
ANNEX I & ANNEX II RESPONSES
Additional Information

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Annex A: FDA Report 483 & Alternative Version

Annex A.

10/3/07 **CONFIDENTIAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER US Food & Drug Administration/Foreign Inspection Team Montrose Metro II, 4 th Floor 11919 Rockville Pike, MD 20852, USA		DATE(S) OF INSPECTION 5/28-31/2007	
		FEI NUMBER 3003118161	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED to: Philip Micallef, Managing Director			
FIRM NAME Amino Chemicals Limited		STREET ADDRESS A61, Industrial Estate	
CITY, STATE AND ZIP CODE Marsa, LQA 06 Malta		TYPE OF ESTABLISHMENT INSPECTED API Manufacturer	
<small>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</small>			
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:			
QUALITY SYSTEM			
OBSERVATION 1			
Deviations from the manufacturing process are not recognized, recorded, nor investigated.			
Specifically, the firm had the following deviations from the manufacturing process, which were not noted as deviations from the process. Examples include the following:			
<ol style="list-style-type: none">1. On July 10, 2006, BEN-A Batch: 06BZ010100, the first processing step of Benazepril Hydrochloride, was manufactured. The amounts of all of the starting materials, listed under Quantity Prepared (Kg) were not the same as those listed in Quantity Standard (Kg). Yet, the difference in quantity of starting raw materials was not noted as a deviation.2. On September 22, 2006, TER/G Batch: 06TB090200 was manufactured. Step 10 states to "Maintain under continuous stirring at this temperature till complete of reaction (approximately 5-7 hours)". The product went from 22:30 – 6:30 (8 hours), without a deviation being noted.3. On February 21, 2007, TER/G Batch: 07TB030200 was manufactured. Step 10 states to "Maintain under continuous stirring at this temperature till complete of reaction (approximately 5-7 hours)". The product went from 8:00 (February 23, 2007) until 8:30 (February 24, 2007) for a total of approximately 24.5 hours, without a deviation being noted.4. On September 27, 2006, TER-1 Batch: 06TB090300 was manufactured. The step before IPC-drying 1 states "Drying time approximately 12 – 16 hours". The product was dried from 17:25 (Sept. 28, 2006) until 13:00 (September 29, 2006), which was approximately 20 hours, without a deviation being noted.			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Tricia Y. Samaniego</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Tricia Y. Samaniego, Investigator	DATE ISSUED 5/31/2007
	<i>Ivis Negron Torres</i> <i>Regulatory Program Expert</i>	Ivis Negron Torres, Regulatory Program Expert	

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 2

Customer complaints, leading to associated customer returns, do not include a thorough investigation.

Specifically, the firm received multiple complaints where communication with the customer was initiated, the product was returned to the firm, but the discrepancy was not thoroughly investigated, nor concluded in a timely manner.

Example of these customer complaints include the following:

Product name	Batch #	Date of Complaint	Date Product Returned	Status of Complaint/Return
Benazepril Hydrochloride	05BZ0107009	Jul. 19, '06	Sept. 6, '06 (Return #0009/06)	Quarantine; Awaiting Decision
Benazepril Hydrochloride	03BZ010706	May 5, '05	Jul. 1, '05 (Return #0006/05)	Quarantine; To be reprocessed
Benazepril Hydrochloride	05BZ010500	May 6, '05	Aug. 24, '05 (Return #0007/05)	Quarantine; Awaiting Decision
Venlafaxine	03VF030200 - 050200	Oct. 18, '05	Jul. 3, '06 (Return #0008/06)	Quarantine; To be analyzed at later date

LABORATORY SYSTEM

OBSERVATION 3

Your firm lack of laboratory mechanisms to avoid the use of laboratory reagents that were out of specification during the analytical test of Batch 06TL010300 (Tolterodine Tartrate). Specifically, during the qualification of Karl Fisher reagent lot "A279363114" conducted during February 2007 that reflects OOS results for 3 consecutive weeks. Even though it was approved and used for analysis.

