

GOOD MANUFACTURING PRACTICE GUIDE PART I FOR MEDICAL GASES

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EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL

AVENUE DE L'ASTRONOMIE 30 • B – 1210 BRUSSELS
Tel: +32 2 217 70 98

E-mail: info@eiga.eu • Internet: www.eiga.eu



GOOD MANUFACTURING PRACTICE GUIDE PART I FOR MEDICINAL GASES

Prepared by WG-7

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EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL
Avenue de L'Astronomie 30 B 1210 Brussels Tel +32 2 217 70 98
www.eiga.eu e-mail: info@eiga.eu

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Amendments to 99/15

Section	Change
Doc	Re-affirmation without any changes

1 Introduction

Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use [1]¹ and as amended by Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 [2] defines a medicinal product as any substance or combination of substances:

- presented for treating or preventing disease in human beings; and
- which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

This Directive requires that the manufacture of all medicinal products shall be controlled following the principles of Good Manufacturing Practice (GMP), detailed in the EC Good Manufacturing Practice Guide and defined in Commission Directive 2003/94 of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [3].

The EC GMP Guide details the principles of the quality management system (QMS) that should be established by every manufacturer or importer of medicinal products and is laid out in nine chapters, dealing with each aspect of the QMS. The purpose of the EC GMP Guide is to ensure that the manufacturing process is controlled so that the medicinal products are produced to the quality level specified in the appropriate marketing authorisation, where required, or the product specification.

The EC GMP Guide recognises the differences between the manufacture of traditional pharmaceutical products and medicinal gases and prescribes in Annex 6 of the Guide the specific elements of the QMS to be used to control the manufacture of medicinal gases. The requirements of Annex 6 have to be followed in addition to those of the main EC GMP Guide.

To assist the Medical Gas Industry in the interpretation of the overall requirements of the EC legislation with respect to GMP, this EIGA GMP Guide has been prepared. It has been structured so that it integrates the specific requirements of the Annex 6 of the EC GMP Guide into the parts of the main text that are relevant to medicinal gas manufacture. Where the requirements of the EC Guide have no relevance to the manufacture of medicinal gases, these requirements have been omitted from the EIGA GMP Guide.

Hence, this EIGA GMP Guide may be used by all medicinal gas manufacturers to assist them in the preparation of a quality management system to ensure that all medicinal gases are manufactured to a defined product specification.

This EIGA GMP Guide mainly addresses the quality requirements for the manufacture, storage and distribution of medicinal gases. These activities shall also comply with all of the other appropriate operational, safety and environmental requirements detailed within EIGA publications and any relevant national / international legislation and regulations.

This version of the EIGA GMP guide covers the:

- EU Guidance on GMP Part I: Basic Requirements for Medicinal Products of 2003
- -Annex 6 Manufacturing of Medicinal Gases of July 2010

It does not specifically cover any International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. (ICH)

¹ References are shown by bracketed numbers and are listed in order of appearance in the reference section.

2 Scope and purpose

2.1 Scope

This EIGA GMP guide is intended for use by all manufacturers of medicinal gases and fillers of medicinal gas cylinders. It covers the:

- manufacture and storage of all medicinal gases on licensed gas company premises;
- filling of medicinal gas cylinders; and
- distribution of bulk medicinal gases and medicinal gas cylinders.

It specifies the requirements necessary to meet the specifications set in the relevant Pharmacopoeia standards and, where required by the national authorities, in the relevant marketing authorisations.

Where medicinal gases are covered by a marketing authorisation, issued by a national authority, the requirements detailed in this guide may be replaced with specific requirements detailed in those marketing authorisation.

This guide does not cover manufacturing and handling of medicinal gases in hospitals, which will be subject to national legislation. However relevant parts of this guide may be used as a basis for such activities.

The contents of this EIGA guide covers only the requirements set out in the chapters 1 to 9 of Part I of the EC GMP guide and in Annex 6, covering the manufacture of medicinal gases.

