps of the conventional film coating are :

MIXING **PLASTICIZER + POLYMER + PIGMENTS**

SPRAYING

DRYING

The film forming substances, usually a cellulose derivative such as hypromellose, methylcellulose, hydroxypropyl cellulose, or ethylcellulose or acrylate polymers, form brittle and hard films. In order to avoid that these substances are mixed with plasticizers which lowers the glass transition temperatures of the polymers in use. The ratio of polymer to plasticizer is 10 to 1. It is essential that the coating solution adheres to the tablet surface. Pigments are almost always used in film coating. All these have to be mixed well before being applied to the tablets. Due to environmental considerations, these materials are currently dispersed in water instead of being an organic solvent.

Film coating can also be carried out in coating pans but spraying process is more popular with the manufacturers. The coating materials are sprayed on to the tablets which are rotating in a perforated rotating drum.

The drying can be done in the same drum where the film is applied to the tablets. The hot air is blown over the tablets through the perforations of the drum and then extracted from under the tablet bed.

In fluidized bed coating method the equipment is able to atomize the spray liquid and agitate the tablet so that every thing passes through the spray. Fluidized coating equipment operates with the same mechanism as the fluid bed granulators.

Some coating materials are required to be gastric fluid registant but easily permeable to intestinal fluids. The tablet mass does not increase very much by this process and the engravings on the tablet are always protected.

CAPSULES

Capsules are defined as solid preparations with hard or soft shells, of various shapes and capacities containing a single dose of active ingredient intended for oral administration, according the pharmaceutical codex. The elegant form of dosage, ease of swallowing, and the masking ability of unpleasant smell and taste contributes towards its popularity among patients. The manufacturers also like this form of the dosage because it requires less compressing equipment, it can be filled with powders, ganules, pellets, and even tablets if required, the dose can be changed simply by changing the fill weight, and many machines can fill up to three components in to the shell at the same time. There are two types of capsules namely the hard shell capsules and the soft shell capsules. An out line giving a step by step description of hard shell capsule formulation is given below. It should be noted that

the formulation of hard shell capsules is essentially the same as that of tablets except for the final stage where capsule filling replaces the compaction step. Since the initial steps are already described in the previous section only the capsule filling stage will be described.

HARD SHELL CAPSULES

The hard shell capsules are a dosage form consisting of two forms - the shell and the filling contents. The shells are almost always of gelatin and have two sections - the body and the cap. Both sections are cylindrical in shape and have one end sealed. The body is first filled with the drugs and other excipients and then the cap is fitted to the body to seal the capsule.

CAPSULE FILLING

The contents of a hard shell capsule are most often powders but granules, pellets, and even tablets can be used as capsule fillers. There are several different capsule sized available and the contents must be formulated so that the dose is properly contained in the volume represented by the capsule size being used.

The degree of dilution is determined by the bulk density of the drug which is dependent on the compression degree of the filling machine being used. In numerous cases, the same excipient and equipment are used as that of tablet formulation. Therefore, the same aspects are considered to mix the chemicals and avoid the segregation of particles. Since most capsule fillers are in the powdered form,disintegrants are not required. Diluents, coloring agents, and any other additive must be innocuous and without influence on the therapeutic efficacy of the drug in use.

A number of filling methods are in practice. For small scale production, the body of the capsule is held so that the powder can be flowed in and then the cap is fitted on top. The uniformity of the product is ensured by the use of a glidant such as finely divided silica to give the powder the essential flowing property.

QUALITY CONTROL

The tablets and capsules thus formulated are subjected to a number of quality control tests in order to be permitted to go to the market. Some of these tests are - uniformity of weight, content of active ingredient in each tablet, uniformity of content, disintegration, dissolution. Any deviation from the standards set by the local drug administration is carefully detected for and if the deviation is larger than the set percentage the products are discarded. Only the products getting the green stickers from the quality control personnel of the manufacturer goes to the packing room and the rest are sent for rework. This is very important to a pharmaceutical formulation plant and the Good Manufacturing Process (GMP) provides incentive both for the prsoanel and the management to be careful to meet the requirements of the products.

REWORKING

The drugs used in the formulation plants are very expensive. Therefore, the products failing to meet the requirements of the drug administration cause great financial loss. Sometimes these rejected products are milled into powders and with slight variations recompressed into tablets. This step of the formulation plant is exceptional because it is rare that reworking will give the required qualities in a product and GMP requires that the specifications of the products are met.

PACKING

All the products, after obtaining the green signal from the quality control department, are then packed in either strip or blister packaging and boxed. Blister packaging is done by the following mechanism - a rolling conveyer belt spreads the blister packs where the holes are filled by tablets or capsules manually and a pressing device seals the top with one layer of aluminum foil to protect the product from out side contamination. Strip packing is also done in a similar fashion. The size of the blisters or the strips are reduced to a minimum (?)% of

the previous size) to reduce cost and landfill by the consumers after use. The label on the container must state the name of the tablet, date of production, date of expiration, the quantity of the active ingredient(s) contained in each tablet and the recommended dosage. These boxes are then packed into master cartons and sent to the wholesalers to be distributed to pharmacies, hospitals, and doctors.

ENVIRONMENTAL POLLUTION FROM THE FORMULATION PLANT

A major activity in a formulation plant is the handling and packing of pharmaceutical powders. This requires careful dust control to avoid contamination of the pharmaceutical compounds. The high cost of these powders to the formulation plant provides a strong incentive to the industry to minimize any losses of such products to the atmosphere. The use of Good Manufacturing Practice for pharmaceuticals leads to high standards of air filtration into the plants to avoid contamination of medicines for human and animal consumption.

The main activity which has impact on emissions to water is the washing down of equipment and floors. This can be significant in finishing plants. This results in a relatively high volumes of aqueous wastes depending on the scale of production. Due to the labor intensive nature of such plants the domestic use of water can be also significant if the production scale is large. The majority of the formulation plants discharge their liquid effluents untreated into municipal sewers under licence.

Formulation plants also produce significant quantities of solid wastes. These include damaged product containers, concentrated washing of highly active or toxic substances, out of date pharmaceuticals or material which fails quality control tests and cannot be recycled. The preferred disposal route for many of these materials is incineration because of the risk of claims against the pharmaceutical manufacturer if any of the products were to be recovered from a landfill. Disposal by incineration may require a move away from PVC packing materials for fear of dioxin formation upon incineration.

There is very little threat of air pollution from a pharmaceutical formulation plant. Still every step of such formulation plant can contribute to the air and water emission as well as the landfill. Therefore, careful monitoring of the whole process under the close supervision of a competent pharmacist is required by regulation in many countries. A full measure of the possible pollutions from every step of the formulation plant in Tangi is discussed in the following section.

SOURCES OF AIR EMISSION

.Transportation in and out of the Plant

-Dust of the powdered chemical - blown by accident
-Exhaust fumes of the trucks

.Warehouse Storing the Raw Materials and Finished Products

-Chemicals in the ventillation extract
-Vapor losses from liquid storing tanks

.Weighing Room

-Chemicals in the ventillation extract
-Vapor losses of liquid ingredients
-Chemicals wasted by accident and then blown by the air

.Pretreatment

-Dust explotion from the mixer
-Chemicals in the ventillation extract
-Emission of volatile organic solvents

.Compaction

-Powders blown when transferring the granules to the granulator
-Chemicals in the ventillation extract

.Capsule Filling

-Powders wasted in the filling process
-Chemicals in the ventillation extract

.Tablet Coating

-Chemicals in the ventillation extract
-Emission of volatile organic solvents

.Quality Control

-Dust emission from the rejected material
-Chemicals from the labs in the ventillation extract

.Packing

-Dust from the final products and packing materials

The threat to air pollution from a pharmaceutical formulation plant. The main pollutant in this case are the pharmaceutical substances and the volatile oragnic solvents. Even so, they can cause harm to the environment if not taken care of properly.

Dust explosion is the most dangerous threat in this stage. Dust of particles are always floating in the rooms and sometimes the solvents as well. Due to the collision between these particles a small spark can occur and creat an explosion. The threat of dust explosion in the rooms in next to nothing in such plants but significant in the equipment.

Since the pharmaceutical substances are toxic or poisonous by ingestion in some extent, special care must be given in the handling of these materials.

When the materials are being transported in and out of the plant, some of the packing boxes might break and cause this powder materials to be blown off by air. The same thing can happen in the warehouse while storing these substances.

In the weighing room, when these materials are taken out to be proportioned for the production, chemical dust contaminates the air if the air flow is not laminer and proper ventillation system does not exit.

During tablet compaction and capsule fillling, the pressing dies and the dosator or tamping device of the capsule filling process are weighed before the actual process is performid. The extra weight is swept off the surface of work. This extra powder can sometimes be blown off by air and contaminate the air.

In tablet coating, the dus emitted is not very great since mostly solutions are handled in this step of the process. Still some powder is lost to the atmosphere from the unpolished tablets.

In quality control laboratories the chemicals and products are tested for their expected standards. Samples of material fly off if the air flow is not horizontal.

In the packing room, dust from tablets and capsules always finds ways to create problems. Also dust from the packing material can cause dust emission problems too.

More and more manufacturers are leaning towards aqueous solvents as the granulating and coating agents. Therefore the volatile organic solvents previously used in the industry are becoming obsolete and so is the threat to the environment through toxic vapor emission.

Polyethylene glycol is used to polish sugar coated tablets in the plant. The solvent is always kept in closed container to avoid loss to the environment through evaporation. No organic dyes are used.

If the chemicals used have a lower flammable limits between 35-55 degrees celcius or lower, then there is a potential hazard for fire. Most of the pharmaceutical chemicals emit toxic fumes of NOx, SOx, NH_3, HCl, Cl, Br etc upon decomposition on heating or oxidization.

In the plant being discussed, all the rooms are equipped with proper dust extractors to catch the dust from both out going and in coming air. All the solvents are kept in closed containers to prevent evaporation. And finally, the incinerator flue gas is guided through a scrubber before being let out of the environment.

SOURCES OF EMISSIONS TO WATER

.Trasporation in and out of the Plant

-Spilled chemicals
-Transportation fuel

.Warehouse

-Leakage in liquid containers
-Wash water of the storage area
-Fire water run off
-Contaminated storm water

.Weighing Room

-Wash water from the equipment
-Wash water of the room

.Pretreatment

-Wash water of the room and the equipment
-Spillage of the organic solvents used in the granulator

.Tablet Compaction

-Wash water of the room
-Equipment wash water

.Capsule Filling

-Wash water of the room
-Equipment wash water

.Tablet Coating

-Wash water of the room and equipment
-Spillage of the coating solution

.Quality Control

-Aqueous solution from the labs
-Organic solutions from the labs
-Wash water of the room and equipment

.Packing

-Wash water of the room and equipment
-Domestic wash water by the workers

Therefore, the main source of contamination of water by a formulation plant are the wash water of the equipment and floor and the aqueous and organic solvents used in the granulation and coating process. A brief description follows

Depending on the production scale the volume of the aqueous and the organic waste from a formulation plant can be very large. Although in most of the cases these effluents are discharged to the municipal supply, they often require proper treatment due to the nature of their content prior to discharge

Wash water is the major water pollutant in a formulation plant. The plant is washed at regular intervals starting from the loading zone to the packing room. Even the equipment are washed before they are used to weigh, granulate, compress, or fill one product and right after they have been used for those purposes. This is done to avoid any cross contamination of the products. Besides, the carcinogenic and toxic nature of the compounds also does not allow the compounds to be left alone in the rooms or equipmet for a long period of time

Aqueous and organic solvents are used to produce the granules and coating solutions. These liquids are often spilled on the ground if not handled with care. They are potential sources of water contamination if the content level is not kept low. This plant mostly uses aqueous solvents in their production with few exceptions such as poly ethylene glycol

The domestic wash water - water used by the workers - is also a water contaminant. The workers come in contact with the pharmaceutical chemicals and wash them off. This water is also guided to the main effluent stream

The quality control laboratory uses various different solutions and solvents to check the content and amount of active ingredient(s) in the products and effluents. Their contaminated water is discharged at the effluent stream as well

Formulation plants have sprinkler systems in the warehouse and other areas to fight against possible fire. In the case of a fire hazard, the sprinkler system sprays water throughout the plant. This water can be contaminated by the chemicals or the combustion products and therefore, should not be let out to the municipal supply without being properly treated

In the case of a big storm, where water may stand above ground level for a long period of time, the excess water can also be contaminated in the same way and the same applies to this situation as well

Wash water, solvents, and run off water can pollute the water in three ways - they can be dumped in a catchpit where they will gradually contaminate the ground water, they can be discharged to the municipal supply

where the town water supply will be contaminated, or they can be discharged at the river or sea mouth where the aquatic life would be affected.

In this case, the effluent is treated in a biological cleaning unit before discharge to the municipal supply. The inlet and outlet of the cleaning unit are constantly monitored to detect any toxic element which might need further treatment. Provisions exit in case of any possible deviation from standard behavior of the effluent.

SOURCES OF SOLID AND VISCOUS WASTE

.Transportation in and out of the Plant

-Packing materials
-Solid chemicals

.Warehouse

-Reject pharmaceutical substances
-Packing materials
-Solid chemicals
-Finished products if accidentally dropped and contaminated

.Weighing Room

-Dust collected at the air filters
-Empty storage boxes
-Chemicals collected at the dust collectors

.Pretreatment

-Dust collected at the air filters
-Chemicals collected at the dust collectors

.Tablet Compaction

-Solid waste from cleaning the equipment
-Dust collected at the air filters and the dust collectors

.Capsule Filling

-Solid waste from cleaning the equipment
-Dust collected at the air filter and the dust collector

.Tablet Coating

-Dust collected at the air filter
-Chemicals collected at the dust collector

.Quality Control

-Rejected pharmaceutical products
-Dust collected at the air filter and the dust collector

.Packing

-Contaminated packing material
-Discarded packing material
-Wasted/excess packing material

The volume of the solid waste in a formulation can be very large depending on the production scale and the operation style.

The major contributors to the solid waste are the rejected pharmaceutical substances and products failing to meet quality control tests, excess, rejected, or used packing materials, empty containers, and contaminated clothing of the workers.

The in coming air in a formulation plant is very carefully filtered to avoid contamination of the chemicals. Also the whole unit equipped with dust control equipments to collect dust form the source of generations. These equipment are regularly cleaned to prevent cross contamination. Significant amount of solid chemicals are extracted from the filters of these equipment.

All the pharmaceutical substances come in some form of containers which are emptied when the chemicals are used. Since it is a pharmaceutical formulation plant, the containers cannot be recycled for fear of cross contamination.

All the chemicals go through quality control tests before being processed and substances failing to meet the standards are discarded. They occupy a large portion of the solid waste.

Finished products also go through stringent quality control measurements and any products failing those tests are either reworked or discarded. Also out of date products are returned by the whole salers which are discarded as well.

Formulation plants use PVC film, aluminum or polythene foil, and papers as their packing materials. These materials are usually not biodegradable and can be found in the landfill many years after they have been disposed. A significant number of packing material is wasted through cutting and shaping of the packaging and quite a few are contaminated in some way. Also the consumers throw the packing materials away after use. All these have to be discarded in an enviroment friendly way.

The workers in a formulation plant use special protective clothing and hand gloves as well as nose masks and eye goggles to prevent intoxication. These materials are discarded in a regular basis when they are contaminated.

The volume of these solid wastes can be reduced by a large degree by some simple preventive measures. The responsibility of the workers to waste the least and protect the environment helps the implementation of the preventive measure to a large extent. The Good Manufacturing Practice serves as good incentive for the manufacturers to actually have a pollution reduction program.

HAZARDS AND RISK FACTORS INVOLVED IN THE FORMULATION PLANT

A formulation plan has many health hazards and risk factors involved besides its environmental impacts. Since it is a very labor intensive plant it requires safety measures to protect health of the workers. The major risk factors that need serious consideration in a formulation plant are fire risk, dust explotion, electrostatic charge build up, intoxication, noise, light, heat, ventillation, and energy consumption.

FIRE RISK

Fire risk is the most common risk factor in all chemical industries. All the chemicals are stored in warehouses. Substances with lower flammable limit less than 35° celcius are the most dangerous. Therfore, the common practice is to store the liquids separately out side the warehouse to avoid any fire incident. The walls of the warehouses are usually fire resistant for atleast 2 hours so that the mangement has plenty of time to evacuate the premesis. Some of the equipment used require enough energy to create a fire hazard any time.

DUST EXPLOSION

The floating particles in the rooms collide with each other and cause separation of charge. The same process occurs inside the equipment as well. Sometimes, this can cause a small spark and if there is enough solvent vapor in the vicinity for the particles to ignite an explosion can occur either in the room or in the equipment.

TOXIC HAZARD

In case the chemicals lose their containment or catch fire they can pose toxic threat to the work force. Large in take of these substances are very toxic for the human system. Some of the chemicals used in formulation plants are poisonous through multiple routes to human beings. Some of the materials emit combustion fumes that are dangerous for the workers. The laborers should be well protected from the adverse effects of these compounds to avoid any health complications.

NOISE POLLUTION

More and more people are paying recognising the adverse effects of prolonged and continuous exposure to elevated noise levels. This can affect the personnel seriously, often in an insidious manner. The granulating and compressing machines can make significant noise to create this problem. The air compressors and the ventilators create the most significant noise disturbance.

IMPROPER LIGHTING SYSTEM

Lighting levels should be carefully selected to avoid ny strain on the eyes of the personnel due to inadequate or excess lighting levels. While inadequate lighting causes fatigue, excess light results in glare and dazzling - all of which is harmful for the personnel. Clear day light is therefore, preferred over artificial light.

HEATING SYSTEM

Some process requirements such as low humidity or excess heat generation by equipment can conflict with the maintenance of a comfortable environment. If not properly heated a formulation plant can cause great harm to the personnel.

INADEQUATE VENTILLATION

Without adequate ventilation the working condition of the plant becomes unbearable. Again, some process requires operations under enclosed rooms to avoid cross contamination of the products and proper measures are needed to provide personnel safety.

ENERGY CONSUMPTION

The equipments used in the production process requires energy input in some form. Some of these equipment can generate static discharge. A large amount of energy is released in the incineration process depending on the scale of production. Energy wastage should be reduced to a minimum.

ELECTROSTATIC CHARGE BUILD UP

As explained in the dust explosion section the separation of charge due to the collision of particles may build up electrostatic charge which is dangerous for any working environment.

In the plant being discussed, all of the hazard and risk factors exist to some extent. Since the plant is rather small and do not have that large a scale of production, the potential danger is not very high. All the employees are environmentally cautious to act responsibly.

PREVENTIVE MEASURES TAKEN AGAINST ENVIRONMENTAL POLLUTIONS IN THE PHARMACEUTICAL FORMULATION PLANT

We have discussed the production process of a pharmaceutical formulation plant and the environmental aspects of it in the previous chapters. Now we will move on to measures and technologies aimed to contain the emissions and to minimize the waste.

Waste management is defined as a system of equipment, structure, or transport mechanism used in handling, storage, treatment, or disposal of waste. The best way to handle waste is to minimize it. The prevention or restriction of waste generation at its source by redesigned products or the pattern of production or consumption. It includes any source reduction or recycling activity undertaken by a generator that results in either 1) the reduction of total volume or quantity of hazardous waste 2) the reduction of toxicity of hazardous waste, or both, as long as such a reduction is consistent with the goal of minimizing present and future threats to human health and environment.

There are a few types of wastes polluting the air, water, and the land. They are either easily biodegradable or nonbiodegradable wastes. Some waste products are more harmful for the environment than the others. Care should be taken to waste and produce minimal amount of toxic material. The waste, regardless of the amount and toxicity, should always be properly disposed of. There are many environmental measures that can be taken. Some of the important ones are discussed below.

Some preventive measures against hazard and pollution increase the production cost but in some exceptional cases this decrease the cost as well. Ciba Geigy in Bangladesh has reduced their non-biodegradable capsule packing foil by 30% which reduced their production cost as well as the landfill. Some very simple and carefull considerations can provide such easy waste management systems.

Pharmaceutical formulation plants deals with chemicals which are often harmful for human being when ingested in small amounts. The cost of such materials is one good incentive for reducing waste. Also the awareness of the workers and the management of the potential dangers in handling such materials and the effect they have on the environment is increasingly becoming another incentive for such stringent environmental considerations.

Formulation plants do not synthesize any chemicals for their production purpose. Since the consumption rate is very low in developing countries, synthsis plants are not cost effective in such countries. All the materials are provided by out side suppliers. Therefore, the hazardous materials are the pharmaceutical chemicals themselves if ingested in large amounts or heated to decompose. So most of the preventive measures are geared to control the loss of such material to the atmosphere.

Since the main liquid effluent is of the wash water of the rooms and equipment, they can all be collected and treated at the same site. In fact, if there are a number of formulation plants in one area they can have joint venture to clean their effluents together before discharging to the municipal supply.

The solid wastes are not landfilled to a large extent these days for fear of redisscovery after a long period of time and possible manufacturer's liability. But all the solids can not be incinerated either because of the dioxin formation from chlorohydrocarbons. Therefore, the solid wastes has to be categorized in order to be incinertaed or landfilled.

In developing countries, a separate industry can be formed to prevent environmental pollutions. If all the pharmaceutical industries cooperate, there can be common effluent treatment sites, incineration facilities, and a common landfill area with every company having a quota on their share of landfill.

The best way to solve this problem is to reduce the pollution as much as possible by replacing the current technology by one which does not contribute to pollution in any way. But to find such a perfect technology is not feasible and therefore, other preventive methods are looked for. The control methods must be installed on the basis of some recognised guidelines and standards.

Air Quality Management

A system comprising coordinated measures necessary to reach and maintain an acceptable level of ambient air quality is known as the air quality management system. The system consists of 1) the assessment of present air quality, emissions, related factors, 2) the comparison of projected emissions and ambient air quality with standards, criteria, guidelines, 3) the development, implementation, revision of abtement strategy plans, including economic aspects and interactions with other environmental media

A formulation plant should have ample facilities to assess their emission level to the atmosphere both in present and in the future. Based on their assessment the plant officials will underake appropriate measures to control their emissions. They will also consider the cost effect of any new technology they have to adopt instead of the old one

Measures Aimed at Containing Air Emission

Care should be taken in the handling of all materials at all times so that the material is not lost to the atmosphere. Since the pharmaceutical substances are toxic when ingested by small amounts, the whole production unit should be equipped with effective dust collecting systems which will collect the dust from its source and filter the out going air. These dust collectors should be cleaned at regular intervals to avoid any kind of cross contamination. All the unloading of powders are done in laminar air flow so that the particles don't fly out in every direction

The granulating, coating, and polishing solvents should be prepared and kept in closed containers to minimize vapor emission. Also any liquid form of ingredient should be stored properly to avoid spilling and consequent vapor emission

The pharmaceutical products emit toxic fumes when heated to decompose often their combustion products are toxic as well. Therefore, special care must be taken to fight fires through proper sprinkler systems. The incineration fumes shohuld also be nuetralized prior to discharge to the environment

Measures Aimed at Reducing Air Emissions

According to the production and need of the plant under local regulations, formulation plants take various measures to reduce the air emission. Some of these measures are catalytic or regenerative vapor incineration, thermal vapor incineration, carbon adsorption, selected chemicl reaction scrubbers to remove acids and odors, HEPA filters, air or stream stripping of effluents for recovery or treatment, biofilters on waste water treatment units etc

The measures taken at our case study plant Ciba are the followings - Dust Control Equipment, HEPA (High Efficiency Particulate Air) Filters, Scrubbers for Incinerator Flue Gas, Liquid Vaporization Minimization

Water Qulaity Management

The presence of enough harmful or objectionable material to damage the water quality is known as water pollution and a system which can assess the present and future quality of water and the amount of pollutants in water and provide a sound solution against the pollution either to prevent it or to reduce it to its minimum, is known as water quality management

The main waste water effluent from a formulation plant is the wash water of all the rooms and equipment. To avoid the cross contamination of the pharmaceutical products the rooms are frequently washed and so are the equipment, especially right after or before the prosduction of one product. Even the filters from the dust collecting equipment are cleaned and washed regularly. All these water stream might contain pharmaceutical substances, which are often organic compounds or their derivatives and thus harmful to aquatic life as well as the human life. One advantage of these pollutants are that they are mostly biodegradable and the suspended solids can easily be filtered out to allow the solid waste to do so. Another threat to the water from such plants are the fire water and

contaminated storm water run off. Since a significant amount of flammable pharmaceutical substances are stored in warehouses, the fire risk is high and the water used to fight the fire is then collected at the catch pit where it is tested for any harmful chemical present and then treated accordingly before letting out to the municipal supply. The same is done for the storm water that stands on the vicinity for a long period of time. This is done to ensure that any reaction that might have taken place during the hazard does not leave the reaction products in the run off water which can subsequently pollute the ground water or the municipal supply.

Measures Aimed at Containing Water Emission

The main water pollutant from a pharmaceutical industry is the wash water of the equipment and rooms. Care should be given in the handling of the material so that the amount of chemicals in the wash water of the floor and room is minimal.

All the wash water should be filtered for undissolved solids before being directed to the effluent stream. The wash water of the equipment often carry significant amounts of pharmaceutical substances which should be taken as well.

In the case of possible fire hazard or storm situation, the run off water should be collected in a catch pit and treated accordingly before being discharged to the municipal supply. The combustion products of these substances are often harmful and hence this process is extremely important.

Measures Aimed at Reducing Water Emissions

The guideline set up by the local authorities require the manufacturers to undertake measures to reduce the water emission such as steam stripping for removal of organohalogens, heavy metals removal, mechanical treatment, pH correction, coagulation, trickling filter, anaerobic digestion, extended aeration, etc.

The key technologies used in this field are on or off site biological treatment, activated sludge process, wet air oxidation, etc.

For a formulation plant such as Ciba Geigy in Bangladesh, a simple biological cleaning device is sufficient enough to handle the effluent stream. In case of possible fire or storm proper drainage system should exist to prevent the storm water to stand or the fire water run off to go into the municipal supply untreated.

Solid Waste Mangement

Any solids that can contribute to the landfill or be incinerated are known as solid waste. Solid wastes contaminate the ground and in turn the ground water. The minimization of solid wastes and proper disposal of such waste is known as solid waste management.

There is a wide variety of solid wastes from the formulation plants including reject raw materials and products along with the reject packing material and contaminated clothing. Also the solids collected at the dust filters and the sludge from the waste water effluent is among the solid wastes. The easiest way to handle them is to incinerate them. But one should be very careful to separate the PVC materials before incinerating other solid wastes as they produce dioxins. The PVC material should be encapsulated in nondegradable packing materials and landfilled where allowed.

All the other solids can be incinerated in a formulation plant of this kind. The incinerated ash has to be landfilled appropriately, meaning that if the ash is degradable it can be encapsulated in degradable material and landfilled to be subsequently decomposed. But if this is not possible, other measures have to be taken. Recovery of some compounds from the ash might be possible which can be recycled for some important use as well.

Measures Aimed at Containing Solid Wastes

All the reject materials should be properly incinerated along with the rejected products that failed quality control tests

All the packing material should be carefully monitored before being sent to the incinerator for any PVC material or other chlorohydrocarbons. Since these materials form toxic dioxin upon incineration, such materials should be separated

Also, incinerated ash has to be properly disposed off. This catches the most public concern due to the dioxin content fear. Usually the ash is encapsulated and landfilled

Lastly biodegradable wastes are landfilled in fibre drums. Therefore, both the drum and the waste is degraded subsequently. Careful thought should be given into the selection of this process because if some nonbiodegradable substance is discovered in the future, the manufacturer will be held responsible

Contaminated clothings should be washed first and then either landfilled or incinerated. The wash water again should be directed to the main effluent stream where it will be treated before being discharged

Measures Aimed at Reducing Waste disposal

No matter how well a formulation plant manages its wastes to minimize the solid waste, there is still a significant amount of solid wastes from such plants. Measures aimed to reduce them are sludge incineration, waste encapsulation, incinerator ash vitrification, on and off site incineration, engineered landfill of hazardous wastes, etc

Ciba incinerates all its solid wastes at their on site incinerator. Since the flue gas coming out of the incinerator is acide, it is guided through an alkaline scrubber to neutralize the acidity

KEY TECHNOLOGIES USED IN THE TANGI PLANT

Since pharmaceutical substances are often fine particles and run a high risk of flying around, proper dust extraction system is essential for such plants. These dust extraction systems consist of suction units which sucks away the dust particles through hods, pipes, ducts, etc. to the filters of the Dust Control Equipment. The chemicals and dust are collected at the filters and the cleaned air is let out to the atmosphere. All the suction units are connected to the central Dust Control equipment. The plant, starting from the weighing room to the packing room, has to be equipped with proper dust extraction units. Some areas may need more care than others such as the granulation room.

In the warehouse, the QC samples are taken only in the sampling cabin which is provided with laminar air flow. Therefore, the risk of powdered material floating in the air is negligible. In the weighing room, the chemicals are taken out to be portioned to their required amount for individual products. The possibility of dusts flying out is much higher here as the powders are being handled by the workers. Therefore, the dust extraction unit is high powered as well. The granulating room poses the greatest danger of dust explotion as the more modern form of granulation, Fluid Bed Granulation, is used. Most of the equipment in this room is therefore operated under closed condition. Even so the room is equipped with three high powered dust ventillation spots apart from the regular A/C returns to filter out the chemicals from the out going air. In capsule filling and tabletting rooms, all the operations take place under closed containment. The flying powders are either collected through suction spots connected to the DCE or sucked out by vacuum cleaners attached to the equipment being used. Tabletting produces more dust than capsule filling and therefore, only a vacuum pump is attached to the filling machine to catch the flying powders. The coating room also produces considerable amount of dust when the coating material is dissolved into a proper solvent. Therefore, this process is also performed in closed containment and equipped with extra high power air extraction system. Even in the quality control lab, the chemical reactions performed to determine the required quality of the products are done in fume chambers, which in turn is connected to the DCE, to prevent any harmful fume or powder to go in to the ambient air.

The suction units are usually what their names suggest. They simply suck the air from the equipment which might have powdered chemicals in it, and passes it through the filters of the DCE. It works like vacuum pumps.

Dust ventillation spot systems are systems which carries away the dust particles from its source of generation and as usual passes it to the DCE. They have some way of attracting dust particles from point they are generated.

HEPA or high efficiency particulate air filters are used to filter any in coming air into the production unit of the plant since these plants are producing drugs that can be contaminated very easily by the particles in the incoming air, the air coming in has to be filtered out from any contaminent it might be containing. The mechanism of such a filter is as follows [ ].

Organic solvents are used to polish coated tablets and as granulating agents while aqueous solutions are used as coating agents. These solutions and solvents are often dangerous for the environment if allowed to mix with the ambient air. Therefore, the solutions are made in closed containers and kept there to minimize the vapor loss to the environment.

Finally, when all the solid wastes are incinerated to decompose, the exhaust fumes becomes highly toxic with NOx's and SOx's as most of the pharmaceutical substances emits toxic fumes of NOx's, SOx's, HCl, HF, Cl, and Br. The flue gas therefore, has to be treated before being discharged to the atmosphere. Since, all these gases are acidic, a wet scrubber with alkaline solution to nutralize the gas is sufficient. The incinerator and scrubber work as the following description [ ].

A biological cleaning device can be used to clean the wash water of a formulation plant. It consists of three major parts a sump, a septic tank and a biospiral unit. the 15 feet deep sump has anaerobic bacteria living there where all the effluent is collected. When the effluent level has reached a certain height the pressure of the fluid activates a pump which pumps a prespecified amount of effluent into the septic tank while most the suspended degradable solids are eaten by the bacterias in the sump. The septic tank has three compartments again to allow primary settlement of the solids. These septic tanks are again inhibited by anaerobic bacteria that can eat up the degradable solids in the sediment. The tank bottoms are tilted on side to initiate settlement and they hold only the prespecified amount of effluent at a time. After a certain time the effluent is then pumped to the biospiral unit. It is collected in the collecting chamber of the unit where a circulating disk with a bucket measures out appropriate amount of effluent to enter the spiral drum. The drum consists of ~70, 1/16 inch rotating PVC disks with bacterias on them. Oxygen is allowed to come in from one inlet and the effluent is always maintained at the same level for a fixed amount of time. After the aeration time the effluent if filtered once again and discharged to the municipal drain. Samples are taken from every steps to monitor the pH, DO, BOD5, COD, total settelable solids, total dissolved solids, total volatile solids, toatl fixed solids, total suspended solids, chlorinity,and Pb content. Any deviation from the set standards are promtly detected and taken care off, especially in the out let stream.

The warehouses run a high risk of catching fire from flammable pharmaceutical substnces. Therefore they are equipped with proper sprinkler systems to fight he fire. These compounds also form harmful substances on decomposition by heat. When mixed with the fire fighting water, they often form very toxic water and therefore is not allllowed to go to the municipal supply. Proper drainage system is provided for the run off water to flow into

a catch pit of 200 cubic meters. This water is eventually pumped out and tested for the presence of any harmful substances and eventually treated accordingly. If it only contains degradable organic compounds,the run off water is led to the main effluent stream to be treated together. In case of possible big storm, the run off water is alos caught in such catchpits and handled similarly.

All solids can be incinerated in a formulation plant of this kind. It works as the follows. The incinerated ash has to be landfilled appropriately, meaning that if the ash is degradable it can be encapsulated in degradable material and landfilled to be subsequently decomposed. But if this is not possible, other measures have to be taken. Recovery of some compounds from the ash might be possible which can be recycled for some important use as well.

To act against the possible fire risk in the warehouse, it is equipped with a sprinkler system. There is a sprinkler water reservoir of 200 cubic meters, about 110 meters away from the sprinkler control system. The sprinkler system has sprayers which fuses at 60 degrees centigrade to spray water thoughout he warehouse where the water is held at 8 bars of pressure. The contaminated solution is the taken to the catchpit and treated as described earlier.

The risk involving warehouse should be separated from other establishments by a minimum distance of 10 meters (the warehouse height). It is best to separate them by 40 meters or so and have 2-4 hour fire resistant walls. Particular attention should be given to certain buildings such as schols and hospitals. Toxic products should not be stored in residential areas or places where flooding ocurs regularly.

Section G

Transfer of Technology and International Investment Related to Installations in Non-OECD Countries

The premise of this Section is that hazardous installations in non-OECD countries should meet a level of safety equivalent to that of similar installations in OECD countries. In this regard, it should be emphasized that the foregoing Guiding Principles should apply to all hazardous installations irrespective of location. This Section highlights certain points and sets out additional Principles which should be taken into account in order to achieve this equivalent level of safety when OECD-based enterprises transfer technology to, or invest in, hazardous installations in non-OECD countries. It should be pointed out that general Principles related to transfer of technology and to acquisitions and affiliated operations are set out in paragraphs B.4.18-B.4.22 and B.4.23-B.4.30, respectively.

This Section is not meant to be comprehensive in indicating how the Principles set out in previous Sections may need to be elaborated in order to take into account situations in which technology or investment flow from an OECD country to a non-OECD country. Rather, it is meant to illustrate the types of local requirements, circumstances and cultural aspects which should be considered, as well as the need in some cases to redefine the roles and responsibilities of public authorities, industry and employees in order that the overall objective of an equivalent level of safety is achieved.

