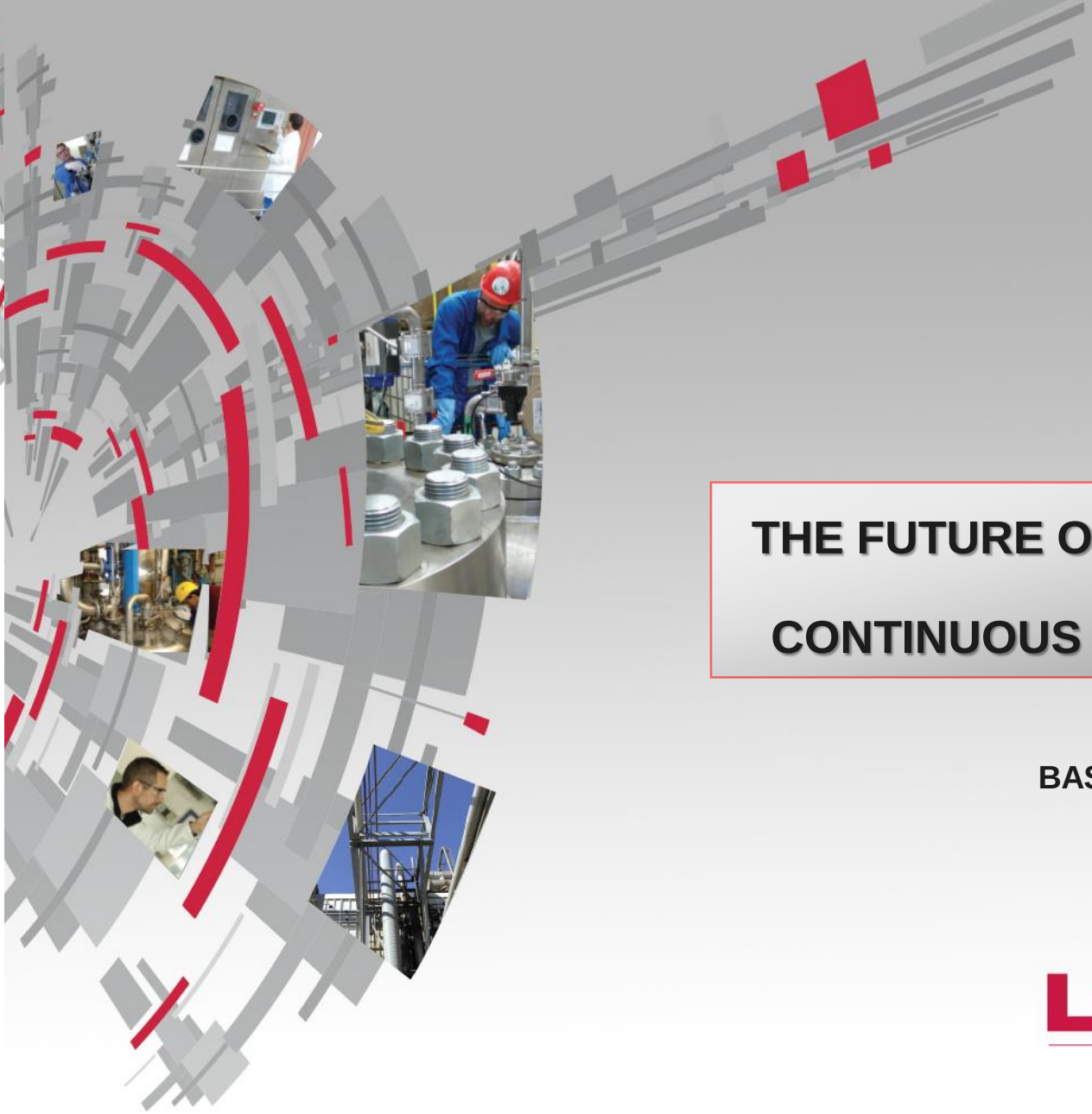


THE FUTURE OF THE CHEMISTRY:

CONTINUOUS FLOW REACTIONS

BASEL 2016

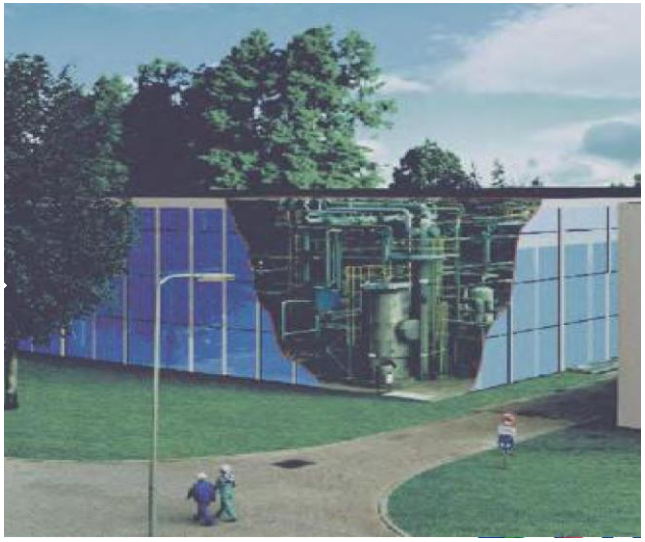
La mesta

CHIMIE FINE

CONTINUOUS INNOVATION FOR FINE CHEMICALS

CHEMICAL PLANT

La mesta
CHIMIE FINE



CONTINUOUS FLOW REACTOR

La mesta
CHIMIE FINE

The continuous flow reactor is a safe system, running chemical reactions in reduced volume with an efficient heat and mass transfer

<u>PROCESS INTENSIFICATION</u>:

Temperature, Pressure, Molar Concentration

<u>Micro and Mini Reactors</u>

Laboratory → ***Industrial***

CONTINUOUS FLOW REACTION

La mesta
CHIMIE FINE

COMPETITIVE ADVANTAGES vs BATCH

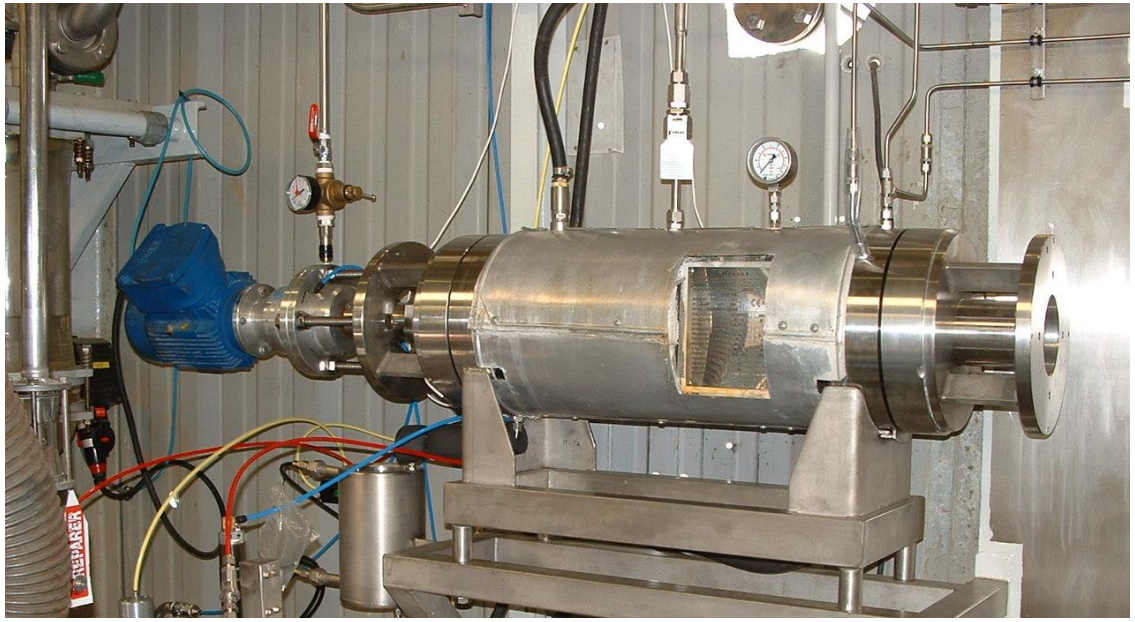
- ***Faster reactions: reduce reaction times down to 1 min***
- ***Safer reactions***
- ***Less energy, solvent and reagents consumption***
- ***Lower waste management***
- ***Better control of highly exothermic reactions***
- ***Ability to manage very high pressure and temperature reactions***
- ***Ability to manage highly toxic and corrosive reagents***
- ***Rapid reaction optimization: easy scale-up***
- ***Low capital investment***
- ***Miniaturization***

INNOVATION

La mesta
CHIMIE FINE

La Mesta has developed a proprietary Plug Flow Reactor called

RAPTOR

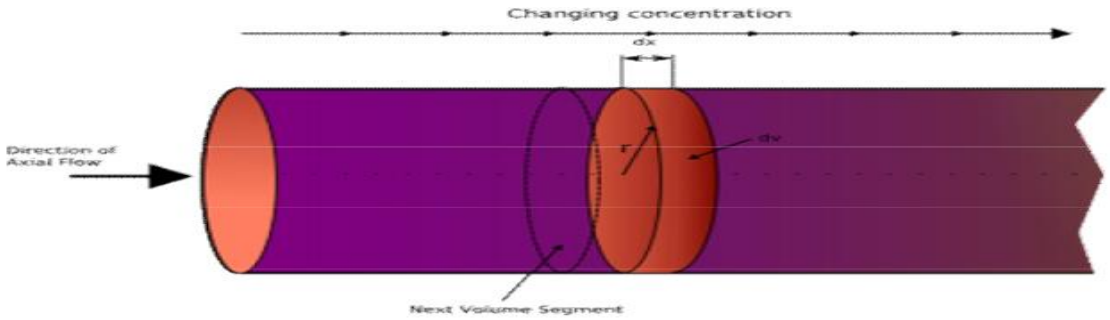


RAPTOR is a tubular continuous agitated reactor, equipped with heating/cooling jacket and a longitudinal shaft having impellers.