It currently does not cover the specific requirements detailed in:

- Annex 15, Qualification and validation;
- Annex 16, Certification by a qualified person and batch release;
- Annex 17, Parametric release;
- GMP Part II, Basic requirements for active substances used as starting material; and
- GMP Part III, Site master file.

Certain aspects of the above requirements are covered in the EIGA GMP guide where they have been referred to in the text of the main EC GMP guide.

This guide provides the minimum standards that are required to meet the requirements of the EC Directive 2001/83 [1]. Although the terminology of the EIGA Guide refers to activities that 'shall' be carried out, it may be appropriate to utilise alternative procedures provided that:

- It can be demonstrated by risk assessment that the alternative method provides at least the same level of protection to ensure that the quality of the final product is maintained.
- Any risk assessment is formally documented.
- Appropriate approval is obtained from the national authorities to deviate from the requirements of the EC GMP guide.

Certain national authorities define some of the medical gases that do not fall strictly under the definition of a medicinal product, as medical device gases. These gases, normally used in conjunction with medical devices, do not strictly fall under the control of the EC GMP guide, but for the purposes of this publication can be considered in the same way as for other medicinal gases. Within the text, any

reference to the manufacture, filling, storage or distribution of medicinal gases shall apply equally to any medical device gases.

2.2 Purpose

The purpose of this publication is to provide manufacturers and importers of medicinal gases and fillers of medicinal gas cylinders with a comprehensive guide for the development of a quality management system (QMS) to control their relevant manufacturing processes to meet the GMP requirements. Other requirements for management systems, such as ISO 9001, and may also be used as a guide during pharmaceutical inspections by the national authorities.

3 Definitions

There following terms have the specific meanings detailed below when used in the context of the EIGA GMP guide.

Shall / must	Indicates a requirement that is mandatory that is either prescribed by the legislation or is considered to be the best operating practice by the medicinal gas industry.
Should / may	Indicates a requirement which is preferred method of achieving a requirement but may be substituted by an alternative method provided that this method achieves the same requirement to at least the same standard.
Good Manufacturing Practice	Is that part of quality assurance which ensures that medicinal gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.
Medicinal gas	Gas used for treating or preventing disease in human beings or administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions through pharmacological effect.
Medical device gas	Gas classified as a Medical Device according to Directive 93/42/CE as a substance used alone or in combination intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of : • diagnosis, prevention, monitoring, treatment or alleviation of disease, • diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, • investigation, replacement or modification of the anatomy or of a physiological process, • control of conception.
Marketing authorisation	An authorisation issued by the national authority to permit a medicinal gas to be marketed within their territory, as described by Article 6 of EC Directive 2001/83EC [1]. The marketing authorisation details include the specification of the medicinal gas, the method and sites of manufacture, the method of supply, including specification of the cylinder or container and the valve closure, clinical indication and contra-indications and precautions for use. Currently, not all national authorities require a marketing

	authorisation for all medicinal gases to allow them to be marketed within their territory.
Manufacturing authorisation	An authorisation issued by the national authority to permit the manufacture of specified medicinal gases on specific sites as described by Article 40 of EC Directive 2001/83EC [1]. The manufacturing authorisation specifies the medicinal gases that may be manufactured and filled into cylinders on specific sites, the names of the responsible persons on each site and the name of the Qualified Person, where required by the national authority.
Qualified person	Nominated person responsible for the final certification of all medicinal gases prior to supply to the patient, as described by Article 48 of EC Directive 2001/83EC [1]. The qualifications required by the qualified person are described in Article 49 of EC Directive 2001/83EC [1].
Test	Unless otherwise stated, the term test refers to either the sampling and analysis of the medicinal gas at various stages in the process of manufacture or cylinder filling or to the process of validating that the specification of the finished conforms to the requirements of the marketing authorisation or product specification.
Pharmacopoeia monograph	Refers to the specification and test methods for specific medicinal gases prepared and issued by the European Pharmacopoeia.
Manufacturing site	Refers to any site, covered by a manufacturing authorisation, where medicinal gas cylinders are filled.
Bulk medicinal gas	Gas supplied directly to the end user or to a medicinal gas cylinder filling site, where it has to be further processed before it can be used by the patient.

