

DOCUMENT REFERENCE NUMBER
001/AMINO

Company Master File

SITE MASTER FILE

**AMINO CHEMICALS LTD
MARSA**

SEPTEMBER 2003

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1.1 Company Information

Amino Chemicals is a company involved in the manufacture of Active Pharmaceutical Ingredients in bulk. The Company was founded in 1992 and in 1999 was bought by the Dipharma Group.

In the past two years the company has gone through an intense period of restructuring and modernization. One of the major projects was the construction and completion of a new drying section.

The laboratory has been equipped with modern qualified instrumentation.

The target of the company is to achieve the industrial objectives by adopting a Quality System that is integrated to the management system with the purpose of ensuring that its customers receive products that are fit and adequate to their purposes.

1.2 Pharmaceutical manufacturing activities as licensed by authorities

1.3 Other Activities

No other activities carried out at site.

1.4 Name and Address

Company name: Amino Chemicals Limited.
A61
Industrial Estate
Marsa LQA06
Malta

Telephone number: ((+356) 21249223

Fax number: ((+356) 21249226

24 hour contact tel number N/A

1.5 Type of Actual Products Manufactured

The company manufactures ACTIVE PHARMACEUTICAL INGREDIENTS in bulk.

No specifically toxic and hazardous substances are produced at the site.

*Site Master File***1.6 Site Description****The location and immediate environment**

The company is located in a segregated industrial estate. The building are surrounded by other companies (pharmaceutical companies producing medical devices, textile companies, food manufacturers, plastic manufactures).

Size of the site, types of building and their ages

The Plant is located on a plot of land of about 3000 square meters, the laboratory and offices occupy 200 square meters. The manufacturing plant is housed in a concrete building. Equipment is located on steel structures. Flooring is concrete or corrosion-proof tiles or steel plates. Flooring may be flushed to ensure adequate cleaning. Since the plant is multipurpose, written procedures exist to avoid cross contamination. Adjacent structures house services such as solvent recovery, dryers, steam generators, water production system, repair shop, warehousing, offices and laboratories are shown on the chart attached which provides a view of the location.

Separate areas prevent mix-ups as follows:

1. Holding rejected products
2. Storage of released products
3. Storage of in-process materials
4. Packaging and labelling operations
5. Quarantine storage before release of drug substances
6. Manufacturing and processing operations
7. Control and laboratory operations

No canteen is present in Plant, operators go eat to an outside canteen.

The Plant also employs the service of a professional pest control company.

Solid waste or liquid waste not treatable at plant is given to authorize outside contractors for disposal.

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1.7 Employees

Production

Number of employees 11

Quality Assurance/ Quality Assurance

Number of employees 5(4 Quality Control and 2 Quality Assurance)

Storage

Number of employees 1

Technical

Number of employees 2

Commercial

Number of employees 3

Total of Company

Number of employees 27

*Site Master File***1.8 Outside Contractor****Contractor**

The only outside contractor currently being used by the company is for pest control. The company used is Capital Pest Control that is a member of the British Pest Control Association. This company undertakes to inspect the premises thoroughly for pest once monthly and issue a service report that is filed by the Quality Assurance.

Other

On certain occasion the Chemistry Department at the University of Malta is used to carry out some analysis namely ^{13}C -NMR, ^1H -NMR and Atomic Absorption Spectrophotometry.

1.9 Company Quality System

Amino Chemicals quality policy is to achieve its industrial objectives, has deemed necessary to adopt a Quality System that is integrated with the Company's Management System with the purpose of ensuring that its customer receive products which are fit and reliable for their purpose, together with a service adequate and punctual at all levels.

This is achieved through adoption of a system of procedures that reflect the Good Manufacturing Practice Regulations.

Achievement of this policy involves all staff, who are individually responsible for the quality of their work, resulting in a continually improving working environment for all. To achieve and maintain the required level of assurance the Managing Director retains responsibility for the Quality System with routine operation controlled by the Quality Assurance Manager.

The objectives of the Quality Assurance System are:

- a) Products offered completely satisfy, the present and future requirements of the customer and are in compliance to the law and regulations.
- b) The quality is of the highest level whilst controlling the costs
- c) That quality is the objective of all the employees,
- d) All the employees pursue the objective of a constant and continuous improvement to quality.

