

DOCUMENT REFERENCE NUMBER  
011/AMINO

Waste Stream Analysis of Core Production

We enclose a waste stream analysis of our core production products.

## Foreword

A technical package will be supplied for each process containing the following documents:

1. A short description of the process.
2. The chemical reaction(s) involved by the process.
3. A table listing all raw materials with the corresponding chemical name, the internal name abbreviation, formula, and quantity used for each batch of product.
4. A table listing all raw materials containing the identification numbers when available (CAS, EEC, EINECS) and a short summary of hazard features (hazard symbol, R phrases, S phrases).
5. A series of block diagrams detailing all elemental operations which must be carried out. Every block diagram will contain the quantities of inlet materials (raw materials, solvents, reactants, catalysts etc.) and outlet materials (product(s), wastes, solvents to be recovered etc.).
6. A table listing all liquid wastes going to be stored and disposed externally. The amount of each waste and its approximate composition will also be given in the table.
7. A list of control points for gaseous emissions, i.e. the phases of the process where most likely an organic pollutant may be conveyed to the scrubbers. During such phases sampling and analysis of the outlet flow are foreseen.

## Products

The following products are to be carried out on industrial scale :

### 1. FOSINOPRIL SODIUM

Fosinopril sodium is the sodium salt of fosinopril, the ester prodrug of an angiotensin converting enzyme (ACE) inhibitor, fosinoprilat. It contains a phosphinate group capable of specific binding to the active site of angiotensin converting enzyme. *Fosinopril Sodium is Designated Chemically as* : L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxyl](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, *trans*-. Its empirical formula is  $C_{30}H_{45}NNaO_7P$ , and its molecular weight is 585.65.

Since the first industrial trials are actually running, all of the items of the above-mentioned technical package are available.

### 2. FEXOFENADINE HYDROCHLORIDE

Fexofenadine HCl is a histamine  $H_1$ -receptor antagonist with the chemical name ( $\pm$ )-4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1-piperidiny]-butyl]-a,a-dimethyl benzeneacetic acid hydrochloride. The molecular weight is 538.13 and the empirical formula is  $C_{32}H_{39}NO_4 \cdot HCl$ .

The process is under development and the industrial production is going to be started in the next months. Some pilot trials are foreseen to take place during 4<sup>th</sup> quarter 2003.

Items 1 – 2 – 3 – 4 of the technical package are available.

### 3. LOSARTAN

Losartan potassium, the first of a new class of antihypertensives, is an angiotensin II receptor (type  $AT_1$ ) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is  $C_{22}H_{22}ClKN_6O$ .

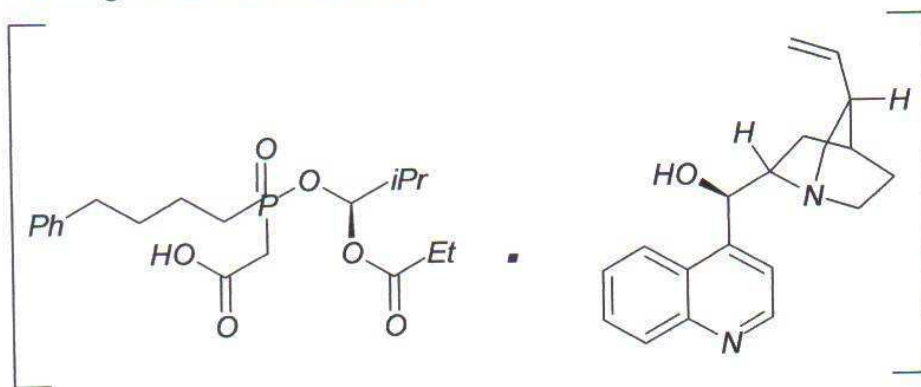
The process is under development and the industrial production is likely to be started during year 2004. Some pilot trials are foreseen to take place during 4<sup>th</sup> quarter 2003.

Items 1 – 2 – 3 – 4 of the technical package are available.

## FOSINOPRIL PRODUCTION PROCESS.

### CHEMICAL REACTIONS

Step 1. cleavage of the cinchonidine salt

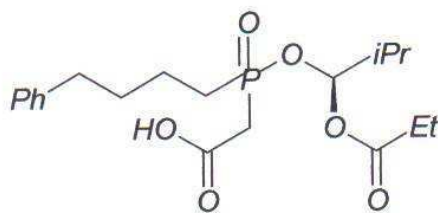


ZP7 (FOS-1 cinchonidine salt)

$C_{38}H_{51}N_2O_7P$

$Fw=678.81$

HCl - cinchonidine hydrochloride salt



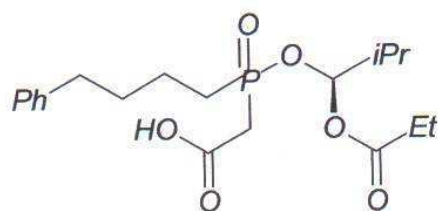
FOS-1

$C_{19}H_{29}O_6P$

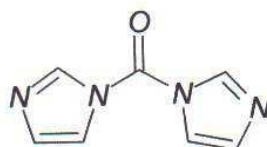
~~$Fw=678.81$~~

384.41

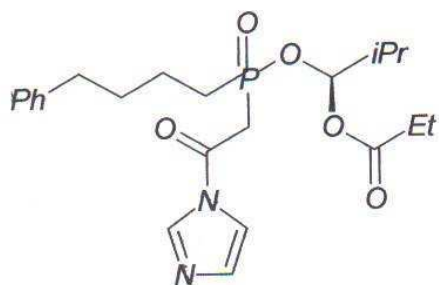
Step 2a. Activation of the acid component



FOS-1  
 $C_{19}H_{29}O_6P$   
 $Fw=678.81$   
384.41



CDI  
 $C_7H_6N_4O$   
 $Fw=162.15$

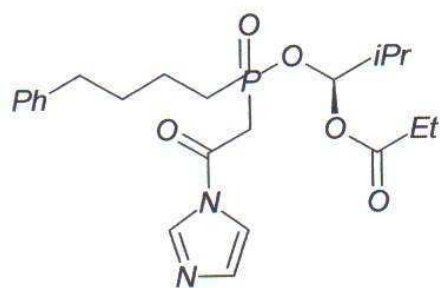


FOS-1 azolid  
 $C_{22}H_{31}N_2O_5P$   
 $Fw=434.47$



Imidazole  
 $C_3H_4N_2$   
 $Fw=68.08$

Step 2b. Coupling reaction



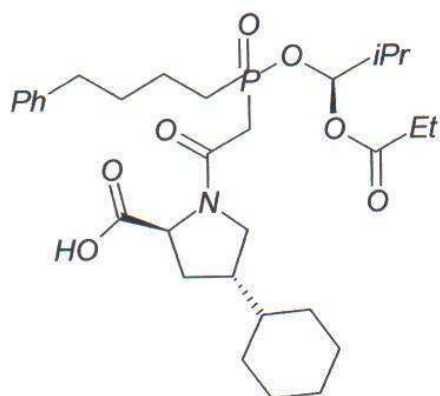
FOS-1 azolid  
 $C_{22}H_{31}N_2O_5P$   
Fw=434.47