4 Quality Management (EC GMP Chapter 1)

4.1 Principle

Any manufacturer of medicinal gases or filler of medicinal gas cylinders, holding an appropriate Manufacturing Authorisation, shall ensure that the medicinal gases they produce are:

- fit for their intended use by the patient;
- compliant with the requirements of their marketing authorisation, where required; and
- safe, of an appropriate defined quality and efficacious so that they do not place patients at risk.

The attainment of this quality objective is the responsibility of the senior management and requires the participation and commitment of staff in many different departments, at all levels within the company, and by the company's suppliers and distributors.

To achieve the quality objective reliably there shall be a comprehensively designed and correctly implemented quality assurance system, incorporating the principles of Good Manufacturing Practice and quality control. (Note: the ICH Q10 refers to Pharmaceutical Quality System [4]). The quality assurance system shall be fully documented and have its effectiveness monitored on a regular basis.

All parts of the quality assurance system shall be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. In addition, where required by the national authority, all medicinal gases shall be formally released for patient use by the Qualified Person.

EC Directive 2001/83 [1] specifies the specific legal responsibilities for both the holder of the Manufacturing Authorisation and the qualified person.

The basic concepts of quality assurance, Good Manufacturing Practice and quality control are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of the manufacture of medicinal gases and the filling of medicinal gas cylinders.

4.2 Quality assurance (QA)

Quality assurance is a wide ranging concept which covers all matters which individually or collectively influences the quality of the medicinal gas. It is the total of the organised arrangements made with the object of ensuring that medicinal gases are of the quality required for their intended use. Quality assurance therefore incorporates the principles of Good Manufacturing Practice as well as other factors outside the scope of this EIGA GMP Guide.

The system of quality assurance appropriate for the production of medicinal gases and the filling of medicinal gas cylinders shall ensure that:

- The equipment and procedures used for the production of medicinal gases and the filling of medicinal gas cylinders are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice.
- Production and quality control operations are clearly specified and the principles of Good Manufacturing Practice and Good Laboratory Practice adopted.
- Managerial responsibilities are clearly specified.
- All necessary controls on starting and packaging materials, intermediate products, and any other in-process controls and validations are carried out.
- The bulk medicinal gases and the filled medicinal gas cylinders are correctly processed and checked, according to the defined standard operating procedures and individual work instructions.
- Where the national regulations specify, medicinal gases are not sold or supplied before a qualified person has certified that each production batch has been produced and controlled in accordance with the specifications of the marketing authorisation and any other regulations relevant to the production, quality control and release of medicinal gases.
- Satisfactory arrangements exist to ensure, as far as possible, that the medicinal gases are stored, distributed and subsequently handled so that safety and quality of the gas and the condition of the containers are maintained throughout their shelf life.
- There is a procedure for self-inspection and quality audit which regularly appraises the effectiveness and applicability of the quality assurance systems

4.3 Good Manufacturing Practice (GMP) for medicinal gases

Good Manufacturing Practice is that part of quality assurance which ensures that medicinal gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.

Good Manufacturing Practice is concerned with the quality control of the production, filling and distribution of medicinal gases.