Quality Assurance Responsibility

- Internal Audit
- Resolution of Quality Assurance System Discrepancies
- Control & Maintenance of the Quality Assurance System
- Documentation & Change Control (Quality System Documents)
- Training
- Release of Finished Goods

Quality Assurance System

The Company has established, documented, implemented and maintains a Quality Management System in accordance with requirements of the ICH guidelines. The company is committed to continually improve the effectiveness of its QMS.

The Company's Quality Management System:

- Regulates the issuance of Standard Operating Procedures
- Controls and regulate the various entities (Production, Stores, Laboratory etc)
- Identifies the processes needed for its operations and their application through out the organisation
- Determines the sequence and interactions of these processes
- Determines the criteria and methods needed to ensure that both the operation and management of these processes are effective
- Ensures the availability of resources and information necessary to support the operation and monitoring of these processes
- Ensures monitoring, measurement and analysis of the processes
- Ensures implementation of actions necessary to achieve planned results and continual improvement of these processes.

The quality systems are based on the ICH guideline.

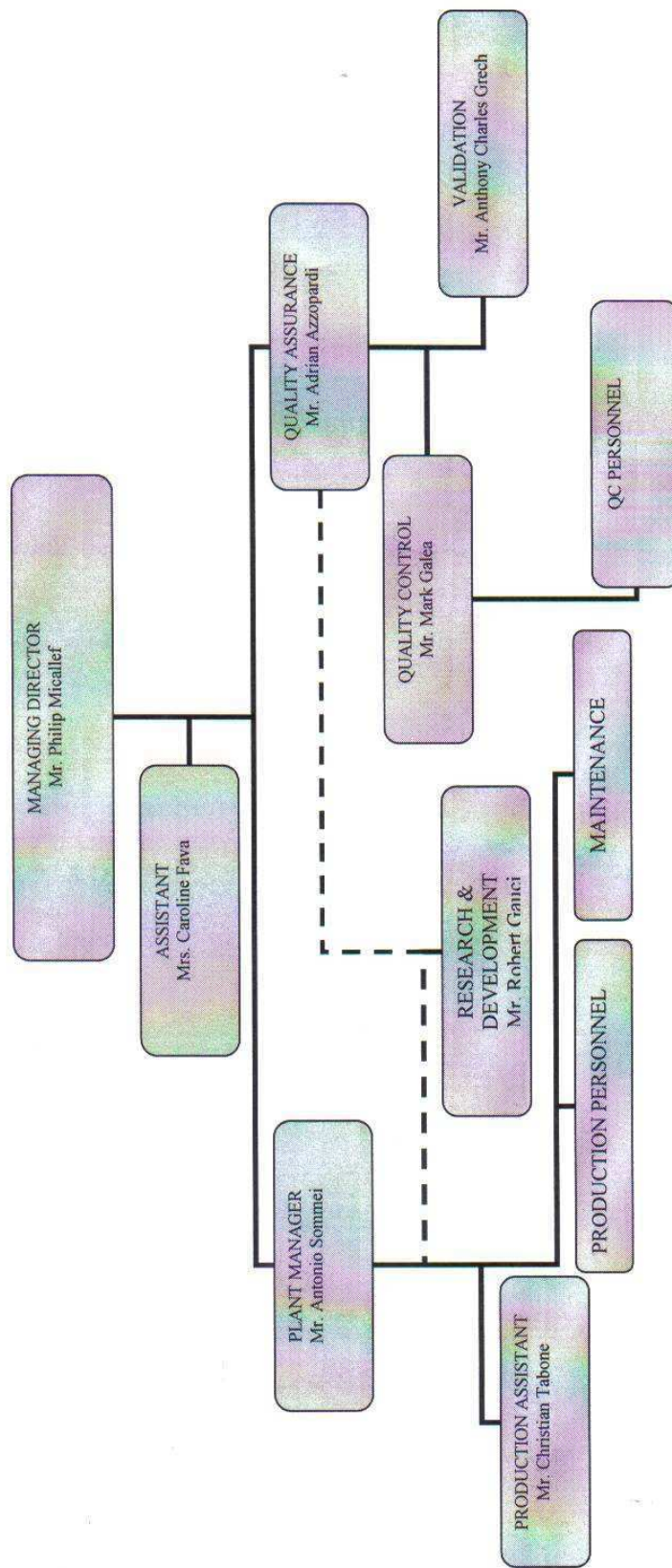
Audit Programmes

An internal audit program is planned on a yearly basis

Release for Sale Procedure.