+



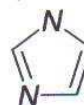
ZPA6  
 $C_{11}H_{19}NO_2$   
Fw=197.28

$ET_3N$



FOSINOPRIL  
 $C_{30}H_{46}NO_7P$   
Fw=563.67

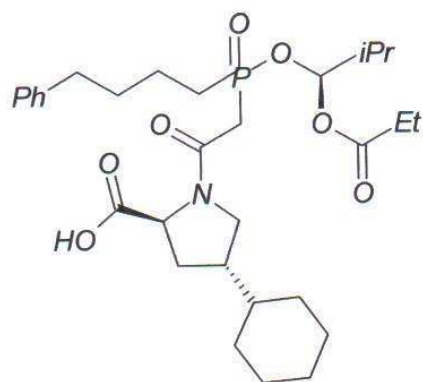
+



Imidazol  
 $C_3H_4N_2$   
Fw=68.08



Step 3. Synthesis of FOSINOPRIL SODIUM.

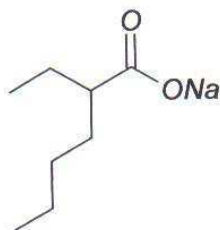


FOSINOPRIL

$C_{30}H_{46}NO_7P$

Fw=563.67

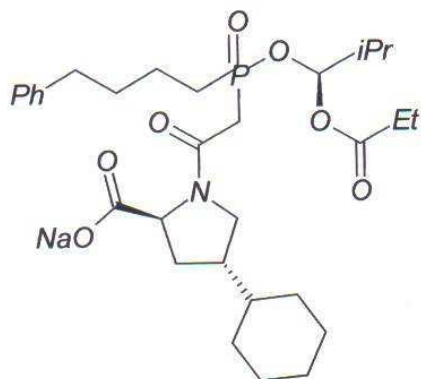
+



Sodium 2-ethylhexanoate

$C_8H_{15}O_2Na$

Fw=166.20



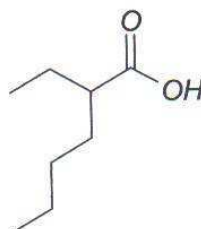
FOSINOPRIL - sodium

$C_{30}H_{46}NO_7P$

Fw=563.67

585.65

+

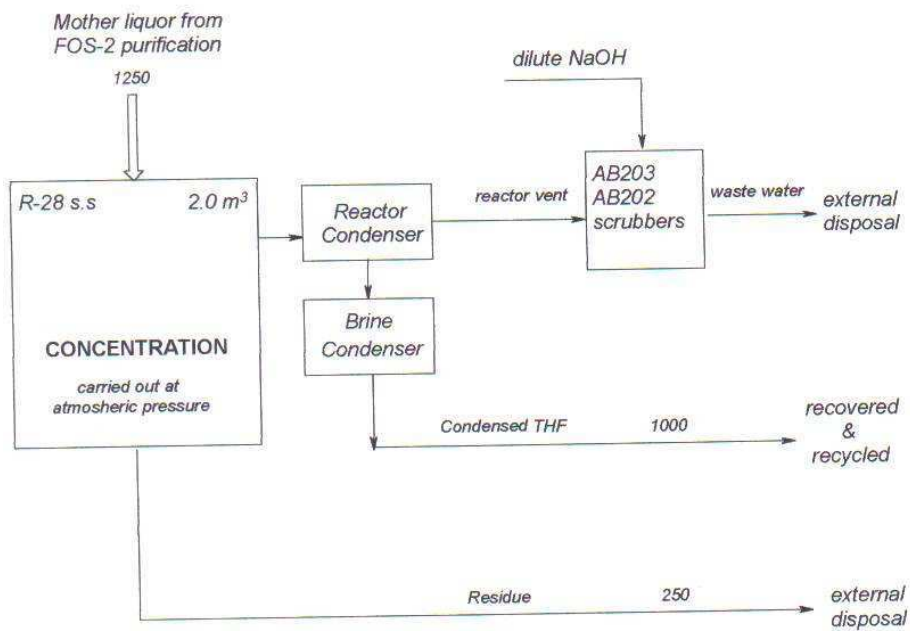


2-ethylhexanoic acid

$C_8H_{16}O_2$

Fw=144.21

**TETRAHYDROFURAN RECOVERY.**





## FOSINOPRIL PRODUCTION PROCESS.

### LIST OF RAW MATERIALS

Raw material		Formula	Data			Amount used for 1 batch ( 100 kg of FOSINOPRIL SODIUM)		
Name	Abbrev.		Physical state	Molec. weight	Density [kg/l]	[kg]	[kmol]	[l]
(*)	<b>ZP7</b>	$C_{38}H_{51}N_2O_7P$	solid	678.81		145	0.214	
Toluene	Tol	$C_7H_8$	liquid	92.14	0.865	855		970
Hydrochloric acid 20% w/w	HCl	HCl	liquid	36.46	1.09	217	1.190	199
1,1'-Carbonyldi- imidazole	CDI		solid	162.15		33	0.204	
N,N-Dimethyl- formamide	DMF	$HCON(CH_3)_2$	liquid	73.10	0.944	583		618
(**)	<b>ZPA-6</b>	$C_{11}H_{19}NO_2$	solid	197.28		43	0.218	
Triethylamine	TEA	$(C_2H_5)_3N$	liquid	101.19	0.726	22	0.217	30
Ethyl acetate	EtOAc	$CH_3CO_2C_2H_5$	liquid	88.11	0.902	489		542
Tetrahydrofuran	THF	$C_4H_8O$	liquid	72.11	0.889	2283		2568
Sodium Ethyl hexanoate	NaEt Hex		solid			36		
Methanol	MeOH	$CH_3OH$	liquid	32,04	0,791	100		126
Aqueous ammonium hydroxide 25%	$NH_4OH_{aq}$	$NH_4OH$	liquid	35.05	0.900	34		38
Demineralized water	Water	$H_2O$	liquid			2500		