Section G relates to the roles and responsibilities of public authorities, industry and employees (and employee representatives where they exist) in the OECD countries from which the technology or investment originates. Clearly the public authorities, industry and employees (and their representatives where they exist) in the non-OECD, recipient countries also have critical roles and responsibilities related to the safety of hazardous installations, and it is ultimately the responsibility of the host government to establish and enforce appropriate safety objectives. Since these Guiding Principles have been developed within the OECD, however, it was considered appropriate to limit this Section to the provision of guidance only to parties from OECD countries, with the recognition that Guiding Principles relating to the roles and responsibilities of recipient countries should be developed in a forum in which the views of representatives of non-OECD countries would be represented. Nevertheless, it should be recognised that these Guiding Principles, in general, have been drafted so as to apply in all countries including non-OECD countries, and it is therefore hoped that they will be utilised world-wide.

A basic premise of these Principles is that there should not be any discrimination in treatment between domestic and foreign enterprises, and that these Principles should be implemented in a non-discriminatory fashion: the same standards should apply to domestic technology and investments as to imported technology and foreign investments. In this regard, the provisions of the General Agreement on Tariffs and Trade (GATT) should be followed.

In addition, the Environment chapter in the Revised OECD Guidelines for Multinational Enterprises, set out in Annex IV, should be taken into account.

terminology at the international level through professional associations and other means.

F.8 National and international inventories of research activities should be established in order to facilitate the dissemination of research information and results, including research financed by industry, public authorities and academia. There should be rapid exchange of information on planned and on-going research and research results, so as to stimulate the appropriate use of scarce resources and minimise unnecessary duplication.

F.9 Special attention should be given to how research results should be disseminated to those potential users who may not have regular access to existing channels of information. For exampl efforts should be made to target resea results related to safety technology ar management processes to small and medium-sized enterprises. In additio information of interest to public authorities should be disseminated, as appropriate, to local communities and public authorities in non-OECD countries.

F.10 The curriculum and research programmes of science and engineeri departments of universities and colle should include, as an integrated elem safety aspects of design, operation an management of hazardous installatio and the transport of hazardous substances. These issues should also incorporated in the relevant activities professional organisations.

Consideration was given as to whether this Section of the Guiding Principles should incorporate a type of "prior informed consent" procedure for particularly hazardous technologies, paralleling the activities for banned or severely restricted chemicals. It was concluded that, while the objective of such a procedure is appropriate, technology cannot classified as banned or severely restricted. Furthermore, such a procedure would appear unnecessary given the general provision of G.1.1. indicating that the degree of safety of th technology being transferred should be the highest level of safety reasonably practicable. number of provisions in this Section do, in addition, call for the exchange of the types of information associated with prior informed consent procedures.

G.1 General Principles

G.1.1 The degree of safety of installations which result from an investment by an OECD-based enterprise, or which incorporate process or other safety-related technology transferred from an OECD country, should be the highest level of safety reasonably practicable according to the current state of knowledge and local circumstances. All parties should promote a level of safety for hazardous installations in non-OECD countries equivalent to that for similar installations in Member countries. Equivalent level of safety does not preclude the public authorities or enterprises from seeking to achieve a higher level of safety.

(i) Good design, engineering, construction, operational procedures and management practices should be followed at the installation in order that safety is maintained on a continuing basis. Account should also be taken of the need for education and training, as well as the need for provision of information concerning the installation.

(ii) The transfer of technology, or the investment, should only take place once there is reasonable assurance that safe operating conditions can be achieved.

(iii) Responsibilities, including costs, associated with meeting the objectives of these Guiding Principles may be allocated by agreement amongst the parties concerned.

G.1.2 When an OECD-based enterprise invests in a new hazardous installation a non-OECD country, or provides process or other safety-related technol for such an installation, the process should be chosen and the installation should be designed to take into accoun local factors which may affect the safet of the installation. These include, amo other considerations:

- geographical and climatic condition
- cultural and socio-economic factors
- infrastructure, including emergency services;
- legal and administrative framework
- land-use policies;
- local legal and control systems;
- local availability of labour;
- information systems; and
- available construction materials and equipment.

G.1.3 Technology suppliers and invest should, in conjunction with technology receivers and relevant public authoritie prepare a site-specific hazard assessme that includes, among other things, an

evaluation of the culture and practices in the non-OECD country that may prompt a re-design of the safety engineering system, and an evaluation of the potential impacts of any design assumptions that may affect the safe use of the technology at the specific location. These might include, for example, assumptions regarding the capacity and size of existing public emergency services, the reliability of steady electrical supply, the size of the pool of safety engineers, and the availability of spare parts and maintenance equipment.

- The hazard assessment should be used in deciding whether to go forward with a proposed technology transfer or investment.

G.1.4 The Guiding Principles relating to provision of information to employees and to the public should be applicable to all hazardous installations, irrespective of location, recognising however that the location of the installation may affect the relative roles of industry and public authorities. For instance, if local public authorities do not have adequate resources to implement public information schemes, the management of a hazardous installation should undertake to make relevant information available to the public, consistent with Section D of these Guiding Principles.

- The approaches used for risk communication in OECD countries cannot effectively be transferred wholesale to non-OECD countries. To ensure that the information provided is accurate, comprehensive and understood, the approaches used in non-OECD countries should take into account such differences as social and family structures, religious influences, language/dialect differences, resource limitations, and available information dissemination technology.

G.1.5 International organisations should continue to take action to support the principle that transfers of technology and investments concerning hazardous installations should only take place when accompanied by the related safety technology and "know-how", together with the assurance that safe operating conditions can be achieved in the recipient country.

G.2 Transfer of Technology: Role of Technology Suppliers

Subsections G.2 and G.3 concern the transfer of process or other safety-related technology by an OECD-based enterprise to a hazardous installation in a non-OECD country. The transfer of technology could be either: between independent parties; or within the framework of a relationship between companies. In the latter case, the relationship can range from minority participation to full ownership. The nature of this relationship may affect the allocation of responsibilities between the technology supplier and receiver, or may influence the means of carrying out their respective responsibilities.

These Guiding Principles should be read in conjunction with the general Principles on Transfer of Technology (paragraphs B.4.18-B.4.22).

G.2.1 The responsibilities of all parties involved in the transfer of technology related to a hazardous installation should be clearly defined at a preliminary stage of the transaction. There should be a written contract between the supplier and the receiver which specifies the duties of each with respect to the safety aspects of the technology being transferred, recognising that responsibility is linked to effective operational control. Such arrangements should take into account the amount of resources needed to

comply with safety requirements, as well as the corporate Safety Policy and guidelines.

G.2.2 The technology supplier should export only those technologies for which sufficient experience has been gained to permit an appropriate hazard analysis of the safety of the technology at the location where it will be used.

G.2.3 Transfer of technology related to hazardous installations should only take place if accompanied by the appropriate safety technology and the information necessary for the safe operation of the installation.

G.2.4 Consistent with the principle that technology transfer should only take place when accompanied by related safety information, the technology supplier should make available to the technology receiver and, on request, to competent public authorities in the importing country, the following information relating to the technology to the extent relevant to safety:

- national regulations, legal or administrative requirements, and accident prevention practices in the major areas where the technology is in use;
- generally accepted safety standards, voluntary codes, trade association rules, and other technical guidance documents relevant to the technology design, construction or operation;
- description of the process, including all necessary data on the substances handled, the chemical reactions involved, etc.;
- operating instructions and critical operating parameters during routine and non-routine conditions;
- a hazard analysis indicating, among other things, significantly hazardous features of the technology, known or suspected safety problems associated with the technology, possible products of runaways and domino effects during an accident, the minimum and maximum safe operating zones for each industrial process, and the normal quantities of hazardous, toxic and flammable substances present during processing or storage;
- any additional information relevant for hazard assessment and control, for the safe operation of the technology and the safe handling of any hazardous substances used or manufactured, and for review of safety performance;
- directions for maintenance, including the recommended frequency of surveillance and of maintenance of vital components as well as the installation as a whole, estimates of the prospective maintenance costs, monitoring equipment needed, and the skills required; and
- manuals and programmes for the education and training of employees.

(i) The above information should be available in an appropriate language and should be provided as early as possible and, to the extent appropriate and in accordance with the contract, before the transfer of technology takes place. The schedule for the provision of information should be acknowledged in the negotiation process for the transfer.

(ii) Recognising that this paragraph applies to the provision of information to the extent necessary to ensure safety, appropriate arrangements should be in place to

ensure the protection of legitimate trade secrets, taking into account paragraph D.13. The above in no way diminishes the intellectual property rights associated with the product or process which is the subject of the transfer of technology.

G.2.5 The technology supplier should indicate to the technology receiver and, as appropriate, to the public authorities in the technology importing country, if the technology being transferred involves activities which are classified as hazardous in the supplier's country and/or, if known, in any third country.

G.2.6 The technology supplier should be responsible for safe process design, supervision of commissioning, initial technical education and training, and start-up assistance, and for providing information needed for safe operation and safe handling of products used or manufactured, recognising that there should be a contract specifying the duties of the supplier and receiver in accordance with paragraph G.2.1.

G.2.7 The technology supplier, through its own staff or consultancy services, should make technically qualified people available to provide assistance to the technology receiving enterprise for training and education regarding the safety of the technology, including the adaptation of the transferred technology to local conditions and its implementation in the local industrial infrastructure. Such assistance should be made available during the design, construction, start-up and initial operation of the hazardous installation (see paragraph G.2.1).

(i) Normally, the technology receiver should be responsible for detailed engineering, plant construction, process operation, plant maintenance and modifications, alteration in design or operating procedures, provision of information to local authorities on safety issues, training and supervision of the workforce, and the establishment of safety and security checking systems.

(ii) Specific contractual provisions can require the technology supplier to exercise control over some of these tasks.

G.2.8 The technology supplier should, as appropriate, continue to provide information and assistance necessary for the safe operation of a hazardous installation following start-up, although the extent of this responsibility and the period during which it applies can vary depending on the type and context of the specific contract. In all cases, the technology supplier should provide any relevant subsequent information related to safety which was not identified at the time of the transfer including, for example, information concerning the investigation of an accident or near-miss involving related technology (see paragraph G.2.1).

G.3 Transfer of Technology: Role of Technology Exporting Countries

G.3.1 Upon request by public authorities in the technology importing country, the public authorities in the technology exporting country should make available, to the extent reasonably practicable, the following information concerning a proposed or actual transfer of technology related to a hazardous installation:

- national and local legal and administrative requirements and regulations applicable to the situation in which the installation is sited and operated;

- government-prepared information relevant to the risks and safe operation of the technology being transferred and the purpose for which it is intended to be used; and

- publicly available post-accident and incident-review studies and reports, to the extent relevant.

(i) Public authorities in the technology exporting country should be able to recover the costs of providing this information from the technology supplier, as appropriate.

(ii) Efforts should be made to develop an international mechanism for the collection, collation and dissemination of this type of information on a worldwide basis.

G.4 *Investments by OECD-Based Enterprises in Hazardous Installations in Non-OECD Countries*

Subsection G.4 relates to international investment by an OECD-based enterprise in a hazardous installation in a non-OECD country. This can involve a wide range of activities, including those in which the hazardous installation is under the actual control of the OECD-based enterprise (defined as a subsidiary relationship) and those in which the OECD-based enterprise is a minority partner and does not have actual control of the installation through contractual or other means (defined as an affiliate relationship). The nature of the investment could be, for example, an acquisition of an existing installation, the construction of a new installation, or participation in a joint venture partnership.

It should be noted that many of the provisions relating to the transfer of technology also apply to investments. Often the investment requires a transfe technology, or a technology transfer is needed to bring the installation in issu to the necessary degree of safety.

These Guiding Principles should be re in conjunction with the general Princi on Acquisition and Affiliated Operatio (paragraphs B.4.23-B.4.30).

G.4.1 The prevention of accidents sh be one of the fundamental business considerations taken into account by OECD-based enterprises, as well as b international service organisations an financial institutions, in any investme related to a hazardous installation in a non-OECD country. The amount of resources needed to comply with safe requirements as well as corporate safe policies and safety practices, based or these Guiding Principles, as well as th influence of local needs and culture, should be taken into account in determining the levels of funding and assistance required in conjunction wit the investment.

G.4.2 Investments by OECD-based enterprises resulting in new enterprise should be accompanied by good desig engineering, construction and operati practices in order that a high degree o safety can be maintained on a continu basis. Account should be taken of the needs for education and training, as w as for the transfer of information, concerning the installation and its operation in the local community.

G.4.3 To the extent reasonably practicable, an OECD-based enterpris should ensure that subsidiaries apply policies and practices concerning accident prevention and emergency preparedness and response which are equivalent to those followed by the enterprise in the home country. Equivalent does not preclude the publ

authorities or enterprises from seeking to achieve a higher level of safety.

(i) The means of implementing these policies and practices should be adapted to the particular local needs and circumstances, including legal, policy, administrative, technical and similar factors.

(ii) Line management of individual installations should develop its own safety programmes to implement the enterprise's Safety Policy;

(iii) Information concerning the hazardous installations and measures to adopt in the event of an emergency should be provided to employees, contractors and the local community in a manner equivalent to that done by the enterprise in its home country; and

(iv) Employees should have rights concerning participation in safety-related activities at the hazardous installation equivalent to those of employees in the home country.

G.4.4 The corporate Safety Policy of an OECD-based enterprise should be publicised in the relevant national language(s) in all hazardous installations of subsidiaries and, to the extent possible, in hazardous installations of affiliates.

G.4.5 An OECD-based enterprise should endeavour to have affiliates adopt safety policies and practices which are comparable to its own, and should offer assistance to facilitate this objective.

G.4.6 An OECD-based enterprise with investments in hazardous installations in non-OECD countries should co-operate with local officials to ensure that an appropriate infrastructure exists for emergency preparedness and response, siting/land-use planning, and provision of information to the public.

G.4.7 Safety experience including, among other things, experience relating to operation, training, maintenance, emergency preparedness and response gained by an OECD-based enterprise operating in a non-OECD country should be shared among local enterprises within that country, while recognising the need to protect trade secrets.

G.4.8 International service organisations, particularly engineering firms, law partnerships, consultancy firms, financial institutions and financial advisors, should take reasonable steps to ensure that their practices encourage the application of these Guiding Principles by, for example, following the relevant Principles in their own activities and by bringing the Principles to the attention of the appropriate corporate or government clients.

CASE STUDY 1

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SWISS INFO CENTER

CIBA-GEIGY

A REPORT ON THE COMPANY'S ENVIRONMENTAL AND SOCIAL PERFORMANCE

INVESTORS & CORPORATE RESPONSIBILITY RESEARCH AND INFORMATION
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SEPTEMBER 1992

CIBA-GEIGY

Sector: Chemicals/Pharmaceuticals
Headquarters: Basel (Switzerland)

Investment conclusion:

Ciba-Geigy shares are recommended to the investors wishing to have the chemical/ pharmaceutical branch represented in their portfolio - or who must buy such shares for diversification reasons . Ciba-Geigy has, in this branch, better than average performances in the ecological and social implications of their investments.

As for the investors who wish to invest in the ecological or social sector strictly speaking, they should not for the time buy Ciba-Geigy shares. Indeed, Ciba-Geigy products encompass risks for man and the natural environment; moreover, the company is active in controversial fields such as animal testing and gene technology.

Contents:

0. SUMMARY

Business Profile

Ciba-Geigy is the leading Swiss chemical group and ranked 7th world-wide with sales of SFr. 21.1 billion in 1991. About a third of the sales is realized by agricultural activities, 20% by pharmaceuticals and 37% by chemical specialities. In the recent years Ciba-Geigy has developped activities in biotechnology and in contact-lenses. The group covers 12% of the world agricultural market and is among the ten most important producers of seed. More than 2 billion SFr. are spent in research and development, partly to develop a vaccine against AIDS.

Stock capitalisation is about SFr.19 billion held by some 65,000 shareholders. Nobody controls more than 2% of share capital. The rules limit the ownership of Ciba-Geigy-stocks to a maximum of 2% of share capital and to 5% the voting rights of a simple shareholder.

Ciba-Geigy had in his history many problems either with products or with sales methods. But when Alex Krauer became CEO, a new policy of dialogue with all opponent groups has started. This policy is characterized in the document «Vision 2000», which states that the company is commited to a long-term-policy, aimed at an equal responsibility for economical, social and environmental concerns. The company runs an open-door-policy and gives many informations to make possible to the public to monitor the activities. Environmental standards in Swiss factories are valid in all group companies and branch offices all over the world. Since February 1990 the company has commited itself to deliver to thirld-world-countries only products which are registred in at least one OECD-country.

Due to the scarcity of such events, the creation of a Ciba-Geigy-foundation for cooperation with developing countries has to be appreciated. The task of this foundation is to help the board of directors and make them more aware of the problems of thirld-world-countries and to verify the company's policy in these countries. Servipharm, a group company, was specifically founded to produce essential drugs for the developing countries.

Nuvacron came under pressure from press and environmental groups. In 1990 the company had to admit that it delivered DDT to Tansania, although internal restrictions prohibited sales of it since 1989. Furthermore, the company is engaged in ethical controversial areas like animal testing and biotechnology.

Ciba-Geigy reported the use or the release of some Greenhouse gases for its world-wide operations.

Ciba-Geigy: Greenhouse Gases

Gases		tons (1990)
Carbon Dioxide	released	1,100,000
Methane	used	158,000
Nitrogen Oxide	released	8,000

Ciba-Geigy: Stratospheric Ozone Depleters

Gases		tons (1990)
CFC's	used in refrigerators	10-15
Halons	used in fire-extinguishers	0
HCFC's	not used/released	0
Methyl chloroform	used	80-90
Carbon tetrachloride	used	80-90

CHANCES:

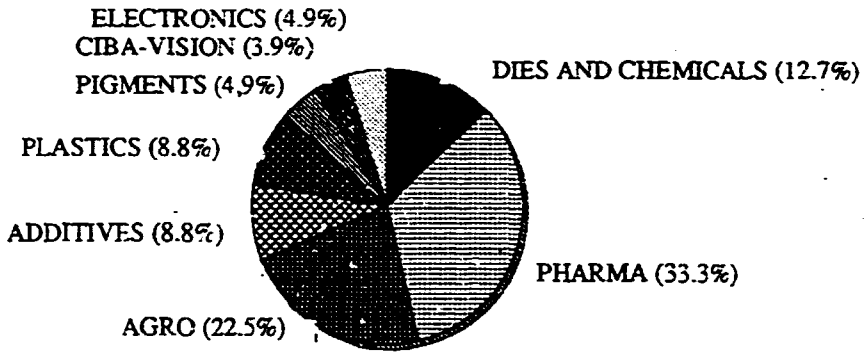
- Policy of security of the enterprise's long-term existence
- Public commitment to an adequate balancing of economic,social and environmental responsibilities (Vision 2000)
- Accurate and open information policy
- Goal of comparable ecological standards worldwide up to the year 2000
- Leading role in the protection of the environment generating competition advantages
- Reduction of air and waste water pollution in Switzerland over the last ten years
- Anchoring of ecological thinking in management and staff
- Large participation of staff in share capital
- Commitment with respect to developing countries
- Opening of share ledger to foreign investors and introduction of participation certificates on the New-York stock exchange
- Intensive research in the field of vaccines (e.g. against the AIDS-virus) through the Biocine Company
- Possible separation of pharmaceutical and chemical fields into two companies could lead to higher quotation.
- Activities in promising bio and gene technology.

RISKS:

- Debate on reduction or prohibition of certain pesticides (pesticides make up approximately 20% of total turnover) weighs on the agricultural sector
- Fast rising waste disposal and environmental costs
- Expenditures for the clean-up of old disposal sites amount to SFr. 50-100 mn per year. Ciba-Geigy is examining whether it is concerned with other old disposal sites.
- Accidents, an inherent risk to the chemical branch, cannot be excluded despite strengthened safety measures.
  Growing liability and image risks therefore justify a relative depreciation of the shares of the chemicals branch as compared with the overall market.
- Ownership of Ciba-Geigy shares limited to a maximum of 2% of share capital and to 5% of the voting rights of a simple shareholder.

ETHICALLY CONTROVERSIAL FIELDS:

- Ciba-Geigy carries out experiments on animals
- Ciba-Geigy is active in bio and gene technology and has already carried out several experiments in the field with genetically manipulated plants.
- Ciba-Geigy group company in South Africa, active in research, production and sales.



Overall strategy

«Vision 2000» of 1990 sets the following priority commitment for the company: «By striking a balance between our economic, social and environmental responsibilities we want to ensure the prosperity of our enterprise beyond the year 2000».

In «Vision 2000» Ciba-Geigy pledges not to jeopardize the long-term future by taking short-term profits. Utility and risks should be carefully balanced in all activities, processes and products. Products and processes should be developed so as to fulfil their purpose with the least possible harm done to the environment.

In the last years, Ciba-Geigy has endeavoured to enforce the standards of the parent company in Basle in all countries hosting group companies. In accordance with an internal guideline issued in February 1990, products are commercialized in developing countries only if their additives are registered in at least one OECD-country.

Shareholders and General Meeting

Ciba-Geigy is a public company with about 65"000 non- majority shareholders. A quarter are foreigners.

Main shareholders	
Company/person:	Participation:
Swiss Bank Corporation Intra, Bilbao (Spain)	2% 1%

Share	SFr. 8/19/92	Earnings in %	P/E 1992	Aver. vol. per day	Beta	Volatility in %
Bearer	663	1.7	12	10 mn.Fr.	1,29	33
Registered	665	1.7	12	25 mn.Fr.	1,22	31
PC	655	1.8	12	3 mn.Fr.	1,28	32

P/E (price/earnings-ratio): figure resulting from the division of stock exchange rate through earnings per share.
Beta: the Beta-value of a share stands for the historical evolution of the share price in relation to the evolution of the global market.
Volatility: historical fluctuation scope of the stock exchange rate

2. PRODUCTS

For the companies active in the chemicals and pharmaceuticals sectors, innovative, safe, user-friendly and non-polluting products will be decisive in the battle for market shares. Ciba-Geigy has acknowledged this and taken on the challenge. Nonetheless, the enterprise still manufactures products that are hazardous from the ecological viewpoint.

Ciba-Geigy is the leading manufacturer of pesticides worldwide, with a market-share of 13%. In 1990, sales with pesticides amounted to Sfr. 3,594 mn. Ciba Geigy distributes three of the so-called dirty dozen pesticides, namely Lindane (only for seeds), Paraquat and Parathion. According to Pesticide Action Network (PAN) International, these dangerous pesticides are targeted for strict controls or even prohibited. PAN aims at having parathion, the worst pesticide, banned world-wide. Pesticides penetrate the water and the ground through agricultural use. Residues have been identified in food, drinking water and cosmetics.

In the next years more stringent regulations regarding the use of pesticides and insecticides in important markets like the USA will affect the company's turnover in the agricultural sector. Problematic pharmaceutical and agricultural products could represent possible liability and image risks for Ciba-Geigy.

Problematic products:

- Atrazin: On April 1st 1991, this product was prohibited by the German Government because it surpassed the limit value of 0.1mg er liter of drinking water. This limit value is also fixed in the relevant EC-regulation. An EC-comittee presently discusses its possible further application on a scientific basis. With a market-share of 60% Ciba-Geigy is the main producer of Atrazin which contributes approximately 500 mn. Sfr. to company sales.

- Dichlorvos: this pesticide is on the North Sea Conference's «Red List» of substances most hazardous to the aquatic environment. Originally developed for plant protection, Dichlorvos came to be used to combat parasites in salmon farms. Although the pesticide biodegrades rapidly and does not accumulate in aquatic organisms, this lattter application is controversial. Given the acute toxicity of the substance, dosage leaves little margin for manoeuvre. Though granting a two-year license for Dichlorvos, the British Government has asked Ciba-Geigy for an environmental report.

- Seed: With a turnover of 213 mn.Sfr.(1987) Ciba-Geigy is one of the ten leading seed companies in the world. The fact that almost only pesticide-dependent seed is being offered strengthens the dependency of Third-World countries upon industrialized countries.

- Until 1990, Ciba-Geigy manufactured and sold PVC stabilizers containing cadmium. Then, for security reasons - cadmium can generate damage to the liver and kidneys when entering human or animal organisms, e.g. through the food chain

- The company, so far the first and only one among its competitors, put a complete stop to the manufacturing and sale of these products although the migration of Cd-stabilizers integrated in the plastic is not documented.

- 1986: The New England Journal of Medicine publishes an article according to which Tegretol (anti-epileptic) can cause malformations in unborn children. Ciba-Geigy refutes the study as being methodically inconsistent.

- In Bangladesh, plant protection substances are sometimes used without the necessary precautions despite the instructions of suppliers.

- The drug «Cibalgin» figures on a list of «especially hazardous drugs». In Africa and Pakistan, the composition of Cibalgin is not the same as in Switzerland.

- 1983: according to a survey by the Canadian agronomist Michael B. Loevinshon, Ciba-Geigy is co-responsible for the death of Philippine farmers.

belief. Employees are involved in the company's development and decision-making processes.

Working conditions, training and further training

The relatively low fluctuation rate of employees, about 5% per year, can be interpreted as positive for the working climate. But with the on-going restructuration measures in Switzerland, there is talk of decreasing satisfaction. Ciba-Geigy has recruitment problems in the academic circles. The chemical industry is not much liked according to enquiries among graduates. However, Vision 2000 is liable to lend a better image to Ciba-Geigy in public opinion, thus enhancing its attractiveness as an employer in this branch.

Besides the contractual partnership with external trade unions (e.g. GTCP), partnership is presently being set up with in-house personnel organisations. However trade- union circles fear that their audience could be restricted by the revalorization of internal unions. According to KIWI, Ciba-Geigy's internal union's publication organ, the internal employee representative bodies are meant to «counterbalance the external trade unions who, for some time now, have been endeavouring to strengthen and widen their influence and representation claims amongst employees».

Several Ciba-Geigy employees work in shifts of up to 12 hours a day, especially on Saturdays and Sundays. Chemical processes which cannot be interrupted and economic motivations justify shift-work.

Ciba-Geigy estimates that it spends about 3200 Sfr. per employee (1.5% of total turnover) on training and further training. This sum includes the salary for the working hours missed during training.

Safety at work

Safety audits carried out in Ciba-Geigy groups abroad have shown that safety there is largely comparable to safety in the Swiss works. The results of the 1990 audits were satisfactory; their contents were not disclosed.
In the parent company, the number of accidents and occupational diseases is about one third of the chemical industry's average. In 1989, there were two deaths. Compared with all the employers ensured with the SUVA, Ciba-Geigy has one of the lowest accident rates. In 1989, Ciba-Geigy was awarded the OSHA-Star for its McIntosh plant, the highest reward of the American authorities for safety at the work place.

8. THIRD WORLD INVOLVEMENT

Key points:

1. Ciba-Geigy is active in 80 developing countries.
2. The sales percentage of Third World countries amounts to 15% of total turnover.
3. The share of profits attained in Third World countries is not divulged.
4. Staff employed in Third World countries: 15,000 employees (about 20% of total staff).
5. 98% of the staff in Third World agencies are employed locally.

Ciba-Geigy runs a Third World Department with six collaborators who act as advisors to management and divisions. Since 1979 a Ciba-Geigy Foundation, to which Ciba-Geigy allocates a yearly grant of 10 mn.SFr., is responsible for cooperation with developing countries. This foundation supports the development of agriculture, public health and education in the poorest countries and regions of the world. It also manages the Risk-Fund and the Leprosy-Fund. The Risk-Fund, endowed with 5-10 mn. Sfr., serves to encourage the Divisions to finance projects in Third World countries with high start investments. As for the Leprosy-Fund, created in 1986, it grants a yearly 1 m. Sfr. towards the care of leprosy patients. Safety audits are carried out in Third world countries in order to prevent possible accidents. These audits are not made public.

According to its own declarations, Ciba-Geigy practices a progressive personnel and social policy tailored to local needs and conditions. However, trade unions pretend that in matter of labour rights and decision-sharing, Ciba-Geigy is very restrictive.

The Group supports the WHO policy with regard to essential drugs. According to a "Erklärung von Bern" survey of 1989, 62% of the 300 medicaments Ciba-Geigy supplies to Third World countries can be assessed positively (against 49% at Roche and 42% at Sandoz. 19% of all Ciba-Geigy preparations are listed among the essential drugs (Roche 15%, Sandoz 8%).

Criticism:

Transgressing internal guidelines relating to sales in Third World countries, Ciba-Geigy delivered 125,000 litres of insecticides containing DDT (Ultracide) to Tanzania (Dec.'90), this being the final supply of an earlier order.

The head of the responsible Division took the following steps:
1. Offer to the Tanzanian cotton authorities to buy back the entire bulk of the

9. ENVIRONMENT

Environmental self-assessment by Ciba-Geigy: · 7
(ranking between 1 (poorest) and 10 (best))

Current and capital expenditure for environmental protection (in SFr.mn.)

	1990	1989
Capital expenditure	235	265
Current expenditure	455	460

Environmental policy

Ciba-Geigy considers the environment with a high strategic significance. In contrast to other chemical manufacturers Ciba-Geigy's environmental policy is decentralised. That means that environmental targets are set by the local management and compliance with national regulations is in the responsibility of each Group company.

The company's policy made first explicit mention of environmental principles in 1973. The Sandoz disaster of 1986 in Basle lead to a significant improvement of environmental consciousness of the giants of the Swiss chemical industry, Ciba-Geigy, Sandoz and Hoffmann-La Roche. Ciba-Geigy has recognized that only an environmentally sound chemical industry can survive. The company made great efforts inside of its plants but also in developing environmentally sound products. In spite of these efforts, further measures are still necessary.

In 1990, Ciba-Geigy published the so-called «Vision 2000», a document which states that «Respect for the environment must be part of everything we do. We design products and processes to fulfill their purpose safely and with as little environmental impact as possible. We use natural resources and energy in the best possible way and reduce waste in all forms. It is our duty to dispose safely of all unavoidable waste using state of the art technology.»

Ciba-Geigy was one of the first chemical manufacturers to carry out safety and environmental audits. Their experiences with this fairly new instrument were

Waste management

All facilities now have waste-water-treatment systems. In Switzerland alone, 400 m.SFr. were spent on disposal between 1988 and 1991. In 1990 the Works of Basle transferred to public sewage-treatment plants 18.5 tons of water polluting metals such as chromium, copper and zinc. After elimination of 90% by the public sewage-treatment plants, 1.85 tons were released into the Rhine River. In 1980, 70 tons of water pollutants were released.

Since 1988 Ciba-Geigy Switzerland has taken the lead in innovative waste-treatment system which includes a database with identity-numbers for more than 4,000 different types of waste. 6,000 tons of solid waste and 27,000 tons of waste solvents are registered anually.

The amounts of solid waste have decreased in recent years but are still high (1990: 6,113 tons).

Waste disposal in Switzerland is still a problem. Ciba-Geigy therefore exported part of its waste to disposal sites in other European countries. In 1986 as much as 10,000 tons of solvents had been deposited abroad. Until April 1988 Ciba-Geigy disposed part of its solid waste by burning it at sea. The disposal costs have increased heavily in recent years. In the Works of Basle they increased from 1.5 mn.SFr. in 1981 to 22 mn.SFr. in 1990.

457 appeals were lodged against the projected waste-incinerator, but in July 1991 the Cantonal authorities granted the construction permission. According to CEO Alex Krauer, the incinerator is a typical example of applied environmental protection. In contrast to this opinion the World Wildlife Found states that waste-avoidance is the sole solution because of the environmental impacts of such incinerators. The environmental-compatibility-report was conducted by a subsidiary company of the Swiss Bank Corporation in which Ciba-Geigys Chairman Alex Krauer is a member of the Board of Directors.

The company is involved in many old disposal sites. The clean-up programmes are very costly. They accounts for 50 to 100 mn.SFr. p.a. The clean-up of just one site in Switzerland (Bonfol) costs Ciba-Geigy over 16 mn.SFR.

Stock management

Warehouse security was checked Group-wide in 1986 and 1987. In Switzerland the amount of potentially dangerous substances was reduced significantly. According to environmental pressure-groups, however, in 1991 in the Canton of Valais, Ciba-Geigy temporarily stored poisonous pesticides in railway waggons without any appropriate safety precautions.

1. Environmental management as among the highest corporate priorities
2. Developement of products that have no undue environmental impact
3. Conduction of regular environmental audits

Until now the company hasn't signed the Valdez Principles, a catalogue of ten environmental measures.

Cooperation with organisations

Ciba-Geigy regularly communicate with different environmental and pressure groups, e.g. Greenpeace. Since 1989 the company has been a member of the American National Wildlife Foundation and the Swiss Union for Environmental Consciousness Management, where it is active in different working groups.

Furthermore Ciba-Geigy is the initiator and member of the International Environmental Bureau (IEB), which transfers environmental know-how to Third-World companies. Ciba-Geigy also participate in the OECD-program for the examination of toxicology and environmental impact of chemical products. Nevertheless Greenpeace U.S.A. mentions Ciba-Geigy as one of the worst environmental violators.

In collaboration with the University of Basle, the Company is conducting empirical tests of a new scientific method (Eco-Rational-Path-Method) with two pigments and dyestuffs to optimize economical and environmental efficiency.

Lawsuits and regulation

In the U.S. the amounts of fines imposed by the E.P.A. (Environmental Protection Agency) are increasing. Thus it can be assumed that the financial burden for Ciba-Geigy will also increase, because the company was fined several times in the past. In the long-term its ecological efforts will pay for themselves in the sense of avoided fines.

In 1992 the Toms River Work was fined by the E.P.A. with 9.0 m$ for illegal dumping of hazardous waste into its landfill between 1981 and 1984. The same Work was fined by the E.P.A. with 50 m$ because of water polluting between 1952 and 1977. 120 different chemicals could been identified in the ground-water. In 1991, 28 companies, Ciba-Geigy among them, were fined with the total amount of 3.5 m$ for violating land disposal rules.

Nevertheless the Toms River Works in the U.S.A. was awarded the 1990 National Environmental Achievement prize by a consortium of 22 national environmental protection organizations.

10. POLITICS AND LOBBYING

Ciba-Geigy is in the center of a dense network of economic, political and scientific interests. Five of its fourteen directors are represented on the board of directors of banks, five others are professors in scientific departments. Up to 1991, Felix Auer, deputy head of Ciba-Geigy, represented the company's interests at parliament as a national councillor.

In 1990, Ciba-Geigy supported 5 opponent groups in the United States with 376"000$ in a successful combat against the Big Green Legislation in the State of California. This law was directed against the use of pesticides. In the framework of the USA election campaign of 1989/90 the Ciba-Geigy Employees Good Government Fund supported the Democratic Party with 55"850 $ and the Republican Party with 63"675 $.

11. MILITARY CONTRACTS

Ciba-Geigy is not active in the military branch and observes the Warning List containing 40 forerunners of chemical weapons. In 1989, Ciba-Geigy supplied 44 m. SFr. worth of drugs and agricultural products to Iraq, not intended for the production of toxic gas.

12. SOUTH AFRICA

Ciba-Geigy has a group company in South Africa, Ciba-Geigy Ltd, in Isando, active in research, manufacturing and sales. According to Joe Mahlangu, warehouseman in the Johannesburg Work «racial discrimination and support for apartheid in the South-African Ciba-Geigy are widespread». On the other hand, the press attaché maintains that for some years now «Ciba-Geigy supports all measures in favour of the peaceful abolition of apartheid».