Each finished active pharmaceutical product has its own set specifications. The product is meticulously tested by the Quality Control department according to the set specification. The result of analysis together with the raw data are reviewed by the Quality Assurance who in turn releases the product for shipment. Product release for shipment are labelled using the appropriate approved label.

2.1 Organisation Chart



2.2 Personnel qualification and their responsibilities

Plant Manager/Production Manager

Antonio Sommei –Plant Manager

He received a Diploma in Chemistry and Biology at IPSIA Perugia in 1984

From 1985 to 1986 he worked as a laboratory analyst in a Chemistry Laboratory at ULSS Perugia.

From 1986 to 1993 work as a production responsible at Sterling S.N.I.F.F. Perugia

From 1993 to date he is working as Plant Manager and Production Manager.

Quality Control

Mr. Mark Galea - Quality Control Manager

He received a degree in Bachelor of Pharmacy from the University of Malta in February 1988.

He worked for Pharmamed in the QC/QA from 1988 to 1999. From 1999 to 2002 he worked for Blaschem Ltd as a Quality Assurance Manager.

Since October 2002 he is working with Amino Chemicals as QC and reports directly to the Quality Assurance manager.

Quality Assurance

Mr. Adrian Azzopardi - Quality Assurance Manager

He received a degree in Bachelor of Science in Chemistry and Biology from the University of Malta in 1994.

He worked for Amino Chemicals in the Quality Control Section from 1995 to 1996.

From 1996 to 1998 he worked for Marsovin Ltd as a Quality Assurance Manager.

From 1998 to 2000 he worked for Euro Chemie Products as Quality Assurance Manager.

Since January 2001 he is working with Amino Chemicals as QA and reports directly to the Managing Director.

2.3 Training Program

A procedure has been formulated to describe the modality adopted by Amino Chemicals for identifying the training needed and/or qualifications of the personnel and provide for the same. The training program is applicable to the technical personnel and of production, with special attention being applied to newly employed. The Managing Director has the obligation of incorporating training of personnel in the budget. The Quality Assurance Manager plans and programs personnel training, legal aspects with regards to quality are to be approved by the Managing Director. The Quality Assurance has the duty of compiling the training program for the personnel Responsible for areas or function. The Quality Assurance, together with the Responsible for areas / function, has the duty of compiling a training program, which is relative to primary arguments. The Responsible for the functions have the duty of compiling the training program for their personnel, asking for collaboration by the Quality Assurance where issues on quality are concerned. The QA has the duty of filing at the end of the year the training schedules, eventual training programs and frequency or exam passing.

The training has to be documented in the module "TRAINING SHEET" showing the following information:

- Training date (dd/mm/yy)
- Duratation of the training (hours)
- Topics discussed (concise description, with references to the course program if these exist)
- Teacher (name, in the eventuality that the teacher was an external one it is sufficient to attach, if available, a copy of the certificate of attendance/progress or otherwise a copy of the program and the application voucher)
- Participants (signatures)
- Area/function responsible (signature)
- Verify effectiveness (date and signature of the verifier or an attached certificate of progress)

Once training is completed the schedule is filed by the Responsible who has conducted the training, he will also send a copy to the QA.

At the end of the year the QA has the duty of filing all the training sheets to the company's quality, planned training programs, and certificates of attendance or exam results.

2.4 Health Requirements for Personnel Engaged

The Company makes use of an external Doctor who monitors the health of employees. Prior to employment the employee to be, is sent for a thorough examination. The Doctor issues a document that the employee is fit for the job.

The company's doctor visits employees who report sick. The doctor will ensure that the employee only returns to work when he is fit to do so.

Employees reporting back from sickness are asked to provide a doctor certificate that justifies their absence.

2.5 Employees Hygiene

Facilities

Adequate washroom facilities are provided both at the plant and at administrative buildings.