RAPTOR TECHNOLOGY

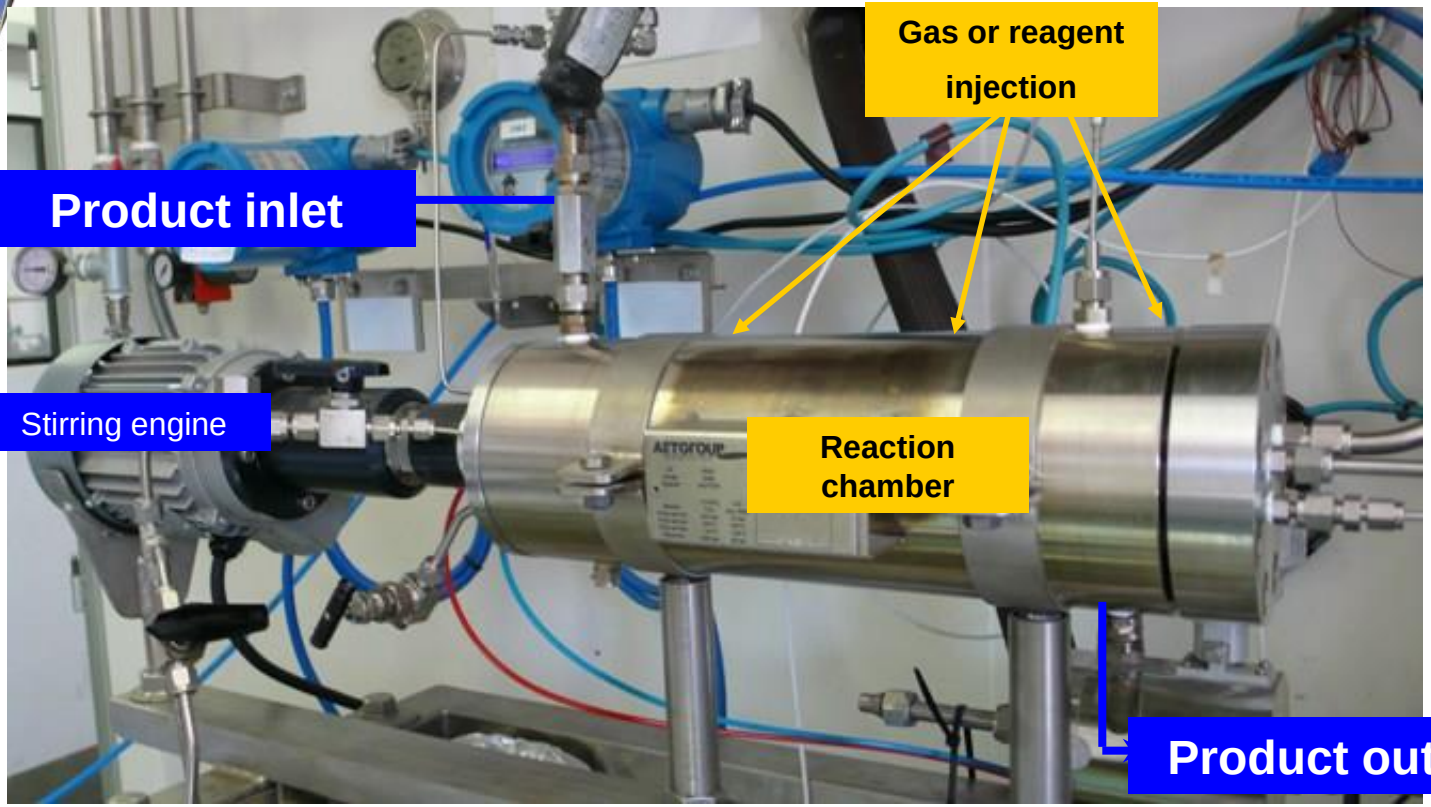
La mesta
CHIMIE FINE

Plug Flow Reactor has a series of thin coherent "plugs", each with an uniform composition, travelling in the axial direction, perfectly mixed in the radial direction but not in the axial direction. Each plug is considered as a separate entity, without a forward or a back mixing.

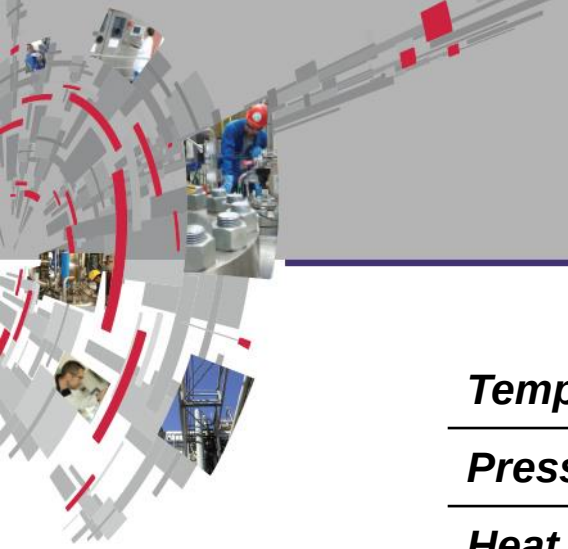


RAPTOR TECHNOLOGY

La mesta
CHIMIE FINE



RAPTOR TECHNOLOGY



Temperature	***-100°C +300°C***
Pressure	***300 bar***
Heat exchange (area/vol.)	***150 m^2/ m^3***
Residence Time	***10 sec to few min***
Flow rate	***5 to 400 liters / h***
Stirring	***1500 rpm***

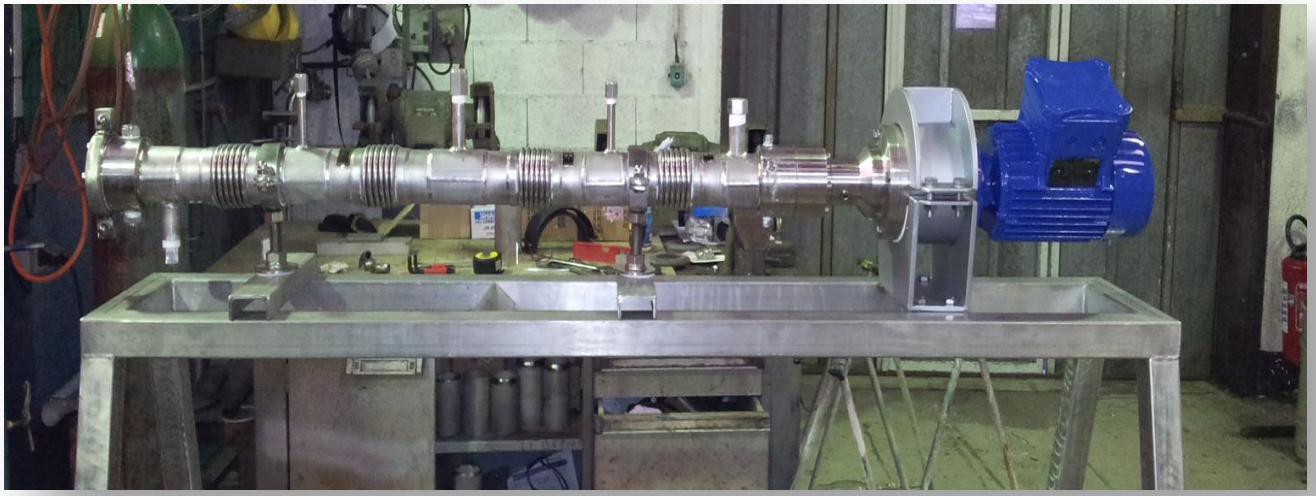
- ***Gas / Liquide / Solid phase reactions***
- ***Handling of toxic or highly corrosive reagents (Triflic acid, CO, Phosgene)***
- ***Highly exothermic, high temperature or cryogenic processes***
- ***Viscous reactions***
- ***Solid suspension up to 30% (as starting materials or during reaction)***