15. TOBACCO

Ciba-Geigy does not produce tobacco. It sells an anti-smoking drug «Nicotinell».

16. ALCOHOL

No activities in this branch.

17. GAMBLING

No activities in this branch.

18. ATOMIC ENERGY AND NUCLEAR TECHNOLOGY

No activities in this sector. But on the whole, Ciba-Geigy representatives are in favour of using nuclear energy. This is hardly surprising as the energy consumption of the Swiss Works is covered up to 20% by electricity.

19. TROPICAL WOODS

No activities in this branch.

20. BIO AND GENE TECHNOLOGY

In July 1991, Ciba-Geigy obtained the building permit for the Biotechnicum in Basle, all 620 objections against the project having been dismissed. The WWF Switzerland and the «Basler Appell gegen Gentechnologie» appealed against the building permit. According to these opponents, release of small quantities of manipulated organisms in the Rhine is taken lightly. The same organizations accuse Ciba-Geigy of withholding relevant information on the safety aspects of the project.

Ciba-Geigy relocated the Biotechnicum-project in nearby French Huningue. In the future, biotechnological additives are to be produced here. About 200 employees are already working in Switzerland in R&D in biotechnology.

Ciba-Geigy intends to further develop bio and gene technology abroad, in case, despite strengthened efforts to overcome the population's distrust, social acceptance of this key-technology cannot be attained in Switzerland. For Alex Krauer, not the «whether», but only the «how» and the «where» are the topical questions. In 1991, a controversial PR-campaign was launched on so-called «responsible gene technology» pointing out only positive effects of gene technology, which Ciba-Geigy supported with 350"000 Sfr.

Ciba-Geigy uses gene technological methods in research and production. Each application field is assessed differently, as there are as yet no relevant legal bases in Switzerland. Interventions on human embryos are prohibited. However, Ciba-Geigy advocates the use of genetically manipulated test-animals. Ciba-Geigy also carries out research projects in genetically manipulated plants. In the laboratories and hot-houses of the Ciba-Geigy research center in St.Aubin (Switzerland) different genetically manipulated plants are being tested.

In the biotech-unit of the Agro Division in North Carolina (USA), researchers are developing genetically manipulated plants highly resistent to herbicides, insects, diseases and unfavourable climatic and soil conditions.

Permitted tests in the field of genetically manipulated plants:
- 1986/87/90: North Carolina: various plants
- 1991: Colmar (France): genetic corn

For these tests, Ciba-Geigy has concluded neither a conventional nor a special liability insurance.

As for safety, Ciba-Geigy follows four principles:
- self-control
- OECD-guidelines
- guidelines of the National Institute of Health (NIH)
- regulations of the Environmental Protection Agency (EPA)

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BAER VERLAG. Who Owns Whom, Der Schweizerische Beteiligungsatlas, Zürich 1992

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- ELSA (Electronic Selective Archives)
- EBUS (Infomat International Business)
- FNTL (Financial Times Abstracts Database)
- INFO (Abi/Inform)

Newspapers and magazines

- Anti-Apardheid-Nachrichten
- Basler AZ
- Basler Zeitung
- Bilanz
- CASH
- CH+6 Nachrichtenbulletin
- Ciba-Geigy-Magazin
- Ciba-Geigy-Zeitung
- Der Bund
- Der Spiegel
- Die Gewerkschaft
- Finanz und Wirtschaft
- Index
- Info des Basler Appell gegen Gentechnologie
- infoline ph9 (Ciba-Geigy)
- Katapult (11/90 und 2/91)
- Med in Switzerland

SWISS INFO CENTER

Purpose

The INFO-CENTER seeks to promote ecological and social investments through research and by providing relevant information on enterprises and investment opportunities.

In the past, investment aspects focused essentially on data and information of a financial nature. More and more, investors with long-term concepts are also taking ecological and social components into consideration in their investment decision. This trend is also of the utmost significance for companies. Recent experience has shown that ecologically orientated companies are able to finance themselves at more favourable terms on the financial markets than companies with heavily polluting products or product processes. The shares of companies with better ecological and social performance records than other companies in their respective industries are traded with a growing premium on stock exchanges. This is confirmed by the U.S. Good Money Index, which over the past few years has achieved above-average performance.

Services

1) Ecological and social corporate research

We offer corporate studies on Swiss companies. In co-operation with foreign partner organisations we also provide studies of European and U.S. corporations.

Examples of criteria in eco-studies:

- Environmental compatibility of production and products
- Environmental sensitivity of management and personnel
- Scope and significance of the ecological information

Examples of criteria in social studies:

- Social compatibility of products
- Relations between the company and its personnel, shareholders, clients, suppliers and the general public
- Relations with Third World countries

REGIONAL

SPECIAL WASTE INCINERATOR

(RSMVA) K-930

CIBA BASLE WORKS

Dr. H. Tschudin

December 1994

Introduction

The Swiss Federal Office of Environment, Forest and Landscape (BUWAL), in its nation-wide waste disposal concept, has foreseen a need for a total of three to four special waste incinerator plants, one of them to be located at Basle. On request of the cantons of Basle-City and Basle-Country, Ciba has accepted the task to build and operate the regional special waste incinerator plant (RSMVA).

Fire in this new plant will be ignited for the first time in December, 1994. Incineration test runs will start in January, 1995. In this testing period, the entire plant will be thoroughly checked out, with determination of the optimal operating data. The begin of routine operations is planned for May, 1995.

With this plant, appropriate means for the disposal of special waste will be available to the entire region. Thermal treatment is a means to dispose of such wastes with specific inherent hazard potentials with minimal environmental impact, to reduce the quantities of waste drastically and, at the same time, to save valuable primary sources of energy (fuel oil, natural gas) by heat recuperation

Demand and plant capacity

Ciba planned and built the RSVMA with an investment of approx. SFr.120 million. To cover the financial operating risks, Ciba concluded contracts with four partners (Hoffmann-La Roche, Sandoz, Canton Basle-City, Canton Basle-Country). Of the total incineration capacity of 16'000 tons per year, 11'400 tons are covered by commitments of these four partners. The remaining capacity for 5'600 tons is freely available.

The thermal design of the plant is for an average throughput of 2.4 tons per hour of special waste with an average calorific value of 16'000 KJ/kg; this corresponds to a total capacity of 16'000 tons per year

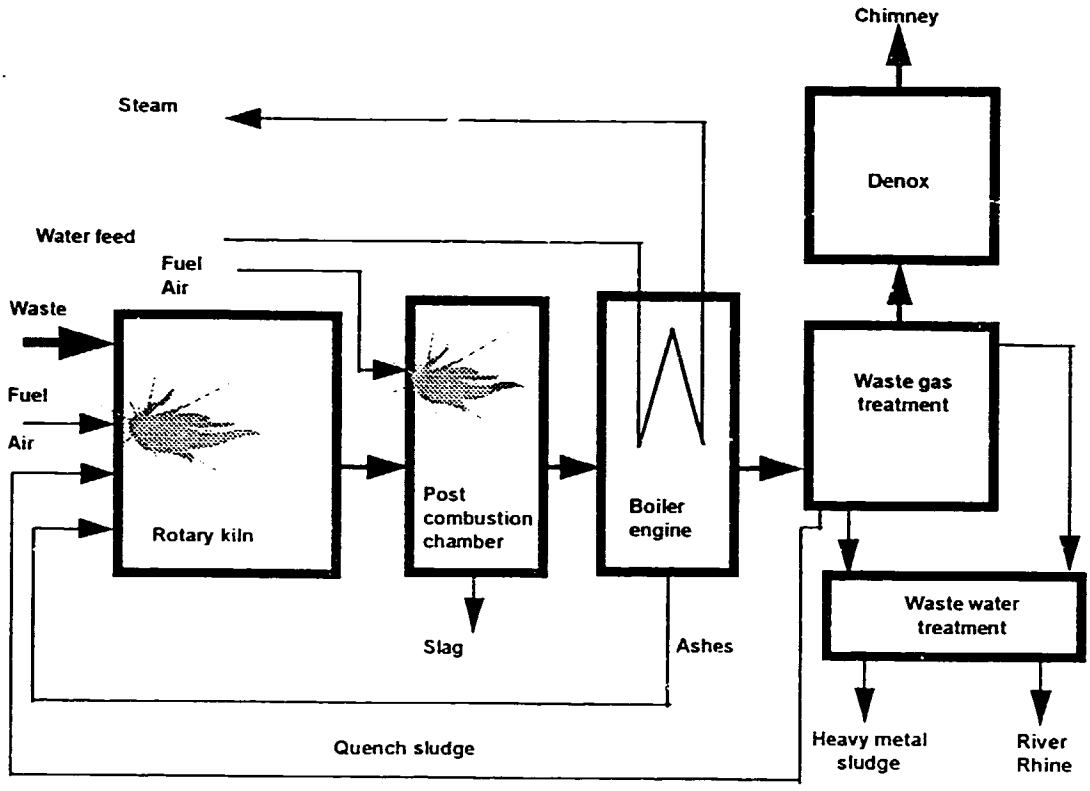
Logistic aspects

The rotary kiln may be used to dispose of special wastes in the form of liquids, gases, solids, as well as of substances with a pasty consistency. All waste materials must be delivered to the incinerator in suitable containers, i.e. loose or bulk materials cannot be charged. The range of containers includes a wide variety of sizes, e.g. from 5 l polyethylene cans or 200 l "Mauser" drums made of polypropylene, up to 4 m^3 tank trailers ("Swiss Containers") or full size road and rail tankers. The wastes may be delivered either by road or by rail.

For each waste material, plant management specifies the incinerator feed rate. This rate depends on the calorific value of the material, the halogen or sulphur content, the tendency to soot formation (important in the case of fine dusts) and other criteria. Liquids and pastes can be fed continuously by means of pumps. The specified feed rate ensures an optimal operation of the incinerator and is also of great importance for the adherence to the very strict emission limits. A special ordering system permits to order the waste materials directly from producers in specified containers. Thanks to this "just in time" logistic system there is no need to store solid or liquid special waste in large quantities in the immediate vicinity of the incineration plant. This means a substantial reduction of the risk potential. To ensure smooth operations over the weekend a storage capacity for two days is sufficient

Description of the plant RSMVA K-930

To build the plant, approx. 1'500 tons of steel and 9'000 m^3 of concrete were used. The main parts of the plant are shown in the block scheme below:



Block scheme of special waste incinerator RSVMA K-930

1. The incinerator with heat recuperation

- **Rotary kiln** (Austrian Energy and environment)

  By means of several different charging devices, the waste to be incinerated is fed to the rotary kiln through the front end. The kiln is 10 m long and has a diameter of 4 m. It rotates with 2 RPM. To ensure the longest possible service period of the kiln, special corundum bricks were used for the lining. The expected service life of the lining is approx. 8'000 operating hours.

  The incineration temperature is maintained in the range of at least 1'000 °C to 1'200 °C. Fuel oil extra light is used as a supplementary fuel. The entire waste combustion process takes place within the rotary kiln.

- **Afterburner chamber** (Wehrle-Werk AG)

  The flue Gases leave the rotary kiln after a residence time of 2.5 seconds. Combustion of the gases is completed in the afterburner chamber at a minimum temperature of 1'200 °C. The geometrical design of the chamber ensures a low gas velocity, intensive mixing and a high residence time (4 seconds). As in the rotary kiln, fuel oil extra light is used as a supplementary fuel also in the afterburner chamber. At the outlet of this chamber, a minimum temperature of 1'200 °C is required.

- **Steam boiler for heat recuperation** (Wehrle-Werk AG)

  In the steam boiler, energy is recuperated from the hot flue gases in the form of steam (45 bar/300 °C). Recuperation efficiency is approx. 60%. The steam is fed to the factory grid with a pressure of 40 bar. The flue gases leave the boiler at a temperature of 250 °C.

  The boiler has 3 drafts: two radiation drafts and one convection draft with blocks of "Eco"-heating surfaces (Ecoheizflächenblöcke). It operates by natural circulation. The boiler contains 32 km (20 miles) of pipes with a total weight of 850 tons. The water volume is 150 m^3. Heat generation is in the order of 12.4 megawatt, 17.2 tons of steam are produces per hour. This corresponds to an energy recuperation efficiency of approx. 60%.

2. Ecology equipment

- **Flue gas treatment** (Ciba Engineering and Process Technology, IVT)

  The flue gases contain various harmful components which must be removed before the gases may be released to atmosphere. In a washing process, dusts, hydrogenhalogenides, halogens, sulphur dioxide and aerosols are eliminated in six consecutive stages. Each group of components is treated specifically in a separate washing stage. This permits to intercept even peak loads of contaminants without surpassing the emission limits for pure gases. To keep the height of structures within limits, the gas treatment tower with a total height of 54 m is subdivided in a four-stage countercurrent column followed by a two-stage uniflow column.

  In **stage 1**, the quenching stage, the hot flue gases are cooled down from 250 °C to 68 °C. Simultaneously, the majority of entrained dust particles are eliminated. For reasons of corrosion protection and mechanical strength, the lower part of this column is brick lined.

  Stage 2 consists of a group of ring jets. Here, coarse dust particles are separated, and the ions of heavy metals and hydrogenhalogenides are eliminated.

  Stage 3 is designed to reduce elementary bromine and iodine. Simultaneously, part of the sulphur dioxide which - in the form of sulphite - serves as a reducing agent, is washed out.

  In **stage 4**, finally more than 90% of the sulphur dioxide entering this stage is eliminated. In four bubble columns the sulphur dioxide is oxidised to sulphate with air. The sulphate solution then goes on to further wastewater treatment.

  Stage 5 has a buffer function. It is designed to ensure that even in case of extreme peak loads the emission limit values are not surpassed.

  Finally, in **stage 6**, high pressure ring jets serve to separate finest particles and aerosols.

  Spent waters from the columns are sent to wastewater treatment in two separate streams to facilitate specific treatment of contaminants.

- **Elimination of NO_x "flue gase denoxing"** (Babcock)

  The flue gases leave the washing tower with a temperature of 68 °C. They carry a high load of nitrous oxides (approx. 1'500 mg/m^3 NO_x). To ensure adherence to the limit value of 80 mg/m^3 specified in the Swiss clean air ordinance (LRV), they are passed through a special "denox"-stage with a titanium/vanadium catalyst, where NO_x is reduced in presence of ammonia to nitrogen and water (SCR-process). The RSMVA is the first plant of its kind with a "denox"-stage. The treated and "denoxed" flue gases are released to atmosphere at 120 °C through a 60 m stack.

3. Wastewater treatment

Wastewater treatment is done in an adjacent building. After separation of sludge, the quenching water is combined with the spent water from the wet slag discharge, for elimination of heavy metals. The combined stream is first pre-neutralised with lime slurry; thereby fluorides and phosphates are precipitated as calcium salts. Then the pH-value is increased further, organosulphides are dosed in, and the heavy metals are precipitated as hydroxides or sulphides corresponding to their low solubility.

The pH-value of the wastewater stream containing the sulphate is regulated with caustic soda to avoid the precipitation of large quantities of gypsum. Subsequently the heavy metals are precipitated with organosulphide as described for the quenching water.

The precipitated heavy metal salts from both streams are combined in a "sludge thickener" and isolated from time to time in a filter press (dry content approx. 30%).

Remaining waste materials

The materials remaining from the incineration of special wastes are:

- Incinerator slags 1'600 - 2'400 tons per year
- Metal sludges 1'200 tons per year

Incinerator slags shall be disposed of in a landfill provided that they meet legal specifications. But studies have already been initiated to use the slags as an aggregate for building materials in civil engineering or road building.

The method to dispose of metal sludges shall be decided during the commissioning phase. A likely possibility is the disposal in an underground mine. Ashes (160 tons per year) and quenching sludge (140 tons per year) are recycled to the kiln to integrate these materials into the incinerator slags.

Automation

A plant of the size and complexity of the RSMVA, operating at high temperatures and being subject to very stringent safety requirements needs a high degree of automation. The entire plant is monitored and controlled from a central control room. A TCD 3000 unit of Honywell was selected as process control system.

Analytics

To meet the very strict requirements imposed by authorities when giving building permission, sophisticated analytical equipment is required. In the treated flue gases, eight different parameters must be measured continuously (on-line) before the gases leave the stack, and seven more criteria must be controlled at regular intervals (dioxins, mercury, cadmium and others).

Furthermore, for all special wastes to be incinerated, analytical certificates and acceptance checks with random sampling are required.

Advisory Committee

To ensure that the operation of the RMSVA is transparent for interested groups and the general public, Ciba has proposed that an advisory body be nominated, to which the interested parties could delegate representatives:

- Ciba 2 representatives
- Basle chamber of commerce 1 representative
- Neutraler Quartierverein Kleinhüning (representing the inhabitants of the city quarters in which the plant is located) 2 representatives

- Basler Arbeitsgemeinschaft zum Schutz von Natur und Umwelt (working group for the protection of nature and the environment) 2 representatives
- Canton Basle-City 2 representatives

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ATTACHMENTS

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ANNEX IA

MODEL APPROACH FOR PREPARING A STATUS REPORTS ON NATIONAL CHEMICAL SAFETY INFRASTRUCTURE

INTRODUCTION

The level and rate of change of economic development in the country particularly in relation to use of chemicals in agriculture, large scale industry, small scale urban and rural workshops, and the home environment and the scale of use of pharmaceuticals and pesticides in preventive health and vector spray programmes are fundamental to the scope and requirements of national chemical infrastructure needs. There may also be recognised diseases of environmental chemical origin, e.g. fluorosis (fluoride excess), including venoocclusive disease due to pyrrolizidine alkaloids, Kashin-Beck disease (due to selenium). The main actual and perceived health and environmental problems concerning chemicals and chemical residues in the country need to be identified. The level of awareness of these problems among public and occupational health and environmental authorities, other government authorities, commercial/industrial sector and the public are integral to addressing the problems. In addition the division of responsibilities between Federal and/or State and local governmental agencies for promulgation and implementation of regulations, promotion of educational programmes and training of public and occupationally potentially exposed people, paying particular attention to sub-populations at special risk with regards to chemicals, needs to be defined.

PROBLEMS OF CHEMICALS AND THEIR IDENTIFICATION

(a) Procedure for Collecting and Sources of Information on Chemicals in the Country

The Status Report should identify the national procedures for collecting information on the chemicals manufactured, imported, exported or transported. The data base developed should include the volume of chemicals in the economy and toxicity information on their potential hazards. The report should identify what national and international sources of information, or databases, national or international for classes of chemicals and specific toxicants, are used by the public and occupational health and environmental authorities when seeking data on chemicals.

(b) Monitoring Activities

The Status Report should also include the various types of monitoring undertaken, to identify which toxic chemicals and their residues occur in the country, either as air pollutants, or as contaminants in water, soil, or food and include consideration of resource priorities. For example, the implementation of

national chemicals management will be closely linked with the availability of analytical facilities and which public and private organisations undertake such monitoring?

For the assessment of hazards and quantification of risks the Status Report should include consideration of local and site specific surveillance and monitoring programmes. The Report should, as a minimum, include public and occupational health monitoring activities through environmental and workplace assessments; human bioassay for the assessment and remediation of individual exposures; and health screening for assessing health effects of exposures.

(c) Assessment of the Chemical Risks in the Country

A number of internationally promulgated guidance documents have been prepared to facilitate development by countries of the assessment of their chemical risks. These include:

Toxicological Evaluations

IARC Monographs on Carcinogens

IPCS Environmental Health Criteria documents

WHO/FAO, JECFA and JMPR Monographs on Food additives, contaminants, pesticides residues and veterinary drug residues

Water

drinking water quality guideline limits (WHO)

water quality guideline limits for surface water (UNEP/WHO)

water quality guideline limits for fresh water used for fishing (UNEP/WHO/FAO)

water quality guideline limits for estuarine and marine waters UNEP/WHO/FAO)

aqueous effluent limits for industrial effluent and treatment outfall (WHO/UNEP/UNIDO)

guideline limits for the use of waste water in agriculture and aquaculture (WHO/UNEP/FAO)

Air

air quality (ambient or indoor) limits for gases, vapours, fibres, particulate matter (WHO/UNEP)

air quality guideline limits for gaseous or smoke emissions from industries (WHO/UNEP/UNIDO)

Occupational

occupational health limits for gases, vapours, dusts, aerosols in the workplace air and substances absorbed through the skin, mucous membranes or alimentary tract (ILO/UNIDO/WHO)

occupational health limits for pesticides and agrochemicals (WHO/ILO/FAO)

Soil

limits of certain chemicals in soil (WHO/FAO/UNEP)

Agricultural Chemicals (WHO/ILO/UNEP/FAO)

limits for certain contaminants in agrochemicals (fertilisers)

limits for application rates of pesticides

Chemical Waste (WHO/UNEP/UNIDO)

limits for disposal of chemicals as waste products:

waste (including liquids and solids);

industrial chemicals (including mixed industrial chemicals), dumps, surface water and deep-well injection;

municipal (UNEP/WHO/FAO);

surface and ground water contamination, use of sludge in agriculture - atmospheric effluent and residual ash from incineration;

Ecosystems (UNEP/WHO)

limits for exposure to ecosystems and non-human biota.

Which of these information sources are being used to assess the risk to health and environment of chemicals under local situations? What other sources are used for this purpose? Has a national register of potentially hazardous industries or situations involving chemicals been developed? Are chemical data banks and information systems available in the country?

MANAGEMENT OF CHEMICAL RISKS IN THE COUNTRY

Outline the national institutional arrangements for the control of hazardous chemicals, with the responsibilities of various governmental authorities. Is there a coordinating mechanism amongst the various responsible authorities? If so, describe how this mechanism functions.

Legislative Framework

Using the framework outlined below, list the areas covered by existing legislation for each of:

pharmaceuticals
pesticides, plant growth regulators and other agrochemicals
explosives, including petroleum products
drugs of addiction
industrial chemicals
domestic chemicals
industrial (hazardous) wastes
clinical hospital wastes

requirements for notification and toxicity evaluation;

protection of occupational health and welfare;

protection of public health;

protection environmental effects:

- land use planning
- environmental impact assessments
- controls on release to the open environment

controls on importation of chemical substances withdrawn, banned or severely restricted in their country of manufacture;

regulations on manufacture;

registration/approval for wholesale and retail marketing;

licensing for possession;

packaging and labelling regulations for air, road, rail and shipping;

Packaging and labelling requirements for bulk and consumer packaging;

regulations on storage including licensing of premises;

regulations on use;

transport regulations for air, road, rail and shipping:

- mixed loads
- manifest requirements
- training
- licence to transport hazardous materials (quantities)
- dangerous goods/explosives

regulations on disposal;

- incineration
- landfill
- municipal dumping

regulations on control of emissions;

laboratory registration/certification;

specialist legislation in regard to international obligations;

The Report should describe what are the most important sources of chemical emergencies: which chemicals (e.g. pesticides, industrial chemicals, household goods, pharmaceuticals, natural toxins such as poisonous plants and venomous animals); what are the main circumstances involving such emergencies. Have epidemiological studies been undertaken to identify the extent, nature and severity of poisonings both acute and chronic in the country?

Which commercially available computerised data and modelling systems are available for chemical emergency reference? Has a full understanding of their strengths and weaknesses been developed by all relevant personnel?

Is there a system for collecting available and relevant information, e.g. Material Safety Data Sheets, from product manufacturers? If so, has a full understanding of their strength and weaknesses been developed by all relevant personnel?

Are the UN Substances Identification Numbers and Hazard Classification, used at storage facilities and reprocessing plants and during transport of chemicals? How are operators made aware of their importance?

Has a system, e.g. a proforma, been developed to help the officer in charge at the site of an accident to obtain all relevant details for communication to local emergency control centres?

Describe the plans made to handle communication with the media and the public at the time of an accident.

(b) Organization and Planning

The Report should describe the chemical emergency plans. Indicate in the Report which authority has responsibility for coordinating overall on-site awareness and preparedness plans (e.g. local government or civil defence). What are the roles of other authorities? Are they playing their part in a local awareness and preparedness programme, e.g. an APELL or similar programme?

Describe arrangements carried out by local authorities for an identification and evaluation of chemical hazards in the area. Have local health authorities actively sought information on potential hazards from local industry?

Does a coordinated chemical emergency plan exist for each major area of the country? Are local health authorities and health care professionals contributing to this? Do the emergency medical plans mesh with the emergency plans of other services (e.g. local government, civil defence, emergency rescue services, etc.)? do they link with the activities of national Chemical Emergency Centres and/or Poisons Information Centres, where these exist?

Are local health authorities contributing to the process of identifying and evaluating hazards in the local community? If necessary, are they taking the initiative in this process?

ANNEX IB

MODEL APPROACH FOR PREPARATION OF COUNTRY STATUS REPORT ON PREPAREDNESS FOR AND RESPONSE TO CHEMICAL EMERGENCIES

INTRODUCTION

For preparedness, and to assess the resources required after impact, a community profile is a pre-requisite of comprehensive chemical accident preparedness planning. Where people live in areas prone to natural disasters or where there were hazardous installations such profiles are essential as major regional and local demographic, social and infrastructural elements are required to be known before any relief can be provided. Information is necessary for example on important elements related to food such as diet, distribution; existing health care installations and teams, (e.g. structure, the location, first aid skills) and transport for health services. Environmental data relating to housing, water, air, sanitation, food, animal health, and, where appropriate, environmentally sensitive areas and species, need also to be included.

Within the community profile data should be included on installations, including a hazard map for each site, and for each chemical. Information should be included on the storage, disposal, transportation, toxicology, analytical and back-up facilities in the area. The people at risk also need to be identified including those in the plant and in the surrounding area, e.g. squatters, dwellings, hospitals, clinics and personnel, schools and other special groups such as the elderly and the handicapped. This information, as well as resources at risk e.g. water supply, and food; and a list of services, contact names and phone numbers must be available to those responsible for developing and implementing disaster plans.

A reliable communication system must be developed for anticipated emergency situations, and the drill practice of such systems should be conducted periodically to ensure their reliability in an emergency situation. This type of preparatory work is essential for a successful emergency response, otherwise communication during an emergency may be faulty and may cause panic and chaotic responses.

(a) Information Needs, Systems and Services

The Report should describe the information requirements which have been considered, planned for and tested as part of the emergency planning process, i.e. in advance of an emergency actually occurring.

It should outline the arrangements established with the national Chemical Emergency Response Centre, if any, or Poisons Information Centre, if any. Otherwise, it should indicate which institution or persons where to contact to get immediate expert advice.

Have contacts been established with armed forces medical services in connection with chemical emergency awareness, preparedness and response?

Describe the chain of command and lines of communication in case of a chemical accident which have been put in place in advance of an accident, as part of the planning process. Has the possibility been considered of creating a coordinating team or command group to be located at the perimeter of the accident site?

Do plans provide for adequate physical means of communication in the case of an accident - radio, telephone, fax, pager, any combination suitable to local circumstances?

Do plans provide for guidance to emergency telephone operators? In particular, do these give instructions about how to obtain the maximum possible information from the initial information?

Do plans provide for information, e.g. on relevant medical treatment and local medical resources, to be available to first responders as they arrive at the scene of an accident? Is there a system for registering emergency workers in the accident area?

Do plans provide for direct communication between medical professionals on-site and at the receiving facilities?

Describe the arrangements made by hospitals and other receiving facilities for chemical accidents, patient identification, documentation and management.

Do hospitals and other receiving facilities in the area have Major Accident Plans? Do these take account of the possibility of large-scale chemical accidents and their special requirements (e.g. the need to have a record of those medical practitioners in the area with experience in toxicology and intensive care)?

Do plans pro[illegible]e for the determination of the accident area and of the area for dealing with exposed patients at the receiving facility, so that contamination of health se[illegible]or personnel can be avoided.

Have the drugs (including antidotes), medical equipment and protective clothing for health care personnel likely to be required in the event of a chemical accident been provided? Has consideration been given to the best place to store them? Are their availability and their condition checked regularly and frequently?

Do plans provide for a "winding-down" procedure, so that the withdrawal of various groups of personnel can be coordinated?

Describe in the Report the national or regional mechanism existing for post-accident review reporting for chemicals. What major accidents involving chemicals have occurred in the country during the last decade? If so, were they associated with agricultural, industrial, transportation or with other activities?

Identify the extent of such accidents and their acute and chronic effects on human and detriment to the environment. Has an inventory been developed for hazardous installations or activities in the country?

Are there plans for investigation of chemical accidents and for collection of data on accidents and "near-miss", for the purpose of analysis, corrective action and improved training? Are local health authorities and health professionals contributing adequately to this process?

(c) Preparedness of the Health Sector for Chemical Emergency Medical Response

Do plans provide for initial care by health care professionals at the accident site?

Do planning and training draw attention to the need to set priorities, according to the nature and extent of the accident, between life-saving first aid, commencement of antidotal therapy and decontamination?

Do plans provide for the setting up of decontamination stations at the site of the accident, for adequate supplies of warm water for decontamination and the availability of clothes and blankets for those whose contaminated clothing has to be removed?

Do plans provide for the setting up of temporary treatment stations in cases where it may not be possible to transport the victims to hospital for some time? Have alternative lies within the accident area? Do the hospital's plans include preparedness measures in the case that the hospital is itself within the accident area (e.g. shutting off ventilation systems)?

Do vehicles for the transport of victims to hospitals or other receiving facilities have suitable equipment, e.g. ventilators and equipment for eye irritation?

Does the hospital have adequate provision for on-site decontamination stations?

Are Poison Information Centre protocols available at the hospital or other receiving facilities, to ensure consistent treatment of similarly affected patients?

Have plans been made for the taking and recording of samples from patients?

Does the hospital have an inventory of ventilators? Does it know where to obtain additional equipment and trained personnel quickly or, alternatively, where to transfer patients to receive this treatment?

Do existing Major Accident Plans contain provision for treatment of large numbers of patients with thermal burns, which can be activated in the case of a chemical accident producing victims with this type of injury?

Have plans been made to set up observation units, e.g. in schools or hotels over a period of several days?

Do plans include:

- identification of groups at risk for stress reactions;
- assessment of information available to the public and of networks through which it is likely to pass;
- provision for immediate monitoring of stress reactions; and
- provision for informing the public at different stages of the emergency, including through a telephone information service?

Do plans provide for inclusion in the emergency medical team of a psychiatrist and/or psychologist?

Does provision exist for treating cases of stress syndrome, preferably through existing mental health services?

In addition to samples from individuals, do plans provide for the taking of environmental samples?

Has consideration been given to the planning of epidemiological studies?

Has there been communication with local veterinarians on the use of animals as "sentinels"" for human disasters?

Has consideration been given to the follow-up of those who have been exposed but do not have symptoms and therefore do not necessarily present as casualties?

(d) Training and Education

Is there in your community a program of public education and training in what to do in the event of a chemical emergency? Are you doing all you can to encourage industry to accept responsibility for organising this? Are local health personnel contributing fully to these activities?

Are members of health profession available to advise and assist occupational health and safety specialists or industry management with incorporating information on emergency situations into health and safety training of workers?

Are members of health professions available to advise and assist rescue services managers in the initial training and regular in-service education of rescue service staff?

Are regular in-service programs arranged to keep health professionals' knowledge up to date in this area and to supply specific information on local emergency procedures?

Are all those health professionals with specific responsibilities in chemical emergency response receiving joint theoretical and practical education in the use and implementation of jointly agreed emergency response plans? Does this training cover information gathering and local emergency information systems? Have the medical aspects of on-site and off-site plans been tested under simulated conditions? Have the results of such tests been evaluated and disseminated? Are the lessons learnt from these evaluations fed back into the training process?

(e) Emergency Contingency Planning

Identify the procedures for classification of chemical accidents in the country according to chemicals involved, source of release, type of area, number of people involved, exposure route and major medical consequences.

Has preparedness planning been implemented for hazardous chemicals and industries? Does this plan involve each of central, provincial and local government? Have linkages been developed with the relevant international agencies and is their documentation (e.g. APELL) taken into consideration in developing the national responses?

What bodies have a role in contingency planning and the management of major chemical accidents (industries, government, emergency services, health and medical services, media, telecommunications, civic defence, chemicals and poisons information and management centres etc.)? What are the roles, responsibilities and interrelationships of these agencies? How is the requirement for interagency coordination and cooperation developed and maintained?

What is the role of the health and environmental sectors in providing emergency medical responses at the time of the accident for triage, decontamination and treatment? Is provision made for the follow up of affected persons including systematic collection of data on exposures, treatments and outcomes and epidemiological post accident evaluation?

Within the preparedness planning processes what provisions are made for training and education for those involved? Do the plans include details of the availability of appropriate equipment and methods to contain and minimise the impacts of the accident?

(f) Information Systems, Hazard Mapping and Community Participation

Does the preparedness planning incorporate a profile of the potentially impacted communities adjacent to hazardous facilities? Is information available on each of disposal of residues, analytical facilities, medical services and resources at risk?

(g) Communication Management

Is there a reliable communication system in place for every anticipated emergency situation? What is the frequency of testing of the communication system to evaluate its reliability? What provision is made for communication to the local community and the media?

(h) Post Accident Review Procedures

(i) Chemical Accidents during Transportation

Does a national or regional mechanism exist for post accident review reporting for chemicals? Have there been any major accidents involving chemicals during the last decade? If so, were they associated with agricultural, industrial, transportation or with other activities. Identify the extent of such accidents and their acute and chronic effects on human health and detriment to the environment. Has an inventory been developed for hazardous installations or activities in your country?