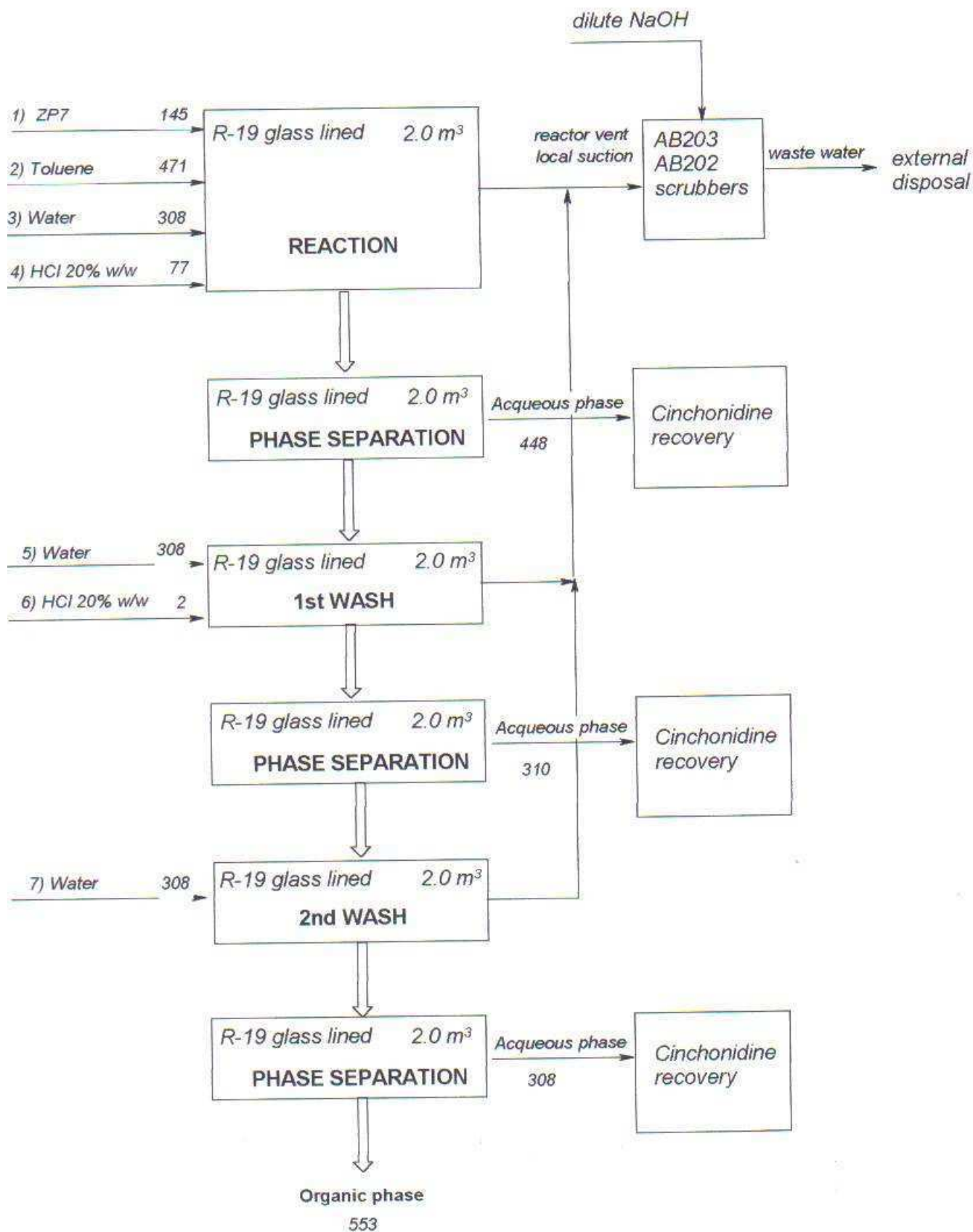
(\*) cinchonidine salt of  $[R, -(R^*, S^*)]-[[2\text{-methyl-1-(1-oxopropoxy)-propoxy-(4-phenylbutyl)phosphinyl}]acetic\ acid.$

(\*\*) (trans)-4-cyclohexyl-L- proline.

Raw material	Identification numbers			Labelling		
	CAS	EEC	EINECS	Hazard symbol	R phrases	S phrases
ZP7						
Toluene	108-88-3	601-021-00-3	203-625-9	F, Xn	11 - 20	2 - 16 - 25 - 29 - 33
Hydrochloric acid 20% w/w	7647-01-0	017-002-01-X	231-595-7	C	34 - 37	1/2 - 9 - 36/37/39 - 45
1,1'-Carbonyldiimidazole	530-62-1		208-488-9	C	34	26 - 27 - 36
N,N-Dimethylformamide	68-12-2	616-001-00-X	200-679-5	T	20/21 - 36 - 61	45 - 53
ZPA-6						
Triethylamine	121-44-8	612-004-00-5	204-469-4	F, Xi	11 - 36/37	2 - 16 - 26 - 29
Ethyl acetate	141-78-6	607-022-00-5	205-500-4	F, Xi	11 - 36 - 66 - 67	2 - 16 - 26 - 33
Tetrahydrofuran	109-99-9	603-025-00-0	203-726-8	F, Xi	11 - 19 - 36/37	16 - 29 - 33
Sodium Ethyl hexanoate	19766-89-3		243-283-8	Xi	36/37/38	22 - 26 - 37/39
Methanol	67-56-1	603-001-00-X	200-659-6	F, T	11 - 23//24/25 - 39/23/24/25	1/2 - 16 - 36/37 - 45 - 7
Aqueous ammonium hydroxide	7664-41-7	007-001-01-2	215-647-6	C	37 - 34	7 - 26 - 36/37/39 - 45