The basic requirements of Good Manufacturing Practice are that:

- All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing or filling medicinal gases to the required quality so that they comply with their specifications.
- Critical steps of the manufacturing processes and any significant changes to the process are validated
- All necessary facilities for Good Manufacturing Practice are provided including:
 - appropriately qualified and trained personnel;
 - adequate premises and space to carry out all operations;
 - suitable equipment and services;
 - correct materials, containers and labels;
 - approved standard operating procedures and work instructions; and
- Suitable finished product storage and methods of distribution.
- Work instructions and standard operating procedures are written in an instructional form in clear and unambiguous language, applicable to the facilities provided.
- Operators are trained to carry out procedures correctly and their competency assessed against a documented programme.
- Records are made, manually or electronically during manufacture of the medicinal gases and the filling of medicinal gas cylinders. These records shall demonstrate that all the required steps, defined by the standard operating procedures and work instructions, have been taken and that the quantity and quality of the medicinal gas is as defined. Any significant deviations from these requirements are fully recorded and investigated.
- Records of the manufacture and distribution of the medicinal gases provide the complete history of the batch and are retained in a comprehensible and accessible form. These records shall be comprehensive enough to allow the batch to be traced in the event of a product recall.
- The method of storage and distribution of the medicinal gases minimises any risk to their quality.
- A system is available to recall any batch of product, from sale or supply.
- Complaints about marketed products are examined, causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent reoccurrence.

4.4 Quality control (QC)

Quality control is that part of Good Manufacturing Practice which is concerned with sampling, testing and specifications of medicinal gases. It is also concerned with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that medicinal gases are not released for patient use until their quality has been judged satisfactory.

The basic requirements of quality control are that:

- Adequate facilities, trained personnel and approved procedures are available for the sampling, inspecting and testing of starting materials, packaging materials, bulk medicinal gases and filled medicinal gas cylinders for Good Manufacturing Practice purposes.
- Samples of starting and packaging materials, bulk products and filled cylinders are taken by personnel and the test methods approved by the quality controller.
- Test methods are validated.
- Records are made, manually or electronically by recording instruments, to demonstrate that all the required sampling, inspecting and testing procedures are carried out. Any deviations are fully recorded and investigated.
- The bulk medicinal gases and the filled medicinal gas cylinders comply with the qualitative and quantitative specification of the finished product and are correctly labelled.
- Records are made of the results of inspection and testing of starting materials, bulk medicinal gases and filled medicinal gas cylinders. These records shall be formally assessed against the specification by the relevant quality controller. Product assessment shall include a review of the relevant medicinal gas production and filling documentation and a review of any significant deviations from the specified procedures.
- Each batch of bulk medicinal gas or medicinal gas cylinders is released for patient use and certified by the qualified person, where required by the national authorities, prior to supply, confirming that it is in accordance with the requirements of the marketing authorisation and the product specification.

4.5 Product quality review

Regular periodic or rolling quality reviews of the authorised medicinal products, including export only products are to be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

4.6 Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

5 Personnel (EC GMP Chapter 2)

5.1 Principle

The establishment and maintenance of a satisfactory system of quality assurance for the correct production of medicinal gases and filling of medicinal gas cylinders relies upon people. For this reason there shall be sufficient qualified and trained personnel to carry out all the tasks involved in the production of medicinal gases and the filling of medicinal gas cylinders.

Records shall be maintained to demonstrate that individuals clearly understand their specific responsibilities.

All personnel involved in the manufacture and assembly of medicinal gases shall receive initial and continuing training relevant to their needs and responsibilities. Specifically they shall be trained and assessed in their awareness of Good Manufacturing Practice and be made aware of the critically important aspects of their roles and the potential hazards for patients from the medicinal gases should they not follow the specified procedures.

5.2 General

5.2.1 Personnel requirements

The manufacturer of medicinal gases and the filler of medicinal gas cylinders shall have an adequate number of personnel with the necessary qualifications and practical experience available to carry out all operations. The responsibilities placed on any one individual shall not be so extensive as to present any risk to quality of the gas supplied for patient use.