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ODOR THRESHOLDS IN AIR (PPM VOLUME)

CHEMICAL	RESPONSE 50 %	RESPONSE 100 %
Acetaldehyde	0,21	0,21
Acetic Acid	0,21	1,0
Acetone	46,8	100,0
Acrolein	0,1	0,21
Acrylonitrile	21,4	21,4
Allyl Chloride	0,21	0,47
Amine, Dimethyl	0,021	0,047
Amine, Monomethyl	0,021	0,021
Amine, Trimethyl	0,0001	0,00021
Ammonia	21,4	46,8
Aniline	1,0	1,0
Benzene	2,14	4,68
Benzyl Chloride	0,01	0,047
Benzyl Sulfide	0,0021	0,0021
Bromine	0,047	0,047
Butyric Acid	0,00047	0,001
Carbon Disulfide	0,1	0,21
Carbon Tetrachloride (Chlorination of CS2)	10,0	21,4
Carbon Tetrachloride (Chlorination of CH4)	46,8	100,0
Chloral	0,047	0,047
Chlorine	0,314	0,314
O-Cresol	0,00047	0,001
Dimethylacetamide	21,4	46,8
Dimethylformamide	21,4	100,0
Dimethyl Sulfide	0,001	0,001
Diphenyl Ether (Perfume Grade)	0,1	0,1
Diphenyl Sulfide	0,0021	0,0047
Ethanol (Synthetic)	4,68	10,0
Ethyl Acrylate	0,0001	0,00047
Ethyl Mercaptan	0,00047	0,001

CHEMICAL	RESPONSE 50 %	RESPONSE 100
Formaldehyde	1,0	1,0
Hydrochloric Acid Gas	10,0	10,0
Hydrogen Sulfide (From Na2S)	0,001	0,0
Hydrogen Sulfide Gas	0,00021	0,0
Methanol	100,0	100,0
Methyl Chloride	(Above	10 pp
Methylene Chloride	214,0	214,0
Methylene Ethyl Ketone	4,68	10,0
Methyl Isobutyl Ketone	0,47	0,4
Methyl Mercaptan	0,001	0,0
Methyl Methacrylate	0,21	0,2
Monochlorobenzene	0,21	0,2
Nitrobenzene	0,0047	0,0
Perchlorcethylene	4,68	4,6
Phenol	0,021	0,0
Phosgene	0,47	1,0
Phosphine	0,021	0,0
Pyridine	0,01	0,0
Styrene (Inhibited)	0,047	0,1
Styrene (Uninhibited)	0,047	0,0
Sulfur Dichloride	0,001	0,0
Sulfur Dioxide	0,47	0,4
Toluene (From Coke)	2,14	2,6
Toluene (From (Petroleum)	2,14	2,1
Trichloroethylene	21,4	21,4
p-Xylene	0,47	0,4

Source: Odour Control Syste
Montair Anderson BV

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APPENDIX B-1

PHOTOCHEMICAL OZONE CREATION POTENTIAL (POCP) FOR 159 ORGANIC COMPOUNDS

POCPs for a Range of Individual Organic Compounds

	Hydrocarbon	POCP
	Alkanes	
1	methane	1
2	ethane	10
3	propane	40
4	n-butane	40
5	i-butane	30
6	n-pentane	40
7	i-pentane	30
8	neopentane	10
9	n-hexane	40
10	2-methylpentane	50
11	3-methylpentane	45
12	2,2-dimethylbutane	25
13	2,3-dimethylbutane	40
14	n-heptane	55
15	2-methylhexane	50
16	3-methylhexane	50
17	4-methylhexane	45
18	2,4-dimethylpentane	55
18	2,3-dimethylpentane	50
19	n-octane	50
20	2-methylheptane	45
21	4-methylheptane	40
22	n-nonane	45
23	2-methyloctane	50
24	4-ethylheptane	35
25	n-decane	45
26	2-methylnonane	45
27	4-propylheptane	35
28	n-undecane	45
29	branched C11 alkanes	40
30	n-dodecane	40
31	branched C12 alkanes	40
32	n-tridecane	40
33	branched C13 alkanes	35
34	n-tetradecane	40
35	branched C14 alkanes	25
36	n-pentadecane	40
37	branched C15 alkanes	25
	Cycloalkanes	
38	cyclopentane	50
39	methylcyclopentane	50
40	C6 cycloalkanes	25
41	cyclohexane	25
42	C7 cycloalkanes	35
43	methylcyclohexane	35
44	ethylcyclohexane	40
45	C8 cycloalkanes	40
46	C9 cycloalkanes	50
47	C10 cycloalkanes	40
48	C11 cycloalkanes	40
49	C12 cycloalkanes	40

50	C13 cycloalkanes	30
51	C14 cycloalkanes	30
52	C15 cycloalkanes	30
	Olefins	
53	ethylene	100
54	propylene	105
55	1-butene	95
56	2-butene	100
57	2-methylprop-1-ene	65
58	1-pentene	70
59	2-pentene	95
60	2-methylbut-1-ene	80
61	3-methylbut-1-ene	90
62	2-methylbut-2-ene	80
63	1-hexene	50
64	C6 internal alkene	80
65	C7 terminal alkene	40
66	C7 internal alkene	75
67	C8 terminal alkene	35
68	C8 internal alkene	65
69	C9 terminal alkene	30
70	C9 internal alkene	60
71	C10 terminal alkene	25
72	C10 internal alkene	60
73	C11 terminal alkene	25
74	C11 internal alkene	60
75	C12 terminal alkene	20
76	C12 internal alkene	55
77	C13 terminal alkene	20
78	C13 internal alkene	55
79	C14 terminal alkene	20
80	C14 internal alkene	50
81	C15 terminal alkene	20
82	C15 internal alkene	50
83	1,3-butadiene	105
84	isoprene	100
85	cyclopentene	70
86	cyclohexene	65
87	alpha pinene	50
88	beta pinene	50
	Acetylenes	
89	acetylene	15
	Aromatic Hydrocarbons	
90	benzene	20
91	toluene	55
92	ethylbenzene	60
93	o-xylene	65
94	m-xylene	100
95	p-xylene	90
96	n-propylbenzene	50
97	i-propylbenzene	55
98	o-ethyltoluene	65

99	m-ethyltoluene	80
100	p-ethyltoluene	75
101	1,2,3-trimethylbenzene	115
102	1,2,4-trimethylbenzene	120
103	1,3,5-trimethylbenzene	115
104	C10 monosubstituted benzene	45
105	C10 disubstituted benzene	65
106	C10 trisubstituted benzene	115
107	C11 monosubstituted benzene	40
108	C11 disubstituted benzene	50
109	C11 trisubstituted benzene	120
110	C12 monosubstituted benzene	40
111	C12 disubstituted benzene	40
112	C12 trisubstituted benzene	120
113	C13 monosubstituted benzene	35
114	tetralin	30
115	naphthalene	35
116	methylnaphthalene	70
117	2,3-dimethylnaphthalene	100

Oxygenated Hydrocarbons

118	formaldehyde	40
119	acetaldehyde	55
120	proprionaldehyde	60
121	butyraldehyde	55
122	i-butyraldehyde	65
123	valeraldehyde	70
124	acrolein	120
125	glyoxal	20
126	methyl glyoxal	65
127	benzaldehyde	-35
128	acetone	20
129	methyl ethyl ketone	40
130	methyl i-butyl ketone	65
131	methanol	10
132	ethanol	25
133	n-propanol	45
134	i-propanol	15
135	n-butanol	55
136	i-butanol	40
137	t-butanol	10
138	but-2-diol	30
139	ethylene glycol	40
140	propylene glycol	30
141	phenol	25
142	alkyl phenols	55
143	methyl acetate	3
144	ethyl acetate	20
145	n-butyl acetate	45
146	i-butyl acetate	35
147	dimethyl ether	20
148	methyl t-butyl ether	15
149	ethyl t-butyl ether	50
150	propylene glycol	

	methyl ether	80
151	propylene glycol methyl ether acetate	30

Chlorinated Hydrocarbons

152	methylene chloride	1
153	chloroform	1
154	methyl chloroform	0
155	tetrachloroethylene	1
156	trichloroethylene	7
157	allyl chloride	55

Other Compounds

158	carbon monoxide	4
159	sulphur dioxide	2

Source: UK Dept. of Environment
Atomic Energy Agency- Harwell

Ann V

Carcinogenic Substances

Class I

Asbestos (chrysotile, crocidolite, amosite, anthophyllite, actinolite, tremolite) as fine dust

Benzo(a)pyrene

Beryllium and its compounds in respirable form,
- indicated as Be -

Dibenz(a,h)anthracen

2-Naphtalamine

at a mass flow of 0.5 g/h or more 0.1 mg/m^3;

Class II

Arsenic trioxide and arsenic pentoxide, arsenious acid and its salts, arsenic acids and its salts (in respirable form),
- indicated as As -

Chromium (VI) compounds (in respirable form), as far as calcium chromate, chromium (III) chromate, strontium chromate, and zinc chromate,
- indicated as Cr -

Cobalt (in form of respirable dusts/aerosols of cobalt metal and cobalt salts of low solubility)
- indicated as Co -

3,3'-Dichlorobenzidine

Diethyl sulfate

Ethyleneimine

Nickel (in form of respirable dusts/aerosols of nickel metal, nickel sulfide and pyritiferous ores, nickel oxide and nickel carbonate, nickel tetracarbonyl),
- indicated as Ni -

at a mass flow of 5 g/h or more 1 mg/m^3;

Class III

Acrylonitril

Benzene

1,3-Butadiene

1-Chloro-2,3-epoxipropane (epichlorohydrin)

1,2-Dibromomethane

1.2-Epoxipropane

Ethylen oxide

Hydrazine

Vinyl chloride

at a mass flow of 25 g/h or more 5 mg/m^3.

Ann VI.

ANNEX I B

LANDFILL SITE SELECTION CRITERIA

Engineering

Geophysical site (geographical criteria). Should be large enough to accommodate waste for life of production facility.

Proximity. Locate as close as possible to production or treatment facility to minimize handling and reduce transport cost. Locate away from water supply (suggested minimum 500 feet) and property line (suggested minimum 200 feet, more for landfill gas).

Access. Should be all-weather, have adequate width and loan capacity, with minimum traffic congestion; one way system on site whenever possible.

Topography. Should minimize earth-moving, take advantage of natural conditions. Avoid natural depression and valleys where water contamination is likely.

Geology. Avoid areas with earthquakes, slides, faults, underlying mines, sinkholes, and solution cavities.

Soils. Should have natural clay liner or clay available for liner, and final cover material available.

Environmental

Surface water. Locate outside 100-year floodplain. No direct contact with navigable water. Avoid wetlands.

Groundwater. No contact with groundwater. Base of fill must be above high groundwater table. Avoid sole-source aquifer. Avoid areas of groundwater recharge.

Air. Locate to minimize fugitive emissions and odor impacts.

Terrestrial and aquatic ecology. Avoid unique habitat area (important to propagation of rare and endangered species) and wetlands.

Noise. Minimize truck traffic and equipment operation noise.

Land use. Avoid populated areas and areas of conflicting land use such as parks and scenic areas.

Cultural resources. Avoid areas of unique archaeological, historical and paleontological interest.

Legal/regulatory. Consider national, regional and local requirements for permits.

Public/political. Gain local acceptance from elected officials and local interest groups.

Economic

Property acquisition. Actual land cost plus related costs.

Site development. Excavation, grading, liner, new roads, and other development costs.

/...

Annual costs. Fuel costs, operating labour, maintenance, land preparation, utilities, and overhead.

Salvage value. Do not consider: site probably will not be an asset.

Conflicts with the objective of setting up and operating towards a stable system particularly in respect of organic matter and in some cases heavy metals (comment seen as relevant to mono deposit with long term storage prospects).

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Annex I

LIST OF SOME COMMONLY USED SOLVENTS

	UN Class	UN Number	Flash Point (°C)	Solution in Water (mg/kg
Aliphatic Hydrocarbons				
- Cyclohexane	3	1145	-18	<1
- Naptha solvents	3	1256	<-20	<1
Aromatic Hydrocarbons				
- Benzene	3	1114	-11	0.2
- Toluene	3	1294	6	<1
- Xylenes	3	1307	25-30	<1
- Decahydronaphthalene		1147		
Halogenated Hydrocarbons				
- Chloromethane	2	1063		
- Methylene Chloride	6.1	1593	bd	1.3
- Chloroform	6.1	1888	nc	0.8
- Carbon tetrachloride	6.1	1846	nc	0.08
- 1,1 dichloroethane	3	2362	-10	0.5
- Trichloroethylene	6.1	1710	bd	0.04
- 1,1,1 trichloroethane	6.1	2831		
- Perchloroethylene	6.1	1897	nc	0.01
- Chlorobenzene	3	1134	29	<1
- o-Dichlorobenzene	6.1	1591	66	0
- p-Dichlorobenzene	6.1	1592		
- Ethylene dichloride	3	1184	13	<1
- Chloronitrobenzene	6.1	1578	127	0
- Ethyl chloride	2	1037		
- Ethylene dibromide	6.1	1605	nc	<1
- Dichlorodifluormethane	2	1028		
Alcohols, Glycols, Ethers, Phenols, Epoxides				
- Isobutanol	3	1212	28	
- Butanols	3	1120	35	
- 3-Pentanol	3	2706		
- Methanol	3	1230	11	100
- Ethylene Glycol Diethyl Ether	3	1153		
- Ethylene Glycol Monobutyl Ether	6.1	2369		
- Ethylene Glycol Monoethyl Ether Acetate	3	1172		
- Ethylene Glycol Monoethyl Ether	3	1188		
- Ethylene Glycol Methyl Ether Acetate	3	1189		
- Dimethyl Ether	2	1933		
- Propylene oxide	3	1280	-44	40
- Cresols	6.1	2076	81	2
- Phenol (molten)	6.1	2312	79	6.7
- Phenol (solid)	6.1	1671		
- Phenol (solutions)	6.1	2821		
- Isopropanol	3	1219		
- Ethanol	3	1170	12	100

Ketones, Aldehydes				
- Aldehydes, toxic	3	1988		
- Aldehydes, n.o.s.	3	1989		
- Formaldehyde (solutions)	9	2209		100
- Formaldehyde (solutions, inflammable)	3	1198	<23	
- Acetaldehyde	3	1089		
- Acetone	3	1090	-20	100
- Acrolein dimer, stabilized	3	2607		
- Acrolein, inhibited	3	1092	<-20	
- Methyln ethyl ketone	5.2	2563	-1	27
- Methyln ethyl ketone	5.2	2550		
- Methyln ethylene ketone	5.2	2127		
- Methyl isobutyl ketone	3	1245		
- Cyclohexanone	3	1915	43	6
- Diethyl ketone	3	1156		
Esters, Amides				
- Ethyl acetate	3	1173	-4	8.7
- Isobutyl acetate	3	1213	19	<<1
- Butyle acetates	3	1123	26	
- Methyl acetate		1231		24
Acids, Nitriles				
- Nitrobenzene	6.1	1662		<1
- Acrylonitrile	3	1093	-5	5
Heterocyclic Compounds				
- Tetrahydrofuran	3	2056	-17	100
- Furfural	3	199	60	8.3

Notes

bd - burns with difficulty
nc - noncombustible

Source: OECD

Table 4 United States 1990 chlorinated solvents statistics

Capacity	[illegible]	720	611	600	1,050	320
Production	375	388	441	526	758	180
Imports	74	84	19	29	[illegible]	[illegible]
Exports	45	53	127	8	124	68
Consumption	404	419	333	547	635	115

Figures are in millions of pounds.
Capacities are flexible. Production of carbon tetrachloride is an industry estimate.

Source: reference 7.

Ann. VIII.

Table 5 Toxic effects of common pollutants in aquatic and terrestrial environments

Carbon Tetrachloride*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hexachlorobutadiene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Benzene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Formaldehyde	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hexachlorocyclohexane - gamma*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Methylene Chloride*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dichlorobenzidine*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
xachlorocyclohexane - Alpha*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hexachloroethane*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hexachlorocyclohexane - Technical	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ethylbenzene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Toluene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hexane (n-hexane)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Chlorophenol 2*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dimethyl Phenol 2,4*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Chlorinated Naphthylenes	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
O-Chlorotoluene	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Methyl Isobutyl Ketone	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Chloroform*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tetrachloroethylenes*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Trichloroethylene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dinitrotoluene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Xylene	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tetrachloroethane 1,1,2,2*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Chlorinated Benzenes*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dichloroethane 1,2*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Trichloroethane 1,1,2*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dichloroethylenes*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Trichlorinated Ethanes	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Trichloroethane 1,1,1*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dichlorobenzenes	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Methyl Ethyl Ketone	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
nochlorobenzene*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Phenol*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

** United States Environmental Protection Agency (US EPA) priority pollutant.*

1. *Has US EPA water quality criterion < 10 mg/l or acute or air quality criterion < 100 mg/m³.*
2. *Listed in RTECS as a carcinogen or suspected carcinogen.*
3. *Listed in RTECS as a teratogen or suspected teratogen.*
4. *Listed in RTECS as a mutagen or suspected mutagen.*
5. *Has bioconcentration factor ≥ 1,000 as documented in PHRED (Public Health Risk Evaluation Database 1987) or in Water-Related Environmental Fate of 129 Priority Pollutants (EPA, 1979).*
6. Has environmental half-life ≥365 days as documented in PHRED.

Key: "+" = has characteristic; "−" = does not have characteristic; blank = no data.

Source: reference 5.

Annex.

Table 1 Common solvents: US exposure limits and health hazards

n-Amyl Acetate	100 ppm[1] (525 mg/m³)	4000 ppm	Eyes, skin and respiratory system.
sec-Amyl Acetate	125 ppm[1] (650 mg/m³)	9000 ppm	Eyes, skin and respiratory system.
Benzene	0.1 ppm[2] 1.0 ppm[3]	3000 ppm	Blood, central nervous system, skin, bone marrow, eyes and respiratory system.
2-Butanone	200 ppm[1] (590 mg/m³)	3000 ppm	Central nervous system and lungs.
2-Butoxyethanol	25 ppm[1] (120 mg/m³)	700 ppm	Liver, kidneys, lymphoid system, skin, blood, eyes and respiratory system.
sec-Butyl Acetate	200 ppm[1] (950 mg/m³)	10,000 ppm	Eyes, skin and respiratory system.
tert-Butyl Acetate	200 ppm[1] (950 mg/m³)	10,000 ppm	Eyes, skin and respiratory system.
n-Butyl Alcohol	50 ppm[1] (150 mg/m³)	8000 ppm	Eyes, skin and respiratory system.
sec-Butyl Alcohol	100 ppm[1] (305 mg/m³)	10,000 ppm	Eyes and central nervous system.
tert-Butyl Alcohol	100 ppm[1] (300 mg/m³)	8,000 ppm	Eyes and skin.
2-Ethoxyethanol	200 ppm[1] (740 mg/m³)	(6,000 ppm)	In animals: kidneys, eyes, blood, kidneys and liver.
2-Ethoxyethyl Acetate	100 ppm[1] (540 mg/m³) (skin)	(2,500 ppm)	Respiratory system, eyes and gastro-intestinal tract.
Acetate	400 ppm[1] (1400 mg/m³)	10,000 ppm	Eyes, skin and respiratory system.
2-Hexanone	ppm[2] (4 mg/m³)	5,000 ppm	Central nervous system, skin and respiratory system.
	5 ppm[3] (20 mg/m³)		
Hexanone	50 ppm[1] (205 mg/m³)	3000 ppm	Central nervous system, eyes, skin and respiratory system.
Isobutyl Alcohol	50 ppm[1] (150 mg/m³)	8,000 ppm	Eyes, skin and respiratory system.
Isopropyl Acetate	250 pp[1] (950 mg/m³)	16,000 ppm	Eyes, skin and respiratory system.
Isopropyl Alcohol	400 ppm[1] (980 mg/m³)	12,000 ppm	Eyes, skin and respiratory system.
Methyl Acetate	200 ppm[1] (610 mg/m³)	10,000 ppm	Eyes, skin and respiratory system.
Methyl Alcohol	200 ppm[1] (260 mg/m³)	25,000 ppm	Eyes, skin, central nervous system and gastro-intestinal tract.
Methyl Cellosolve	ppm[2] (80 mg/m³) (skin)	(200 ppm)	Central nervous system, blood, skin, eyes and kidneys.
Methyl Cellosolve Acetate	25 ppm[3] (120 mg/m³) (skin)	(4000 ppm)	Kidneys, brain, central nervous system and peripheral nervous system.
Methyl Chloroform	350 ppm[1] (1900 mg/m³)	1000 ppm	Cardiovascular system, central system, skin and eyes.
Methylene Chloride			Skin, cardiovascular system, eyes, central nervous system
Naphthalene	10 ppm[1] (50 mg/m³)	500 ppm	Eyes, blood, liver, kidneys, skin, red blood cells, central nervous system.
2-Pentanone	150 ppm[2] (530 mg/m³) 200 ppm[3] (700 mg/m³)	5000 ppm	Respiratory system, eyes, skin and central nervous system.
n-Propyl Alcohol	200 ppm[1] (500 mg/m³)	4,000 ppm	Skin, eyes, respiratory system and gastro-intestinal tract.
Tetrachloroethylene	25 ppm[3] (170 mg/m³)	(500 ppm)	Liver, kidneys, eyes, upper respiratory system and central nervous system.
Toluene	100 ppm[1] (375 mg/m³)	2000 ppm	Central nervous system, liver, kidneys and skin.
1,1,2-Trichlorethane	10 ppm[3] (45 mg/m³)	(500 ppm)	Central nervous system, eyes, nose, liver and kidneys.
Trichloroethylene	50 ppm[3] (270 mg/m³	(1000 ppm)	Respiratory system, heart, liver, kidneys, skin and central nervous system.
1,2,3-Trichloropropane	10 pp.m[3] (60 mg/m³)	(1000 ppm)	Eyes, respiratory system, skin, central nervous system and liver.
Xylenes (o-, m-, p-isomers)	100 ppm[1] (435 mg/m³)	1000 ppm	Central nervous system, eyes, gastro-intestinal tract, blood, liver, kidneys and skin.

[1] *NIOSH/OSHA limit.*
[2] *NIOSH limit.*
[3] *OSHA limit.*
[4] *Occupational carcinogen, no threshold developed.*

Source: adapted from reference 4.

Auxiliary Ingredients

AHS

Aluminum : Inhaaltion of finely devided aluminum powder reportedly cause pulmonary fibrosis. The dust is moderately flammable/explosive by heat, flame, or chemical reaction with powerful oxidizers.

Arosil 200 : It is a poison by intraperitoneal, intravenous, or intrathracheal routes. It is also moderately toxic by injestion but much less so in crystalline form. Carcenogenic data raises question to its carcenogenic property. Mutation data has been reported also. It does not cause silicosis.

Avicol : It is poisonous by intraperitneal, intravenous, subcuteneous, and tracheal routes. Whenheated to decompose, it emits toxic fumes of HCl and NOx's.

Calcium Phosphate : A skin and eye irritant, this compound is also a nuisence dust.

Cellulose : Also a nuisance dust and emits acrid smoke and irritating fumes when heated to decompose.

Disperse Orange : It is a confirmed carcinigen with carcenogenic, tumorigenic, and neoplastigenic data. When it decomposes by heating, it emits toxic fumes of NOx's.

Glycerine : It is apoison by subcuteneous route. Shows mild toxicity by ingestion. Effects on human system by ingestion - nausea, headache, vomitting. Experimental reproductive effects. Human mutation data reported. Also an eye and skin irritant. In the form of mist, a nuisance particulate and inhalation irritant. A combustible liquid with heat, lame, or powerful oxidizing agents, and explosive with nitric and sulfuric acids.

Iron Oxide : Explosive with certain compounds and metals or when heated with specific metals. A poison by subcuteneous route and questionable carcenogen with tumorigimic data.

Lactose : Moderately toxic by intravenous route. Questionable carcenogen with experimental teratogenic and tumorigenic data. Mixtures with oxidants may be explosive hazard. When decomposed by heat emits acrid smoke and irritating fume.

Nymcel : It is mildly toxic by ingestion. Experimental reproductive effects. Questionable carcenogen with neoplastic data. It can migrate to food from packing material. Emits toxic fumes of sodium oxide when decomposed.

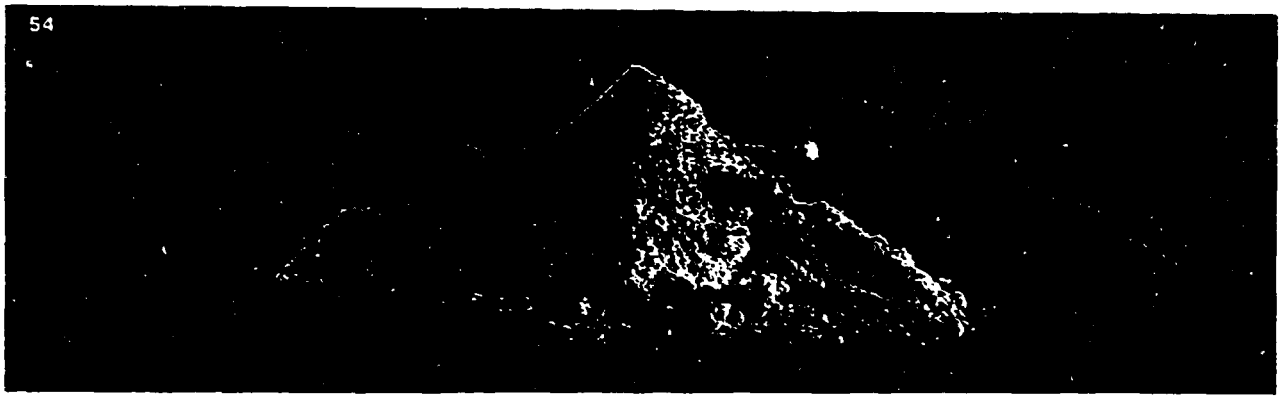
Pharmagel : An experimental teratogen and reproductive effects. Emits acrid smoke and irritating fumes on decomposition.

Polysorbate : It is moderately toxic by intravenous route and mildly so by ingestion. Experimental reproductive effect. Human mutation data reported. Questionable carcenogen with experimental teratogen c data. Emits acrid smoke and irritating fumes when heated to decompose.

Sodium Citrate : A poison by intravenous route. Moderately toxic by intraperitoneal route. Emits toxic fumes of sodium oxide on decomposition.

Starch : A nuisance dust and allergen. Flammable when exposed to flame or strong oxidants.

A-112



MIKE DEAN

FDA Regulation of Bulk Pharmaceutical Chemical Production

David B. Barr, William C. Crabbs,* and Dale Cooper

FDA's interest in the manufacture of bulk pharmaceutical chemicals (BPCs) seems to many to be a new phenomenon; however, the agency has a long history of active regulation in this area. It is true that FDA has intensified its inspectional coverage of BPC producers, particularly those located overseas, and has also provided its investigators with more inspectional guidance in this area. But FDA has recognized for a considerable time the need for manufacturers to exercise the same high level of control over BPC production as they have to finished dosage form production. Controls over BPC production will not always be the same as those found in finished dosage form plants. But these differences are simply reflections of different manufacturing processes, not inherent differences in the importance of GMPs for the two types of production. This article will provide a series of necessary definitions followed by a general discussion of BPCs and the regulatory context in which they are produced. The discussion will then cover some of the situations, problems, and issues — including those involving validation — that FDA investigators encounter in their inspections. Finally, the article will offer a few comments and conclusions about the current regulatory status of BPCs.

BPCs are usually made by chemical synthesis, recombinant DNA technology, fermentation, enzymatic reactions, recovery from natural materials, or combinations of these processes. In almost every case, the starting materials or derivatives of the starting materials undergo some significant chemical change. Impurities, contaminants, carriers, vehicles, inerts, diluents, and unwanted crystalline or molecular forms that may be present in the raw materials are largely removed by various treatments in the production process. Purification is the ultimate objective and is accomplished by various chemical, physical, and biological processing steps.

Sources. BPCs are manufactured by a variety of companies. The majority of them are outside the United States and are involved in the production of BPCs or BPCs and other chemicals. In general, they are more closely associated with the chemical industry — concerning their environmental conditions, equipment, and operational techniques — than they are with the pharmaceutical manufacturing industry. Some firms, however, manufacture both BPCs and finished pharmaceuticals.

BPCs are drugs under the Food, Drug, and Cosmetic Act. The manufacture of all drugs sold in or imported to the United States is subject to inspection. Foreign companies are inspected by FDA under the Foreign Inspection Program, or if a company is in a country that has a bilateral inspection agreement with FDA, they may be scrutinized by that country's inspectorate.

REGULATORY STATUS

What is the regulatory status of BPCs? Section 501 (a)(2)(b) of the Food, Drug, and Cosmetic Act requires that all drugs be manufactured, processed, packed, and held in accordance with CGMPs. No distinction is made between BPCs and finished pharmaceuticals. Failure to comply with CGMPs constitutes a failure to comply with the requirements of the act, and the drug is deemed to be adulterated.

What constitutes CGMPs for BPCs? GMP regulations in 21 *CFR* §210 and 211 apply only to finished dosage forms. The preamble to the GMP regulations (1978) states: "Although these CGMP regulations are not applied to the manufacture of bulk drug components, there are numerous instances where Good Manufacturing Practices

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for bulk drug components would parallel the requirements set forth in part 211. For this reason FDA will use the standards of part 211 as guidelines during inspections of manufacturers of bulk drug components under their jurisdiction of the act."

Regulation. BPCs are regulated by FDA in ways that parallel finished dosage forms. The same personnel inspect the manufacture of both BPCs and finished dosage forms. Requests for these inspections come about in many ways:

- Each FDA district maintains an inventory of companies under the agency's jurisdiction. This inventory is managed by the district, and if a firm has not had an inspection within an established time frame — two years for drug manufacture — the district will schedule the inspection.
- The preapproval inspection program also applies to the manufacture of BPCs. When an application for the manufacture of a drug is filed, all components and their sources must be listed. In the event that this is a new drug substance, or the listed BPC manufacturer has not received a recent CGMP inspection for the same process — e.g., chemical synthesis, fermentation, sterile bulk production, etc. — an inspection must find the manufacturing process satisfactory prior to the recommendation for approval.
- There may be many other reasons for inspection of a BPC manufacturer, such as complaints, injuries and illnesses, and requests under the Governmentwide Quality Assurance Program preliminary to a government purchase. Districts may also conduct inspections at their discretion for surveillance or any other circumstances they believe warrant the inspection.

Guidance documents. A variety of guidance documents issued by FDA do relate to BPC manufacturing. "Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing" was revised in September 1991. This guide is intended to aid FDA personnel in determining whether the methods used in and the facilities and manufacturing controls used for the production of BPCs are adequate to ensure that they have the quality and purity that they claim. This current revision covers agency policy on several issues, including validation and impurity profiles and reference to the preapproval inspection program.

"Guideline for Submitting Documentation in Drug Applications for the Manufacture of Drug Substances" was issued in February 1987. Guidelines represent the formal position of FDA on any matter. Although it is mandatory that regulations be followed, guidelines are not legal requirements but do represent FDA's current position on this subject. This guideline is intended to provide sponsors and applicants with procedures acceptable to FDA for complying with regulations pertaining to the submission of adequate information on the production and control of new drug substances. This guideline addresses new drug substances manufactured by chemical synthesis, fermentation, or isolation from natural sources. It does not cover recombinant DNA synthesis.

The "Biotechnology Inspection Guide for Investigators" was issued in November 1991. The guide is intended to aid FDA personnel in determining the adequacy of facilities and manufacturing controls used in the production of biotechnologically derived products.

FDA also issues compliance programs that provide specific instructions for conducting inspections in specialized areas. Compliance Programs 7356.002F (Bulk Pharmaceutical Chemicals) and 7356.002A (Sterile Drug Process Inspections) are two such programs; the former covers nonsterile BPC's and the latter addresses sterile BPC's. These documents will be used by FDA investigators during inspections of BPC manufacturing.

The BPC manufacturer may file a drug master file (DMF), a submission to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation but is submitted solely at the discretion of the holder. The information in a DMF may be used to support an investigational new drug application (IND), a new drug application (NDA), an abbreviated new drug application (ANDA), another DMF, an export application, or amendments and supplements to any of these. A DMF is not a substitute for an IND, NDA, ANDA, or export application. It is not approved or disapproved, nor does the assignment of a DMF number indicate approval. Technical contents of a DMF are reviewed only in connection with the review of an application or an export application. DMFs are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file.

Center activities. The Center for Drug Evaluation and Research (CDER) is responsible for establishing regulatory policies, reviewing DMFs, reviewing and approving/nonapproving applications, and establishing program responsibilities regarding the manufacture and shipment of human drugs within the United States.

Domestic inspection program. The manufacture of bulk drugs has been covered by FDA inspection programs for many years. These inspections typically determine the acceptability of the manufacturing process and manufacturing controls. GMP regulations are used as a guideline. The site and product-specific acceptability of the manufacture of drug substances named in applications is covered under the recently revised preapproval inspection program. Applications are received by CDER for review and name the sources of the drug components. Whenever the source of a component has not been recently inspected for the process used to produce the substance — e.g., chemical synthesis or fermentation — or has not had a recent acceptable CGMP inspection, the agency will conduct a site-specific inspection. If the bulk drug is a new drug substance, the agency will conduct a site- and product-specific inspection. FDA may also conduct inspections for surveillance and other reasons. During these inspections, the investigators will evaluate production capability in terms of equipment, systems, and controls and determine the company's compliance with current CGMPs.

Foreign inspection program. Foreign manufacturers of drugs and drug substances who wish to export to the United States are also subject to inspection. FDA made its first foreign inspection in 1955 as part of the former antibiotic certification program. By 1961, the total number of drug inspections had grown to 13 and continued to grow slowly throughout the sixties. In fiscal year 1971, inspections doubled to 80 as a result of organizational and policy changes within FDA. Growth continued in the seventies and leveled off at about 160 drug inspections/yr throughout the eighties and early nineties. In fiscal year 1993, FDA experienced its second major one-year increase in the number of inspections planned — 340. Most of these inspections have been and continue to be BPC inspections. To ensure equivalency with domestic inspections, these inspections are made by investigators from the district offices, who also perform domestic inspections. This helps to ensure that manufacturers outside of the United States are subject to the same requirements as domestic manufacturers.

In addition to inspections by FDA investigators, there are bilateral agreements with three foreign governments, which allow for exchanges of inspectional information. These countries are Canada, Sweden, and Switzerland.

FDA INSPECTIONS

Although this article has been organized in a sequence going from raw materials to final packaging and release, an actual FDA

inspection may be conducted in any sequence, depending on the circumstances of the inspection and the judgment or habits of the investigator.

We have also attempted to briefly address, under several of these headings, some issues directly and indirectly related to validation. This is an area that demands cautious discussion. The bulk manufacturing industry is diverse, and the degree and extent of the validation required may vary depending on the process and the point in the process under question. Although the general concepts in FDA's May 1987 guideline covering process validation are, for the most part, well understood by industry, there is no agreement about all of the specific, detailed applications of these principles to all areas of bulk production. Added to this problem is the lack of consistency in the use of validation terminology, which occasionally leads to confusion and misunderstanding. Clearly, the bulk pharmaceutical industry is faced with an evolving state of validation interpretation and application.

PREPARATION FOR THE INSPECTION

Before making any inspection, an investigator will review the report of the previous inspection for background information and any conditions that needed correction. That review represents the minimum preparation for an investigator, assuming that there is good knowledge of the BPC inspectional guide and compliance program. Before making an NDA or ANDA preapproval inspection, the investigator may review the most relevant sections of the application and associated DMF, if any. In most instances, this type of review is also done before making routine inspections covering approved NDA and ANDA products. (Actually, it is the finished dosage form in which the BPC is a component that is approved or disapproved.) The investigator knows that a substantial part of the upcoming inspection will be devoted to confirming that the commitments made in these documents are being met. In addition to this standard preparation, the investigator may be asked by the center to gather special information not contained in the application or the DMF to meet special needs and to help speed up the evaluation process. The preparation described above represents only the minimum and not the average amount of preparation that is undertaken by an investigator before making a BPC inspection.

In a relatively new development, our investigators have asked companies to send them selected documents in advance of preapproval inspection to save inspectional time for both the investigator and the company. These documents include validation reports, annual reports, complaint reports, and other documents not normally available to an investigator beforehand. Also, the agency issued a proposed rule on 28 January 1991, which, when finalized, will require applicants to submit a third copy of the chemistry and biopharmaceutics sections of their drug applications. Such copies will be provided to field units for use by investigators in preparation for preapproval inspections.

RAW MATERIALS

The term *raw materials*, as used here, loosely refers to the wide range of materials extending from fine chemicals to crude plant and animal matter that is used in BPC production. It also includes solvents and chemicals used in processing. FDA investigators have no single, rigid set of controls they insist upon when they inspect the handling and control of raw materials. Rather, they gear their expectations to the type of material and the process of which it is a part. But they do always expect to find a well thought out system of controls appropriate for the material and the process.

Investigators will determine whether there is a control system that ensures that the incoming materials meet approved specifications and are properly stored. Usually such systems will involve some type of temporary quarantine system based on physical separation and status identification or rigorous paper or computer controls. (However, they do want to be reasonable. For example, they do not demand that quarantine, under-test, release, and rejected stickers be affixed to each of 2000 cloth bags of a fermentation nutrient, although some companies, fearing the worst from FDA, have done so.)