OBSERVATION 4

The Laboratory SOP-QC-027 "Calibration of Gellenkamp Melting Point Determination Equipment" is deficient. Specifically, it does not provide specific set-up instructions for the qualification of it at the working range of manufactured products.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Tricia Y. Samaniego</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Tricia Y. Samaniego, Investigator	DATE ISSUED 5/31/2007
	<i>Ivis Negron Torres</i>	Ivis Negron Torres, Regulatory Program Expert	

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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to: Philip Micallef, Managing Director

FIRM NAME
Amino Chemicals Limited

STREET ADDRESS
A61, Industrial Estate

CITY, STATE AND ZIP CODE
Marsa, LQA 06 Malta

TYPE OF ESTABLISHMENT INSPECTED
API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 5

Inadequate training for the Quality Control Unit. Specifically, the review of analytical records by a second person, use of laboratory reagents OOS (out-of-specification), use of laboratory equipment without a qualified analyst, unable to recognize problem with laboratory equipment, etc.

OBSERVATION 6

Inadequate laboratory mechanism to demonstrate adequate qualification of:

- Analytical balances used on the Quality control unit. Only six replicates are performed without taking into consideration the uncertainty and tolerance. The actual qualification indicates a Tolerance of 1% for laboratory balance as well for the ones located on the process area.
- Certification of Secondary Standards used on a daily basis. The actual practice is to take one weight and compare against primary standard without taking into consideration the weights variability.

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Tricia Y. Samaniego
Ivis Negrón Torres

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Tricia Y. Samaniego, Investigator

Ivis Negrón Torres, Regulatory Program
Expert

DATE ISSUED
5/31/2007



September 2007

Re: FDA Inspection of Aminochemicals

Aminochemicals exports active pharmaceutical substances to the United States of America.

Aminochemicals Ltd was inspected by the **United States Food and Drug Administration (USFDA)** for compliance to the principles of **Good Manufacturing Practice (GMP)**.

The inspection was carried out from the 28th till the 31st of May 2007.

The inspection covered the following systems: Quality, Facilities & Equipment, Production and Laboratory.

The USFDA inspectors recommended approval of Aminochemicals as active pharmaceutical substance manufacturer and exporter to the United States of America.

A handwritten signature in blue ink, appearing to read "Jonathan Farrugia", with a long horizontal line extending to the right.

Jonathan Farrugia
QA Manager
Aminochemicals Ltd

Annex B: Amino Chemicals Fire Fighting Course Details



FIRE WARDEN



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FIRE WARDEN



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Fire Warden

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The role of a Fire Warden

Fire wardens form an organization front line of defence against fire. Working with the person responsible for fire safety, they carry out a variety of tasks to ensure that premises and their occupants are safe from fire.

The roles and responsibilities of a fire warden can be placed into five main headings,

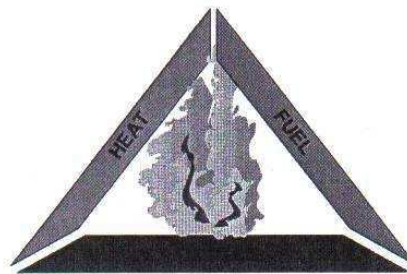
1. Prevention
2. Confinement
3. Communication
4. Evacuation
5. Suppression

Prevention

For a fire to initially start and then develop, 3 things are required,

1. Fuel
2. Heat
3. Oxygen

This can be best shown in the form of the fire triangle. If the triangle is complete, a fire will start and continue to burn.





Fuel

Could include any of the following,
Wood, paper plastics, flammable gases, cooking oils or petrol

Heat

From any of the following or similar sources,
Matches, lighters, welding torches, overheating machinery, electrical faults or hot surfaces.

Oxygen

From any of the following or similar sources,
The air around us, oxygen cylinders, medical gases or manufacturing processes.

Using the fire triangle, we can apply the easiest form of fire prevention. By keeping the three elements of the triangle apart, we can stop a fire ever starting.