5.2.2 Organisation chart

Manufacturers of medicinal gases and fillers of medicinal gas cylinders shall have an organisation chart detailing the reporting structures throughout the organisation. All personnel in responsible positions shall have their specific duties recorded in their written job descriptions and adequate authority to carry out their responsibilities. These duties may be delegated to designated deputies of a satisfactory qualification level.

There shall be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application and control of GMP.

5.3 Key personnel

5.3.1 Responsibilities

The holder of a manufacturing authorisation shall have available on every manufacturing site a nominate person:

- responsible for production; and
- responsible for quality control.

Normally these key posts should be occupied by full time personnel. If these persons are not resident on the site they shall still retain the overall responsibilities for production and/or quality control.

The heads of production and quality control shall be independent from each other. In large organisations, it could be necessary for the nominated head of production or quality control to delegate some of their responsibilities to another suitably qualified person.

The manufacturing authorisation holder shall have permanently and continuously at their disposal a qualified person, who shall be responsible for the final release of all bulk medicinal gases or filled medicinal cylinders prior to the supply to the patient. The duties of the qualified person are fully described in EC Directive 2001/83 EC [1].

5.3.2 Independence

The level of independence of quality control to production is considered fundamental to the satisfactory operation of quality control. The quality controller shall have the authority to prevent any finished medicinal gases that do not meet the specification from being supplied for patient use.

5.3.3 Person responsible for production

The person responsible for production is generally responsible for:

- ensuring that the manufacture of medicinal gases and the filling of medicinal gas cylinders follows the authorised procedures detailed on the marketing authorisation, where required, in order to obtain the specified quality;
- checking that the maintenance of the equipment and premises under his control are carried out correctly;

- ensuring that the appropriate process validations are completed;
- ensuring that the required initial and continuing training of his department personnel is carried out and adapted according to the identified need; and
- ensuring that any agreed self-inspection programme is completed and that the appropriate actions are taken to correct any identified non-compliances.

5.3.4 Person responsible for quality control

The head of the quality control department is generally responsible for:

- approving or rejecting, as they see fit, starting materials, packaging materials, and intermediate bulk and finished product;
- evaluating batch records;
- ensuring that all necessary testing is carried out.
- approving specifications, sampling instructions, test methods and other QC procedures;
- approving and monitoring any contract analysis.
- checking the maintenance of their department, premises and equipment;
- ensuring that the appropriate quality control validations are completed; and
- ensuring that the required initial and continuing training of their department personnel is carried out and adapted according to need.

5.3.5 Joint responsibilities

The persons responsible for production and quality control generally have some shared or jointly exercised responsibilities relating to the quality of the medicinal gases.

These responsibilities can include:

- authorisation of written procedures and other documents, including amendments;
- validation of procedures;
- training;
- designation and monitoring of storage and distribution conditions for materials and products;
- retention of records;
- monitoring of compliance with the requirements of GMP; and
- control of any changes to procedures or equipment, including any relevant validations.

5.3.6 The qualified person

Where required by the national authorities, the qualified person's responsibilities shall include:

- Ensuring that each batch of bulk medicinal gas or filled medicinal gas cylinders has been produced and tested /checked in accordance with the relevant directives and the appropriate marketing authorisation.
- Certifying in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of the EC Directive 2001/83 EC [1].
- Approving specifications, sampling instructions, test methods and any other quality control procedures
- Verifying that the appropriate validations are completed.
- Verifying that the required initial and continuing training of their department personnel is carried out and adapted according to the identified need.
- Approving and monitoring of suppliers and materials.
- Approving and monitoring of contract manufacturers.
- Making the decision to recall potentially defective finished product and to assist, as necessary, in the investigation procedure and any follow-up actions when informed of any product non-conformance

The person responsible for the qualified person duties shall meet the qualification requirements laid down in EC Directive 2001/83 EC [1] and shall be permanently and continuously at the disposal of the holder of the manufacturing authorisation to carry out these responsibilities.

The qualified person's responsibilities may be delegated to another qualified person with the appropriate experience.