Upon receipt, lots are usually checked for condition, labeling, and lot number and the information recorded. In most cases, there should be at least a visual or chemical identity test of a physical sample. This minimal type of examination is, however, usually combined with a certificate of analysis from a qualified vendor showing that all specified test requirements have been met. For critical materials and intermediate compounds, a full analytical work-up may be required. There are synthetic processes that depend upon a high degree of purity of key starting materials and intermediates to ensure the purity of the final bulk pharmaceutical. These processes are important exceptions to the general rule that, in BPC production, impurities present in starting materials are largely removed in processing.

Solvents used for crystallization and other final processing steps require special attention. If contaminated, these solvents can directly contribute to the contamination of the finished bulk material. Two problems stand out: the reuse of drums for different solvents by suppliers and bulk tankers used for multiple products. Investigators will want to know how a firm's control system precludes the possibility of contamination. Because of past experiences with contaminated tankers, some companies take a substantial sample of solvent from a tanker delivery hose rather than taking a small 100-mL sample through the tanker hatch. Tested lots of solvents may be commingled in bulk holding tanks, but an investigator will expect to see a periodic check of the quality of the solvent in the holding tank. If the tank is underground, periodic integrity testing is desirable.

If you have a solvent recovery system, the investigator will be interested in how you control it and will generally expect to see some type of chromatographic control, particularly for solvents used in different operations. Recovered solvents, with few exceptions, should meet the same specifications as new incoming solvents.

During an inspection, it is likely that the investigator will want to know if you have a written supplier qualification plan. The agency generally encourages audits of suppliers' operations. On the other hand, it is also important that the supplier understand a company's needs and how changes would affect its process. This approach, combined with complete analysis of several lots of incoming material over a significant period of time, will allow a company to qualify its supplier.

For companies that have strong qualification programs, accepting critical raw materials based on certificates of analysis combined with minimal identity testing is usually an acceptable procedure. However, a full analytical examination should be undertaken periodically. Surprisingly, FDA sometimes finds companies whose qualification programs simply consist of performing analyses on three successive lots. If the lots all meet specifications, then the company considers that the supplier has been validated. This does not represent a thoughtful evaluation of the supplier's operation, and it does not represent an adequate sampling of the supplier's material over time.

MANUFACTURING PROCESSES

The wide range of manufacturing processes used in bulk pharmaceutical chemical production precludes absolute statements about what an FDA investigator will be primarily interested in during an inspection. Normally, investigators pay the most attention to that part of the process that begins with the first reaction step that produces the key

intermediate. The key intermediate has been defined in the February 1987 FDA "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" as: "An intermediate in which an essential molecular characteristic(s), usually involving the proper stereochemical configuration required for structure/activity (pharmacological and/or physiological activity of the drug substance), is first introduced into the structure ..."

For nonsynthetic processes, such attention would start with the first step in the isolation or recovery of the pharmaceutical entity. FDA's inspectional coverage will, in almost every case, extend through final processing, with close attention paid to the purification steps employed. However, during most inspections, at least some GMP coverage will be given to earlier steps in the BPC manufacturing process. And these earlier steps may be considered critical steps if they affect the purity of the finished BPC. Although usually it is neither feasible nor required to apply rigid controls during early processing steps, the documentation system for such steps must provide a chain of documentation but need not necessarily be as comprehensive as in later parts of the process.

Validation of the manufacturing process. Currently, the number-one issue related to inspection of bulk pharmaceutical chemicals is the validation of the manufacturing process. Until 1991, agency policy covering BPC process validation was left unstated. Current policy is that the agency has not insisted that all BPC manufacturing processes be validated at this time, but it does expect all BPC producers to be actively engaged in a validation program for their products. The agency does not anticipate taking legal action when a company has an adequate program in place, including milestones, unless there is lack of validation and evidence of a significant number of failed batches.

A new BPC production process usually goes through a pilot production phase during which the critical processing parameters, operating ranges, and in-process testing requirements are established. Specifications for equipment, raw materials, in-process materials, and finished product, including impurity limits, are also usually established during this phase. Prospective validation of a new process begins here with a documented scientific investigation that leads to an understanding of the process and how to control it. A plan or protocol is usually developed for scaling the operation up to commercial batch sizes. A company first qualifies processing equipment and begins processing batches under close scrutiny to ensure that the equipment, operating ranges, and in-process controls developed during the pilot phase are adequate to reliably produce a finished product meeting all specifications. A company obtains and evaluates documented processing and analytical control history for multiple batches in relation to the validation protocol to determine if the process can be considered validated.

For a process that has been used for an extended period of time, a company may attempt a retrospective validation. Some firms have mistakenly thought that a thorough evaluation of all existing records associated with three batches would be sufficient to retrospectively validate a production process. FDA has not established the number of past batches that must be evaluated, but it would rarely consider three batches to be adequate for retrospective validation; the number of such batches needs to be determined relative to the number of batches previously manufactured. A successful retrospective validation effort depends on the availability of a documented history of adequate physical and analytical controls exercised over past batches extending from starting materials through the finished batch. Impurity profiles are an important part of the history that must be evaluated. Without this type of documented history, FDA does not believe that a retrospective validation of a process is possible.

Whether a process has been validated prospectively or retrospectively, the process does not automatically remain permanently validated. If changes are made in the controls or process, they need to be evaluated through a formal "change control" procedure involving a careful evaluation of changes by qualified individuals that will determine the extent of any revalidation effort that will be required. This is one aspect of a company's validation program upon which FDA places much importance. Investigators commonly give detailed coverage to change control in inspections, both for bulk and finished pharmaceuticals. And, of course, like all production processes, a validated process should be subjected to a routine yearly evaluation that attempts to detect potential problems through trend analysis.

Validation of equipment cleaning. For many years in inspections of BPC producers, investigators have asked companies for evidence showing that their cleaning procedures for equipment such as crystallizers, reactors, centrifuges, dryers, and blenders used in final processing were adequate. Sometimes they even asked whether the cleaning procedure had been validated. They found in past years that many, if not most, companies processing a drug with high pharmacological activity conducted some type of analytical control of cleaned equipment before changing over to another product. Typically, this control consisted of checking the solvent used for the final rinse for residual drug activity, often with a simple TLC method. The significance of the result, "no residue detected," obviously varied with the sensitivity of the method.

It is now standard practice for investigators to inquire about validation of cleaning procedures for all products. For clean-in-place (CIP) methods, standard validation procedures covering design, equipment installation qualification, operational qualification, and validation test requirements are applicable. For validated CIP procedures, the variables are usually controllable to the point that analytical testing after cleaning may not be required routinely. Companies may choose, however, to continue to do such testing as an additional control measure. In a somewhat different light are those cleaning operations that heavily depend on hand cleaning. Here, the use of the word *validation* signifies less certainty because of the extensive reliance on the human factor. Under these circumstances, FDA believes that analytical testing is necessary. Samples for laboratory analysis are usually taken from the solvent used for the final rinse combined with swabs from difficult-to-clean areas. In all cases, visual examination — including the use of mirrors for hard-to-see areas — should reveal no residual product.

"No residue detected" is now an infrequent finding, given the sensitivity of modern HPLC and gas chromatography methods. These methods are preferable to the TLC methods that were more common in the past. Today, the question is usually not whether there is a residue but rather how much is permitted — which is a difficult question. The BPC industry follows different approaches in developing limits for postcleaning drug residues. (Limits for residues of cleaning agents are also a concern, although generally they are secondary to active ingredient BPCs.) Some establish a limit that is related to the amount left after a heroic cleaning effort. Others establish a limit several orders of magnitude below the minimum known pharmacological or physiological activity level of the BPC that is being cleaned from equipment. This limit is compared to the amount of residual BPC as follows: The amount of residual material is calculated based on a sample or samples from a specified surface of known area. The theoretical amount of material coating the entire vessel is calculated assuming uniform dispersion. It is assumed that all of this material will contaminate the next BPC to be produced. It is further assumed that the contaminated BPC will be used in the finished dosage product with the highest dosage level. The theoretical total amount of contamination is calculated for one dose and compared to the limit. Although

this is a somewhat tortuous method, it is usually acceptable. However, in all such product changeovers, no matter what validation approach is taken, investigators expect that a diligent effort will be made to clean the equipment and, as stated before, that there be no visible residues. The BPC producer needs to quantitate the residue levels after cleaning and have a good rationale for the specified limits upon which the validation effort is based.

BPC plants may operate on a campaign basis. That is, they may produce the same product, batch after batch, using the same equipment for extended periods of time. On the one hand, inspectors would not expect the same cleaning standards to be applied here as in product changeover situations. On the other hand, there should not be clumps of product adhering to equipment walls. Many companies clean enough so that only a dust layer is left between batches. This is generally acceptable. However, companies must consider the stability of the drug product under those exposed conditions and the total amount involved.

Validation of computerized processes. Computer systems are commonly associated with BPC production and are used to initiate, monitor, adjust, and otherwise control manufacturing processes. As a result, it is important that computer systems perform accurately and reliably, be secure from unauthorized or inadvertent changes, and provide adequate process documentation. Computer systems must be validated to ensure their accurate and reliable performance. In general, there are five main areas of consideration for validation of both hardware and software:

- defining the task to be performed and matching the task to the computer system
- identifying the system's operational limits and incorporating those limits in a standard operating procedure (SOP)
- testing the system
- documentation, and
- establishing systems to detect changes and precipitate revalidation.

We consider the end user as primarily responsible for the validation of computer systems, and such users must ensure the suitability of equipment and procedures applied to BPC production. Although the user bears primary responsibility for computer systems validation, much of the actual testing and documentation may be carried out by vendors. Records of system validation must be readily available at the user's facility. However, when a party other than the user — such as a vendor — conducts validation studies, the user's records of the studies need not be voluminous. Rather, the user's records as supplied by the outside party need only be complete enough for the user to reasonably conclude that the validation itself was thorough and accurate.

Although a thorough discussion of the validation of computerized processes is beyond the scope of this article, FDA has provided guidance on this subject in a number of documents, including "Guide to Inspection of Computerized Systems in Drug Processing," February 1983; "Compliance Policy Guides 7132a.07/08/11/12 and 15," issued in 1987; and "Technical Report on Software Development Activities," published in July 1987.

Validation of blending and related problems. This aspect of processing deserves more attention than it often receives. Finished dosage form manufacturers must expend more analytical resources analyzing two 500-kg lots of an active ingredient than for one 1000-kg lot of such an ingredient. As a consequence, finished dosage form producers have sometimes pressured BPC manufacturers to produce larger and larger lot sizes. In turn, BPC producers have, at times, exceeded their legitimate maximum lot size. If lots are produced by the blending of batches — a batch is often defined as a homogeneous quantity of material produced by one crystallization cycle or other purification or isolation process — then the maximum lot size is determined by the maximum working capacity of the largest blender. This limitation has sometimes been ignored. If an investigator finds that a BPC producer is shipping lots of sizes greater than the working capacity of its blender, the plant may lose its acceptability to FDA. This may result in regulatory or administrative sanctions, including withholding of application approvals, import detentions, or other regulatory actions, as appropriate.

For companies with sufficiently large blenders, there is one more step. The company must demonstrate that its blending process produces homogeneous lots. In other words, FDA expects companies to validate their blending systems. Sometimes the term *optimize* is used and correctly suggests that in a blending process, it is possible to blend for either too short or too long a time. Blending for too long may produce a less homogeneous lot as a result of particle size sepa-

Glossary

BPCs are the ingredient chemicals, including actives and excipients used in the manufacture of drug products (finished dosage forms). There are various terms that are used when referring to specific types of BPCs. These terms include drug, new drug substance, drug substance, bulk drug, component, active ingredient, and inactive ingredient. The following definitions may help clarify meaning:

Drug. Defined in the Food, Drug, and Cosmetic Act in Chapter II 201 (g)(1). The term *drug* means (A) articles recognized in the official *United States Pharmacopeia, Official Homeopathic* ... (10 lines)

New drug substance. Defined in the *Code of Federal Regulations (CFR)* Title 21, section 310.3: "New drug substance means any substance that when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance."

Drug substance. Defined in 21 *CFR* section 314.3: "Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient."

Bulk drug. Term in general use does not have a legal definition. Generally refers to drug substance itself; however, [illegible] between bulk drug and drug products packaged in [illegible] equipment.

Component. Defined in cGMP Regulations, 21 *CFR* section 210.3: "Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such product."

Active ingredient. cGMP Regulations 21 *CFR* 210.3: "Active ingredient means any component that is intended to furnish [illegible] effect in the diagnosis, [illegible] disease, or to affect [illegible] other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."

Inactive ingredient. cGMP Regulations 21 *CFR* 210.3: "Inactive ingredient means any component other than an active ingredient."

ration and attrition effects — or even thermal degradation for sensitive products. An optimized process may not achieve the level of homogeneity required by preestablished validation test criteria because of poor mixing equipment or other factors. Caution is required when using the word optimize. To some it means attaining the best possible results, and to others it represents a process that has been designed to achieve the maximum total benefits derived from both the quality of the product (homogeneity) and the efficiency of the process (cost of production). Validation of a blending process demonstrates that predetermined test criteria for homogeneity can reliably and repeatedly be met lot after lot. FDA believes that neither "validation" nor "optimization" should be taken to mean that a blending process must necessarily achieve the highest theoretical level of homogeneity possible for a product–blender combination.

Individual batches must be blended to ensure homogeneity. Separate drying operations, nonuniform drying, particle-size separation during centrifugation, secondary recovery operations, and other factors make it desirable to blend a single finished batch. If a company chooses not to blend single batches before shipment, it should be prepared to produce conclusive evidence that homogeneous batches are consistently produced without blending. (Companies should keep in mind that FDA's policy on blending prohibits blending out-of-specification material with better material so that the final blend will fall within specifications.)

Whenever possible, finished dosage form manufacturers should determine the blending practices of their active ingredient suppliers as part of their qualification program. First, the company can decide if the practices are acceptable and, second, it can adjust its sampling plan for the supplier's material in light of this information.

Validation of water supplies. Water used in the production of BPCs in some instances — e.g., fermentation of antibiotics or early in synthetic processes if high chemical purity is unnecessary — may be potable water obtained from wells or surface sources. This is acceptable, provided that water quality standards are established and are consistent with compendial or other regulatory requirements for source drinking water. In the United States, such water is subject to federal Environmental Protection Agency regulations and is commonly obtained from municipal water authorities. Although it is not possible to validate such a system because it is not under the company's control, FDA expects periodic testing to show compliance with standards from both chemical and microbiological standpoints, including freedom from pathogenic organisms.

Purified water is widely used in the manufacture of BPCs. Because of the well-recognized potential for microbial growth in deionizers and ultrafiltration (UF) or reverse osmosis (RO) systems used to produce purified water, such systems must be properly validated and controlled. Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and adequate maintenance procedures, such as regeneration and sanitation-sterilization. Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process where the water is used. For example, if the water is used in later processing steps, such as for a final wash of the filter cake, or if the BPC is crystallized from an aqueous system, the water quality standards should be higher than those normally specified for purified water. This is particularly important when the BPC is intended for use in parenteral dosage forms, as mentioned below. The frequency of microbial and chemical testing of purified water depends on a variety of factors, including the test results and the point in the process — e.g., final wash in centrifuge — at which such water is used.

USP includes suggested microbial action guidelines for source drinking water and purified water in the "General Chapter on Water for Pharmaceutical Purposes" and includes standards for specific types of water in monographs — e.g., Purified Water, USP. If the company specifies a water of compendial quality in an application, the water should meet the standards given in the compendium.

Principles similar to those discussed above for purified water apply to water for injection (WFI) used in sterile and pyrogen-free BPC processing. The WFI system must be monitored for microorganisms, and the validation data and reports of monitoring should be reviewed as is required for the production of finished dosage forms.

Most purified and WFI water systems, including RO and UF systems, have the potential for the development of endotoxins. If the final BPC is purported to be pyrogen free or sterile, or if it will be used in preparing parenteral products, routine endotoxin testing of the process water — preferably by the LAL method — is indicated. Endpoint testing alone is not adequate, however, and companies should validate the system to control endotoxin development.

Microbial limits for nonsterile material. Up to now, the agency has not provided formal guidance concerning appropriate microbial limits for nonsterile BPCs. *USP* Chapter ⟨1111⟩ has suggested, however, that certain categories of products, such as natural plant, animal, and some mineral materials, should be tested routinely for total counts and specified indicator organisms. In addition, definitive limits are incorporated into specific monographs for some BPCs based largely on the potential for the specified organisms to constitute a hazard in the finished product. Whether or not there are specific compendial microbial limits for a BPC, it is important for manufacturers to apply strict GMPs to minimize bioburden.

In the July–August 1992 *Pharmaceutical Forum*, USP proposed a major revision of Chapter ⟨1111⟩ to include guidelines for microbial count limits for raw ingredients, excipients, and drug substances. The proposal defines total bacterial counts at Microbial Alert and Action Levels on the basis of the material's origin — natural or synthetic — and whether it can be decontaminated. The action levels are five times those of the alert levels. The alert level total bacterial counts are proposed at 200, 1000, and 20/g for synthetic, natural, and materials that can be decontaminated, respectively. The value indicated (20) is for material following decontamination. A scheme for second-tier testing is also proposed for the presence of yeast and mold — with counts specified — and absence of specified indicator organisms where total bacterial counts fall between the alert and action levels.

Sterile and pyrogen-free material. The handling of sterile and pyrogen-free BPCs during processing is critical. Postdepyrogenation exposure of BPCs to water must use WFI-quality water or better. For pyrogen-free material, the final processing environment should be well controlled. If wet material is undergoing final handling, the air should be free of gram-negative organisms. This usually requires the use of HEPA filters. Any manipulation of sterile BPCs poststerilization must be performed as an aseptic process, including the use of Class 100 air and other aseptic controls. If the sterile BPC will be used without further processing by the dosage form producer, except vial/ampul filling, then CGMP regulations for finished dosage forms apply to the sterilization process and subsequent handling.

Pyrogen-free BPCs have been known to fit into several categories:

- BPCs labeled as being pyrogen free or with specifications for being pyrogen free. The BPC producer must ensure that these conform to specifications.
- BPCs not specified by the BPC producer as pyrogen free but intended as such via an NDA/ANDA commitment. This is a component specification. It is the ultimate responsibility of the dosage form manufacturer to ensure that the BPC is pyrogen free.

- The DMF declares the BPC to be pyrogen free. This is a commitment to the NDA/ANDA by incorporation and is considered a product specification. The DMF is the responsibility of the bulk manufacturer.

Packaging and labeling. Producers should label BPC containers with the same care and with controls similar to those exercised over finished pharmaceuticals. Untrained and uncontrolled warehouse personnel should definitely not be used. If the labels are computer generated, that process should be validated. Although the mislabeling of a BPC is unlikely to have the same potential for patient harm as the mislabeling of a finished dosage form, it can damage a company's reputation and thus surely justifies a final control check of all labeled containers.

Manufacturing records. The manufacturing process for a BPC should follow approved written procedures and should be documented. FDA normally expects more detailed documentation in the final phases of the process than in earlier stages prior to the isolation or synthesis of the BPC or its key intermediate. For some operations when there is a continual blending of recycled material with new material, it usually is not practicable to trace back to all the raw or starting materials used to produce the finished BPC. But for most other operations it should be possible to do such a tracing using the manufacturing batch records. Unlike most workers in finished dosage form plants, chemical operators often have to perform a series of operations without stopping or risk compromising the processing step. They cannot stop to make an entry on a processing record every time they turn a valve or push a button. In these situations, the operators commonly stop after the last operation in the series and make the entries at that time. The agency has no objection to this. In most cases, these routine processing operations are unwitnessed. But, typically, the operator's supervisor signs every page of the record, signifying that the process was carried out under the supervisor's general, if not immediate, supervision. This kind of signature system is not objectionable to FDA if it occurs at the time the operator's shift comes to an end and not at some later date. Any in-process strip chart records for significant processing steps should be preserved as part of the manufacturing record and reviewed along with other records before release.

GMP coverage. GMP regulations in title 21 part 211 refer to finished dosage forms. They are used, however, as a general guide where applicable to BPC processing operations. FDA has provided extensive GMP coverage during its inspections of BPC manufacturing operations for at least the last 20 years. That coverage addressed in one form or another most of the control issues that are now being raised through the application of validation concepts to the bulk industry. The agency has always been concerned about a company's control and understanding of the manufacturing process. FDA has never depended solely on finished product testing for its evaluation of a BPC process, nor has it ignored impurity profiles in the absence of formal validation coverage. Inspections continue to cover the basic GMP concepts as in the past. For FDA, validation is an inherent part of GMPs, but it isn't the only part. Validation provides solid evidence that a company understands a process and can carry it out successfully; it doesn't guarantee it. Although validation concepts are of great importance in ensuring the adequacy of manufacturing operations, validation coverage will not be the sole concern of investigators during BPC inspections.

Facilities for final processing. In the past, too many BPC final processing operations were carried out in facilities that had a marked resemblance to an automotive garage or worse. Investigators have inspected integrated manufacturers who took the BPCs from these poor conditions into a dosage form plant where extreme precautions were taken to protect the BPC from contamination. Typically in such situations, the BPC was produced in an industrial chemical setting and delivered to the pharmaceutical division of the corporation. These differences in standards should not be tolerated because any contamination at this stage of the process is unlikely to be removed. If undetected, the contamination will probably be incorporated in the finished dosage form. These final steps, which commonly consist of crystallization, centrifugation, drying, blending, milling, sifting, and packaging, should be carried out in a clean environment with stringent standards to prevent contamination with extraneous substances or cross-contamination with another BPC. In short, the standards for the facility used for finishing BPCs should equal those of an acceptable dosage form plant. This should not be confused with earlier processing in an enclosed system where such environmental control is unnecessary and in many cases may be located outdoors.

CALIBRATION CONTROLS

FDA is paying closer attention to calibration practices during drug inspections, including BPC inspections. The agency believes that without calibration of processing equipment instrumentation and laboratory instruments, a pharmaceutical company is not in control of its operations and therefore is not in compliance. Furthermore, without a formal system of calibration controls, a company cannot adequately validate its manufacturing process. (Any instruments used in the validation effort must, themselves, be validated.) As a consequence, it risks disapproval of its NDA/ANDAs.

Investigators expect to find a rational basis for a calibration schedule — expressed in elapsed calendar time or use time — for all equipment. The working standards used should ultimately be traceable to a national standards-setting organization. Complete and accurate documentation should be maintained, including the follow-up action taken when instrumentation is found to be out of specification. If recalibration is required, FDA expects the company to recalibrate it rather than to simply apply a correction factor to operator or technician readings.

The agency strongly suggests that calibration programs be subjected to internal audits to ensure that calibration schedules are being kept and to ensure that documentation is accurate and complete. The same attention should be paid to these records as to laboratory analytical records. We sometimes find that such is not the case.

LABORATORY OPERATIONS

From FDA's standpoint, nothing is more important in a BPC plant than the operations of the analytical control laboratory. In fact, in some respects, they are more important for BPCs than they are for finished dosage forms. Typically, the finished dosage form manufacturer subjects only incoming lots of active ingredient BPCs to routine compendial testing. In many, if not most, cases this testing is inadequate to detect the full range of possible contaminants that may be present. Any contaminant in the BPC, in almost all cases, will not be removed by the manufacturing process and will be incorporated in the finished dosage form. These contaminants vary from process to process and from manufacturer to manufacturer. They could include

closely related foreign compounds produced by the synthesis, unreacted starting materials, intermediates, stereoisomers, residual solvents, cross-contaminants, microbial contamination, and debris sloughed off processing equipment, usually seen as black specks.

The manufacturer's laboratory is in the best position to know what contaminants are or may be present and to ensure that they do not reach the finished dosage form producer at excessive levels. If they do reach the dosage form producer, they may remain undetected.

Impurity profiles. A manufacturing process cannot be validated nor can changes in that process be evaluated without an awareness of the impurity profile for the product. Impurities and impurity profiles are discussed in the current *USP* at some length. *USP* notes that the analytical tests laid out in the individual monographs cannot anticipate all the possible impurities resulting from the different processes used by various manufacturers to produce the same product. BPC companies should have impurity profile programs and be prepared to discuss them in NDA/ANDA applications or with investigators. The sensitivity and resolution of the analytical methods used are areas that will be covered. For example, if you are not using capillary columns for gas chromatography methods, investigators may want to know why not. Other subjects for discussion will be how limits are established for individual impurities and total impurities and to what degree they have been characterized. Questions concerning their toxicity may very well be asked either by a reviewing chemist at CDER or by a field investigator.

In-process analytical controls. In-process analyses may be performed by either the production department or the quality control laboratory. FDA does not insist that in-process analytical checks be done by the quality control laboratory. But they do expect that these tests will be performed by competent individuals using adequate analytical instruments and that the testing will be documented. In some processes, impurities that could carry over to the final product are checked for during in-process sampling but not in the finished BPC. In these instances, it may be more appropriate for the quality control laboratory to do the testing. For processes that proceed on a campaign basis producing lot after lot of the same intermediate, and then the next intermediate, it also may be more appropriate for the intermediates to undergo testing by the control laboratory before they are released for further processing. Regardless of which group conducts testing, the quality control unit must be responsible for releasing — or rejecting — the material for subsequent processing after each significant step in the process.

Available instrumentation and methodology. A basic part of every investigator's inspection of a BPC operation is to determine whether the laboratory has all the equipment needed to do the testing specified in the company's NDA/ANDA/DMF or the *USP* monograph for the product. (On some occasions, an FDA chemist may accompany the investigator, primarily to evaluate the firm's methodology and technique.) For *USP* tests, the agency does not require that the company validate the methodology, as long as the prescribed analytical procedure is followed. In these instances, however, the company must do related testing specified by *USP*, e.g., system suitability testing in the case of HPLC methods. In general, because BPCs are pure substances, validation of the analytical methods does not pose the same kind of problem as it does for finished dosage forms. A dosage form product often contains several substances in addition to

the active ingredient, and some of these may interfere with the assay. These additional ingredients vary from manufacturer to manufacturer. Consequently, compendial or NDA/ANDA assays may not always work for all dosage form producers producing the same drug product. Generally, this is not a problem for BPC products.

Stability studies. With few exceptions, expiration dates are not now considered to be a general requirement for all BPCs. Thus, the absence of an expiration date may not be objectionable. The chief exception is antibiotic BPCs, for which expiration dates are required by antibiotics regulations.

Most BPC manufacturers conduct stability testing programs for their products; however, such programs may be less comprehensive than the programs now required for finished pharmaceuticals.

Undetected changes in raw materials specifications or subtle changes in manufacturing procedures may affect the stability of BPCs. This, and the generally widespread existence of stability testing programs, makes it reasonable to require such programs for BPCs. In this regard, the stability testing program should be formalized in writing and should include samples from the first three commercial-size batches; thereafter, a minimum of one batch a year, if there is one, should be entered in the program. BPCs are typically stored in small bags made of the same material used to line the bulk drums. These bags, representing different batches or lots, are stored in a drum similar or identical to the ones actually used for marketing. Such samples may be stored in glass or other suitable containers only if there are data developed by the company or others to show that results are comparable. The samples should be stored under conditions specified on the label for the marketed BPC. As is true for finished dosage form testing, the test method must be stability indicating — i.e., able to distinguish between degradation products and the BPC itself. In general, stability problems are fewer for BPCs than for finished dosage forms containing multiple ingredients.

Documentation. To maintain credibility, a laboratory must be able to produce the original laboratory data upon which reports of analyses are based. These data include the original notes and calculations of the analyst, original IR and UV spectra strip charts, microprocessor printouts, chromatographic strip charts, and so forth. More than ever, investigators scrutinize these documents for irregularities and signs of falsification, which are sometimes the work of an individual analyst or technician. But laboratory directors and higher management have also been implicated in past incidents. The systematic falsification of records will result in the unacceptability of a company as a supplier. If the company is a domestic manufacturer, it is likely that regulatory action will be taken.

Standards. A laboratory should have a system that ensures that it uses the current official compendial standard for a given product. It is permissible to use an in-house or working standard for routine analytical work as long as it has been properly equilibrated against the current official standard. Investigators usually pay close attention to this aspect of laboratory operations.

Internal quality assurance audits. Periodic internal audits of laboratory operations are the best protection against unauthorized departures from prescribed procedures. Without an audit program, these departures — which may include the falsification of records — pose a threat to the company. These departures may also result in out-of-specification products that must be recalled. If they are uncovered by FDA during an inspection, they may result in the withholding of application approval or other regulatory sanctions. FDA believes that to be most effective, the internal audit team should include members who are not from the quality control laboratory but who are knowledgeable about laboratory operations.

SUMMARY

This article has defined a number of terms applicable to BPCs and explained how BPCs are regulated under the Food, Drug, and Cosmetic Act. It has also described FDA's inspectional programs, including applicable guidance documents.

In addition to the routine GMP coverage the agency has long provided in its BPC inspections, it has increased emphasis on the coverage of validation issues. This includes validation of manufacturing processes, including equipment cleaning, computerized processing, blending, and water systems. It has also stressed the importance of adequate, properly documented analytical controls and laboratory operations during such inspections. These factors are even more important today because a manufacturing process cannot be validated nor can changes to that process be evaluated without adequate analytical controls — including a knowledge of the impurity profile for the BPC.

FDA expects all BPC producers to be actively engaged in a validation program for their products; however, because the agency recognizes that not all processes for all BPCs can be validated simultaneously, it has allowed some leeway in completing such validation if the company has an adequate program in place, including reasonable milestones. ■

FDA Regulation of Bulk Pharmaceutical Chemicals — An Industrial Commentary: Part I

F. Demmer, N.C. Franklin,* S. Geussenhainer, H. Häusler, R. Kirrstetter, C. Rufer, E. Walter, and F. Zimmermann

The publication of the article "FDA Regulation of Bulk Pharmaceutical Chemical Production" (1) spurred a number of German companies to form an ad-hoc committee to coordinate the views of a representative section of the German bulk-pharmaceutical industry. This committee evaluated the article and compared its guidelines to current bulk pharmaceutical chemical (BPC) industrial practice. The results of these discussions, and the committee's proposals, are presented here. This article was previously published in *Pharmaceutical Technology Europe* 6 (8), 16–23 (1994).

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During the last two years, there has been a considerable increase in US Food and Drug Administration (FDA) activity connected with bulk pharmaceutical chemical (BPC) production. This has been reflected in a number of publications and guides to the subject. To some members of the BPC industry, this FDA interest may be new. However, to companies with a long tradition in the manufacture of BPCs *and* drug products, such an interest is not new. Many such companies have a history of FDA inspections of their manufacturing facilities going back some 20 years or more. The publication of an article — "FDA Regulation of Bulk Pharmaceutical Chemicals" by Barr et al. (1) — spurred a number of German BPC/drug companies to form a committee and present the viewpoint of a sizeable part of the German bulk-pharmaceutical industry. This paper is the result.

The article by Barr et al. is a very timely, welcome, and pragmatic addition to the views of FDA on this topic. It is especially welcome because it combines the views of headquarters staff from the Policy and Guidance Branch of FDA with the views of FDA field practice and is not just the opinion of a single field office or individual investigator. Our commentary will follow the structure of Barr et al. and will cross reference passages where necessary.

A large majority of the BPCs used in the United States are manufactured abroad. A clear interpretation of FDA policy is, therefore, very welcome. Usually, the only contact a non-US firm has with FDA is when an investigator arrives to conduct an inspection. In the past, FDA used investigators who were experienced in the inspection of BPC facilities. However, the recent rapid increase in the number of non-US inspections has resulted in some inspections being carried out by investigators with much less experience of BPC manufacture. During some non-US inspections, this has led to case studies from drug manufacturing being inappropriately applied to the manufacture of BPCs.

In many instances, Barr et al. corrects these views and recognizes that *there are essential differences between the manufacture of BPCs and the manufacture of drug products*. For example, the opening paragraph of Barr et al. states:

> Purification is the ultimate objective and is accomplished by various chemical, physical, and biological steps (1).

This, in a nutshell, is the essential difference between *processes* used in the manufacture of BPCs and *processes* used in the manufacture of drug products. With very few exceptions, a chemical or physical impurity introduced into

RAW MATERIALS

Quarantine. Barr et al. contains the timely comment that the treatment of raw materials will vary with the circumstances in which they are used. The article continues with

> ...such systems will involve some type of temporary quarantine system based on physical separation and status identification... (1).

Unlike drug-product manufacturers, BPC manufacturers do not always have "separate" quarantine areas or systems. It is, therefore, not unusual to find deliveries of raw materials made directly to the manufacturing plant, and stored in fairly close proximity to the future point of use. This is particularly true in the early stages of some syntheses or extractions/fermentations that are carried out in very "chemical" environments due to the nature of the reaction involved.

"Temporary quarantine" in such cases may consist solely of a temporary indication of status (linked chains on poles surrounding the 40-or-so pallets) with a shield saying *in quarantine*. There would be no indication of the status of individual sacks or pallets. Release of such a batch may consist solely of replacing the shield with another saying *released*.

Most serious BPC producers would consider that temporary quarantine of this kind could get out of control. They would, therefore, want to supplement the system with some type of status label — perhaps saying *released* — that appeared at least on the lowest level of the goods on the pallet. However, if the status (quarantine or released) appears solely on a computer screen, and the material management system prevents the call up of a raw material for use in the process whilst it is still in quarantine, then such labelling is generally unnecessary. In such situations, there may be no difference in physical location between raw materials in quarantine and those that are released. This is very often true with flammable materials stored in drums. Such materials must be stored in the open (due to local or national safety regulations) where labels can easily be lost.

Use of lot numbers. The reasonable requirement that there should be a "chain of documentation" implies that it should be possible to trace back the steps of the process to the raw materials used. It is also practice, in many cases, to trace back to the lot of raw material used. However, this is not always possible, for example, where raw materials are stored in silos or tank farms.

It is, however, not unreasonable to expect a BPC manufacturer to *check raw materials on receipt* for condition, correct labelling and identity, and assigned lot numbers, *and to record this information.*

Quality of the raw material. It is quite usual to purchase raw materials with lower levels of purity than those specified in pharmacopeias. Assays of the order of 95 % or even less are not unusual. Sometimes, neither the supplier nor the user knows much about what constitutes the remaining 5 %. This practice is quite acceptable if there is *evidence* that such material will result in a BPC of the required quality. Bearing in mind the core statement

> Purification is the ultimate objective (1)

process development (or, for older products, process history) will have shown that the process is capable of eliminating these unknown impurities, and this is the type of evidence which is acceptable.