For example,

1. No naked flames in flammable areas,
2. Maintaining a smoking policy,
3. Store waste products outside,
4. Store gas cylinders outside in a ventilated and locked store

Common fire hazards

1. Careless disposal of lighted cigarettes or matches,
2. Accumulation of rubbish, paper or other materials that can catch fire
3. Electrical wiring, plugs and sockets in poor condition or overloaded
4. Electrical equipment left switched on when not in use, unless permanently connected
5. Flammable material left close to sources of heat



6. Obstructing the ventilation of heaters, machinery or office equipment
7. Inadequate cleaning of work areas, thus accelerating the fire spread

Confinement

Even after all our preventative measures are in place a fire still occurs, confinement will give the occupants time to safely escape. Fire confinement will also help to prevent fire spread.

For a positive approach towards confinement, a fire warden should ensure that,

- Fire door operation is checked on a regular basis
- Fire doors are not propped open
- When hearing the fire alarm, doors and windows are closed on the way out, If it is safe to do so
- Doors that should remain locked are locked

Communication

Communication can be divided into two areas,

1. Pro-active
2. Re-active

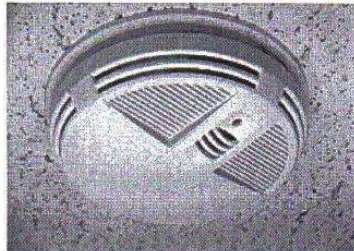
Pro-active communication should include, induction and ongoing training for new staff, visitors and contractors in,

- Hazards and safe practices
- Escape routes
- Fire signs and there meanings
- Actions on hearing the fire alarm
- Actions on discovering fire
- Fire extinguishers
- Fire warden duties
- Fire/evacuation drills



Re-active communications inform us of the detection of a fire. This will include,

Detection devices



Break glass point



Fire signs



Fire Alarm



Evacuation

The main objective is to evacuate everyone from the building (or to a point of designated safety) as quickly as possible. To achieve this, we must make sure,

- Exits are marked and kept clear
- Exit doors operate correctly and are not locked
- Emergency lighting operates
- The fire alarm can be heard
- Persons with mobility disabilities are assisted
- Regular fire drills are undertaken
- Assembly points are designated, marked and kept clear



Fire drills

Fire drills should be conducted on a regular basis and recorded. To make the drill realistic, they should be conducted without warning and if possible exit routes blocked on a random basis to simulate a fire in that area. A roll call should be taken at the assembly points, and a full exercise debrief given.

Assembly point

This is a safe area away from the incident, or building involved in an incident. It is a designated point of safety for persons to gather after the evacuation has taken place so a roll call can be taken

Roll call

This is to be carried out at the assembly point. All persons will give their name, which will be checked against an attendance list. Missing persons can then be reported to the fire incident commander. All persons must remain at the assembly point until directed otherwise by the fire incident commander.

Suppression

Equipment for suppression will include,

- Fire extinguishers
- Hose reels
- Sprinklers
- Co2 flooding

It is important that the above equipment is on a regular schedule of maintenance which is conducted by an engineer. On a regular basis a fire warden should visually check to see that all equipment for suppression is,

- In the correct place
- Is in test
- Is not damaged
- Is not obstructed



The chemistry of fire

Fire is chemical reaction producing,

1. Heat
2. Light
3. Toxic products of combustion (smoke)

As a substance is heated to a specific temperature, it starts to emit flammable vapours. As the heat increases, so does the rate at which flammable vapours are created. It is these flammable vapours which if come into contact with an ignition source or reach spontaneous combustion temperature, that burn.