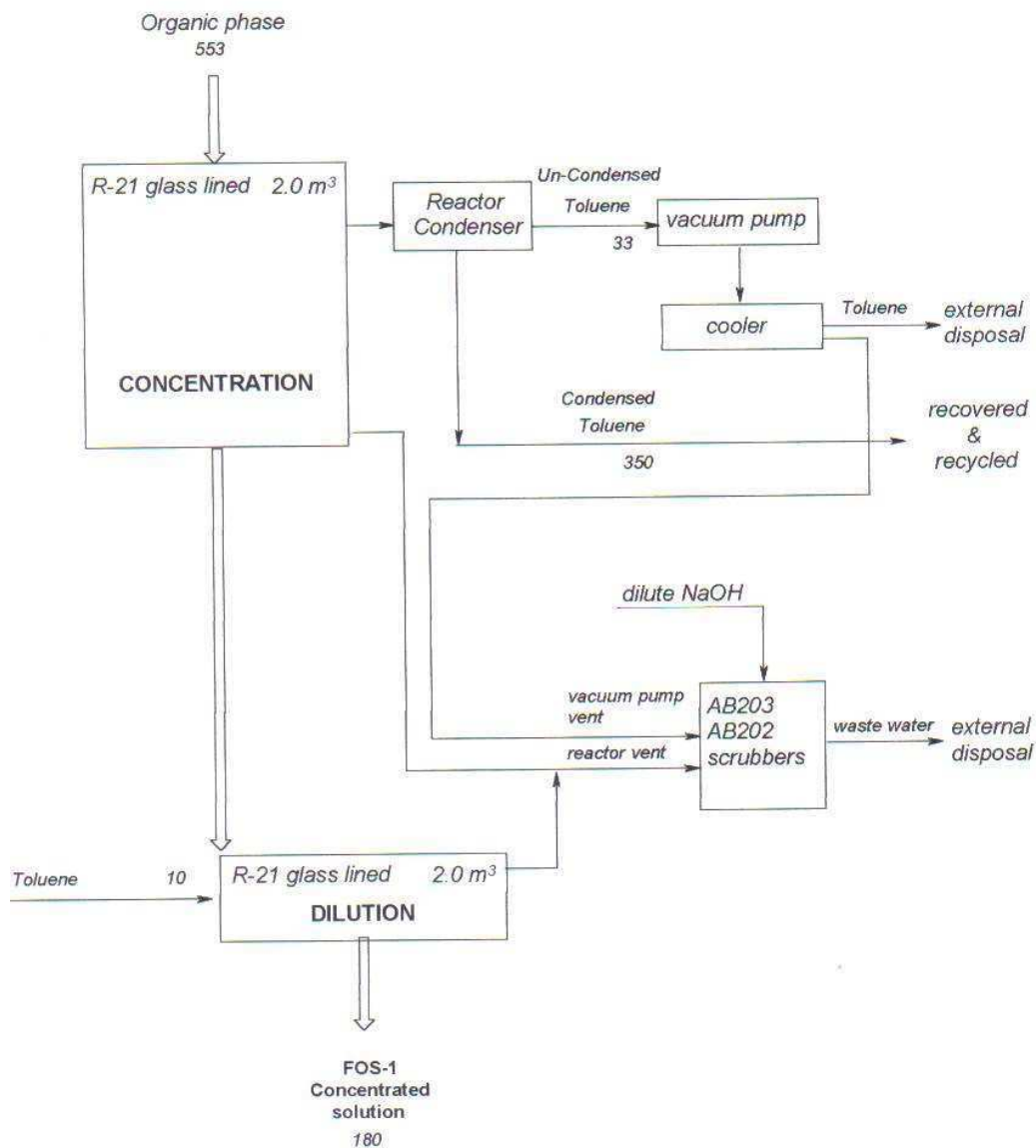


**FOS-1 SYNTHESIS. REACTION & WASHINGS.**



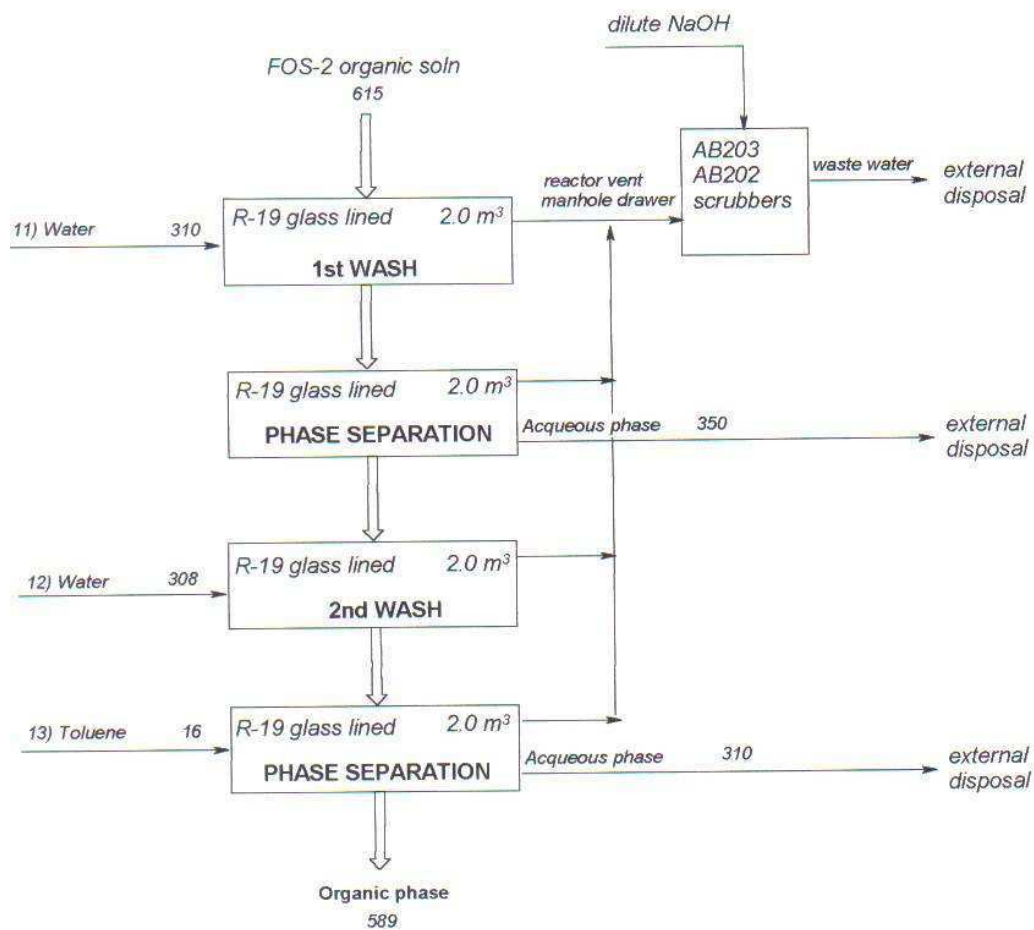
## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 2