FDA states that there is no need to inform FDA when a supplier of a raw material is changed provided the specification is still met (7). In the light of the above paragraph, this statement is a pragmatic acceptance of the reality of BPC production. It recognizes that if the change in supplier has a negative influence upon the process, then either the specification for the raw material will need to be

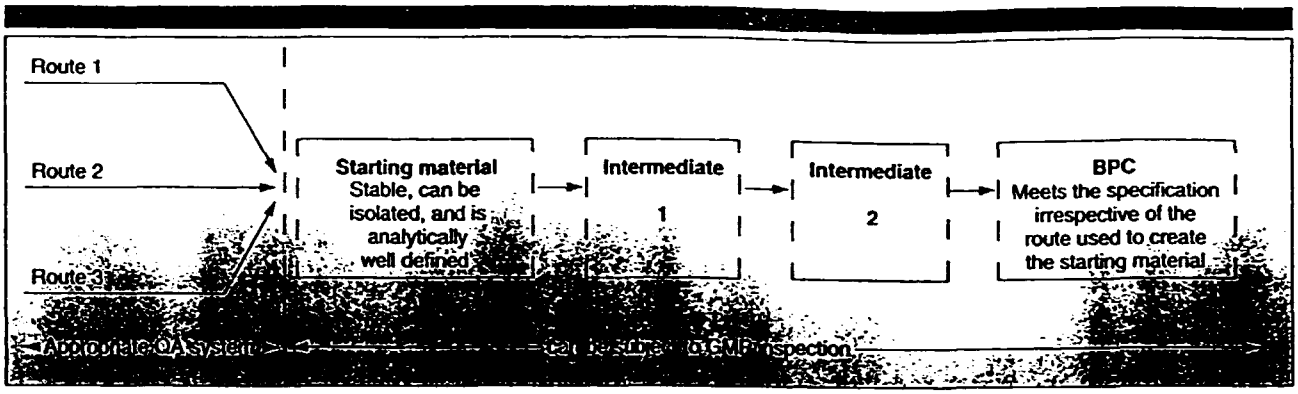

Figure 1: *Defining the applicability of GMP inspection of a BPC.*

can expand the processes subjected to cGMP well beyond that which is scientifically meaningful. According to this definition, the synthesis of ampicillin would start with phenyl glycine, because the D(+) part of the ampicillin molecule is introduced from d(+) phenyl glycine. Likewise, in a twelve-step steroid synthesis, the extraction of diosgenin in the first step would be the key intermediate production step.

Analytical techniques are now so well developed that it is possible to specify very accurately a "key intermediate" (taking into account stereochemistry and optical activity) without even knowing how it was produced. Such a "key intermediate" can be designated as a "starting material", which allows the BPC synthesis to be shortened by starting with a very tightly specified "starting material".

Regrettably, it is still said that this concept is just end-product testing, because it depends upon the analytical testing of a product. Such comments indicate a failure to recognize the capabilities of modern analytical methods to accurately specify such a key intermediate. In addition, such comments fail to recognize that the validation of BPC manufacture would be impossible without such modern analytical methodology because it would be impossible to determine whether impurities from the process had been removed from the BPC.

FDA itself increasingly recognizes the value of such modern analytical techniques, and its "Forensic Samples Program", relying as it does on what some dismiss as end-product testing, is so accurate that it is able to detect the source of a product without, at the same time, having paper evidence for the route of synthesis. Thus, to belittle the characterization of a product because it relies exclusively on well defined analytical testing is an insufficient reason for extending inspectional coverage to the *start* of the synthesis of a key intermediate. Slavish adherence to the Guideline's definition of a key intermediate given above results in subjecting all seventeen steps of a BPC synthesis to cGMP, whilst in the same plant only the last three steps of another synthesis fall under cGMP because of the different points where the optical centre is introduced.

Theoretically, in the case of a new drug substance, this problem should be resolved at an early stage. In the Guidelines previously cited, it is stated:

> Generally the decision about what is the starting material has been reached by agreement between the applicant and the FDA chemist before submission of the NDA (10).

Regrettably, FDA chemists themselves place different interpretations on what is a "starting material" even when the same process is involved. The time has therefore come to reassess which part of a BPC synthesis falls under cGMP and separate the natural curiosity of the reviewing chemist as to the full synthetic route from the legal requirement to apply cGMP to that part of the synthesis where it is essential.

In the light of the pragmatism already exhibited in most of Barr et al., this committee believes that the Policy and Guidance Branch should adopt the following policy statement:

> The investigators will check for compliance with cGMP requirements from that point onwards in the synthesis where analytically well-defined, isolatable, and stable starting materials are introduced into the synthesis, and where the analytical specification of these starting materials is alone sufficient to ensure the quality of the BPC, independent of the method used to obtain the starting material. This point is where lack of adequate control of procedures and products could result in the manufacture of a product not meeting the defined specifications or re-control period. Such investigations will start no later than the step(s) producing the final intermediate.

Such a policy statement covers both non-synthetic and synthetic BPCs. For non-synthetic BPCs, it may be necessary to start with the plant, the animal organ, or the cell, if these are the last materials which satisfy the isolated and stable requirements.

In the case of synthetic BPCs, one could easily start quite a way down the synthetic route. This would permit a BPC manufacturer to purchase even a custom-made starting material in which certain "essential molecular characteristics" are already present because such a starting material would need to be specified in detail, examples being:

- optical purity
- limits on known (and even unknown) impurities
- manufactured under an appropriate quality assurance (QA) system as part of the previous "Suppliers Qualification Programme".

Any subsequent manufacturing would be conducted under cGMP. This approach would strengthen the working relationship between the supplier and the BPC manufacturer. The above policy statement would also provide much clearer guidance to investigators and manufacturers as to where to apply cGMP.

Barr et al. states that

> during most inspections, at least some GMP coverage will be given to earlier steps in the BPC manufacturing process. ...Although usually it is neither feasible nor required to apply rigid controls during early processing steps, the documentation system for such steps must provide a chain of documentation but need not necessarily be as comprehensive as in later parts of the process (1).

Unfortunately, this statement has provoked considerable fruitless discussion between the hawks and the doves as to what counts as "some GMP coverage" and how comprehensive the documentation needs to be in the very early stage of what is essentially the manufacture of a fine chemical in the widest sense of the term.

Our alternative wording

- is in good agreement with the philosophy of the above statement
- but defines more clearly where GMP coverage should begin
- and leaves it to the purchaser of the starting material to agree with the supplie

FDA Regulation of Bulk Pharmaceutical Chemicals — An Industrial Commentary: Part II

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The publication of the article "FDA Regulation of Bulk Pharmaceutical Chemical Production" (1) spurred a number of German companies to form an ad hoc committee to coordinate the views of a representative section of the German bulk-pharmaceutical industry. This committee evaluated the article and compared its guidelines to current bulk pharmaceutical chemical (BPC) industrial practice. This installment continues with the results of these discussions, and the committee's proposals. Part I appeared in the October 1994 issue of *Pharm. Technol.* This article was previously published in *Pharmaceutical Technology Europe* 6 (9), 34–44 (1994).

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Last month, the authors began their evaluation of the article "FDA Regulation of Bulk Pharmaceutical Chemical Production" (1) by Barr et al. They conclude their discussion this month.

Change control. Barr et al. states that, irrespective of how validation was carried out,

> the process does not automatically remain permanently validated (1).

This is a true statement and worth repeating. However, care needs to be taken in requiring revalidation. Barr et al. states that

> changes ... need to be evaluated through a formal "change control" procedure involving a careful evaluation of changes by qualified individuals (1)

This statement is made, not so much because it is specific to GMP, but because it is a basic element of all QA systems. Any change to a validated process needs to be evaluated not only to determine the potential cost savings, environmental effects, or need to revise a drug master file (DMF) or NDA, but also to determine the need to revalidate, and how extensive such a revalidation should be. A recent article by an ad hoc subcommittee of the PMA QC Section's BPC Committee also covers the issues of revalidation (11), and the statement in the article by the PMA QC Section's BPC Committee that

> Sound scientific judgement should determine what, if any, validation studies are required to justify a change in a validated process

and the later statement

> careful evaluation of the batch manufactured with the changes is sufficient

indicated the thinking of the PMA subcommittee members.

However, our committee believes that, although such concurrent validation is acceptable in most cases, this "careful evaluation" should not only include intensive analytical investigation of the initial batch, but normally also the subsequent batch or batches, for example the next two batches.

Having outlined the need for a change control program, which FDA investigators should verify, Barr et al. unfortunately do not give guidance to investigators about checking the effectiveness of the change control programme. Obviously, an investigation into whether changes in the synthetic route of a

validated when three sequential runs have been successfully completed). Such a cleaning validation could therefore extend over two or more years. Additionally, it is quite common that BPC producers verify the results of their cleaning operations by a suitable analytical method, and this is done independently of the documented validation of the cleaning process (there being a clear parallel here between still carrying out an analysis of a batch of a BPC even if this latter was made by a validated process).

Under these circumstances, a clear statement of policy from the Policy and Guidance Branch of FDA's Center for Drug Evaluation and Research (CDER) on the regulation of cleaning for BPCs could help to remove some misinterpretations both from the industry and the regulatory side. Such a statement could be

> The determination of whether the cleaning used in a BPC plant is adequate will be based either on the results of a formal and documented validated cleaning procedure which takes into account the quantity of material removed through cleaning, and risks associated with the quantity found, or on the results of other documented cleaning procedures which have been shown to remove potential residues down to a level which is acceptable. The justification for the fixing of such a level should be determined. Routinely verifying the effectiveness of such validated cleaning procedure is acceptable.

Such a policy would place the burden on a BPC manufacturer to have available evidence that what was, or had in the past been done, was effective in reducing traces of previous products in the equipment down to an acceptable level, without prescribing whether a specific analytical technique should be used, whether specific cleaning procedures were necessary, or whether one should just be looking for the previous "active."

Validation of computerized processes. The short paragraph on this topic in Barr et al. (1) recognizes the complexity of the issue, and provides a pragmatic solution. The expenditure on a data collection system in a BPC plant must be justified, and if the system is not working correctly the analytical department will very rapidly have results to prove this. Thus, the "five main areas for consideration" laid out by Barr et al. (1) remind the serious BPC producer of things he already should be aware of.

"Validation" of blending. This is placed in quotation marks, not because this ad hoc committee questions Barr et al.'s belief in the need for such work, but because there is a call here to apply a modern concept validation to an old problem homogeneity. Historically, pressure has always been placed on a BPC manufacturer to produce as large a lot size as possible. In the past this has resulted

free. This commitment has been entered into by the drug product manufacturer, and the BPC producer cannot be held to such claims unless they were made specifically with his knowledge or authorization. Care obviously needs to be taken when a US agent of a foreign producer makes commitments for an NDA/abbreviated new drug application (ANDA) without the knowledge of the BPC wing of the foreign producer.

Manufacturing records. Even in the early part of a BPC process, where possibly just intermediates are produced, it is good practice to have written instructions available for the operators, and to record that various prescribed parameters, (temperature, time, pH, etc.) were attained. However, as Barr et al. (1) so rightly point out, it is not common practice either to confirm every individual activity, or to have routine processing operations witnessed, even at a very late stage or even the final stages of BPC manufacture. Thus, this committee welcomes the position of the Policy and Compliance Branch that the "grouping" of activities under one sign-off and the indication of who "generally supervised" the operator are acceptable practices in the recording of BPC manufacturing records. This policy recognizes that, in general, BPC manufacture will not proceed if steps are left out. For example, a reaction will not take place if a starting material is not added, but in drug product manufacture, a missing step or a missing ingredient could very easily be overlooked. There is, therefore, no need for the same level of supervision as in the drug product industry.

Facilities for final processing. The principle being established here is the "suitability" of the facilities for the operations being conducted therein. But what is "suitable"? Barr et al. (1) somewhat light-heartedly point out that some facilities resemble an automotive garage (which might be a compliment as there are some very clean garages!); but, what is truly meant by this comment is that some BPC operators have not adequately considered the potential for contamination of the final product after the last purification step. It is obviously not cGMP to remove particulate matter, etc., via a fine filter before the crystallization stage and then expose the crystallized solid product to an open environment full of foreign particles. However, a "pharmaceutical environment" is not the only way of solving this problem. Totally closed processing from that step in the process where chance foreign contamination will no longer be removed is a modern and acceptable solution to the problem of protecting the product from contamination.

Thus, this committee would suggest that the section on "Facilities for final processing" in Barr et al. (1) be supplemented by the following statement.

> Processing of BPCs, from that stage in the process where chance contamination will not be removed, should preferably be carried out in closed systems. Where this is not possible, and the BPC is processed in the open during the final steps, such processing should be conducted in an environment suitable for preventing contamination.

Such a statement continues the logic of protecting the product during early stages of manufacture by using closed systems, and recognizes that equipment such as dryers, centrifuges, dryers, blenders and mills, or sieves are now available as totally enclosed systems, and that it is not even necessary to disassemble these for cleaning. Thus, after the last filtration stage, the product may "no longer see the light of day" until it is used in the pharmaceutical plant. The statement also recognizes that not every plant is fitted with such totally enclosed equipment, and thus where "open product" operations are still carried out, (emptying of a centrifuge, tray drying, combining sub-batches in a blender, etc.) these need to be conducted in an environment which will prevent chance contamination, be it foreign matter or cross contamination.

CALIBRATION

Very little needs to be said about the requirement to calibrate *certain* instruments used in BPC manufacture and control, though this does not mean that *every instrument* in a BPC plant needs to be calibrated. In a typical BPC plant there is quite a bit of instrumentation which is not critical for the process (e.g., a clock used to watch a processing time). Thus, *critical* instruments in a BPC process should be defined and then inspectors can determine whether these are subjected to a calibration programme. Such a programme will then include such topics as

- Are the *critical* instruments in the programme identified?
- Are acceptance limits available?
- Is the method of calibration laid down?
- Is the frequency of recalibration laid down?
- Are records of such calibration available?

LABORATORY OPERATIONS

Barr et al. (1) quite rightly point out the importance of "the analytical control laboratory" (perhaps they intentionally chose this wording rather than "the quality control laboratory" as it places more emphasis on analysis). Certainly, it is not possible to manufacture or validate a BPC without accurate analytical support. Such a laboratory should not only be capable of conducting the "normal" pharmacopeia testing, but also routinely

specified recontrol periods. Other batches should be added to the programme if these were manufactured by a process which was not covered by the process originally submitted in the NDA/ANDA/NADA.

Internal QA audits (self inspections). This section is perhaps a little new for some BPC producers because, in the past, FDA has not particularly emphasized the internal auditing function. However, it is increasingly becoming an international practice, as seen by the European Union or the World Health Organization GMPs, to require that the GMP systems within a company be audited for compliance with the established system standards. Barr et al. points out that

> Periodic internal audits of laboratory operations are the best protection against unauthorized departures from prescribed procedures. (1)

However, this is not the only advantage of such audits, because potential QA *system problems* can also be detected before they get out of hand.

SUMMARY

This ad hoc committee of representatives from eight different major German BPC manufacturers has carefully analysed the recent paper by Barr et al. (1) and compared this with current BPC industrial practice. In most cases, Barr et al. has struck the right balance between what is cGMP in BPC manufacture and what the authorities expect cGMP to be. Where this balance has not been attained, this ad hoc committee has proposed wording which reflects cGMP in a major European country and which simultaneously recognizes that the customer has certain fundamental expectations from a product which is designed to restore health. The ad hoc committee would welcome the publication of specific GMPs for BPCs, and the suggestions made in this article are a contribution to this end.

ACKNOWLEDGMENTS

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We also appreciate the valuable comments made by David Barr, Deputy Director of FDA's Office of Compliance, during the final drafting process.

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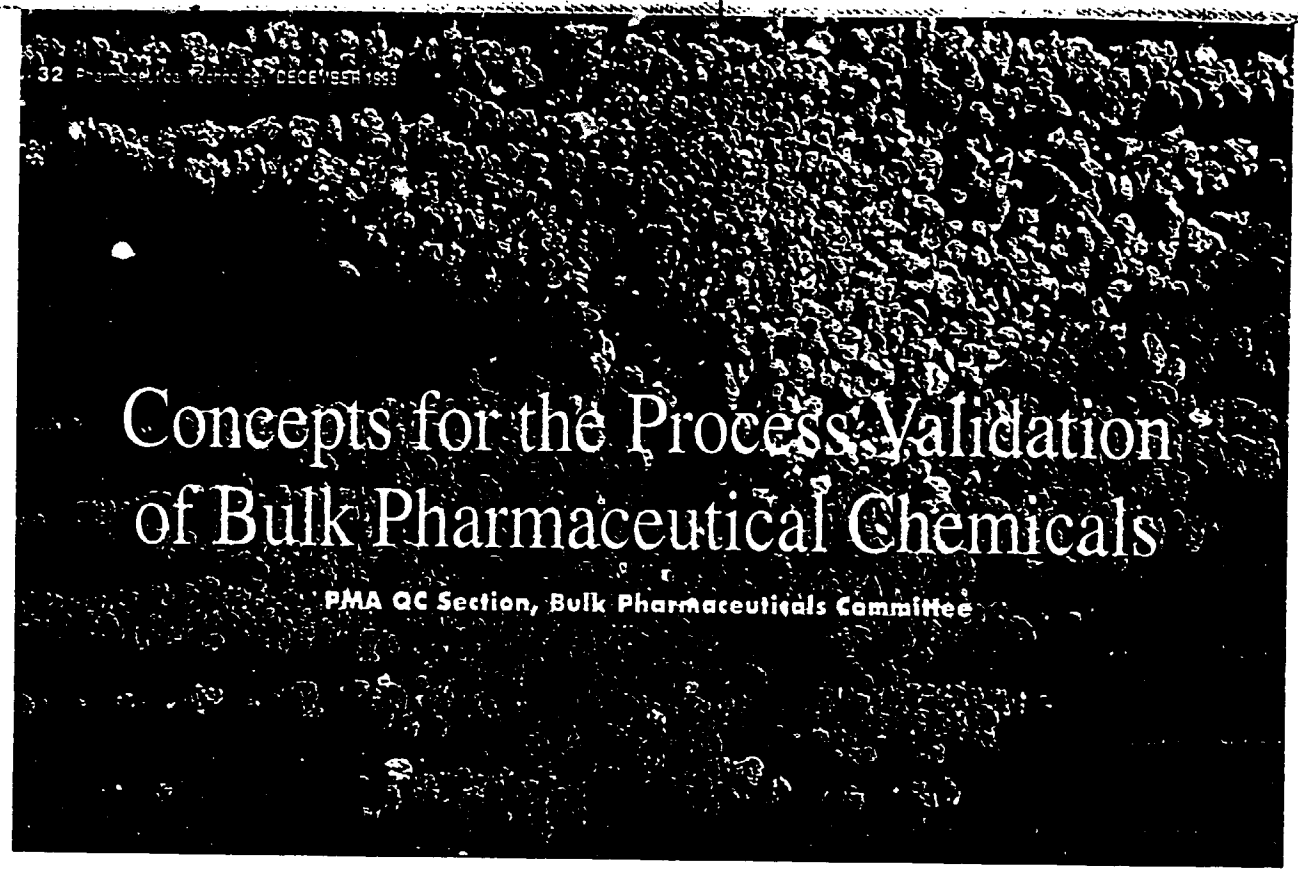

Concepts for the Process Validation of Bulk Pharmaceutical Chemicals

PMA QC Section, Bulk Pharmaceuticals Committee

MIKE DEAN

Since the late 1980s, FDA has increased its attention to and has expanded its inspectional review of bulk pharmaceutical chemicals (BPCs). The agency's focus has been attributed to episodes in which alleged process control failures have resulted in recalled products. There has also been increased awareness that BPC quality plays a potentially significant role in the performance of finished dosage forms. FDA now expects more of the finished dosage form CGMP requirements to be applicable to BPC manufacturing, and it is applying these expectations to all BPC areas, including development, manufacturing, control, and distribution. Among these expectations is extension of the validation concept to bulk pharmaceutical processes. In 1991, FDA issued an update to "FDA Guide to Inspection of Bulk Pharmaceutical Chemicals." The Pharmaceutical Manufacturers Association (PMA) Quality Control Section's Bulk Pharmaceuticals Committee concluded that developing an article that describes BPC validation would be valuable as a supplement to the FDA guide. The committee established an ad hoc subcommittee to develop a concept document for the process validation of BPCs. This article is intended to define the application of validation principles to BPC processes.

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This concept paper is intended to assist bulk manufacturers in the validation of processes for the production of bulk pharmaceutical chemicals (BPCs). It does not include validation of sterilization processes.

A well-controlled process for the production of a BPC may provide a number of benefits, including reduction of rejections, reworks, and scrap; improvement of yields; reduction in process time and process cycle; improvement in product quality; reduction of in-process and/or finished goods testing; increased ease of process automation; greater ability for worldwide standardization; easier investigations of process problems; and enhancement of employee quality awareness. Process validation can contribute to establishing and maintaining a well-controlled process.

The validation of any process should take into account the fundamentals of the process and the resulting product. The characteristics of processes for the production of BPCs have been described in PMA's "Guidelines for the Production, Packing, Repacking, or Holding of Bulk Pharmaceutical Chemicals" (1):

> There are fundamental distinctions between the production of bulk pharmaceutical chemicals and the formulation of drug products. Bulk pharmaceutical chemicals usually are made by chemical synthesis, by processes involving fermentation, or by recovery from natural materials. On the other hand, drug products are for the most part the result of formulation of materials of established high quality.
>
> In the production of bulk pharmaceutical chemicals, purification is effected by various chemical and physical processing steps, and the quality is confirmed by chemical and/or biological and physical tests on the bulk pharmaceutical chemical. In almost every case, the starting materials undergo some kind of substantial and significant chemical change. Impurities and contaminants which may be present in the raw materials usually are removed by various treatments in the production process, such as distillation, crystallization, precipitation, and filtration.

Although principles of process validation are universal, the differences between the processes used to produce BPCs and those used to produce drug products may require differences in application. This concept paper is intended to describe a method and provide a discussion of the concepts by which validation of BPC processes may be accomplished. It is not intended to be all-inclusive; there may be equally appropriate alternatives to the examples given, particularly in the case of processes with unusual characteristics, such as an unusually large or small scale, infrequently produced product, processes producing products of unusually high purity, or those utilizing unusual methods or equipment. Because of the unusual nature of some processes, this concept paper may be inappropriate, in which case appropriate deviations should be employed. Good scientific judgment is necessary to interpret and apply these concepts.

A good working knowledge of the process is essential to process validation. This concept paper presumes that a well-defined quality assurance program has been effectively implemented for the production processes. Such a program would include personnel training; facility and equipment maintenance; validated cleaning procedures; control of process materials, packaging, and labeling; control testing and inspection operations; and documentation of operations. Although it is not part of process validation, a quality assurance program is critical for successful process validation.

Process validation and optimization of a BPC are activities that span the life of the BPC process. These activities frequently start with data from process development at the research or pilot plant scale when critical steps and control ranges are identified. BPC characteristics are commonly identified during process development and production of supplies for clinical investigations. Scale-up activities then generate data to confirm or refine earlier work. Production scale batches generally provide the data to show consistency of the process. A change control system provides the mechanisms for ongoing process optimization and for assuring a continuing state of control. In addition, deviation investigations may provide information for process validation. This idealized life cycle for the BPC process is intended to provide a conceptual context for this article and is not intended to imply that alternative approaches are not acceptable.

SECTION 1: GLOSSARY OF TERMS

Bulk pharmaceutical chemical. An active ingredient that is intended to furnish pharmacological activity.

Process validation. Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Prospective validation. Establishing documented evidence that a system does what it purports to do based on a plan. See Section 2.

Concurrent validation. Establishing documented evidence that a system does what it purports to do based on information generated during actual implementation of the system. See Section 2.

Retrospective validation. Establishing documented evidence that a system does what it purports to do based on review and analysis of historic information. See Section 2.

Installation qualification (IQ). See Section 2.

Operational qualification (OQ). See Section 2.

Performance qualification (PQ). See Section 2.

Process performance qualification. See Section 2.

Critical process parameter. A parameter that could affect a critical quality attribute. See Section 5.

Range for critical process parameters. The range normally used for a critical process parameter. See Section 6.

Validation range. The range for a critical process parameter that has been validated. See Section 6. (Note: It is not the range beyond which a process fails.)

Critical quality attribute. A measurable characteristic of the material that affects its suitability for its intended use.

Process validation plan. See Section 9.

Revalidation. See Section 13.

SECTION 2: TYPES OF VALIDATIONS FOR BPCs

Validation usually consists of several aspects that are conventionally divided in the following way:

Installation qualification (IQ), which is the documented verification that all key aspects of the equipment and ancillary systems installation adhere to the approved design intentions and that the recommendations of the manufacturer are suitably considered.

Operational qualification (OQ), which is the documented verification that the equipment and ancillary systems perform as intended throughout anticipated operating ranges.

Performance qualification (PQ) — or process performance qualification — which is the documented evidence that the process, operated within established parameters, performs effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes.

This concept paper focuses on the BPC performance qualification or process performance qualification aspect of validation. In all cases, the term *process validation,* when used in a context describing process performance qualification, implies that the installation and operation qualification aspects of validation are appropriately addressed.

It is common to define three types of process validation, depending on when the process validation study is conducted. These are:

Prospective validation, which is conducted prior to the commercial distribution of a new BPC or a BPC made by a new or revised process.

Retrospective validation, which is conducted for a BPC already manufactured on a production scale based on accumulated production, testing, and control data. This does not imply that unsuitable material was manufactured but is simply a recognition that a formal process validation was not implemented prior to distribution or use. This would most commonly be used for a process instituted before evolution of the current process validation concepts.

Concurrent validation, which is conducted for a process in which the BPC is being manufactured on a production scale before completion of process validation studies. Examples may include alteration of the validation plan, an existing process with insufficient retrospective validation, or cases in which the number of validation batches is large or the production requirements are small or will be produced over an extended time. In the case of concurrent validation, each batch should meet all process and BPC product validation criteria before release and may require increased sampling or testing.

Process validation, whether prospective, retrospective, or concurrent, will include the same considerations presented in this concept paper. The significant difference between the types of validation is whether the critical process parameters and operating ranges are identified and derived from previously manufactured production scale batches with or without developmental data in the case of retrospective validation or from developmental or scale-up batches in the cases of prospective and concurrent validations. The validation data for the retrospective case are obtained from already manufactured or released batches; for concurrent and prospective validations, the data are produced from batches manufactured, sampled, and tested according to a validation plan.

SECTION 3: DEFINITION OF PROCESS

The processing steps in the later stages in the synthesis and purification used for the formation of the bulk substance or the removal of impurities should be validated in accordance with this concept paper. Although all steps in the production of a BPC must be appropriately controlled, not all steps must be validated.

Each process should be individually evaluated to determine the point in the process after which process validation should be applied to assure meeting the predetermined quality attributes of the finished BPC. Determining this point should be based on knowledge of the BPC and its critical quality attributes, as well as the process and its capabilities. The rationale for the determination should be documented, and the following items should be considered:

- the points at which significant impurities may be introduced into or removed from the process
- the point after which no significant impurities will be removed from the process
- the point at which all the essential structural elements of the BPC are present.

Although these concepts apply to validation of BPC processing steps after the point described, the concepts may be considered appropriate for process validation of earlier steps.

Process validation for a BPC should include an identification or definition of the process to be validated, including:

Facilities. A description or reference to a description of the facility in which the process is performed, including — if appropriate — a description of necessary environmental conditions to which the BPC may be exposed.

Equipment. A listing of all major equipment, its use in the process, and its material of construction. Calibration of appropriate equipment controls should be documented.

Synthesis/purification. A flow sheet or synopsis of the process in terms of the synthesis and purification steps, including identification of process controls employed. Rework or reprocessing operations should be included.

Process. Detailed instructions for the process steps being validated, including necessary control procedures.

Control instrumentation. Identification of instrumentation used to assure the critical quality attributes of the BPC, including computer control systems. Calibration of such instrumentation should be documented.

Personnel. A description or reference to a description of any unusual or specialized personnel training or qualifications required beyond that usually expected under good manufacturing practices.

It is usual to reference existing documents, records, and systems whenever possible in defining the process.

SECTION 4: DEFINITION OF THE BPC

Process validation for a BPC should include a definition of the BPC in terms of its critical quality attributes. Among the attributes that should be considered are assay or chemical purity; qualitative and quantitative impurity profiles; physical characteristics, such as particle size and polymorphic form — particularly for materials to be used in solid drug products; moisture and solvent content; uniformity of attributes (homogeneity); and, in some cases, microbial attributes. Consideration of attributes for newly developed products should include comparisons between clinical production or biobatches and commercial batches.

Table I: Examples of the types of information supporting validation of a bulk pharmaceutical chemical process.

Definition of Process
- synthesis/purification (Section 3)
- point in process where validation begins (Section 3)

Equipment List
- equipment requirement/specifications (Section 3)
- engineering drawings
- cleaning procedures
- control instrumentation (Section 3)

Critical Process Parameters (Sections 5 & 6)
- ranges (Section 6)
- justification (Section 6)

Quality Systems
- raw material/intermediate specifications and test procedures (Section 8)
- specialized training (Section 3)

Definition of Bulk Pharmaceutical Chemical
- quality attributes (Section 4)
- impurity profile (Section 4)
- analytical methods validation

Packaging Materials (Section 8)

Historical Batch Data
- summary of results
- consistency (Section 7)
- investigation(s) of deviation(s)/failure(s) (Sections 12 & 13)

Example of Completed Batch Record and Analytical Data

Stability Data (Section 4)

Process Change Control System (Section 11)

Process Memos/Justification of Process Changes

Approval Signatures

Critical quality attributes known to change upon storage should be considered in terms of an expiration period — e.g., for antibiotics — or reevaluation period, as well as in terms of the material at the time of processing.

SECTION 5: CRITICAL PROCESS PARAMETERS

Process validation for a BPC should include the identification of the critical process parameters that could affect the critical quality attributes of the BPC. Numerous parameters could be critical to the process, such as reaction times, reactant ratios, concentrations, temperatures, pressures, pHs, and impurity levels. The parameters that are critical should be determined by sound scientific judgment, which may or may not require supportive experimentation. Not all parameters that are controlled during a process are critical process parameters. Some variables may be controlled for economic considerations, such as minimizing energy consumption or equipment use — or, in some cases, improving yields — rather than for quality concerns. These noncritical parameters need not be included in the process validation. There may also be situations in which one end of an operating range is imposed for quality concerns and the other for economic considerations, or in which only one end of a range is of concern.

Typically, data used to identify critical process parameters are derived from research or pilot scale batches and do not need to be confirmed on full-scale batches unless the control of the particular parameter can only be adequately evaluated on a production scale.

If the probable adverse consequences of exceeding operating ranges of critical process parameters have been determined either experimentally or through scientific knowledge of the process, the validation

studies should be able to demonstrate that the adverse consequences did not occur within the validation ranges. If, for example, it is known that high temperature causes degradation, then the test methods employed in the validation studies should be capable of determining that the degradation does not occur to an unacceptable level when the process is acceptably controlled.

SECTION 6: RANGES FOR CRITICAL PROCESS PARAMETERS

Experimentation necessary to substantiate the ranges for critical process parameters is generally performed on research or pilot scale batches unless the process or parameter can only be adequately evaluated on a production scale.

Process validation for a BPC should include the determination of the range for each critical process parameter. The limits of the validation range, which indicate capability of producing BPCs with acceptable quality attributes, should encompass the operating range that is expected to be used for routine process control. The limits of the validation range are not intended to be the "edge of failure" limits beyond which the process will fail to produce acceptable BPCs.

Some process steps may have multiple critical process parameters that may or may not be interrelated. It is generally unnecessary to experimentally challenge the limits for each combination of variables. If the parameters are not interrelated — i.e., do not contribute to the same adverse consequence — then the limits of the ranges may be evaluated independently. If the parameters are interrelated, the range limits challenged should be those known to produce the most adverse consequences.

SECTION 7: NUMBER OF LOTS IN VALIDATION STUDIES

Process validation for a BPC should include evidence to show that a process will consistently produce an acceptable BPC. Demonstration of consistency frequently requires the use of multiple batches. The number of batches will depend on the complexity of the process or the magnitude of the process change being considered. Although three consecutive batches can be used as a guide, there may be cases in which three are insufficient to demonstrate consistency, and there may be situations in which fewer than three are appropriate, particularly when revalidation or change control data are being considered in relation to data from previous validation studies.

The need for multiple batches to demonstrate consistency of process should not be construed as a need for multiple batches to demonstrate ranges for critical process parameters. Typically, these ranges are determined from one or more research or pilot scale experiments, and the multiple production scale batches use operating conditions within these operating ranges.

SECTION 8: PROCESS MATERIALS AND PACKAGING MATERIALS

Process validation for a BPC should include control of the quality attributes of materials used in the process. This includes starting materials, intermediates, recycle streams, new and recovered solvents, water, catalysts, gases, and process aids. The quality attributes of materials that affect the quality of the BPC should be identified and controlled. Usually, that is accomplished by using process materials with typical quality characteristics in process validation studies and establishing

routine acceptance criteria reflecting those typical characteristics. It is generally not common practice to perform process validation studies using process materials with intentionally varying quality characteristics unless it is deemed that such characteristics will significantly affect the quality attributes of the resultant BPC.

As is the case for the control of the quality attributes of materials used in the process, process validation for a BPC should include control of the quality attributes of both contact packaging materials and packaging materials providing protection to intermediates and the finished BPC.

SECTION 9: PROCESS VALIDATION PLAN

Process validation studies for a BPC should include a plan indicating how the validation will be conducted, which may include process equipment, critical process parameters and operating ranges, BPC characteristics, sampling and testing, data to be collected, and the decision points as to what constitutes acceptable results. The plan should specify the number of process runs to demonstrate the consistency of the process. The plan should also indicate the types of data intended to demonstrate that equipment and systems performed appropriately, that the process materials were suitable, and that the BPC was acceptable.

The process validation plan should be reviewed and approved by personnel in appropriate functional areas, including personnel in the quality unit.

SECTION 10: VALIDATION DOCUMENTATION

Process validation for a BPC includes evidence that a process will consistently produce a BPC meeting its predetermined specifications and critical quality attributes. Documentation of such evidence should be retained and be retrievable for the life of the process or until it has been replaced by more recent evidence.

Validation documentation should be reviewed and approved by personnel in appropriate functional areas, including personnel in the quality unit.

There should be a system for the maintenance of process validation data; however, there is no single acceptable method of documenting process validation. (An example of the types of information for process validation of a BPC is included in Table I.) The data may be collected and maintained in a single location or file, or there may simply be a reference to where the various data reside throughout the company or a combination in which some data are centralized and some are referenced. The system used should be able to incorporate new data derived from process changes (Section 11) or revalidation (Section 13).

Documentation should include the rationale for choice of the point in the process after which process validation should be applied (Section 3). Summary development reports documenting or referencing the selection of critical process parameters (Section 5) and the determination of operating ranges for these parameters (Section 6) are common but not universal. Validation data derived from production scale batches are frequently maintained in batch records. Records of equipment cleaning and calibration are frequently maintained as part of batch or area records.

SECTION 11: CHANGE CONTROL

Process validation for a BPC should include a system to reassess a process whenever there are changes in process, equipment, BPC, process materials, or packaging materials that would affect the critical quality attributes of the BPC. Such change control should be a sys-

tematic approach to ensure a continued state of validated control. Any changes to equipment, systems, facilities, or processes affecting process validation should be documented and approved by means of a change control system and should include the decision made regarding the need for additional validation.

Anticipated or planned changes are usually handled on a preapproval basis, and proposed changes are documented, reviewed, and approved by personnel in appropriate functional areas. Consideration should be given to the impact of the changes on the critical quality attributes of the BPC.

Unanticipated, nonpermanent, or nonrecurring changes may be addressed via a separate system. Such changes should be documented, reviewed, and approved by personnel in appropriate functional areas to assess the impact of the changes on BPC critical quality attributes.