Clothing

Garments are provided by the company. There are two types of garments being utilised and these are

- Production garments - used during synthesis of product. This is a reusable washable garment.
- Clean garments: - used during various operations in which operator comes in direct contact with the product. The garment here is a disposable garment

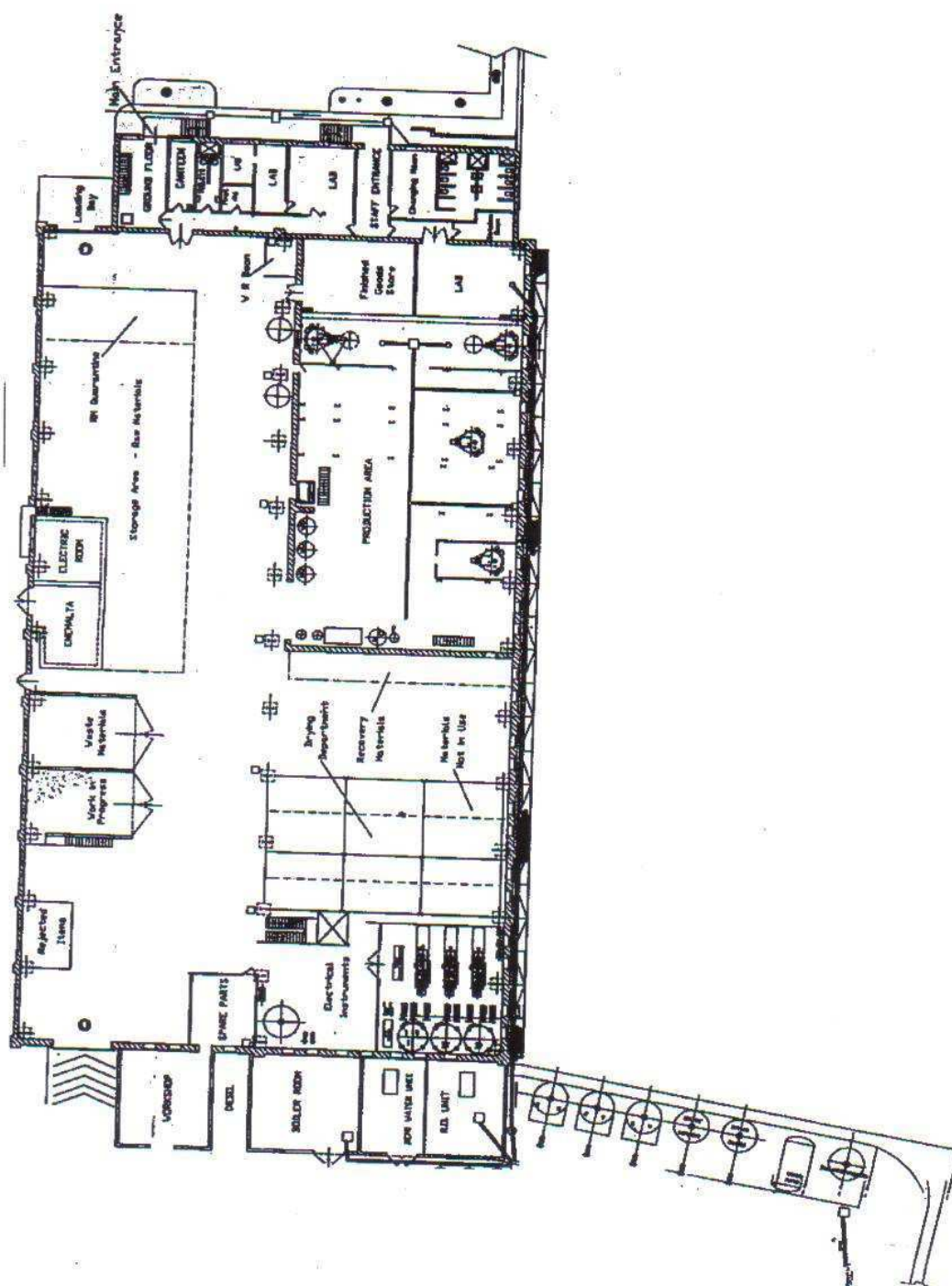
Instructions Protective Equipment

The employees are shown how to use protective equipment and there is a procedure identifying how to use clothing when handling the finished goods. The employees are instructed to wash there clothing on a regular basis. An in house laundry service is used.