### FOS-1. SOLUTION CONCENTRATION.



# FOSINOPRIL PRODUCTION PROCESS. SHEET N. 4

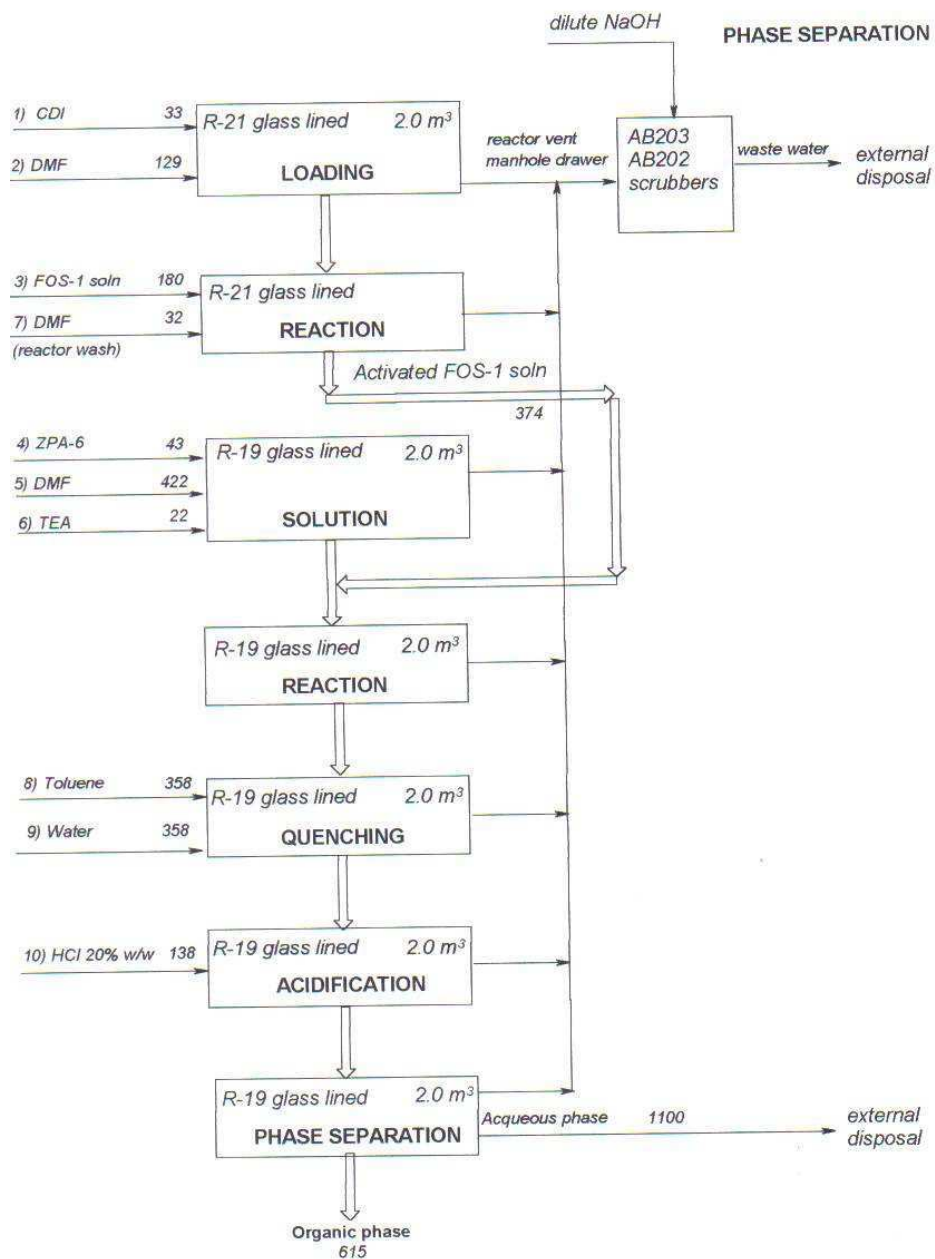
## FOS-2. WASHINGS





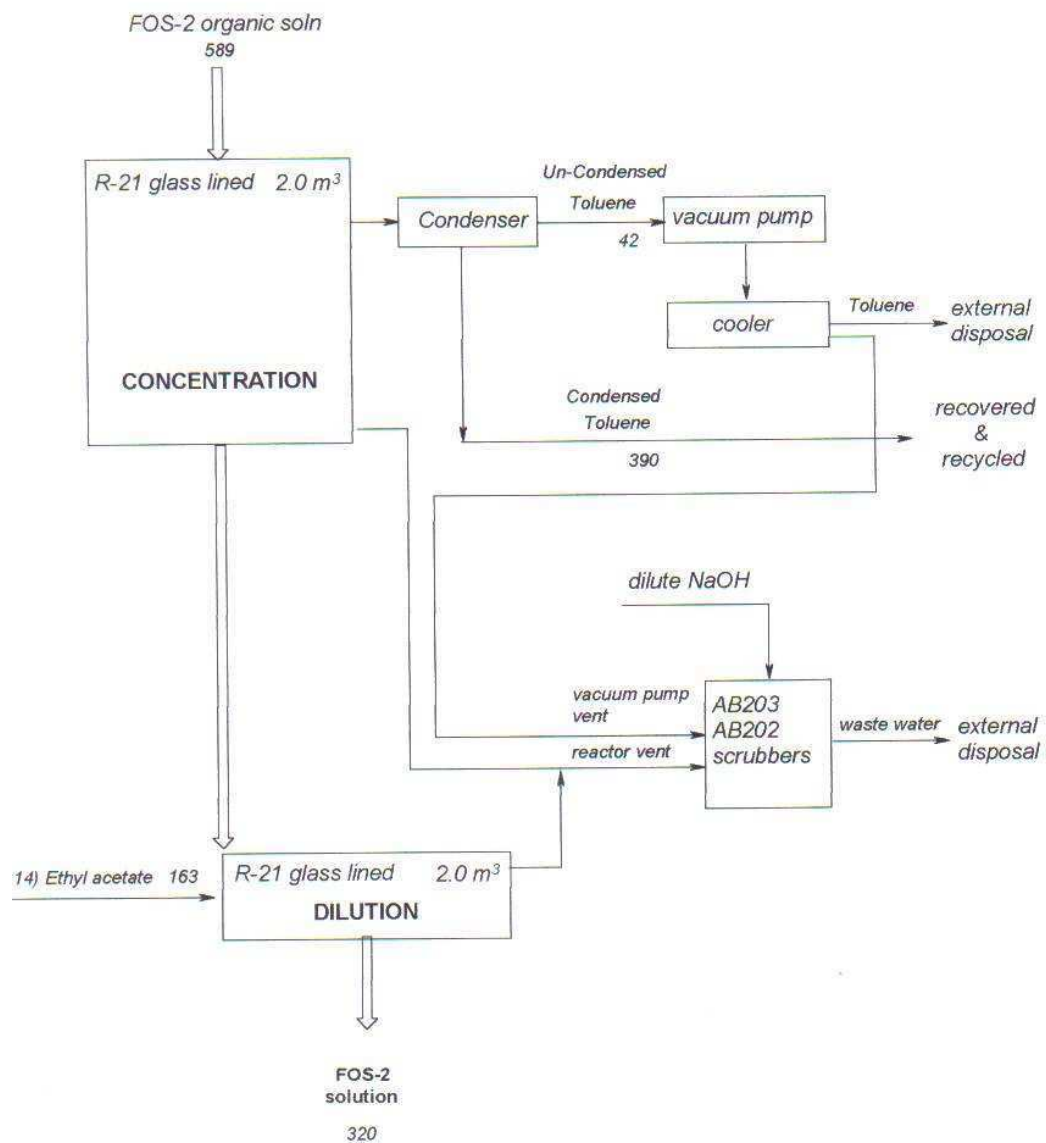
# FOSINOPRIL PRODUCTION PROCESS. SHEET N. 3