RAPTOR TECHNOLOGY

La mesta
CHIMIE FINE

5 Raptors are in place:

- ***#1*** *(hastelloy) : flow rate 150 liters/h*
- ***#2*** *(ss) : flow rate 40 liters/h*
- ***#3*** *(hastelloy) : flow rate 60 liters/h*
- ***#4*** *(hastelloy) phosgene chemistry: flow rate 60liters/h*
- ***#5 (hastelloy) : flow rate 400liters/h***



RAPTOR CHEMISTRY

La mesta
CHIMIE FINE

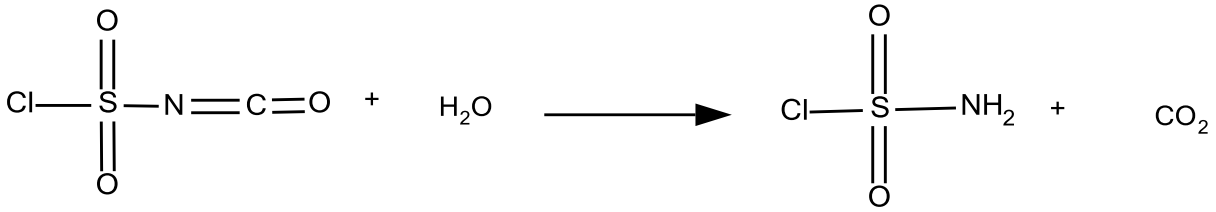
MULTIPURPOSE EQUIPMENT

- ✓ *Ammonolysis*
- ✓ *Carbonylation*
- ✓ *Condensation*
- ✓ *Decarboxylation*
- ✓ *Grignard Chemistry*
- ✓ *Hydrogenation*
- ✓ *Isomerization*
- ✓ *Oxidation*
- ✓ *Phosgene Chemistry*
- ✓ *Reductive amination*

HAZARDOUS REACTIONS

La mesta
CHIMIE FINE

DECARBOXYLATION

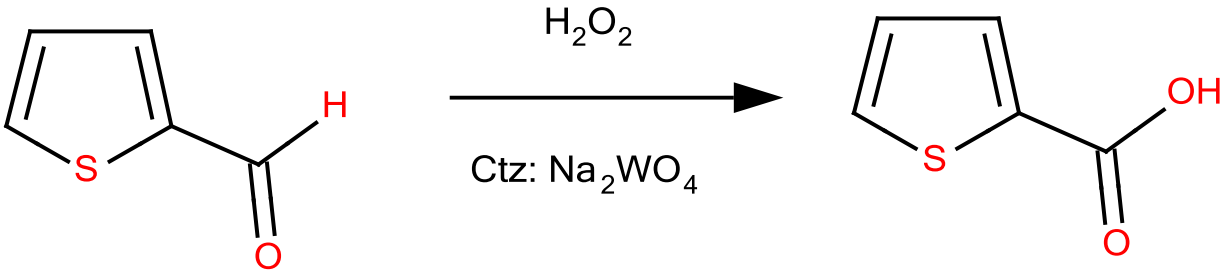


Hazardous Reaction:
Uncontrolled CO_2 gas evolution

Raptor is safe:
small reaction volume and up to 300 bar

HAZARDOUS REACTIONS

OXIDATION with H_2O_2

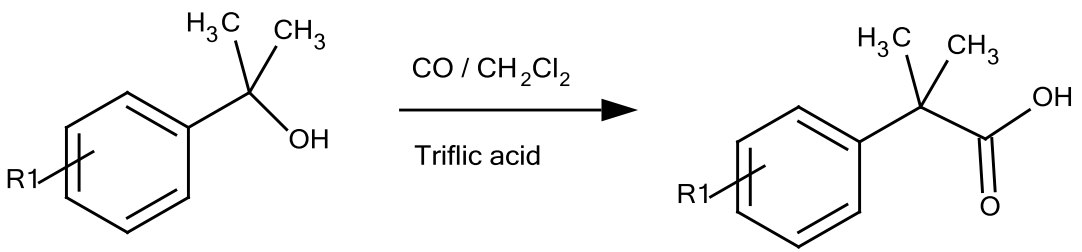


Temperature	*70°C*
Pressure	*10bar*
Reaction Time	*1 min*
Residual H_2O_2	***0% w/w***

CARBONYLATION

La mesta
CHIMIE FINE

Starting Material for API in cGMP

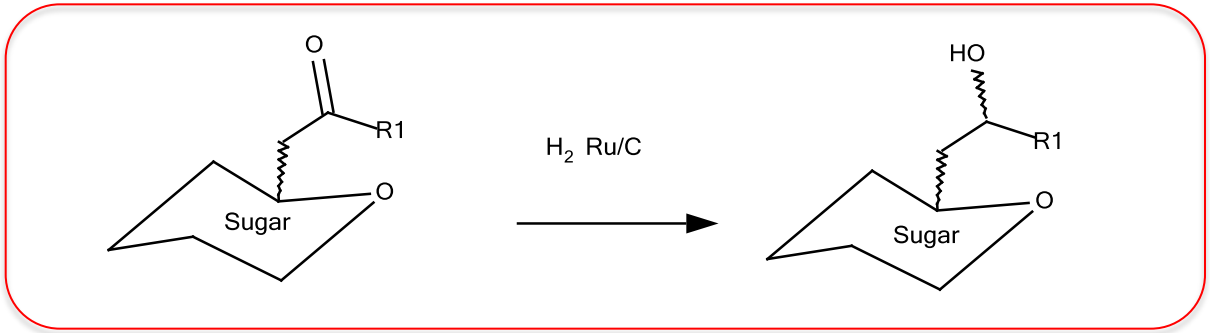


Temperature	*45°C*
Pressure CO	*45 bar*
Alcohol in CH_2Cl_2	*40% w/w*
Residence Time	*30 sec*
Triflic acid	*50% w/w*
Yield	*84%*