MALTA

3 Facility map

3.1.1 Site Plan



3.2 Nature of Construction and Finishes

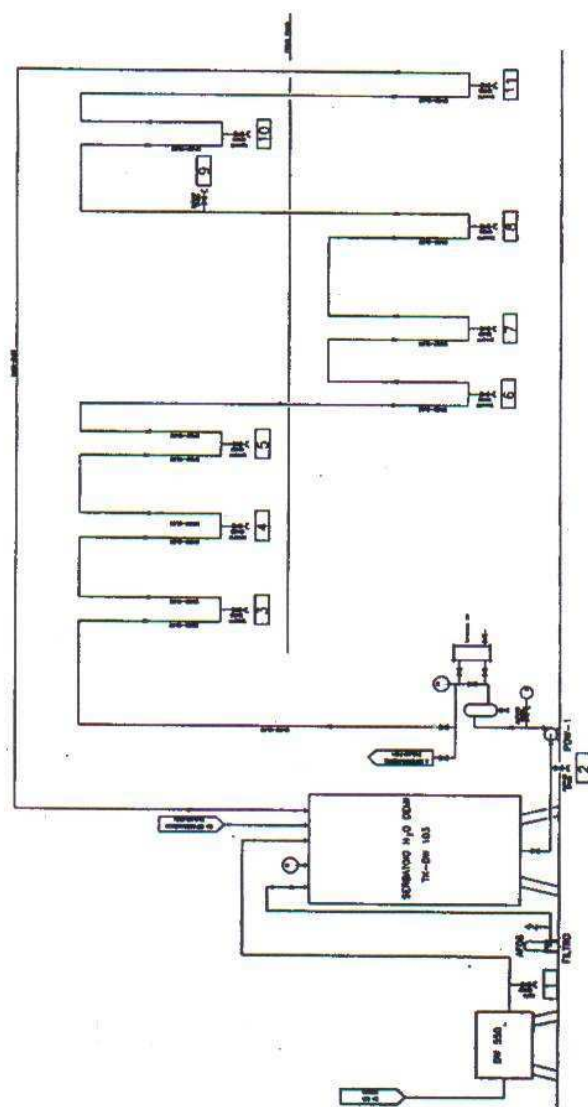
The manufacturing plant is housed in a concrete building. Equipment is located on steel structures. Flooring is concrete or corrosion-proof tiles or steel plates.

3.3 Potentially Harmful Substances

Not applicable

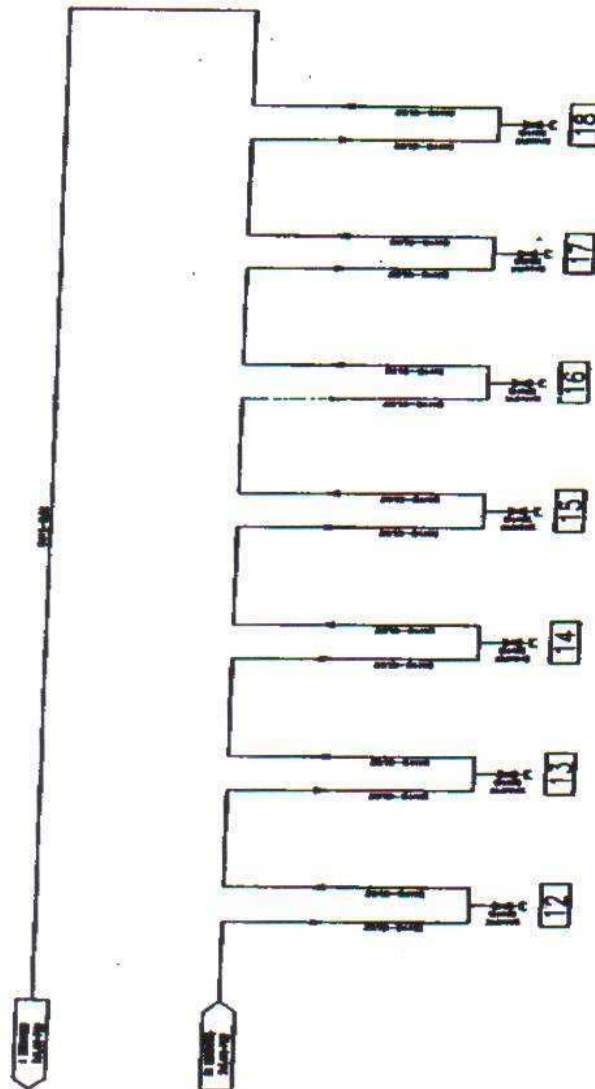
3.4 Water System

Schematic Diagram of Deionised water system Production Plant



Site Master File

Drying Area –water loop



Description of Water System

In the production of API Deionised Water is utilised.