Flash point

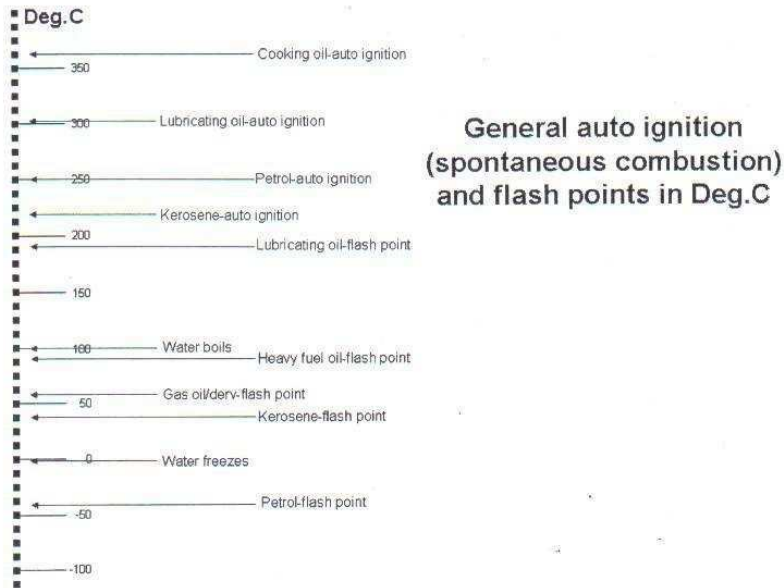
This is the lowest temperature at which a substance gives off sufficient flammable vapour to ignite momentarily when an ignition source is applied.

Fire point

This is the lowest temperature at which a substance gives off sufficient flammable vapour to ignite and continue to burn when an ignition source is applied.

Spontaneous Combustion

This is the lowest temperature at which a substance will ignite without an ignition source being applied.

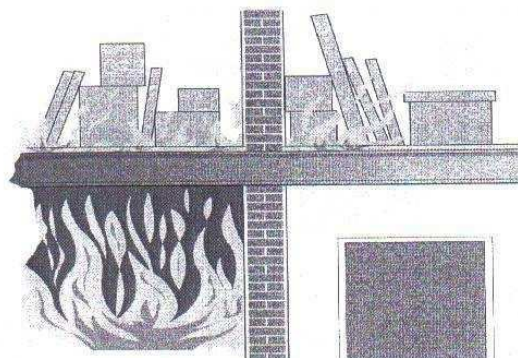


Fire spread

Fire is spread by the following methods.

Conduction

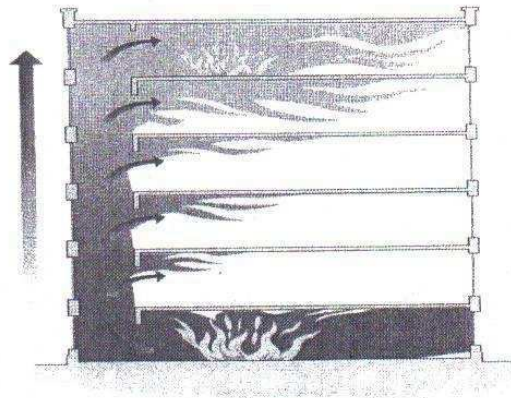
This is the movement of heat through a material, which could be solid, liquid or gas. The ability of materials to transfer heat varies considerably according to its type.





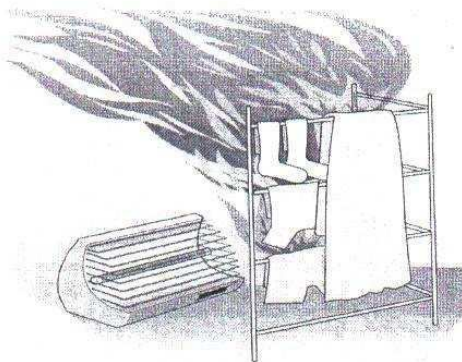
Convection

The transfer of heat via moving air currents.



Radiation

The transfer of heat energy as electromagnetic waves



Direct burning

When a material comes in direct contact with a naked flame.



Extinguishing a fire

To extinguish a fire we need to remove one side of the fire triangle. We can achieve this by either cooling, smothering or starving the fire.