CARBONYL REDUCTION

La mesta
CHIMIE FINE

ALCOHOL

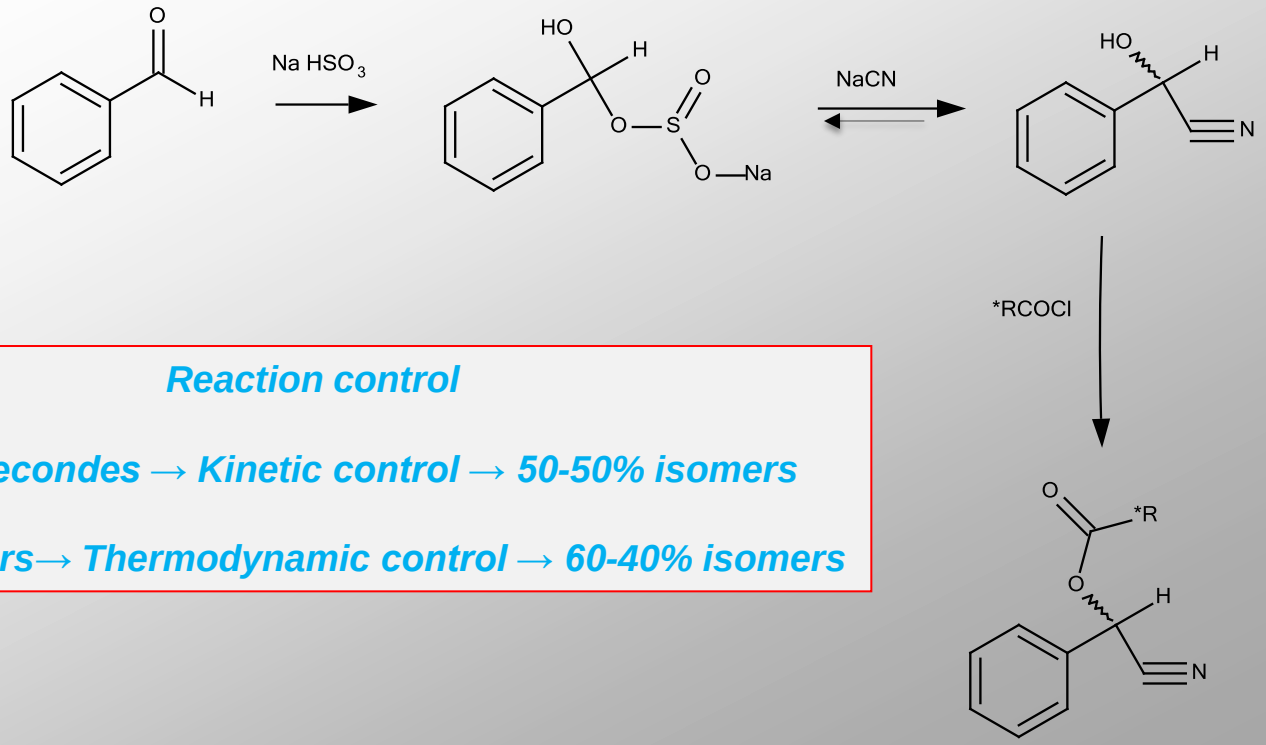


	Batch	***Raptor***
Pressure H_2	*10 bar*	*70 bar*
Temperature	*90°C*	*170°C*
Reaction Time	*12h*	*1min*
Quality (Color)	*Not OK (add. step)*	*OK*

MULTI STEPS SYNTHESIS

La mesta
CHIMIE FINE

Cyanohydrin in RAPTOR



Reaction control

Raptor: 15 secondes → Kinetic control → 50-50% isomers

Batch: 6 hours→ Thermodynamic control → 60-40% isomers

CRYOGENIC IN CONTINUOUS

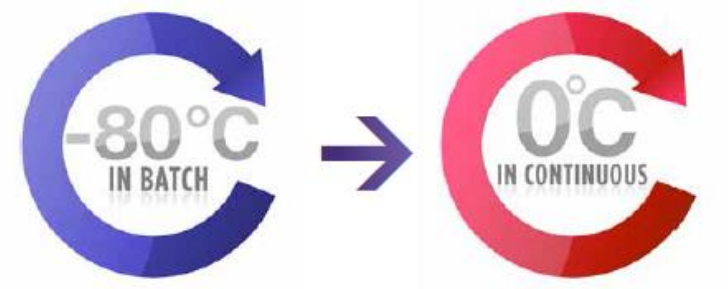
La mesta
CHIMIE FINE

Continuous flow reactor RAPTOR for cryogenic reactions:

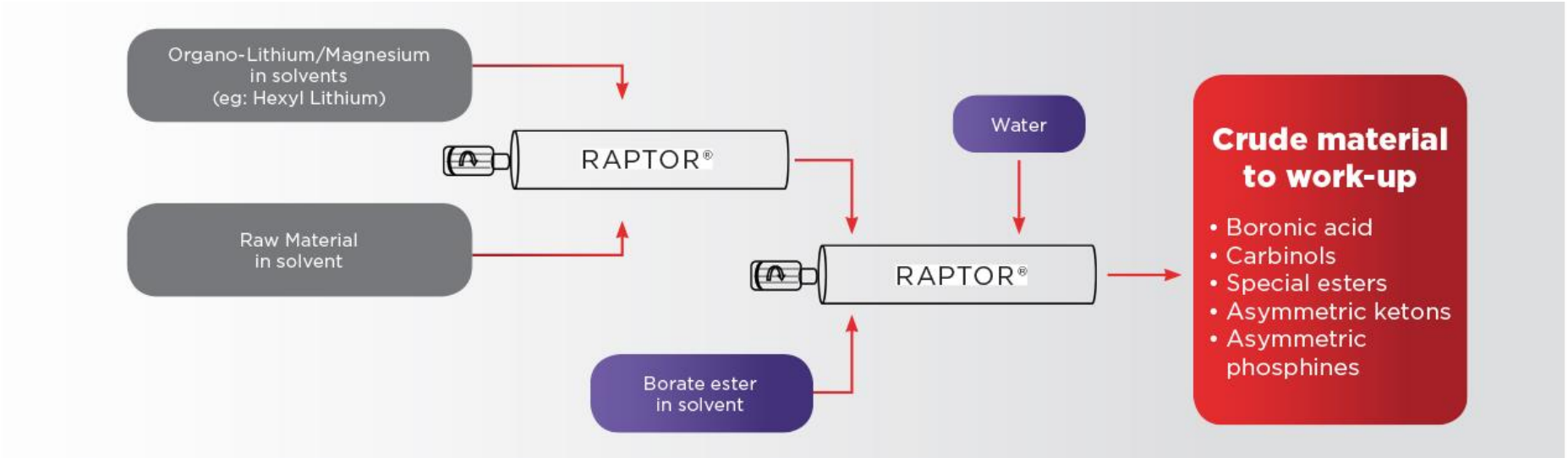
- *Easy to cool down to -90° C but most of the time not needed;*
- *Short reaction time: reaction selectivity and quality improvement;*
- *Use of highly reactive compounds;*
- *Two raptors in line for consecutive reactions (cryogenic + quenching);*

CRYOGENIC IN CONTINUOUS

La mesta
CHIMIE FINE

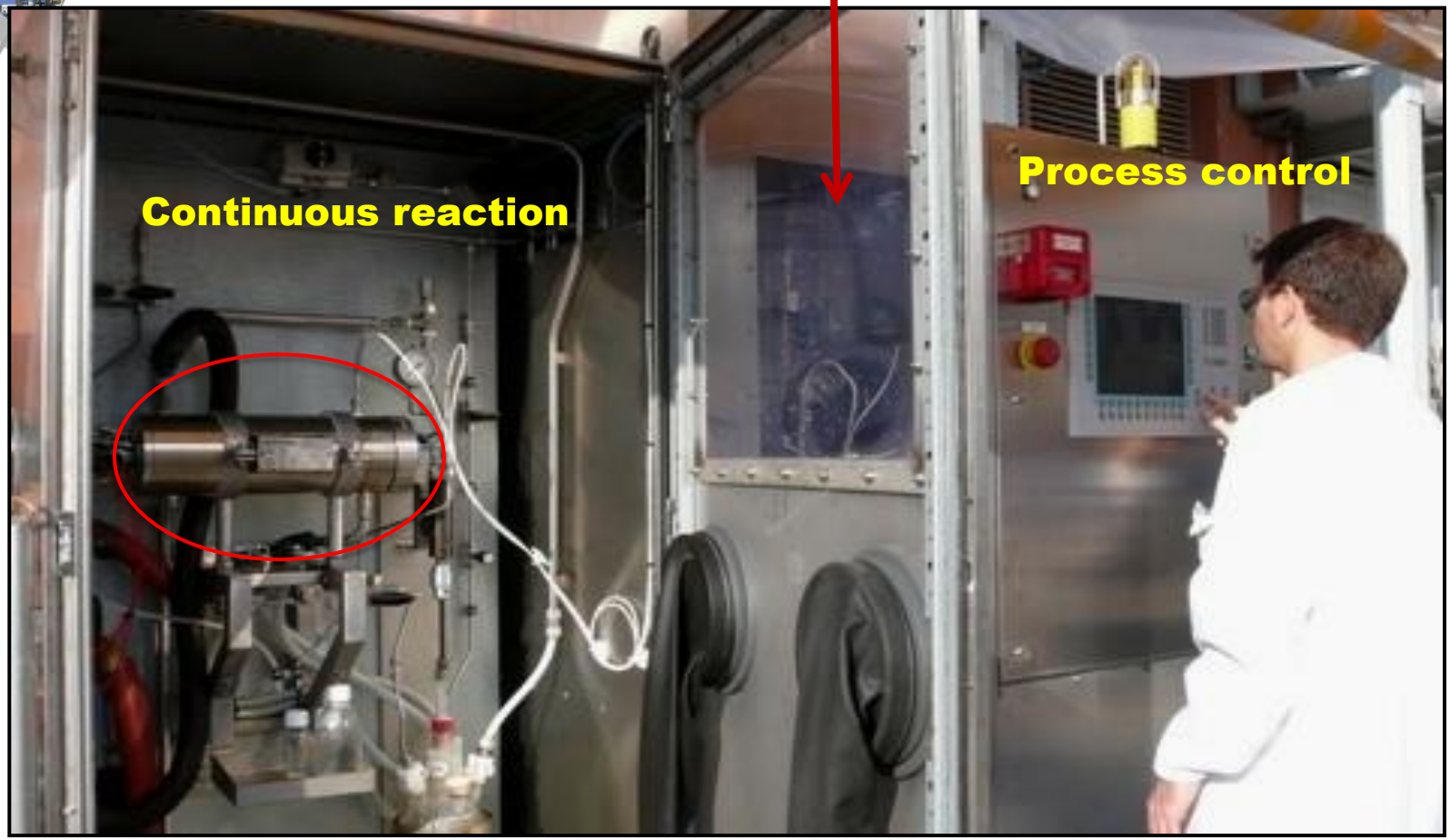


Very low temperature is not necessary in continuous !