The water system is made up of a reverse osmosis plant and a deionisation plant. The water used for the reverse osmosis is derived from the municipal supply, water produced by RO is stored in two fibre glass tanks. These fibre glass tank supply the deionisation plant. The water produced by this plant is stored in a large stainless steel tank. Water from this tank is utilised in the various production areas

3.6 Maintenance

Production laboratory Control Equipment

Production Identification	Description	Nominal Capacity or Diameter
R-20	Glass lined reactor	L300
R-21	Glass lined reactor	L1300
R-19	Glass lined reactor	L2000
R-27	Glass lined reactor	L2000
R-29	Glass lined reactor	L 2000
R-25	Glass lined reactor	L 7500
R-28	Stainless steel reactor	L 2800
R-33	Stainless steel reactor	L 4000
R-31	Stainless steel reactor	L 6400
R-32	Stainless steel reactor	L 6400
R-30	Stainless steel reactor	L 10000
ID-210	Stainless steel centrifuge	D1500
ID-220	Stainless steel centrifuge	D1500
ID-290	Stainless steel centrifuge	D1500
ID-260	Stainless steel centrifuge	D1000
ID-250	Stainless steel centrifuge	D1200
ES-201	Stainless steel dryer	m 2
EV-202	Stainless steel dryer	m 1
EV203	Stainless steel dryer	m 1
ER204	Glass lined dryer	L 1000
EA205	Stainless steel dryer	L 1000
ABB-201	Scrubber tower	
ABB-202	Scrubber tower	
ABB-203	Scrubber tower	
F1	Horizontal plate filter	L200
F2	Filter	
F3	Filter	
F4	Filter	
F5	Filter	
M01	Granulator	
M02	Granulator	
M03	Granulator	
M04	Granulator	
M05	Granulator	

Site Master File

M06

Granulator

M07

Vibrating sieve

Boiler

Boiler

Chiller

Chiller

Chiller

Reverse Osmosis

Demineralised water plant

Drieres

Standard generator

Maintanance work shop

A qualified supervisor performs the necessary maintenance. On certain occasions it might be necessary to use an external service

*Site Master File***Laboratory**

No. 1	HPLC	Waters 2690
No. 1	HPLC	Jasco (UV Vis Det 975 and PU980)
No. 1	HPLC	Water 600
No. 1	Integration program	Millennium Ver 3.2
No. 1	HPLC	Schimadzu
No. 1	Integration program (HPLC)	
No. 1	Varian	CP8400 with auto sampler
No. 1	Varian	CP8400
No. 1	Sampler	DANI HSS89.50
No. 1	Integration program	
No. 1	Digital Polarimeter Jasco	DIP 1000
No. 1	FT-IR spectrophotometer	Jasco 5300
No. 1	UV spectrophotometer	Jasco V-520
No. 1	Apparatus for melting point	Gallenkamp
No. 1	Analytical balance	Mettler Toledo A8204
No. 1	Technical balance	Gibertini Europe 1700
No. 1	Titration	Mettler DL2S
No. 1	Karl Fischer	Mettler DL3S
No. 1	Vacuum oven	Gallenkamp
No. 1	Muffle furnace	Bicasa 8.E43
No. 2	Climatic chambers	Piardi
No. 2	pH meters	Mettler
No. 1	Glass ware washer	
No. 1	Glass ware Dryer	
No. 1	Tapped density	
No. 1	Microscope	Hund
No. 1	Particle Sizer	Malvern

3.9 Qualification, Validation and Calibration

3.9.1 General Policy

The company policy defines the criteria to be adopted in the various operations and equipment that need to be qualified and validated. It also defines the responsibilities of the functions that should control these operations.

In the case of new equipment the following is carried out:

- Installation qualification (IQ)
- Operation qualification (OQ)
- Performance qualification (PQ)

The procedure also defines the criteria to be adopted in the Validation of process.