## FOS-2 SYNTHESIS.



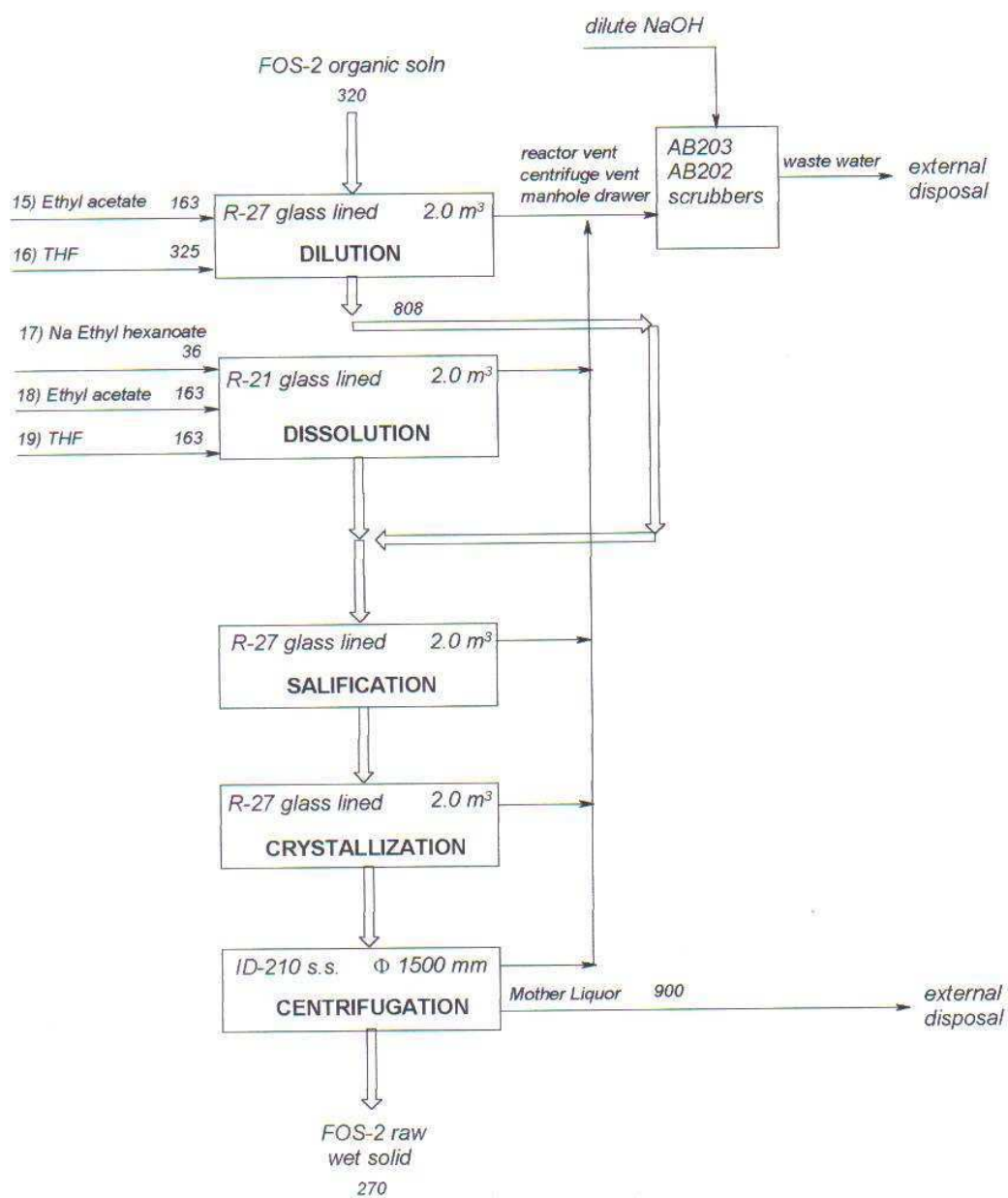


**FOS-2. SOLUTION CONCENTRATION.**



# FOSINOPRIL PRODUCTION PROCESS. SHEET N. 6

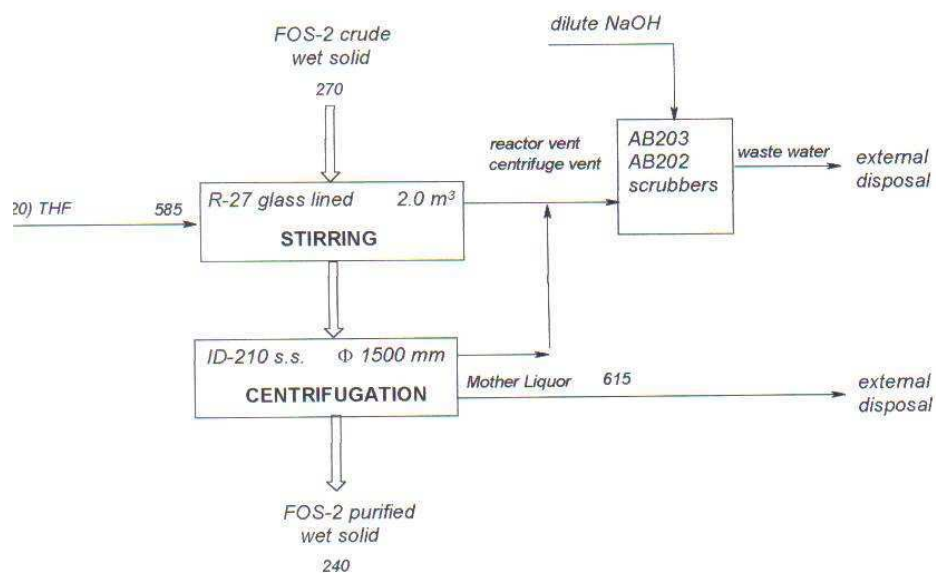
## FOS-2. SALIFICATION & CRYSTALLIZATION.