The qualified person responsible for release of medicinal gases shall have a thorough knowledge of the production and control of medicinal gases.

5.4 Training

Manufacturers of medicinal gases and fillers of medicinal gas cylinders shall provide training for all the personnel whose duties take them into production areas or laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

Besides the basic training on the theory and practice of GMP relevant to the manufacture of medicinal gases, newly recruited personnel shall receive training appropriate to the duties assigned to them.

Continuing training shall also be given, and its practical effectiveness shall be periodically assessed.

Training programmes for all personnel and consultants shall be available, approved by either the head of production or the head of quality control, as appropriate. Training records shall be retained.

5.4.1 Hazard areas

Personnel working in areas where contamination is a hazard or areas where toxic materials are handled shall be given specific training.

5.4.2 Visitors

Visitors or untrained personnel should not be taken into the production and quality control areas.

If this is unavoidable, they should be closely supervised and given the appropriate information in advance, particularly about personal hygiene and the prescribed protective clothing.

5.4.3 Quality assurance training

The concept of quality assurance and all the measures capable of improving its understanding and implementation shall be fully discussed as part of the overall training programme during training sessions.

5.5 Protective clothing

For safety reasons every person entering the manufacturing areas shall wear protective garments appropriate to the operations to be carried out.

Personnel shall be instructed to use gloves when handling medicinal gas cylinder valves.

5.6 Personal hygiene

Separate facilities shall be provided for personnel for eating, drinking or smoking remote from any production and quality control areas. These facilities should include storage for food and drink or any smoking materials. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected shall be forbidden.

6 Premises and equipment (EC GMP Guide Chapter 3)

6.1 Principle

Premises and equipment for manufacture of medicinal gases and the filling of medicinal cylinders shall be located, designed, constructed, adapted and maintained to suit all of the relevant operations. The layout and design of the premises shall aim to minimise the risk of errors and permit effective cleaning and maintenance of the equipment and not have any adverse effect on the quality of products.

The manufacture of medicinal gases and the filling of medicinal gas cylinders is carried out in closed pipework, containers and tanks. Consequently, environmental contamination of the product is minimal, provided that the equipment is suitably commissioned and maintained in an operational condition. However there could be a risk of cross-contamination with other gases if the pipework allows for interconnections between different gases without any suitable backflow protection and the appropriate, validated procedures are not followed correctly.

6.2 Premises

Premises shall provide sufficient space for manufacturing, filling, testing, inspection and storage of medicinal gases to avoid the risk of mix-up. Premises shall be kept clean and tidy to encourage orderly working and have adequate space to permit the storage of cylinders to be correctly laid out with adequate segregation.

6.2.1 Maintenance

Premises and equipment shall be cleaned and maintained regularly to a documented preventative maintenance programme. The repair and maintenance operations shall ensure that they do not present any hazard to the quality of the medicinal gas, and be carried out according to detailed written procedures.

6.2.2 Unauthorised entry

Steps shall be taken to prevent the entry of unauthorised people to production, cylinder filling, storage and quality control areas, which shall not be used as a right of way by personnel who do not work in them.

6.3 Manufacturing areas - Production**6.3.1 Location**

Except where special precautions are taken, production equipment shall be located away from any incompatible activities such as those that generate any chemical or biological emissions

6.3.2 Storage areas

Where starting materials are stored prior to use, they shall be kept in an environment where contamination is avoided and deterioration is controlled.

6.4 Manufacturing areas - Cylinder filling**6.4.1 Layout**

Premises used for the filling of medicinal gas cylinders should preferably be laid out in such a manner as to allow a flow through the area, with cylinder filling steps taking place in areas connected in a logical order corresponding to the sequence of the cylinder filling operations. Cylinder filling areas shall be of a sufficient size and have an orderly layout, providing separately marked areas for different gases and, where applicable, different cylinder sizes.

A typical plant layout is shown in Figure 1,