The procedure also defines the operations that have to be carried out when accessories to validated equipment are changed and production processes.

Computer Validation

The computer validation and software validation is carried by the supplier of the instrumentation. This mainly applies to laboratory equipment.

Equipment calibration policy

There is a procedure that determines the criteria and parameters for instrument calibration.

3.10 Sanitation

To define the operative modality for the sanitation of the demineralized water system, if out of specification microbiologically, when system is stopped for more than 15 days or at the end of a modification or structural change to the system, The procedure is applicable to equipment at Amino Chemicals Limited.

1. Ion exchange resin production system
2. Storage tank
3. Distribution System

The sanitation program has to be carried out when the Quality Control department indicates that the microbiological contamination is higher then the permitted levels.

Due to the **fragility** of the analysis, in the case of out of specification, a second analysis to confirm the first has to be affected prior to sanitation process.

Standard Sanitation

One time a year a sanitation cycle is effected, normally after a summer holidays

Emergency Sanitation

The emergency sanitation is carried out, as stated above, every time that a sample, taken twice, is out of specification from the microbiological point of view.

Site Master File

4 Documentation.

Description of documentation system

It is mainly the responsibility is on the Quality Assurance to prepare, revise and distribute procedures. However certain procedure that deal with production are prepared by the Plant Manager and then distributed by the Quality Assurance.

With regards to the preparation of the production methods and the master batch records it is the Plant Manager that prepares, revise and distributes these documents. This operation is done after the documentation has been reviewed by the Quality Assurance and approved.

All Master documents are stored in a cabinet in the Plant Manager's office.

The format utilised for preparation of master batch records, methods and SOP are themselves controlled by procedures.

The Quality Assurance prepares the documentation that refers to the specifications of raw material , intermediates and finished products.

Changes that are incurred to documentation is controlled by the Change Control System which is managed by the Quality Assurance.

There are other documentation that is available and these are the following:

- Quality Assurance Standard Operating Procedure
- Quality Control Standard Operating Procedures
- Training Procedure
- Documentation control of process deviation
- Calibration and test documents
- Validation documents
- Stability Protocols

5 Production

Production Operations

Manufacturing is comprehensively managed by the Production Manager who has the task of planning the production taking into consideration the following:

- materials requirements (starting materials and packaging materials);
- confirmation of requirements to be turned into purchase orders
- checking of arrival of materials on the established dates;
- checking of materials state (Quarantine/Approved/Rejected);
- issuing of batch records with the raw material requirement;
- scheduling of operations manufacturing on lines and/or machines;
- manufacturing control;
- closure of manufacturing orders and further checking of materials consumption.

The manufacturing flow is organized as follows:

- a) Preparation of the pharmaceutical dispensing area for the starting materials needed for the manufacturing batch;
- b) Manufacture of the intermediate product and storage in the Warehouse system;
- c) Q.C. approval of the intermediate product;
- d) Preparation of the packaging materials and their delivery to the Finishing department, together with the intermediate product;
- e) packaging and storage of the finished product in the finished goods warehouse ;
- f) Q.C. approval of the finished product;
- g) Quality Assurance product release

The materials are prepared on presentation of the batch record to the store keeper, who prepares the materials. The weight prepared is registered on the batch record and the amount withdrawn from stock is registered on the Stock movement card. Each batch entering the warehouse has its stock movement card, in this way it is easier to utilize the first in first out principle.

The prepared materials are consigned to the head of section who controls that the weights are correct.

5.2 Handling Of Materials

5.2.1 Starting materials

All incoming materials are stored in an dedicated area ("quarantine area"). The store keeper separates the materials, and records the following data on a register:

- date of arrival
- GRN number
- name of supplier
- Internal batch number
- supplier's batch number
- name of product according to the official nomenclature
- amount
- number of packages and their sizes
- signature of store keeper

Each batch is labeled with the Quarantine label and the storekeeper fills a request for the Quality Control laboratory analyses in duplicate.

All the quarantined materials are sampled by Quality Control Personnel according to defined sampling procedures. Each container sampled (a space on quarantine label is available) with the sampler's signature and sampling date. After positive analytical controls, the goods are released, and the material state is moved from "quarantine" to "approved". These materials can be used according to the FIFO technique.