PHOSGENE REACTIONS

La mesta
CHIMIE FINE



PHOSGENE GENERATOR

La mesta
CHIMIE FINE

- ***Process:*** *$CO + Cl_2$ + Active Carbon at 150° C*
- ***Production:*** *up to 12kg / hour*

  up to 40kg / hour
- ***Quality:*** *CCl_4 max 49-56ppm*

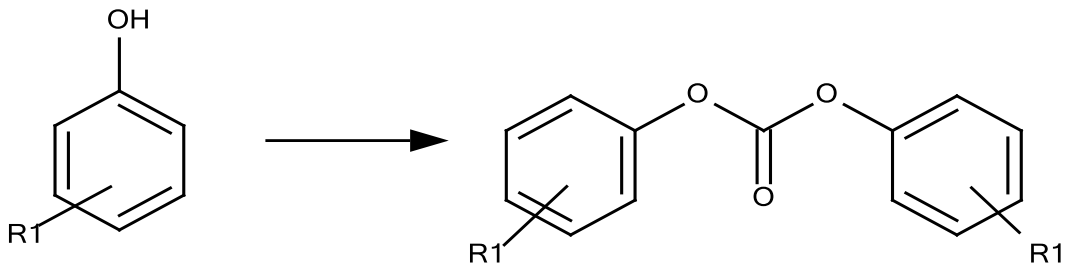
No Phosgene on stock

On demand generation and continuous consumption

PHOSGENATION

La mesta
CHIMIE FINE

Last step of an API synthesis performed under cGMP



Temperature	*35-45°C*
Pressure $COCl_2$	*0 bar*
Phosgene Excess	*5% mole*
Residence Time	*0.2min*
Productivity	*16 kg/h*
Conversion	*complete*

DOWNSTREAM IN CONTINUOUS

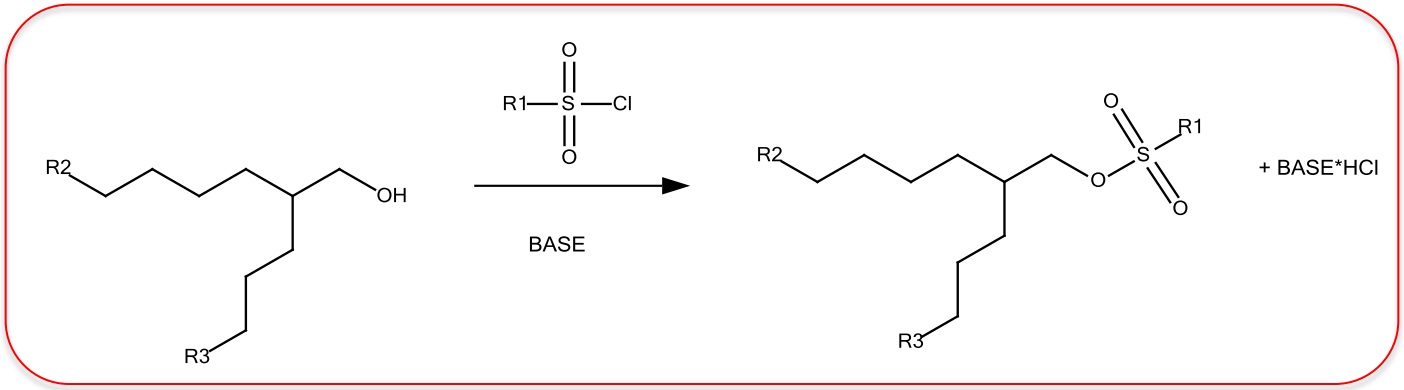
- ***PROVED the EFFICIENCY of the RAPTOR***
- ***NEXT STEP: DOWSTREAM in CONTINUOUS***

- ***Washing – Separation in Continuous***
- ***Distillation in continuous (THIN FILM EVAPORATOR)***
- ***Crystallization and filtration in batch***