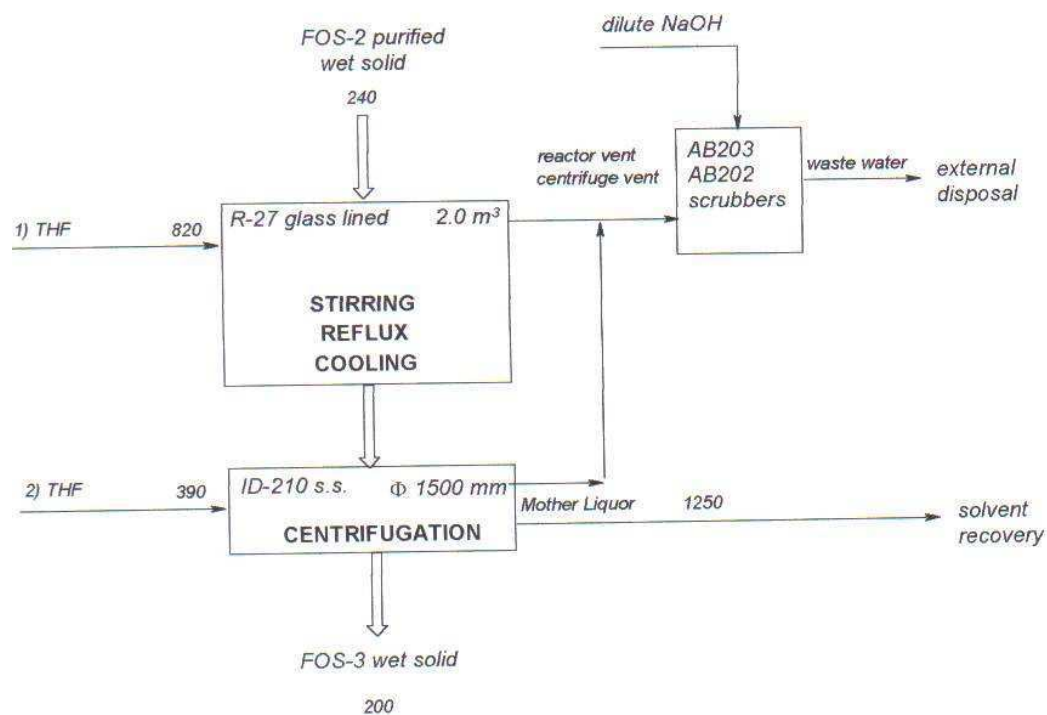
## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 7