All the manipulations needed for sampling and distribution are performed in strict compliance with the rules intended to avoid the risks of cross contamination.

5.2.2 Intermediate Materials

Intermediate products are stored in a dedicated area. They are accepted by warehouse personnel, using the labeling procedure. These materials are withdrawn from the warehouse just before the execution of the production step.

5.2.3 Finished products

The finished products are processed in the same manner.

5.3 Handling Of Rejected Materials

The Rejected items are isolated in a special areas of the warehouse. On the rejected raw material/intermediate/finished/packaging material, a red label with the indication rejected is affixed by the warehouse responsible.

5.4 Process Validation Policy

The general policy for process validation pertains to the following:

5.4.1 New products

The process validation plan is written by the Validation team of Q.A., and describes all the relevant technical and analytical operations. Strict acceptance criteria are then applied to three product batches manufactured and followed by the validation team.

5.4.2 Process revision for routine products

In the case of a process revision due to equipment change or processing upgrade, the new process steps undergo revalidation according to new acceptance criteria, if appropriate.

6. Quality Assurance

Quality Assurance is responsible for monitoring the compliance of the manufacturing process, and for ensuring established rules and procedures are followed. This Department also operates as a permanent auditing organization within the plant.

The Quality Assurance responsibilities ensure:

- production operations are performed in accordance with the relevant procedures;
- products are properly labeled, sealed and stored to enable suitable physical separation of products;
- equipment is cleaned in compliance with the cleaning procedures;
- the production area is neat and orderly;
- the personnel has been suitable trained for the work performed;
- systems operate in a satisfactory manner.

6.1 Quality Control Laboratory

6.1.1 Products specifications and analytical procedures.

For each product requiring a control of quality, specifications are defined and corresponding analytical procedures are assessed in compliance with the Registration Documentation. These include purchased raw materials and intermediates obtained during production of drug and finished products.

Specifications are based on Drug Master File and/or existing pharmacopoeia monographs. Some specifications are also based on data available from scientific literature which have been checked for reliability. Analytical procedures selected from pharmacopoeia or relevant bibliography originate within the laboratories through experimental work. These procedures use international standards when available, or working standards produced in-house.

Approved specifications and related analytical procedures for each product are dated and signed by the Quality Control Manager and by the Quality Assurance Manager, and filed with a code number. Changes may be introduced, if necessary, but only according to the Change Control System requirements (either internal or Corporate).

6.1.2 Working standards

Working standards are stored in Quality Control Laboratories and are used in routine assay of production batches. Working standards originate from a highly pure production batch, or a pilot batch, which is compared with a primary standard in order to be defined "working standard".

6.1.3 Analytical records

All data regarding the performance of an analysis is recorded on working sheets. The sheets are filled in by the analyst with raw data, product reference, and relevant chromatograms or instrumental print-outs.

Analytical activities are performed using internal test methods formally approved by management, and periodically revised.

The analyst's working sheets are checked and signed by the Quality Control Manager, or his deputies. They are maintained in the Quality Control Archives.

All recordings of U.V. and I.R. spectra, chromatographic records are kept together with other analytical data.

7. Contract Manufacture And Analysis

The only outside contractor currently being used by the company is for pest control. The company used is Capital Pest Control that is a member of the British Pest Control Association. This company undertakes to inspect the premises thoroughly for pest once monthly and issue a service report which is filed by the Quality Assurance.

8. Distribution, Complaints And Product Recall

8.1 Distribution System

After Quality Assurance approval for a product, all finished products are sent to a customer. The batch numbers of each product sent to each customer are recorded.

8.2 Procedures For Complaints And Product Recalls

Two written procedures describe the complaints and the product recalls/returns management.

8.2.1 Complaints

The first procedure manages complaints by:

- Q.A. classifies each complaint by importance
- the complaint object is analyzed in order to ascertain the cause that generated the complaint itself;
- the corrective actions needed to overcome the problem are defined and applied.

8.2.2 Return/Recalls

The second procedure manages the procedure to be applied when a product is recalled or returned. Batches that fall under this category have to be re-analyzed and if approved given a different number as is recommended in the procedure for Batch numbering.

9. Self-Inspection

An internal audit program is planned on a yearly basis as is indicated in the SOP-QA-021.