Sound scientific judgment should determine what, if any, validation studies are required to justify a change in a validated process. In many cases — such as minor processing or equipment changes, changes in control points, operating ranges, or procedures — careful evaluation of the batch manufactured with the changes is sufficient. Generally, no revalidation is required in the case of "like-for-like" replacements in which identical or similar equipment is introduced into the process or in which equipment is repaired to its original state.

SECTION 12: DEVIATIONS FROM VALIDATED PROCESSES

Deviations from a validated BPC process on either a planned or unplanned basis are to be expected.

A planned deviation may require justification by supporting data on either research or production scale prior to implementation. The significance of the deviation would determine the extent of the data required, as described in Section 11.

An unplanned deviation may be evaluated by additional testing or by supportive experimentation following the deviation. Similarly, the significance of the deviation would determine the extent of the data required. Frequently, data from such unplanned deviations become part of the data used to justify expanded operating ranges, changed processing steps, and reprocessing or rework procedures.

SECTION 13: REVALIDATION

Revalidation of a BPC process is a verification process that may be initiated periodically or when changes are made to equipment, systems, or processes; the revalidation effort will depend on the nature and extent of the changes. The evaluation and decisions regarding the need for additional validation should be documented.

For validated processes, any change affecting the BPC, process, equipment, facilities, or systems should be evaluated by means of an appropriate change control system as described in Section 11. An assessment should be made regarding the need for additional process validation.

An indication of failure of a validated process should result in an investigation to identify the cause and to take necessary corrective action, and an assessment should be made regarding the need for additional process validation.

In the absence of changes or process failures, there should be a system for periodic review of validated processes to assess the need for revalidation.

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Ad Hoc Subcommittee

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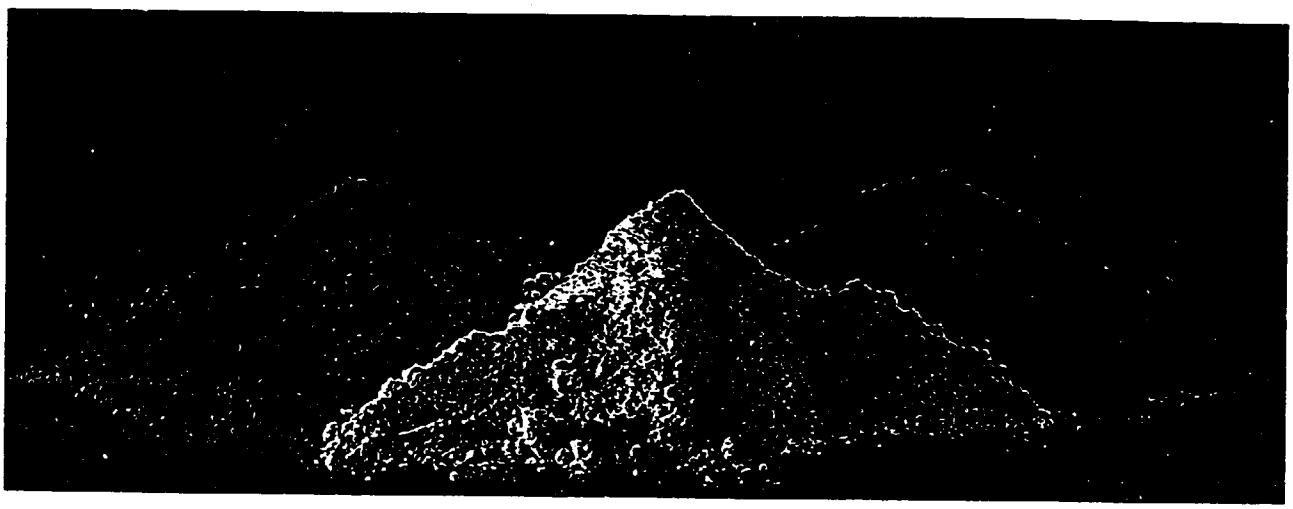
Sterile Bulk Pharmaceutical Chemicals: A PhRMA Position Paper



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PhRMA QC Section Bulk Pharmaceuticals Committee and Sterile Bulk Pharmaceutical Chemicals Subcommittee*

The 1993 PhRMA (formerly PMA) concept paper *(Pharm. Technol.* 17 [12], 32–40 [1993]) on process validation of bulk pharmaceutical chemicals (BPCs) did not address sterile BPCs. General validation considerations, as described in the 1993 paper, should be followed for all bulk pharmaceutical operations. This paper on sterile BPCs is intended to address only the unique considerations that apply to bulk material produced as sterile.

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In December 1993, the Bulk Pharmaceuticals Committee of the QC Section of PhRMA (formerly PMA) published in *Pharmaceutical Technology* a concept paper on process validation of bulk pharmaceutical chemicals (BPCs). That paper did not address sterile BPCs.

Recent FDA initiatives have indicated a need for an industry position on validation practices that should be considered when producing sterile BPCs. General validation considerations, as described in the December 1993 paper, should be followed for all bulk pharmaceutical operations. This paper on sterile BPCs is intended to address only the unique considerations that apply to bulk material produced as sterile.

SUPPORT SYSTEMS

All support systems should be validated or qualified as separate systems to ensure that each is performing in a validated state. It is particularly important to identify potential sources of bioburden in such systems and, where appropriate, maintain programs to ensure that these systems operate at acceptable sterile or minimal microbiological and pyrogen/endotoxin levels. Appropriate change control systems should be used to ensure that these process utilities remain in a validated state. The systems directly affecting production of sterile BPCs that should be considered are the following:

- water — treatment and distribution systems
- compressed air and process gases — storage and handling systems
- filter systems — liquid, gases including vent filters
- clean/pure steam — generation and distribution systems
- heat exchange systems
- vacuum systems
- sterilizing, cleaning, and depyrogenation systems
- solvent handling, storage, and distribution systems
- central HVAC and local HEPA laminar flow stations.

Appropriate preventive maintenance and calibration procedures must also be in place to ensure that the systems remain in a state of control

particulate levels both viable and nonviable) necessary to successfully produce product of the required quality. Appropriate monitoring programs should be in place to detect any objectionable bioburden and nonviable particulate drift before it reaches unacceptable levels. The level of control necessary will vary depending upon the type and timing of operations being conducted. The microbiological and pyrogen/endotoxin levels of the process stream before the sterilization step must be evaluated as part of the process validation and monitored thereafter with appropriate frequency to ensure maintenance of the validated status. Alert and action limits should be established for all environmental parameters.

EQUIPMENT CONSIDERATIONS

Special equipment requirements should be defined or specified during process development and scale-up. Equipment should be designed for ease of cleaning and sterilization. The process should use closed, pressurized equipment and, whenever possible, eliminate manual interventions. This would allow that segment of the process to be considered as part of the systems validation, obviating the need for aseptic processing validation. Engineering design and controls should be incorporated into the operations to ensure the successful processing of sterile BPCs. An example of this might be the inclusion of an integrity test (pressure/vacuum) for all vessels used in the aseptic processing train prior to each usage. The selection and testing of seals, filters, valves, gaskets, etc., are all critical to successful aseptic operation and should be subject to a change control system.

VALIDATION OF STERILE BPC MANUFACTURING

Described in the following sections are the considerations that should be reviewed during the validation of a sterile BPC.

Concept. To maintain sterility assurance of BPC manufacturing, it is generally regarded as appropriate to validate all support and environmental systems and perform extended testing on the drug substance or placebo. This includes the training and monitoring of all personnel involved in manufacturing and support activities associated with the process. It may also be acceptable to exclude certain stages of the aseptic process that take place in a closed system. The scale of BPC manufacturing and the inherent risks associated with the use of culture media make the general use of a culture medium inappropriate and undesirable in a sterile BPC manufacturing area. It would be difficult, if not impossible, to fully simulate all production steps using culture media. Removing media residue from the process train would require impractical, vigorous, and aggressive cleaning methods. Further, a material as crudely formulated and as complex as culture media would present significant cleaning validation problems.

Use of product vs. placebo: The nature of the drug substance should be considered. If it is not antimicrobial, comprehensive testing of the product during the validation lots could be acceptable. Either product or placebo may be appropriate for use during validation. Placebos can vary from inert materials to buffer solutions that can rinse the system and be analyzed subsequently for microbiological content. Appropriate studies should verify that the material used for the validation is not toxic to microorganisms and does not inhibit their growth during testing. If substances other than product are used, the ability to remove the material from equipment should be demonstrated (i.e., cleaning validation). Simulations should encompass all steps in the process in which aseptic manipulations are performed. Processing steps conducted in fully closed, validated systems or vessels need not be simulated.

Number of runs. For the prospective sterile process validation of a new or reconfigured system, three simulation runs are generally appropriate. For processes that have been in operation over many years in the same facility, validation can be retrospectively obtained. Fewer than three simulation runs may be justified when coupled with a satisfactory sterility history of the process train, sound validation systems, and an acceptable environmental monitoring profile.

Validation focal points. These are as follows:

- process stream feed to sterilization step — bioburden
- sterilization step
- sterile crystallization/filtration/drying
- discharge handling and sampling
- blending
- milling
- micronization
- container/closure integrity
- packaging.

For sterilizing filters, it is suggested that a challenge with *Pseudomonas diminuta* would be an appropriate method for validation.

Sampling and testing of material. *Test sample size:* For some small-scale or simple aseptic processes (e.g., a single-vessel, dry blend process) it may be appropriate to perform a sterile simulation on a reduced scale with 100% sterility testing of the material used. However, for many large-scale or complex BPC processes, it is impractical to perform a meaningful simulation utilizing an amount of material that can be fully tested. A significant reduction in the amount of product or placebo may not allow adequate simulation of process steps or vessel contact to accurately reflect the performance of those steps in the full-scale process. For such processes, an appropriate aseptic sampling plan should be developed based upon lot size, system design, locations of manipulations, and the number of containers produced.

Typical sampling plans may include the following:

- one placebo run plus extended testing of a predetermined number of lots
- three lots of product with elevated sampling regime and satisfactory history of the processing unit
- three placebo runs with a defined sampling plan.

It is recognized from a statistical standpoint that testing alone via any individual sampling plan is not adequate to ensure sterility. Nor will reduced-scale simulations reflect conditions and handling present in actual production. The combination of all the factors discussed in this paper will ensure the highest level of sterility that can be reliably achieved.

Although running a smaller lot size through the actual equipment and possibly testing the entire amount of material could address the distribution of microorganisms concerned, it does not represent the operating conditions under which the actual product will be produced. Also, testing the entire amount of material would only define sterility conditions for that lot; it would not ensure or validate sterility of each future lot or the process itself. This can be accomplished by validating and/or qualifying all support systems.

CONCLUSIONS

The validation of sterile bulk pharmaceuticals can be accomplished by implementing the concepts presented in this paper along with those established in the paper published in the December 1993 issue of *Pharmaceutical Technology*. This includes validating all of the support systems. Sterile simulations of open aseptic handling areas using extended sampling and testing of full-scale drug substance or placebo lots, or small scale simulations with 100% testing may be appropriate. While it is recognized that microorganisms do not necessarily distribute uniformly, a combination of environmental and personnel monitoring, personnel training, closed pressurized systems, and extended sampling and analysis contributes to sterility assurance and appropriate pyrogen/endotoxin control. Where processes are operated under a closed, pressurized environment, system validation can ensure sterility. ■

(ii) Since effective communication with the public during an emergency requires the co-ordinated involvement of a number of relevant parties - including, for example, local response officials, corporate spokespeople, employee representatives, community representatives, public authorities, technical experts and the media - the duties of these parties should be established during the preparation of emergency plans.

E.2.3 The media should be involved during the development of emergency plans and should be given information concerning the emergency plans in order that they have the necessary background to be an effective and reliable source of information should an accident occur.

E.3 Medical Aspects of Emergency Preparedness and Response

The subject of medical aspects of emergency preparedness and response is being addressed in greater detail through a joint activity of the International Programme on Chemical Safety, the World Health Organization (Euro), the United Nations Environment Programme and the OECD. A Workshop to consider guidelines in this area will be held in mid-1993. The Guiding Principles in this subsection are, therefore, provisional and will be reviewed and substantially augmented by the guidelines resulting from the Workshop.

E.3.1 Public health authorities should establish their own health sector plans at national, regional and local level as part of the overall emergency preparedness plans.

(i) Each country should establish an information centre capable of providing relevant information in an emergency on the diagnosis, treatment and rehabilitation of persons injured by chemicals.

(ii) This information should be available on a 24-hour-a-day basis throughout the year.

E.3.2 Public health authorities, including experts from the information centre, should be involved in national and local emergency planning related to accidents involving hazardous substances.

(i) They should take part in exercises wit the other relevant authorities involved in emergency response, in order to test emergency plans and train emergency response medical staff.

(ii) They should be consulted when issuing statements to the media concerning health aspects of chemical accidents.

E.3.3 As part of emergency planning, it should be ensured that adequate medical facilities are available including transportation facilities, which may mean in an emergency the rapid transformation of facilities normally used for other purposes.

(i) The availability should also be ensur of up-to-date antidotes and other pharmaceutical substances, including oxygen, necessary for the treatment of persons injured by chemicals.

(ii) Where suitable antidotes exist for treatment of persons injured by chemicals produced or used by industry, the industry should be required to ensure their availability locally if this is a problem for the health authorities. Necessary relevant emergency medicines, kept updated, should be available at

installations handling toxic chemicals.

(iii) Decontamination equipment for on-site and hospital use and, as appropriate, protective equipment for the medical emergency response personnel should also be available.

E.3.4 Public health and education authorities should ensure the basic training of all medical and paramedical professions, as appropriate, in the principles of medical toxicology and emergency medicine. Specialist courses should be provided for those involved in emergency response work.

E.3.5 Industry should be encouraged to provide to the appropriate information centres adequate data for emergency medical response and follow-up, including information on the composition and the toxicological and other relevant properties of chemical products which they produce, use, store, dispose of, or transport. Arrangements should be made to guarantee the confidentiality of data, where appropriate.

E.3.6 Research into new antidotes and decontamination procedures for toxic chemicals should be encouraged by the health authorities and the relevant sectors of industry.

E.4 Emergency Response

E.4.1 Management of a hazardous installation should promptly notify emergency response authorities of all incidents involving hazardous substances which result or threaten to result in potential harm to health or the environment.

(i) Notification should flow as directly as possible from the individual detecting the incident to responders.

(ii) The initial notification should include the following information, if ascertainable:

- the nature of the incident;
- the hazardous substances involved;
- the potential severity of the incident; and
- the incident's potential off-site effects.

E.4.2 The notification from the hazardous installation should trigger the implementation of the off-site emergency response plan, beginning with an initial assessment of the situation leading to a decision on which response actions are required.

E.4.3 Handover of responsibility from management to public authorities, in the case of accidents with potential off-site effects, should be based on criteria contained in the emergency plan. These criteria should make it clear at what stage the handover should take place, and to whom.

E.4.4 The first responders to an accident should have sufficient information, training and experience to be able to assess quickly whether they can deal with the situation, or whether additional equipment and/or persons with particular expertise should be summoned. Mechanisms should be in place for the first responders to obtain whatever additional personnel and equipment are needed for responding to the accident.

(i) Systems should be available to allow immediate, on-the-spot access to the information necessary to assess and respond to an emergency and, in particular, information regarding: all hazardous substances in the installation; how to deal with these substances and their effects; and, as

appropriate, related transport activities.

(ii) Systems should be in place for obtaining assistance, as needed, from emergency responders in neighbouring or other appropriate communities.

E.4.5 Where the safety of the first emergency responders is at risk, or where other difficulties exist in responding effectively, specialists should be called in to assist with such matters as:

- identification of the hazardous substances involved;
- evaluation of the hazard;
- need for protective equipment;
- control and containment of the hazardous substances; and
- decontamination and emergency termination activities.

Such specialists should be able to provide fast, reliable information under stressful conditions so that it can be understood and immediately acted upon by emergency services personnel.

E.4.6 In the case of the release of a toxic substance, the decision on whether the potentially affected public should shelter indoors or be evacuated should be taken by the responsible person designated in the emergency preparedness plan. The decision made should be based on likely exposure and possible health effects.

E.4.7 The systems used for communicating with the public in an emergency to provide initial and continuing information should be well-known and readily accessible and understood.

E.4.8 The media should have ready and continuous access to designated officials with relevant information, as well as to other sources, in order to provide essential and accurate information to the public throughout the emergency and to help avoid confusion. Efforts should be made to check the clarity of the information as it becomes available, before it is communicated to the public.

E.4.9 Official spokespeople should be as open as possible in providing information during an emergency. In this regard they should, for example, admit when information is not available, avoid making promises which cannot be fulfilled, be the first to give bad news, and ensure that the messages provided are consistent with actions taken.

E.4.10 Public authorities should ensure that systems are in place to provide information to the public following the accident and the immediate emergency response.

(i) Such information should cover the off-site effects of the accident, the risks of further adverse off-site effects, and related follow-up information.

(ii) Counselling services should be made available for victims of the accident as well as victims' family, friends and fellow employees.

E.4.11 During the transition between emergency response/rescue operations and clean-up activities, all those involved should co-operate and exchange information in order to maintain safety and protect and/or restore the environment

E.5 Incident Reporting and Investigation

General Principle

E.5.1 Efficient reporting and investigation of all significant incidents should be undertaken by industry and public authorities, as they can provide an important contribution to the safe operation of hazardous installations. Incident reporting and investigation can also help to instill public confidence that proper actions will be taken to avoid similar incidents, or incidents with similar consequences, in the future.

(i) Reporting and investigation should identify causes of incidents and lead to remedial action to correct any deficiencies in technology or procedures which led to the incident.

(ii) All interested parties should encourage, and management should promote, the full reporting and critical examination of accidents and near-misses.

Reporting

E.5.2 All fatalities, regardless of cause, all significant incidents, and other "reportable" events as determined within the enterprise, should be immediately reported by local management to the appropriate members of management of the enterprise.

- Reportable events should include those which occur in conjunction with work by contractors.

E.5.3 Employees and contractors should be positively encouraged by their management to report all incidents to appropriate managers in the enterprise so that the causes can be established.

(i) Employees should be given the appropriate training in hazard identification to facilitate this.

(ii) Employees should also be encouraged to discuss near-misses among themselves immediately after they happen.

(iii) Efforts should be made to foster an environment where reporting incidents and discussing them are considered to be positive activities.

(iv) Employees should be given the assurance that there will be no adverse repercussions for reporting incidents to management or discussing incidents among themselves.

E.5.4 Public authorities should require prompt notification to an appropriate authority of the key elements of major accidents involving hazardous substances. This notification should be followed up by formal written reports.

(i) Public authorities should encourage the voluntary reporting by enterprises to public authorities of accidents and significant near-misses beyond that legally required.

(ii) Similar information on incidents should be provided to relevant trade associations.

E.5.5 Mechanisms to foster the open and frank exchange of information related to accidents and near-misses, both within an enterprise and among enterprises, should be further developed and encouraged. There is an obvious need to capture and share such information widely throughout industry, so that enterprises can learn from the experience of others.

- In addition to the sharing of information within industry, means should be developed to involve public

authorities in this information sharing without jeopardising the enterprises' interests.

E.5.6 Public authorities and industry should promote further efforts to improve the international exchange of information on significant accidents and near-misses in order to promote safety.

- Efforts should be made to co-ordinate reporting by industry at the national and international level, in order to facilitate information sharing.

E.5.7 Public authorities should also establish a structured national system for maintaining statistics on accidents involving hazardous substances. This will facilitate: exchange of information; analyses of this information; and dissemination of the results of the analyses.

Investigation

E.5.8 The local management of an installation should be responsible for ensuring the prompt investigation and thorough analysis of all incidents.

(i) The emphasis should be on identifying the underlying causes, the lessons to be learned, and ways to prevent future accidents rather than identifying the person(s) responsible.

(ii) The use of a computer database for storing the key elements of incidents can facilitate their analysis. By this means, particular trends can be highlighted and historical data can be used proactively in accident prevention, for example by orienting safety training towards the avoidance of the type of incidents which have occurred.

E.5.9 Public authorities should independently investigate all major accidents.

(i) Where appropriate, this investigati should be conducted by a group of experts (for example, a specially designated commission) which includes different individuals than those responsible for inspection of installations and enforcement of th control framework.

(ii) All appropriate interested parties should have an opportunity to be involved in this investigation.

E.5.10 In all accident investigations, efforts should be made to determine the underlying cause(s) in a chain of events leading to an accident, and not to limit the investigation to determining the apparent cause(s).

- Where "human error" is involved, th cause should not simply be so recorded. Rather, investigators should determine exactly what elements contributed to any human error. Such elements could include boredom, stress, overwork, lack of training, inadequate procedures, poo ergonomic design, poor system/technology design, communication problems, management inadequacies, inappropriate safety goals, and simi factors.

E.5.11 Public authorities should publis accident investigation information for a wide dissemination as possible. This should include sufficient information t enable it to be useful in other situations as well as any conclusions arising from the analysis of accident data.

- Public authorities are in a unique position to correlate information, foster exchange of information, and

provide credible analyses. Such information is important in order to gain knowledge useful for public authorities and management in their role in evaluating and making decisions related to, for example, regulation, monitoring, preparation of emergency plans, and development of risk assessment and management techniques.

FDA Proposed Guidance for Che... Manufacturing, and Control Ch... Immediate-Release Solid Dosage Fo... A Review and Industrial Perspective

Leo J. Lucisano* and Robert M. Franz

FDA recently issued an interim guidance document that addresses formulation and m... release solid dosage forms. It represents several years o' initiative and collaboration a... try, and academia in attempting to facilitate the regulatory process while maintaining product qua... a greater number of postapproval changes be implemented before FDA approval, it would provid... maceutical manufacturers to incorporate manufacturing efficiencies and technology upgra... terim guidance places a greater responsibility on pharmaceutical companies to maintain chang... propriately justify and validate the change. This article reviews the content of the interim guidance and discuss... implications for both the preapproval and postapproval processes. The interim guidance is a welc... of the range of changes that it addresses, its clarity, and its basis in pharmaceutical principles. Th... ceutical technology and its regulation should study the document and provide prompt, constructive... pedite the incorporation of the interim guidance into the *Code of Federal Regulations*.

In late 1994, FDA issued an interim guidance document on chemistry, manufacturing, and control changes for immediate-release solid oral dosage forms that has significant and positive effects on filing requirements for this class of drug product (1). The interim guidance was issued as an informal communication under *21 CFR* (10.90(b)) (9) that represents the best judgment of CDER but "does not necessarily represent the formal position of FDA and does not bind or otherwise obligate the agency to the views expressed" (7). The interim guidance was issued in this manner as a means to elicit feedback from the pharmaceutical industry before the expert working group for scale-up and postapproval change (SUPAC ... mendations as a formal gu... *Federal Regulations* (8).

The recommendations contai... worthy because they do the fol...

- affect both postapproval change... process development strategy for n... abbreviated new drug applications (A...
- clarify many of the uncertainties ... (314.70) (Supplements and ... (2) and Office of Generic ...
- allow pharmaceutical ... formulation and ...
- place greater emphasis ... principles during process ch...
- demonstrate the benefit of pharmaceu... on scientific issues of mutual inte...

SCOPE OF INTERIM GUIDA...

The document addresses changes in ...

- components and composition of the dru...
- manufacturing site changes
- scale-up of drug product
- manufacturing equipment
- manufacturing process

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Editor's note: The April 1995 issue of *Pharmaceutical Technology* published an article about the AAPS/FDA workshop report on the scale-up of immediate-release oral solid dosage forms. That report played in integral role in the November 1994 issuance of the interim guidance by FDA's Scale-Up and Coordinating Committee. The present article provides a detailed review of the interim guidance and its potential impact on pharmaceutical manufacturing development.

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Table I: Summary of FDA Interim Guidance on Immediate-Release Solid Oral Dosage Forms, continued.

Category	Description	Filing Documentation	Stability [1]	Batch Records	Dissolution Documentation	In Vivo Bioequivalence
Scale-up of Drug Product	(ICH guidelines for NDAs: pilot-scale batch for biostability batch is minimum 100,000 dosage units) [10]					
Level 1	Scale-up to and including 10 times size of biobatch (Same equipment design and operating principles, SOPs, controls, formula and process same as biobatch, manufactured under cGMPs)	Annual report	Stability commitment (long-term) and submit results in annual report	Yes	Meets test (NDA/USP)	None
Level 2	Scale-up from beyond 10 times size of pilot/biobatch (Same equipment design and operating principles, SOPs, controls, formula and process same as biobatch, manufactured under cGMPs)	Changes-being-effected supplement	Accelerated stability testing Stability commitment (long-term) and submit results in annual report	Yes	Case C testing (see above)	None
Manufacturing Equipment						
Level 1	Change to automated or mechanical conveying Change to alternative equipment of same design and operating principles of same/different capacity	Changes-being-effected supplement	Stability commitment (long-term) and submit results in annual report	Yes	Meets test (NDA/USP)	None
Level 2	Change in equipment to a different design and different operating principles	Prior approval supplement (with justification) [11]	Accelerated stability testing Stability commitment (long-term) and submit results in annual report	Yes	Case B testing (see above)	None
Manufacturing Process						
Level 1	Process changes outside of application/validation ranges (e.g., mixing time, operating speed)	Changes-being-effected supplement	Accelerated stability testing [2] Stability commitment (long-term) and submit results in annual report	Yes	Case C testing (see above)	None
Level 2	Change in process type (e.g., change from wet granulation to direct compression)	Prior approval supplement (with justification) [11]	Accelerated stability testing Stability commitment (long-term) and submit results in annual report	Yes	Case C testing (see above)	Yes

[1] See reference 9
[2] Question marks bracket this requirement in interim guidance document
[3] Expressed as percentage (w/w) of total formulation
[4] Drug solubility and permeability defined on pages 7 and 8 of interim guidance document
[5] Surfactant may be used with appropriate justification
[6] Case A dissolution specification of NLT 85% dissolved in 15 min in 900 mL of 0.1N HCl is also required to satisfy Case B testing
[7] If either Case A or Case B tests requirements are not met, proceed to requirements for Level 3 change
[8] List of narrow-therapeutic-range drugs is provided in Appendix 1 of interim guidance document
[9] *Drugs* is interpreted as being the drug product incorporating the desired formulation and/or manufacturing changes
[10] See reference 10
[11] "Reports containing scientific data and expert professional judgment to substantiate decisions."

terms that attempts to define often-used but poorly understood concepts such as *contiguous campus* and *optimization*.

BACKGROUND

The recommendations contained in the interim guidance represent several years of initiative and collaboration among members of the pharmaceutical industry, academia, and FDA. In April 1990, the American Association of Pharmaceutical Scientists (AAPS) and FDA agreed to investigate guidelines for scaling up dosage forms based on sound pharmaceutical principles. This led to a series of joint FDA–AAPS workshops that focused on the scale-up of immediate- and extended-release solid oral dosage forms; liquid and semisolid disperse systems; and manufacturing site changes (3–6).

Concurrently, FDA established several policy coordinating commit-

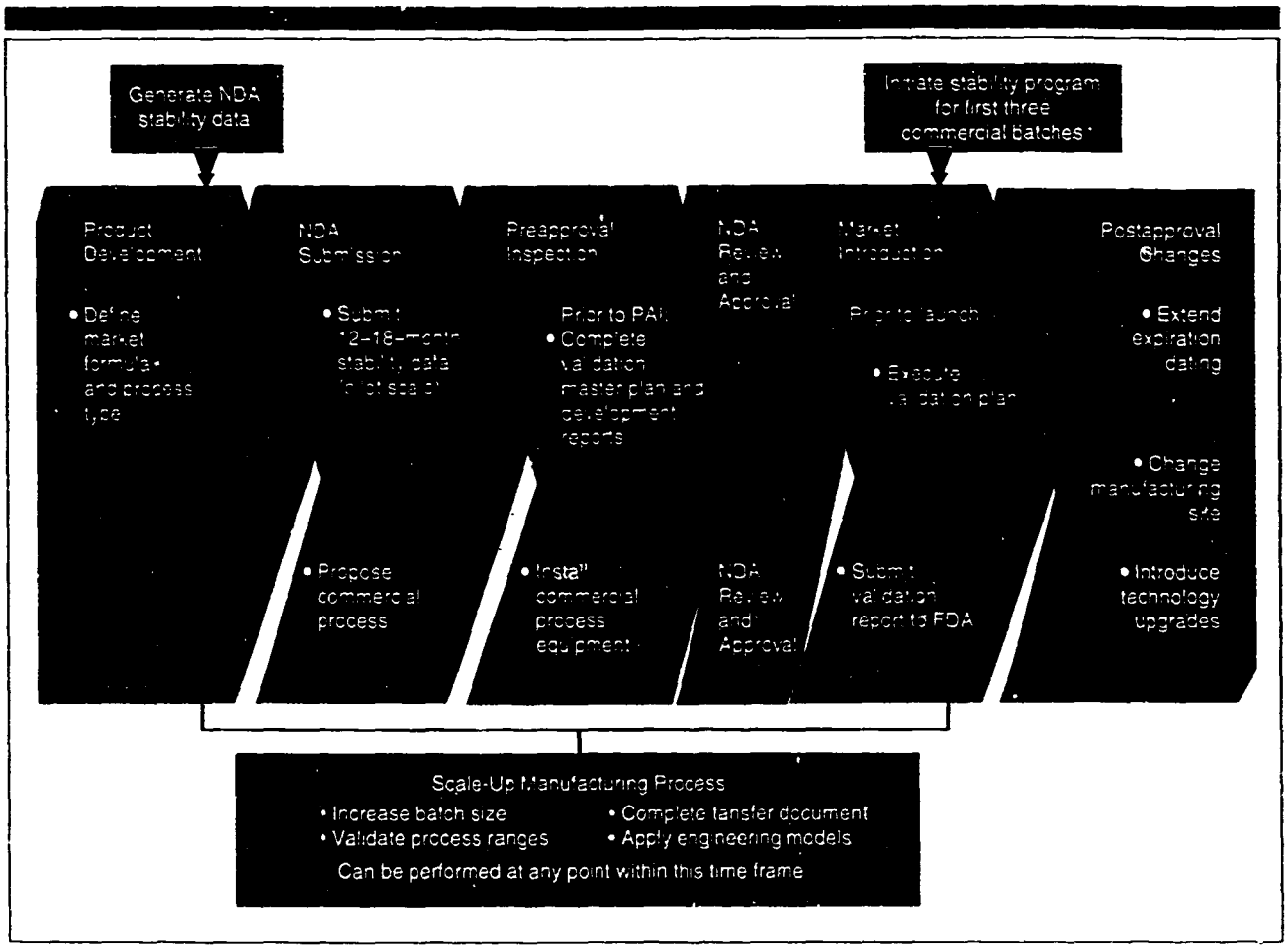

Figure 1: *Process schematic for new drug application.*

ucts is cited in discussing pilot-scale stability requirements for NDAs (10). Note: the interim guidance references the final draft of the ICH guideline that was endorsed by an ICH steering committee on 27 October 1993. This draft was later issued by FDA in September 1994 as a guideline in the *Federal Register.*

Interestingly, submission of updated batch records is requested for every change addressed in the interim guidance, except for filing a level-one change in the components and composition of the drug product via the *annual report.* As part of the *preapproval inspection* (PAI) requirements, FDA issued a ruling in October 1993 that required the submission of batch records in NDAs and ANDAs (11). For an ANDA, the applicant must provide the proposed or actual master production batch record for the commercial manufacturing process. For an NDA, the applicant may provide the same or a detailed description of the production process for a representative batch of its proposed product. The requirement in the interim guidance to submit updated batch records to support changes filed by an annual report and supplemental applications would represent an extension of that ruling.

Dissolution documentation requirements fall into one of four scenarios listed in Table II. The interim guidance requires that all profiles be conducted on at least 12 individual dosage units and refers to the *United States Pharmacopeia/National Formulary (USP/NF)* for general dissolution requirements, although the specific dissolution methodology (e.g., USP Method I at 100 rpm) is not specified for Case A, B, or C testing. The interim guidance also requires that dissolution profiles for the drug product manufactured using the proposed changes be similar to profiles of the approved formulation/method of manufacture, but stops short of defining the means to verify *similarity* (e.g., profile analysis using multivariate statistics).

In vivo bioequivalence study. The interim guidance requires an in vivo bioequivalence study in two instances: a level-three change in the components and composition of the drug product or a level-two change in the process used to manufacture the drug product, e.g., changing from wet granulation to direct compression of dry powder.

Although not explicitly stated, all other manufacturing changes that do not require a bioequivalence study a priori, but which fail dissolution testing, do need an in vivo study to support the change. This is based on the Components and Composition Section, which is the only section in the interim guidance that discusses major changes likely to have a significant impact on formulation performance (i.e., level-three changes). "All other drugs not meeting the dissolution criteria under Section III/B/2/b" (i.e., Case A or Case B testing) is given as an example of a level-three change. In this instance, *drugs* is interpreted as being the drug product incorporating the desired formulation and manufacturing changes.

The interim guidance also proposes a general design for the bioequivalence study (single-dose, two-treatment, two-period crossover study with a minimum of 24 subjects) as well as the appropriate statistical analysis.

Filing documentation. In general, a level-one change can be implemented via annual report or a *changes-being-effected supplement* (CBES). It requires a commitment to perform long-term stability and

Table III: Comparison of FDA documents addressing postapproval changes.

Manufacturing/Formulation Change	Draft Guideline (20) Nonsterile Drug Products	Interim Guidance (1) Immediate-Release Solid Oral Dosage Forms
Change to equipment of a different design and different operating principles	Prior approval supplement	Prior approval supplement
Change to equipment that changes basic methodology of manufacturing	Prior approval supplement	Prior approval supplement
Change to equipment of same design and operating principles	Annual report	Changes-being-effected supplement
Change to same equipment with a different capacity (not greater than 10 times the test batch size)	Annual report	Changes-being-effected supplement
Relocating processing areas or structures within, or through addition to, any portion of the existing facility	Annual report	Changes-being-effected supplement
Use of a different, separate facility or establishment for the manufacture of drug product	Prior approval supplement	Changes-being-effected supplement (different data requirements apply if change is within a single facility/contiguous campus vs different campus)
Reprocessing procedures	Prior approval supplement (to establish a new reprocessing procedure) Annual report (to repeat one step a single time per batch in the approved manufacturing sequence)	Not addressed
Change in components and composition of the drug product	Not addressed	Annual report (Level 1 excipient change) Prior approval supplement (Levels 2 and 3 excipient changes)

requires generating accelerated stability data, conducting multipoint dissolution testing, and providing a commitment to perform long-term stability testing (and then submitting the results in the annual report). These are reasonable requirements for the degree of flexibility provided, especially considering that several pharmaceutical companies have practiced a conservative policy of conducting bioequivalence testing when changing manufacturing sites.

This provision would also permit manufacturers to initially launch a product from one site and then transfer to another facility with a minimum of redundancy. In the past, many companies were forced to maintain two facilities while awaiting the outcome of the review process for a PAS.

The interim guidance still requires the filing of a PAS in two cases of level-two manufacturing changes: (1) if the manufacturer changes equipment to a different design and different operating principles (e.g., converting from tray drying to fluid-bed or microwave drying) and if there is a change in the type of process used in the manufacture of the product (e.g., switching from a wet granulation process to direct compression). Recall that the latter also requires an in vivo bioequivalence study to support the change.