- ***DEDICATED AREA TO THE CONTINUOUS PROCESS***
- ***WORKSHOP is in PROGRESS (SEPT. 2016)***

EXOTHERMIC REACTIONS

SULFONIC ESTERS



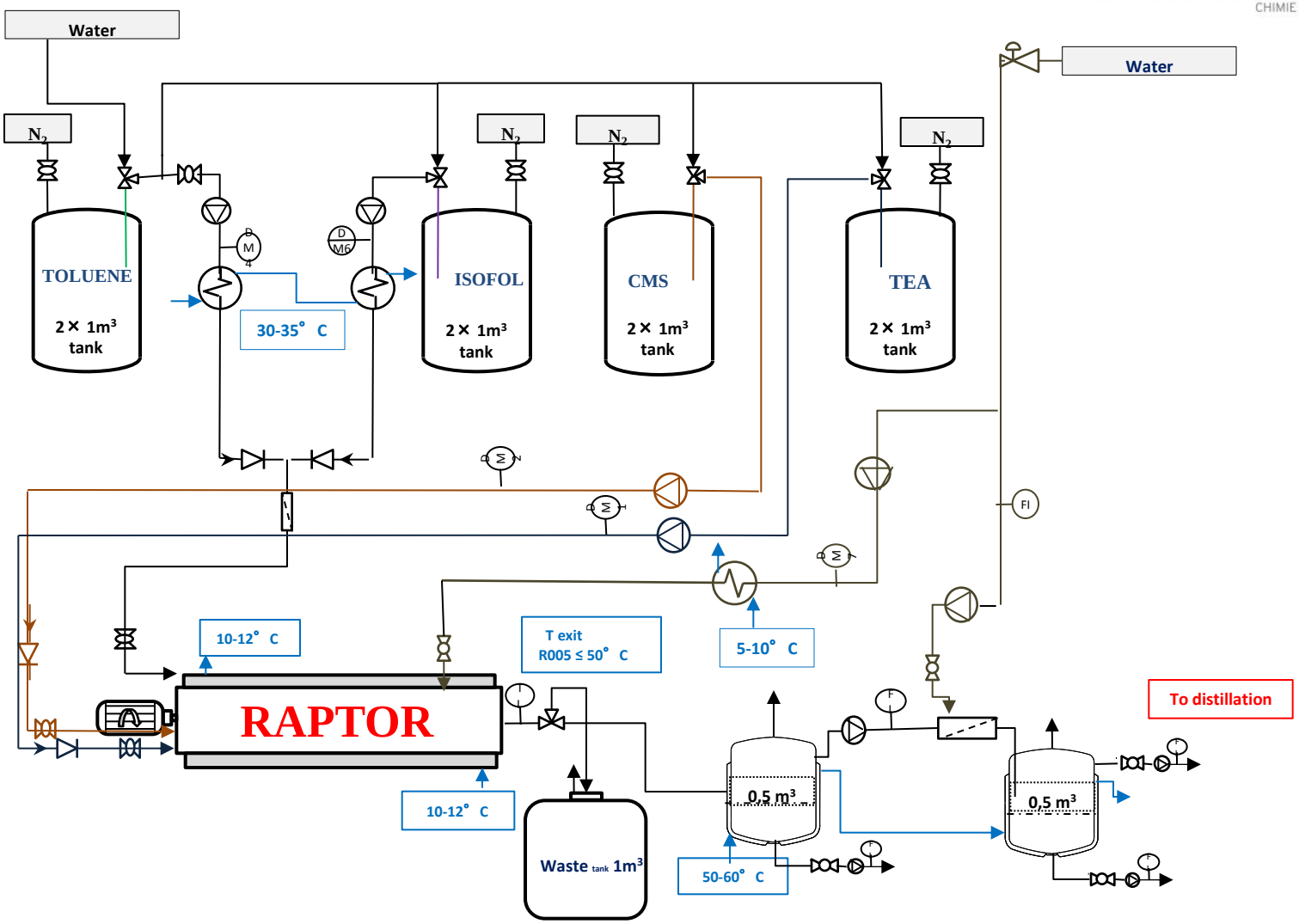
Annual production 60 MT / year

New continuous workshop in 2016

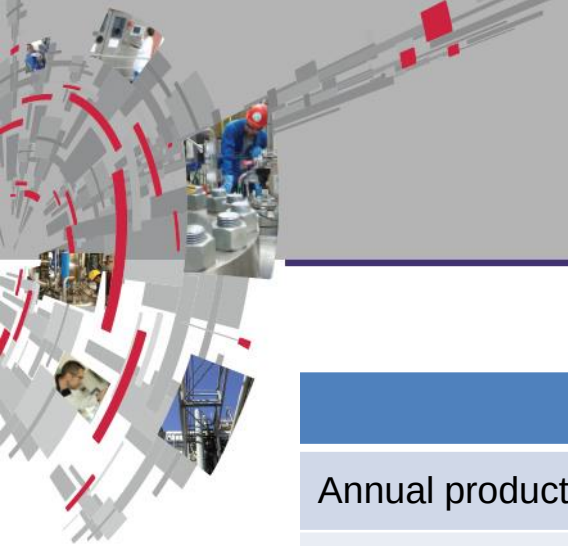
DOWNSTREAM IN CONTINUOUS

La mesta
CHIMIE FINE

CONTINUOUS LAYOUT



CONTINUOUS VS BATCH



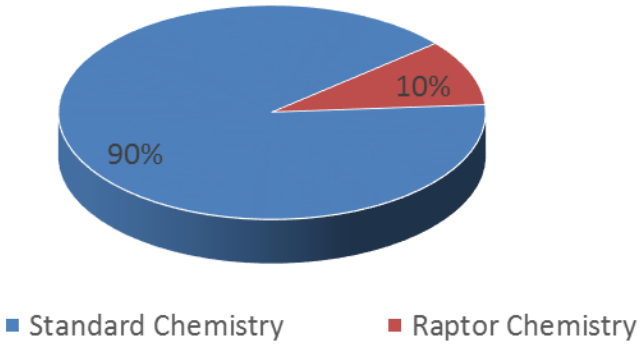
La mesta
CHIMIE FINE

	BATCH	CONTINUOUS
Annual production	**60 MT**	
Equipment used	Vessel (6 rm^3) + tanks	Raptor (0,001rm^3) + tanks
Duration of Production	25 weeks	6 weeks
Productivity	42 kg/h	100 kg/h
Productivity x week	2,4 MT	6 MT
Reaction temperature	10 – 15°C	45°C
Toluene	3,5 vol	1,75 vol
Water (washing)	4 vol	2 vol
Excess CMS & TEA	30%	10%
Product Quality	Orange (purification step needed)	Pale yellow
Disposal	6,2 kg /kg	3kg / kg

RAPTOR SUMMARY

La mesta
CHIMIE FINE

- PROJECTS TESTED IN RAPTOR: 48
- PROJECTS MOVED AT LEAST TO PILOT / PRODUCTION: 15
- MORE THAN 100 MT PRODUCED USING RAPTOR TECHNOLOGY



THANK YOU FOR YOUR ATTENTION

La mesta
CHIMIE FINE

LA MESTA CHIMIE FINE S.A.S.
1336 route de l'Esteron
06830 GILETTE
FRANCE
Tel : +33 492 08 53 00
Fax : +33 492 08 53 40
info@la-mesta.com

www.la-mesta.com