### FOS-2. PURIFICATION.

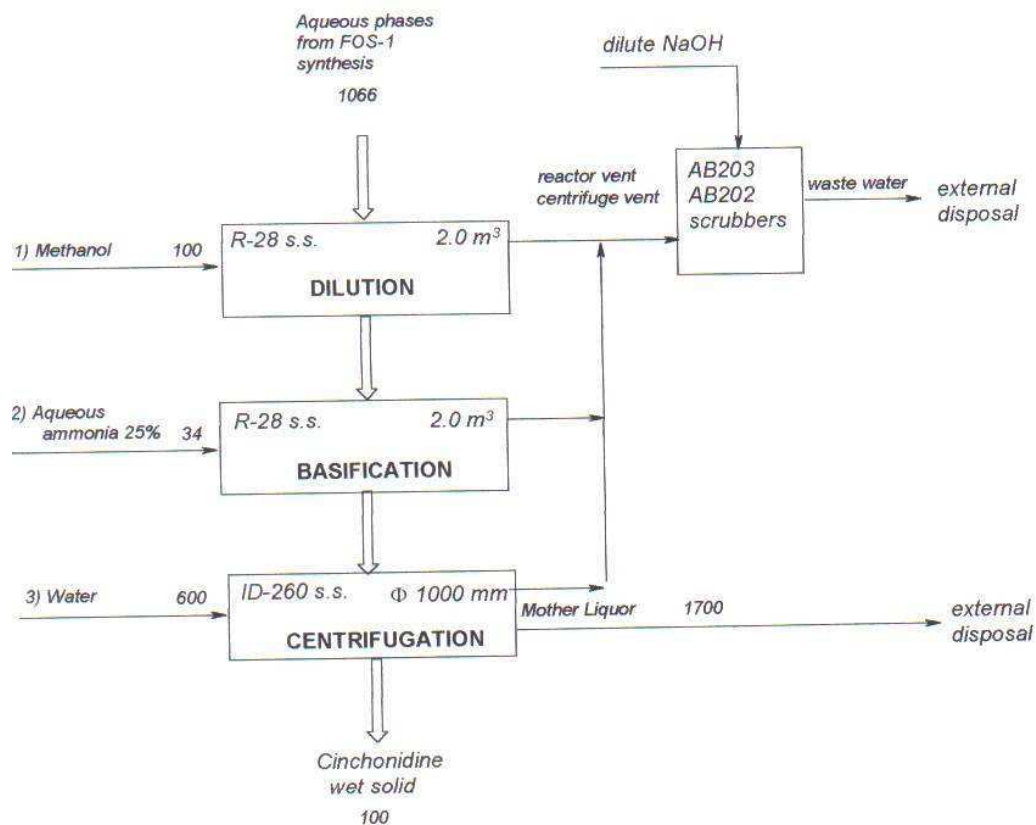


## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 8

### FOS-3 PRODUCTION

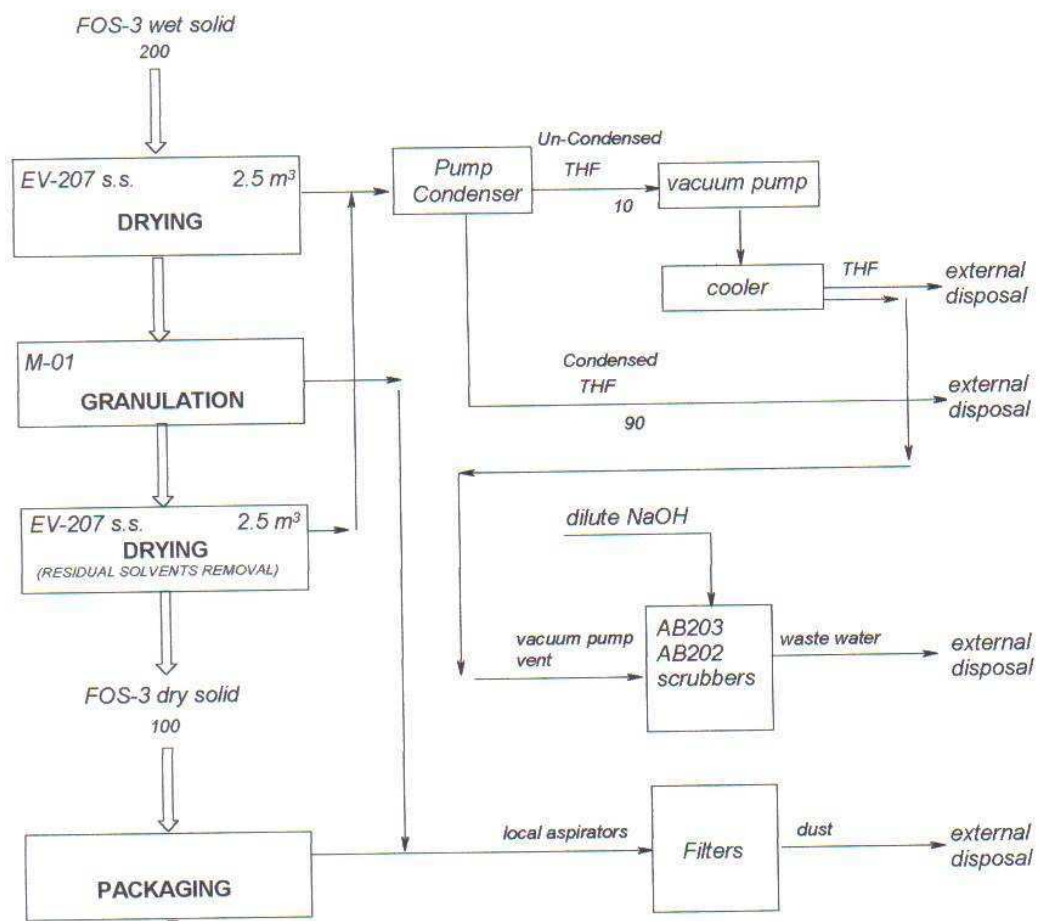


# CINCHONIDINE RECOVERY



## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 9

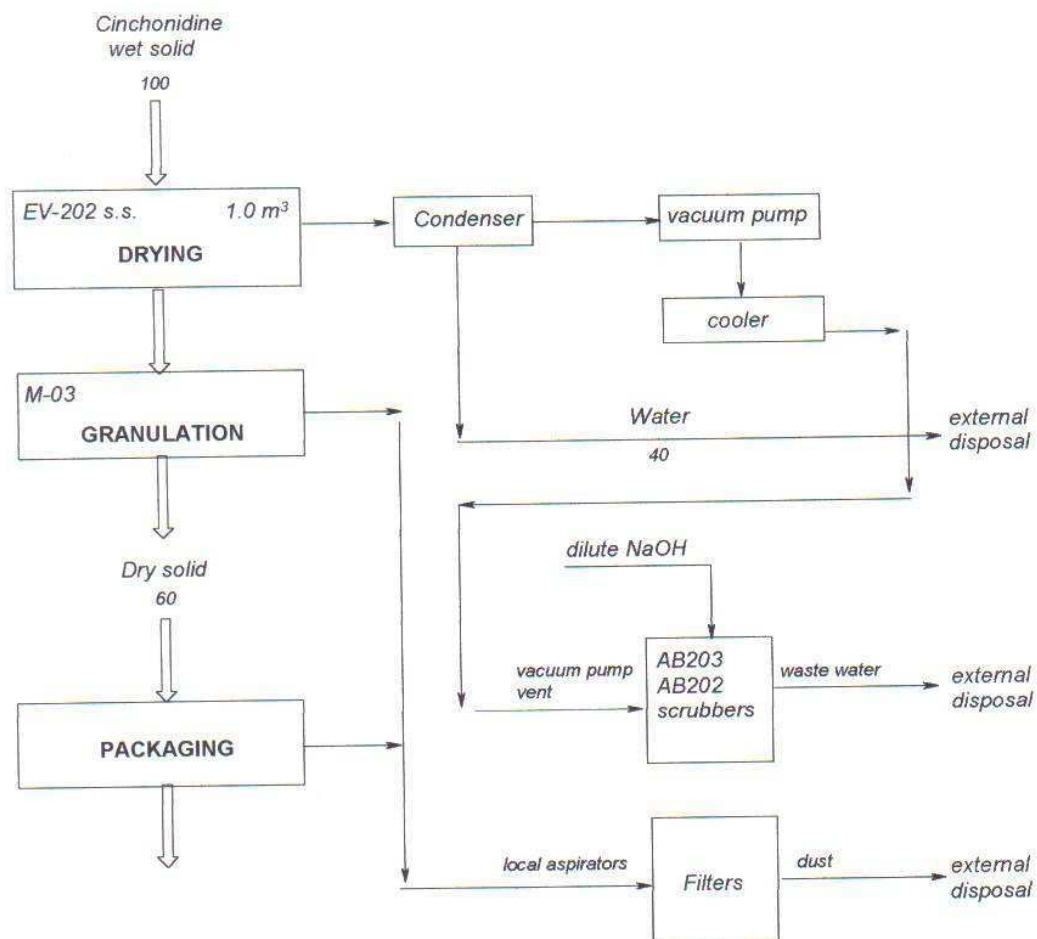
### FOS-3 DRYING





## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 11

### CINCHONIDINE DRYING



## **FOSINOPRIL PRODUCTION PROCESS. GASEOUS EMISSIONS.**

### **Main technical features of the plant**

- 1) All operation are carried out in closed equipment (reactors, centrifuges, dryers)
- 2) Solids are charged in the reactor through the manhole. The charging process is usually quite fast.
- 3) Liquid are either fed with appropriate pump or sucked in by reducing the pressure (by means of the vacuum pump).
- 4) Aspirators are placed near every manhole in order to draw local emissions. The corresponding gaseous stream is conveyed by a fan to a scrubber (AB 202 or AB 203). The emissions during charging are negligible.
- 5) Every reactor is equipped with a shell and tube condenser cooled with refrigerated water (5-7°C). Since reactors are vented through the condenser, the cooling causes the condensation of the main part of the volatile components. The outlet flow is nonetheless conveyed to the scrubber.
- 6) The vacuum pump connected to reactors is equipped with an after-cooler served by refrigerated water. The vent pipe is connected to the scrubber.
- 7) Vacuum pumps connected to driers are equipped with :
  - a) a brine-cooled condenser installed before the pump, which is able to condensate the main part of the volatiles which may reach the pump;
  - b) a cooler served by refrigerated water installed after the pump.

The vents are connected to the scrubbers

### **Main volatile components used in the Fosinopril process :**

- 1) HCl
- 2) Toluene
- 3) Tetrahydrofuran
- 4) Ammonia (very little amount)

The scrubber is operated with a dilute sodium hydroxide solution which is able to scrub both the inorganic acid (by neutralization and dissolution) and solvents (by dissolving them).

### **Control points for gaseous emissions during the Fosinopril process**

The following operating phases are most likely to generate a flow of pollutants to the scrubber:

- 1) Concentration of the FOS-1 solution (see block diagram, sheet n. 2). The evaporated toluene is mainly condensed by the local condenser. The gas flow outcoming from the pump is passed through a cooler which is able to further reduce the toluene content and eventually conveyed to the scrubber. The operation lasts about 3 h for each batch.

2) Concentration of the FOS-2 solution (see block diagram, sheet n. 5). The evaporated toluene is mainly condensed by the local condenser. The gas flow outcoming from the pump is passed through a cooler which is able to further reduce the toluene content and eventually conveyed to the scrubber. The operation lasts about 3 h for each batch.

3) Drying of the product. The out-coming flow from the drier is passed through a brine-cooled condenser installed before the pump, which is able to condensate the main part of the tetrahydrofuran evaporated during the drying process. A guard-cooler served with refrigerated water is also installed after the pump. The flow is finally sent to the scrubber.

A series of analytical controls are actually being carried out during the above-mentioned working phases in order to assess the concentration of the main components (i.e. toluene and THF) in the gaseous stream from the scrubber.

## FOSINOPRIL PRODUCTION PROCESS. SHEET N. 12.

### TETRAHYDROFURAN RECOVERY.