There is one more method of extinguishing a fire, chemical interference with the burning process. This is a method used by some fire extinguishers.

Cooling or removing the heat

By the application of water from a hose reel or extinguisher.

Smothering or removing the oxygen

By the application of a foam blanket or a fire blanket.

Starving or removing the fuel

By turning off a gas valve or fuel supply tap. This could also be achieved by physically removing the fuel.

Classifications of fire

Before we can safely fight a fire, we first need to know what is actually burning. To assist in this decision, five classes of fire have been developed.



Class A, fires involving solid materials. To include, Paper, wood, plastics, fibres, rubber etc.



Class B, fires involving liquids. To include, Petrol, oils, paraffin, paints etc.

Class C, fires involving gases. To include, Acetylene, propane, butane, hydrogen etc.

Class D, fires involving metals. To include, Magnesium, sodium, potassium, titanium, aluminium etc

Class F, fires involving cooking oil and cooking fats.

Fires involving electricity

Electrical fires do not have a class of their own. Electricity is an ignition source, the resulting fire would involve at least one of the other five classes.

What to do if you discover a fire

1. Try to contain the fire by closing the door, if it is safe to do so
2. Raise the alarm
3. Establish what is on fire
4. Select the correct extinguisher to deal with the fire
5. Tackle the fire, only if safe to do so

Fire Extinguishers

Most fires start small. If a fire is discovered in the early stages and the correct techniques and equipment are employed to attack it, both lives and property can be saved. The portable fire extinguisher, hose reel, or fire blanket, for most, is our first line of attack.



Extinguisher colour coding

In accordance with BS EN3 1997, all extinguisher bodies will be colour coded RED. However, up to five percent of the extinguisher body will be coded with the colour of the extinguisher type.

RED- Water

CREAM- Foam

BLUE- Dry powder

BLACK- Carbon dioxide

YELLOW- Wet chemical

Method of operation

Extinguishers are normally operated by the use of gas pressure in the upper part of the container which forces the extinguishing medium out through the nozzle/discharge hose.

The required pressure is produced by either a gas cartridge or by stored pressure.

Before an extinguisher is ready for use, the following steps must be taken,

1. Select it is the correct extinguisher for the class of fire
2. Check details on extinguisher body
3. At arms length, remove safety pin
4. Holding hose and at arms length, charge extinguisher
5. Test extinguisher
6. Extinguisher now ready



Water extinguisher

1. Colour coded red
2. Can only be used on class A fires.
3. Works by cooling

WARNING- Do not use on fires involving electricity

Foam extinguisher

1. Colour coded cream
2. Can be used on class A + B fires
3. Works by smothering
4. There are 2 types. Aspirated and non aspirated

WARNING- Do not use on fires involving electricity

Dry powder extinguisher

1. Colour coded blue
2. Can be used on class A + B + C fires
3. Is safe to use on fires involving electricity
4. Works by smothering and chemical interference

WARNING- Can be a congestant

Carbon dioxide extinguisher

1. Colour coded black
2. Can be used on class B + C fires
3. Is safe to use on fires involving electricity
4. Works by smothering

WARNING- Could be an asphyxiate in confined spaces, and if not held correctly, operator could receive cold burns.



Class D powder extinguisher

1. Colour coded blue
2. Is designed for use on class D fires
3. Specialist fire fighting only

Wet chemical extinguisher

1. Colour coded yellow
2. Can be used on class A + F fires
3. Works by cooling, smothering and chemically interfering
4. Turns burning liquid to soapy residue

WARNING- not to be used on fires involving electricity

Fixed hose reel

Fixed fire fighting hose reels have the advantage of an almost endless supply of water.

1. Can be used on class A fires
2. Works by cooling

WARNING- Do not use on fires involving electricity

Fire blanket

1. Designed for use on deep fat fryers/chip pans
2. Works by smothering
3. Leave on for at least 30 min
4. If possible let the fire service remove the blanket

Annex C: Boiler Operator Course Details