- Validation and quality assurance groups will shoulder greater responsibility to justify, validate, and document manufacturing changes that previously required a PAS.

By allowing a greater number of changes to be implemented before approval (either by annual report or CBES), there is greater liability for pharmaceutical manufacturers that fail to adequately substantiate the changes. If a manufacturer changes the site of manufacture under a CBES, and FDA later finds insufficient documentation (as described in the interim guidance) demonstrating equivalency of the new site with the original, the manufacturer could be faced with recalling all lots of drug product manufactured at the new site. An effective change-control system will be critical to ensure acceptance by FDA.

When requiring a PAS, the interim guidance sometimes attaches the term *with justification. Justification* is defined in the document as "reports containing scientific data and expert professional judgment to substantiate decisions." Although the interim guidance does not explicitly request that validation data demonstrating equivalency of the change be included in annual reports or CBESs, manufacturers should maintain the same level of documentation and supporting data that they are accustomed to providing in a PAS or a PAI.

Simply reporting a change and claiming it has no effect on product integrity will carry a high level of risk.

IMPLICATIONS FOR PREAPPROVAL AND DEVELOPMENT PROCESS

At first glance, the orientation of the interim guidance seems exclusively directed at postapproval changes for immediate-release solid oral dosage forms and consequently would have the greatest impact on those groups located at the production site (quality assurance, validation, technical services, etc.). "Preapproval changes" is also part of the title, however, and those groups involved in new product development, technology transfer, and NDA submissions are also affected by its recommendations.

- The interim guidance echoes the ICH guideline that pilot-scale batches are sufficient for NDA and ANDA submissions.

recorded in an annual report (20). The draft guideline was issued in the *Federal Register* and comments solicited, although the interim guidance was not. The draft guideline addressed many of the same changes covered in the interim guidance but did not offer the same level of detail regarding the documentation required to support the change. The documents use slightly different terminology (especially regarding equipment and site changes) and require a degree of interpretation to adequately compare the consistency of filing requirements between the two. For example, the draft guideline requires a PAS for the use of a different, separate facility for the manufacture of drug product, but relocating processing areas or structures within a portion of the existing facility can be exercised through an annual report. The interim guidance recommends filing a CBES regardless of a change within a single facility/contiguous campus or to a different campus. Table III lists other inconsistencies and similarities between the two documents with respect to manufacturing changes.

CHANGE CONTROL PROCEDURES — THE NEXT HORIZON

By recommending that filing requirements be relaxed for many postapproval changes for immediate-release solid oral dosage forms, the interim guidance should emphasize the need for responsible validation and change control practices. In January, 1994, FDA issued a guide that addressed validation of solid dosage forms for pre- and postapproval inspections (18). Although the document adequately reviewed validation principles and recognized common problem areas in specific equipment for solids processing, it still left the interpretation and application of validation principles to the drug manufacturer. At the Workshop on Manufacturing Site Changes, it was suggested that change control systems be submitted as part of NDAs and ANDAs. Upon approval, an applicant would then be able to implement any change following appropriate validation, and FDA would be able to verify compliance during periodic inspections (6). Perhaps the time has come for serious consideration of such a proposal.

FROM GUIDANCE TO REGULATION

The interim guidance for immediate-release solid dosage forms represents a genuine step toward a degree of rationality in the regulation of pharmaceutical manufacturing. Members of the SUPAC Group and industry colleagues who participated in contributing task forces should be congratulated. The issuance of the interim guidance followed closely on the heels of the Workshop on Manufacturing Site Changes and reinforces FDA's assertion at this workshop to move quickly to streamline and facilitate the process for changing manufacturing processes (21). The pharmaceutical industry, in turn, should study the recommendations in the interim guidance and supply prompt, positive feedback to FDA to assist in ensuring the codification of these recommendations. In the future, the SUPAC Group also expects to release interim guidance documents covering extended-release solid oral dosage forms as well as liquid and semisolid dispersal systems. The momentum is now in favor of industry/FDA partnering that will allow pharmaceutical manufacturing to remain a competitive industry without compromising product integrity.

PROVIDING FEEDBACK TO FDA

Reaction and comments to the interim guidance should be directed to one of the industry groups working directly with the SUPAC Group:

Pharmaceutical Research and Manufacturers of America (PhRMA)
1100 Fifteenth Street NW
Washington, DC 20005
(202) 835-3559

Generic Pharmaceutical Industry Association (GPIA)
200 Madison Avenue
Suite 2121
New York, NY 10016-4090
(212) 683-1881

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a position for a collaborator responsible for womens questions was created to whom the female employees may turn anonymously for advice. Ciba-Geigy also organizes seminars on the professional and personal development of women.

5. MARKETING

The marketing strategy in the pharmaceutical sector is based on the «IFPMA Code of Pharmaceutical Marketing Practices», committing the enterprise, among other things, to accuracy in the indications, guarantee of quality impartiality vis-a-vis the public. Expenditures for marketing and public relations are not divulged. Ciba-Geigy carries out PR-actions amongst the local population. In Basle, for example, Ciba-Geigy cultivates an open dialogue with the population, distributes a free local newspaper and regularly organizes neighbourhood events.

In September 1991, the American authorities accused Ciba-Geigy of having transgressed fair publicity regulations. A base-ball player had promoted the product Voltaren on a publicity tour and had received money to do so from Ciba-Geigy.

6. DISCLOSURE OF INFORMATION

Compared with that of other Swiss companies, the information given by Ciba-Geigy is better with respect to scope, quality, transparency and accuracy. This holds true in particular for social and ecological information. The INFO-CENTER questionnaire was almost entirely completed. For Ciba-Geigy, the goal of information is to strengthen reciprocal understanding and trust between the entreprise and employees, investors and public. Furthermore Ciba-Geigy practices an objective, open and up-to-date open-door policy. Vision 2000 is systematically communicated to the public by the top management, in interviews and conferences. Alex Krauer, CEO, acts as the main mediator of Ciba-Geigy messages to the public. After every mishap, the public is informed in detail on the situation and on the measures taken.

According to a survey of the University of Geneva, the 1989 annual report fulfilled only 37.9% of the EC balancing guidelines. But the latest annual report of 1990 was adapted to the EC-guidelines and in 1993 IAS-standards are to be applied for the first time.

(iii) The responsibility for the actual development and implementation of the off-site emergency plan may rest with local officials or with a designated committee, depending on the laws and policies which are applicable in the locality, and may include involvement by regional or national authorities. It should be clear, however, who has the decision-making responsibility for the development and implementation of the plan.

E.1.32 Management of a hazardous installation should provide, without reservation, information it has which is necessary to assess hazards and to develop the off-site emergency plan to those responsible for preparation of the off-site plan.

- In addition to information concerning the installation, management should co-operate with public authorities in the routing and identification of pipelines which carry hazardous substances outside the boundary fence of the hazardous installation across public land to another part of the site.

E.1.33 Highly technical and specialised information in emergency plans should be presented in a form appropriate for emergency responders. Technical details on a specific chemical should be expressed in terms which provide clear guidance as, for example, in the case of an acute exposure to a high dose.

E.1.34 In the development of an off-site emergency plan, all emergency response participants should be identified. In addition, their roles, resources and capabilities should be realistically established and their commitment and participation obtained. These participants should include, among others:

- police, fire, medical (including hospitals), transport and welfare services;
- emergency management or civil defense agencies;
- public works and utilities;
- the management of the hazardou installations;
- public information/communicati outlets; and
- public health and environmental agencies.

E.1.35 Emergency preparedness pla identifying the roles and responsibili of all the parties concerned, should clearly indicate the chain of comman and co-ordination among the parties, lines of communication and the mea obtaining the necessary technical, meteorological and medical informat

- The plan should identify an emergency co-ordinating officer v the necessary authority to mobiliz and co-ordinate the emergency services.

E.1.36 Emergency planning must tak into account the special situation of l institutions which may have particula vulnerable populations such as schoo hospitals and homes for the elderly.

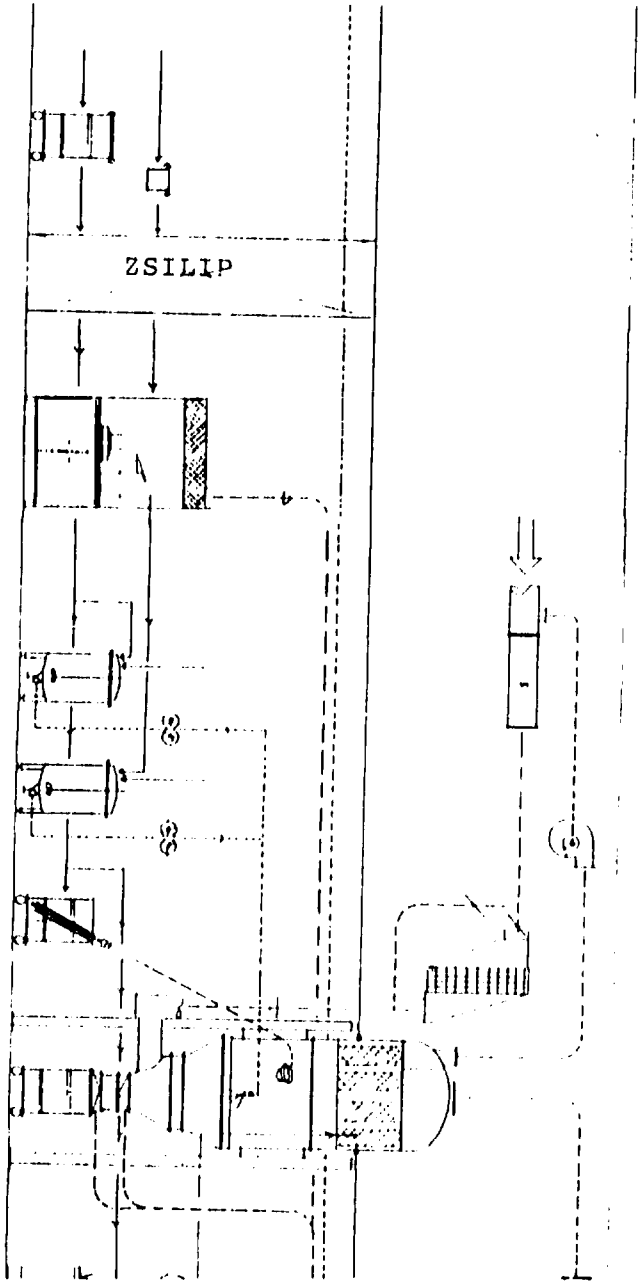
E.1.37 The emergency plan should provide guidance on when the potenti affected public should shelter indoors when they should be evacuated.

E.1.38 The public should be given, o continuing basis, specific informatio on the appropriate behaviour and safety measures they should adopt i the event of an accident involving hazardous substances (see OECD Council Decision-Recommendation

HORMONTABLETTA GYÁRTÁS, TECHNOLÓGIAI FOLYAMATÁBRA

Műveletek:

Hordozó anyag:
- belső fázis,
- külső fázis
- kötőanyag
Bemért mennyiség:
202000,0 g
Átlag nedvesség: 3%



Hatóanyag bemérés mérőfülkében, bemért mennyiség: 360,0 g

Granuláló oldat főzés

Hatóanyag oldás cloroformban és etilalkoholban

Belső fázis felszivatás a fluidizációs granulálóba, fluid állapotban hatóanyag-oldat beporlasztás, szárítás.
Fluidizációs granulálás, szárítás, regranulálás.
Átlag nedvesség:
2,0-2,5 %

Környezeti hatás, környezetvédelem:

A hatóanyag bemérés szívott mérőfülkében történik, az elszívott levegővel esetleg elragadott hatóanyag por a fülkébe épített szűrőn kerül leválasztásra, a szűrőt rendszeres időközönként cserélik, az elhasznált szűrőt égetésre elszállítják.

A készülék falára tapadt hatóanyag maradékot oldószerrel leoldják, ezt az oldatot is beporlasztják a fluidizációs berendezésbe, ezzel egyben átmossák a porlasztó rendszert.

A granulálás során előállt súlyveszteség átlag 1,0 %. Ez részben a nedvességtartalom változásból, részben a berendezés szűrőjének pórusmérete miatt a rendszerből eltávozott szilárd anyag veszteségből adódik. Ezt az eltávozó port az elszívó vezetékbe épített HEPA (DOP 99,95%) szűrő választja le.

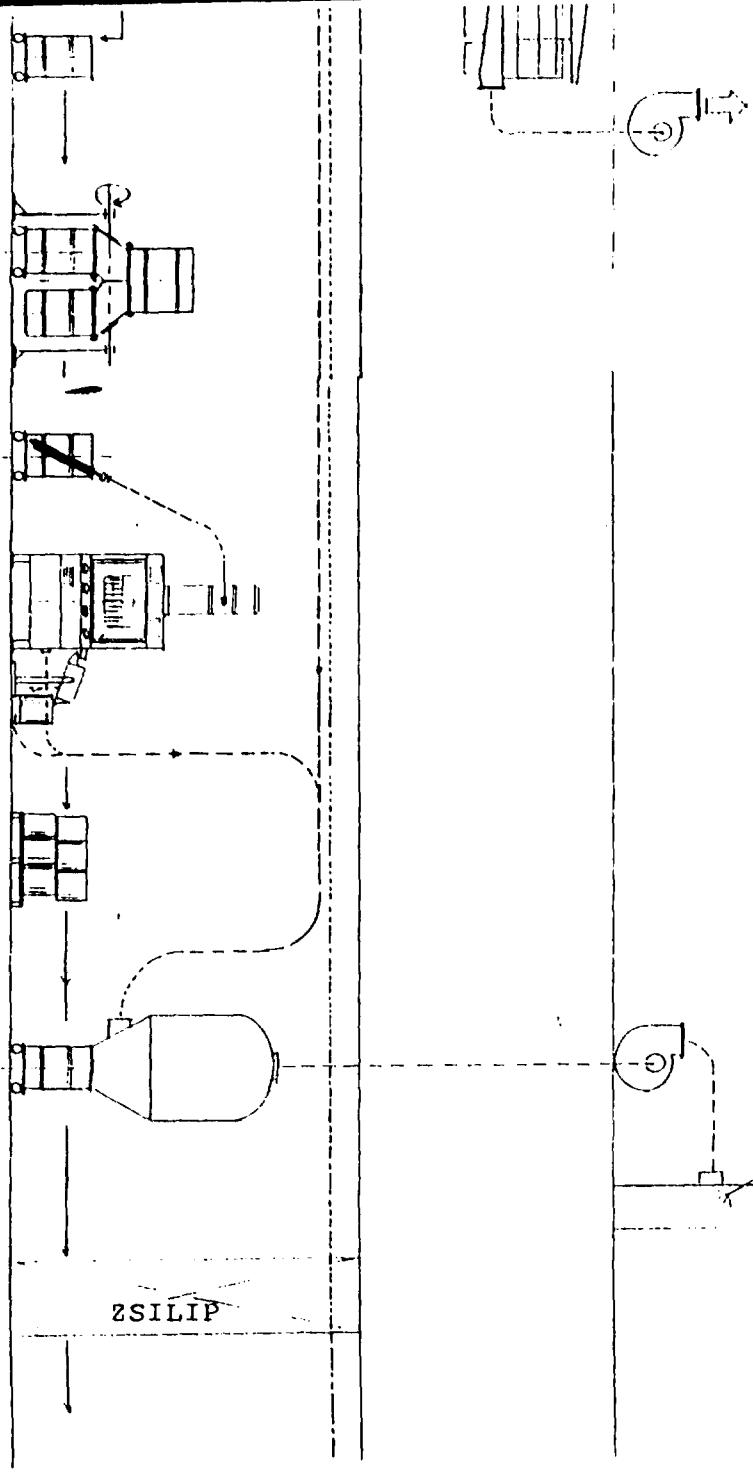
A fluidizációs berendezés mosása, tisztítása 15-20 sarzsonként történik.

Külső fázis hozzátöltés.

Véghomogenizálás

A granulátum felszivatása a tablettázó gép garatába,

Tablettázás.



re elszállítják.
Ezután a szűrőt kiemelik, a készüléket kimossák, a mosóvíz a csatornába van vezetve.
A szűrőzsákot mosógépben mossák, a mosóvíz a csatornába kerül.
A HEPA szűrő betéteket PE fóliatömlő védelemmel kiemelik, égetésre elszállítják.
A mérhető porveszteség sarzsonként átlag 250,0 g.

A tablettázás során előálló veszteség 1,0-1,5 %, ami a tabletta préselés, ill. a tabletta portalanítás során a technológiai elszívással távozik.

A technológiai elszívás a hatóanyag bemérésnél, a granuláló berendezés bontásánál, a tabletta préselés és portalanítás során keletkező porokat szívja el, zsákos porszűrővel, majd ezt követően nedves permetező porleválasztóval (ROTOCLON) leválasztja.
A zsákos porszűrő alatt összegyűjtött port (átlag 2500,0 g/sarzs) égetésre elszállítják.

A nedves porleválasztó által kimosott por a csatornába kerül.

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demonstrate such compliance to others. The standard is also intended to support certification schemes.

In addition to specifying the requirements for an environmental management system, the standard also provides guidance, in annex A, to implementation and assessment. For ease of use, the principal subclauses of the specification and guide have related numbers; thus, for example, 4.5 which requires participating companies to have an internal environmental protection system. The standard specifies the elements of such a system. Additionally, the environmental management audits and environmental management reviews together cover the activities of 'environmental auditing' as described by the International Chamber of Commerce, and in the draft Regulation.

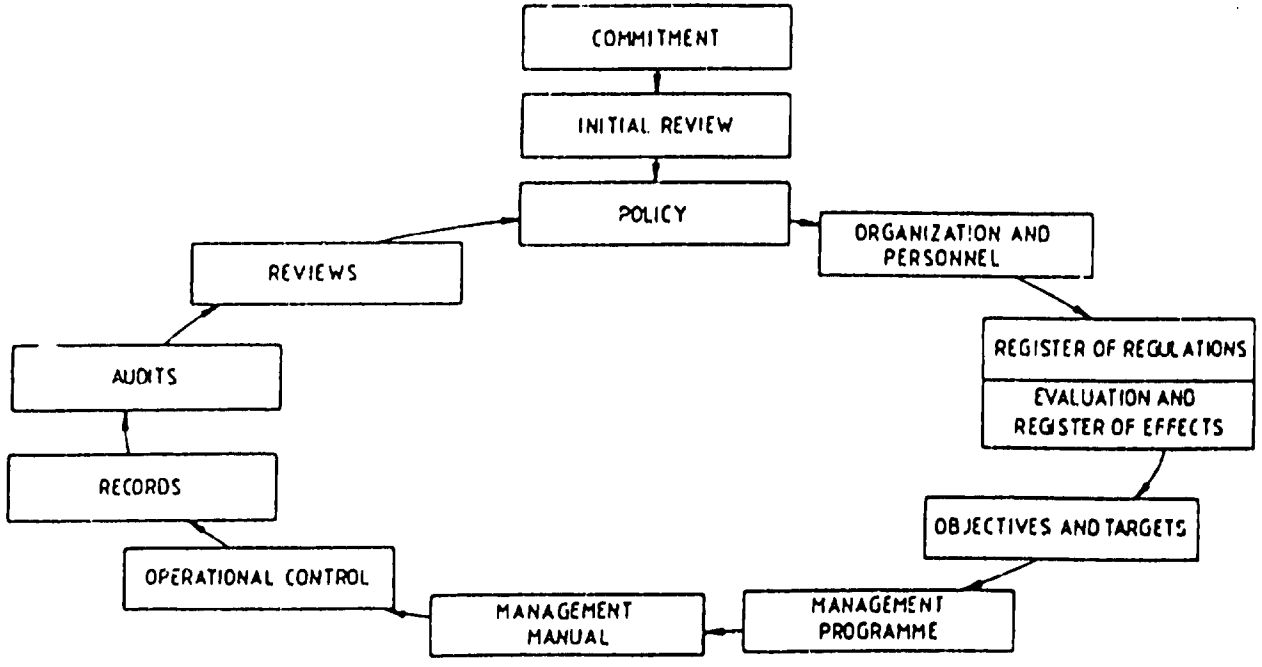
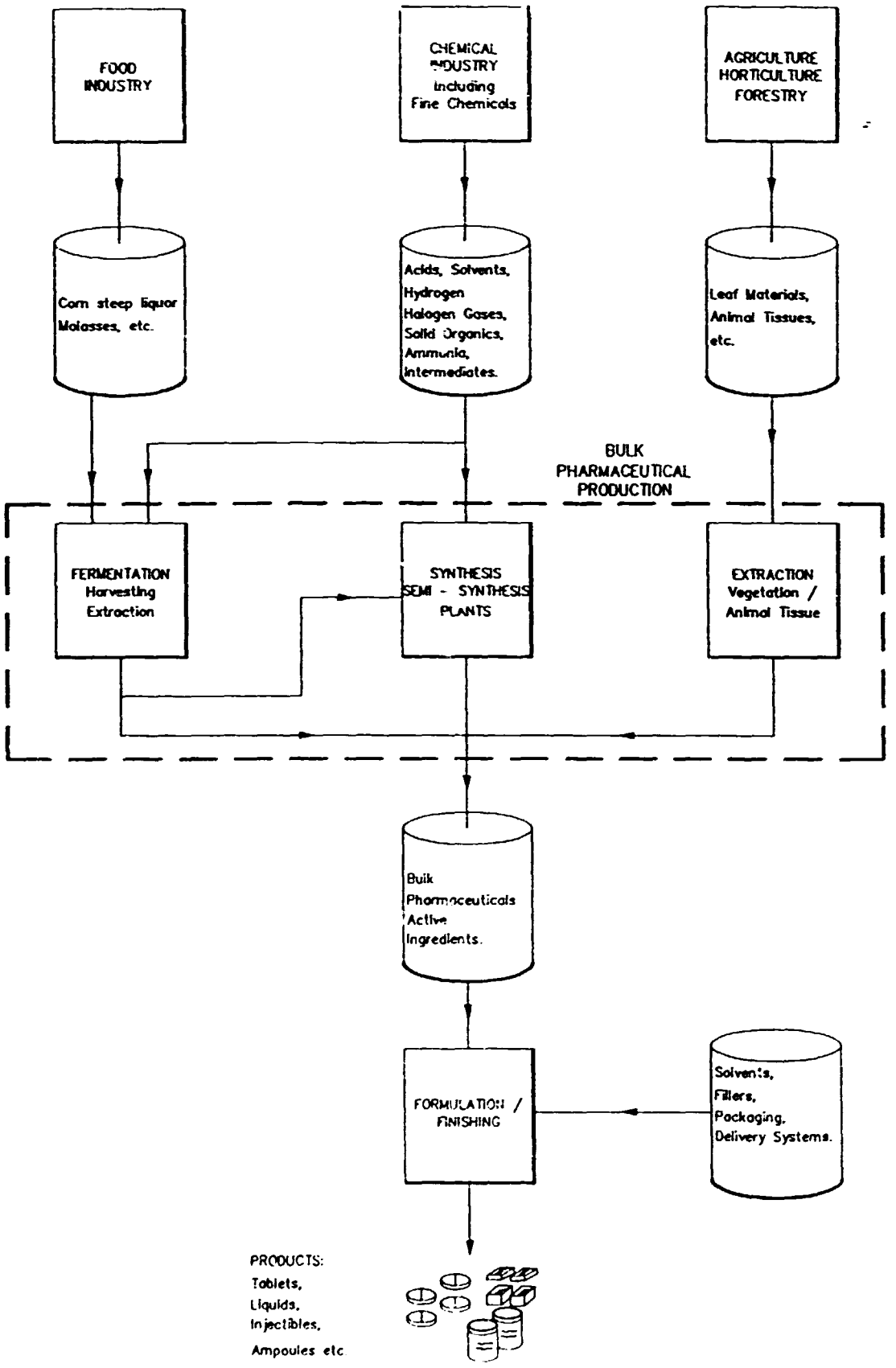


Figure 1. Schematic diagram of the stages in the implementation of an environmental management system



LINKAGES BETWEEN PHARMACEUTICAL MANUFACTURE AND OTHER INDUSTRY SECTORS: CHEMICAL, FOOD AND AGRICULTURE

Fig. 1.1

fig 2.

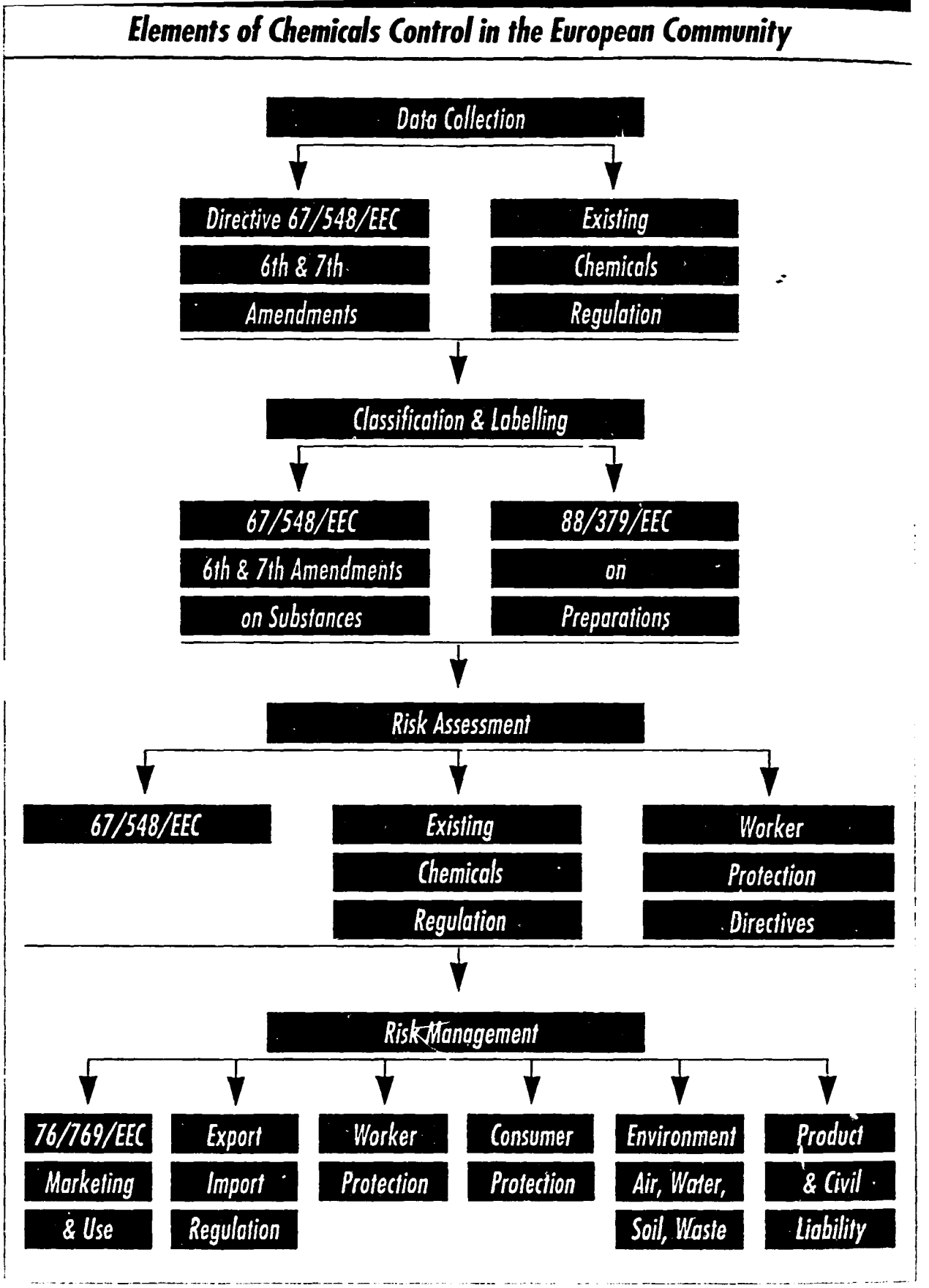

Elements of Chemicals Control in the European Community
Data Collection
Directive 67/548/EEC
6th & 7th
Amendments
Existing
Chemicals
Regulation
Classification & Labelling
67/548/EEC
6th & 7th Amendments
on Substances
88/379/EEC
on
Preparations
Risk Assessment
67/548/EEC
Existing
Chemicals
Regulation
Worker
Protection
Directives
Risk Management
76/769/EEC
Marketing
& Use
Export
Import
Regulation
Worker
Protection
Consumer
Protection
Environment
Air, Water,
Soil, Waste
Product
& Civil
Liability

Fig. 6

FIGURE 1
GENERAL OVERVIEW OF INCINERATION SUBSYSTEMS AND TYPICAL PROCESS COMPONENT OPTIONS

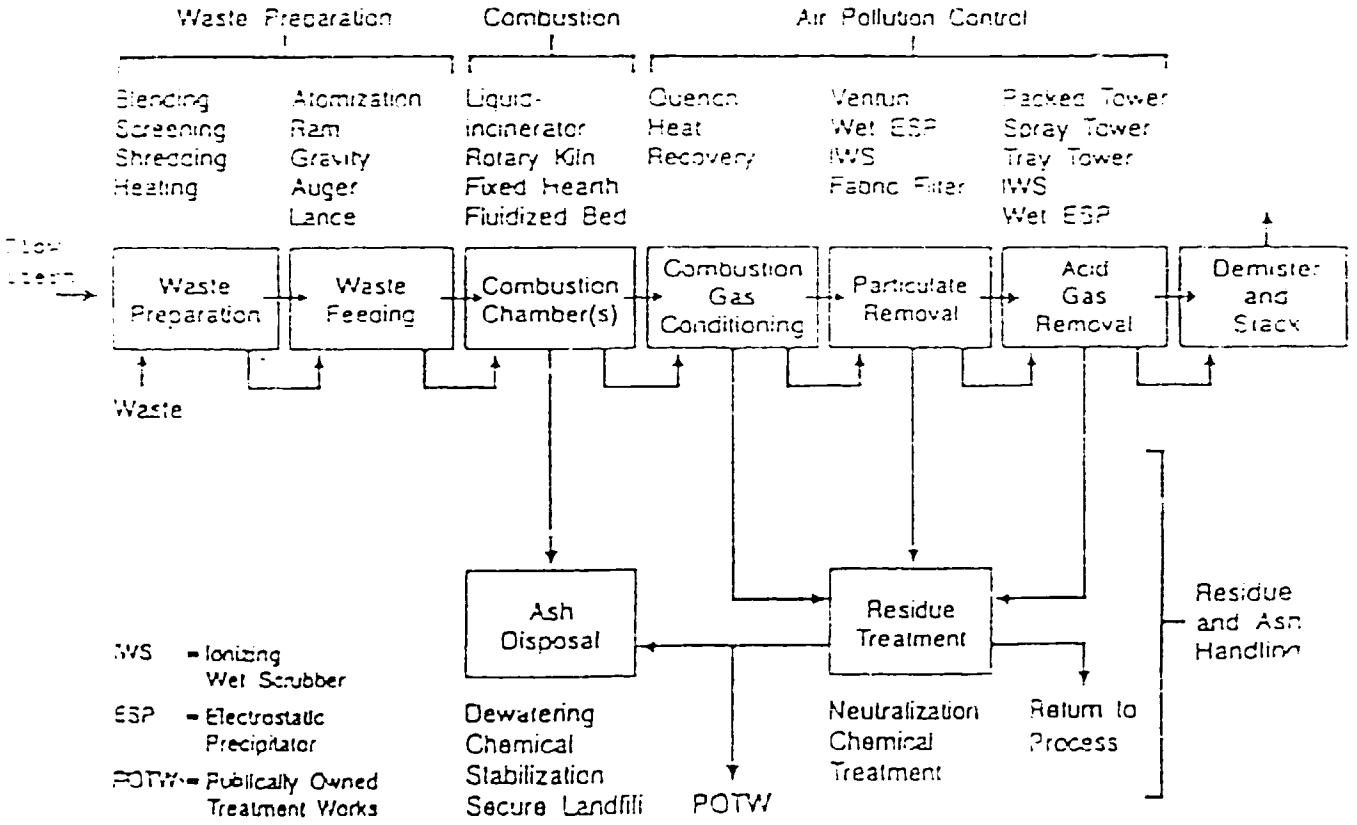


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Fig 7

FIGURE 2
TYPICAL INCINERATOR PROCESSES
(ROTARY KILN)

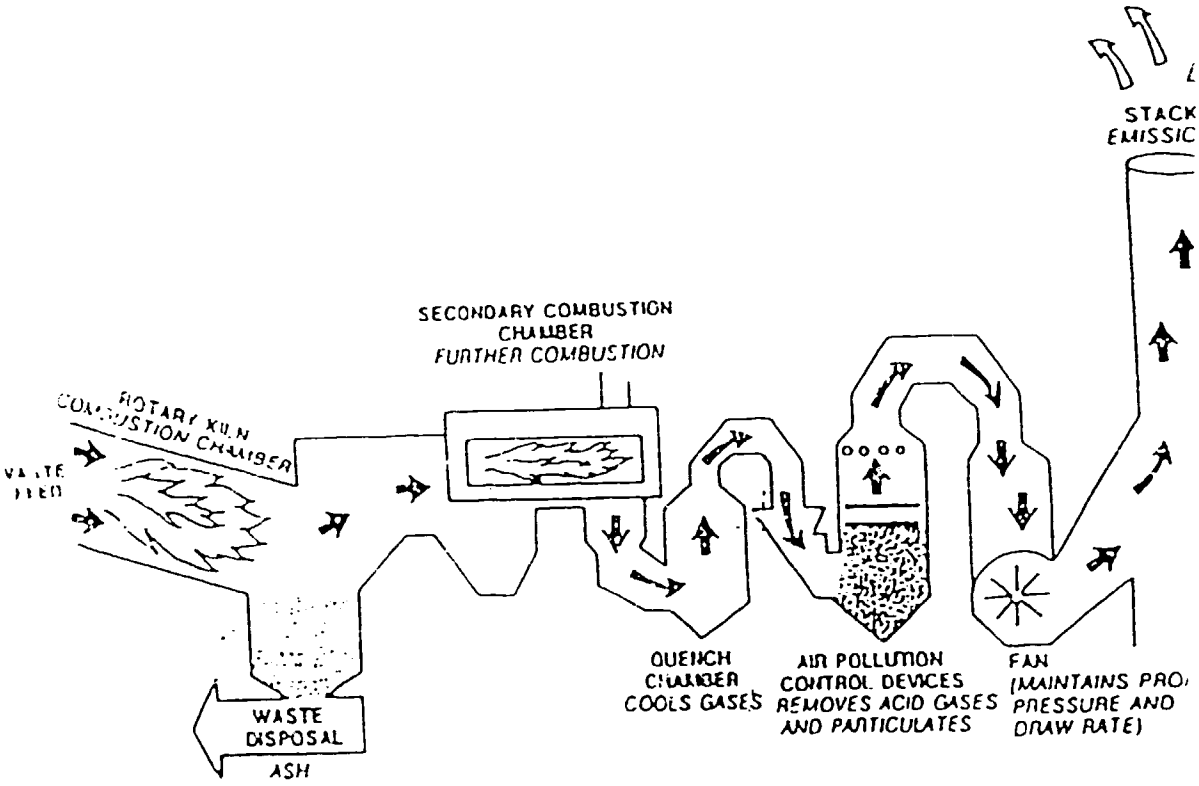

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Fig 8.