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

PROCESS INTENSIFICATION:
Temperature, Pressure, Molar Concentration

Micro and Mini Reactors
Laboratory → Industrial
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
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.
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

Product inlet
Stirring engine
Reaction chamber
Gas or reagent injection
Product outlet
RAPTOR TECHNOLOGY

- 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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>-100°C to +300°C</td>
</tr>
<tr>
<td>Pressure</td>
<td>300 bar</td>
</tr>
<tr>
<td>Heat exchange (area/vol.)</td>
<td>150 m²/m³</td>
</tr>
<tr>
<td>Residence Time</td>
<td>10 sec to few min</td>
</tr>
<tr>
<td>Flow rate</td>
<td>5 to 400 liters/h</td>
</tr>
<tr>
<td>Stirring</td>
<td>1500 rpm</td>
</tr>
</tbody>
</table>
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 60 liters/h
- **#5** (hastelloy) : flow rate 400 liters/h
RAPTOR CHEMISTRY

MULTIPURPOSE EQUIPMENT

- Ammonolysis
- Carbonylation
- Condensation
- Decarboxylation
- Grignard Chemistry
- Hydrogenation
- Isomerization
- Oxidation
- Phosgene Chemistry
- Reductive amination
HAZARDOUS REACTIONS

**DECARBOXYLATION**

\[
\text{Cl-SO\text{\textsc{y}}N\text{\textsc{y}}C\text{\textsc{y}}O} + \text{H}_2\text{O} \rightarrow \text{Cl-SO\text{\textsc{y}}NH}_2 + \text{CO}_2
\]

**Hazardous Reaction:**
Uncontrolled CO\textsubscript{2} gas evolution

*Raptor is safe:*
small reaction volume and up to 300 bar
# HAZARDOUS REACTIONS

**OXIDATION with \( H_2O_2 \)**

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temperature</strong></td>
<td>70°C</td>
</tr>
<tr>
<td><strong>Pressure</strong></td>
<td>10 bar</td>
</tr>
<tr>
<td><strong>Reaction Time</strong></td>
<td>1 min</td>
</tr>
<tr>
<td><strong>Residual ( H_2O_2 )</strong></td>
<td>0% w/w</td>
</tr>
</tbody>
</table>
CARBONYLATION

Starting Material for API in cGMP

\[
\begin{align*}
\text{R1} & \quad \text{H}_3\text{C} & \text{CH}_3 & \text{OH} \\
\text{H}_3\text{C} & \quad \text{CH}_3 & \text{CO} / \text{CH}_2\text{Cl}_2 & \text{Triflic acid} \\
\text{R1} & \quad \text{H}_3\text{C} & \text{CH}_3 & \text{OH}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>45°C</td>
</tr>
<tr>
<td>Pressure CO</td>
<td>45 bar</td>
</tr>
<tr>
<td>Alcohol in CH\text{2Cl}_2</td>
<td>40% w/w</td>
</tr>
<tr>
<td>Residence Time</td>
<td>30 sec</td>
</tr>
<tr>
<td>Triflic acid</td>
<td>50% w/w</td>
</tr>
<tr>
<td>Yield</td>
<td>84%</td>
</tr>
</tbody>
</table>
CARBONYL REDUCTION

**ALCOHOL**

```
\[
\text{Sugar} \quad \text{H}_2 \text{Ru/C} \quad \text{Sugar}
\]
```

<table>
<thead>
<tr>
<th></th>
<th>Batch</th>
<th>Raptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure $H_2$</td>
<td>10 bar</td>
<td>70 bar</td>
</tr>
<tr>
<td>Temperature</td>
<td>90°C</td>
<td>170°C</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>12h</td>
<td>1min</td>
</tr>
<tr>
<td>Quality (Color)</td>
<td>Not OK (add. step)</td>
<td>OK</td>
</tr>
</tbody>
</table>
MULTI STEPS SYNTHESIS

Cyanohydrin in RAPTOR

Reaction control

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

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

Very low temperature is not necessary in continuous!

- Organo-Lithium/Magnesium in solvents (eg: Hexyl Lithium)
- Raw Material in solvent
- Borate ester in solvent
- Water

RAPTOR®

Crude material to work-up
- Boronic acid
- Carbinols
- Special esters
- Asymmetric ketons
- Asymmetric phosphines
PHOSGENE REACTIONS

Phosgene generation

Continuous reaction

Process control
PHOSGENE GENERATOR

- **Process:** $\text{CO} + \text{Cl}_2 + \text{Active Carbon at 150° C}$
- **Production:** up to 12kg / hour
  - up to 40kg / hour
- **Quality:** $\text{CCl}_4$ max 49-56ppm

*No Phosgene on stock*

*On demand generation and continuous consumption*
PHOSGENATION

Last step of an API synthesis performed under cGMP

Temperature: 35-45°C
Pressure COCl₂: 0 bar
Phosgene Excess: 5% mole
Residence Time: 0.2 min
Productivity: 16 kg/h
Conversion: complete
DOWNSTREAM IN CONTINUOUS

- PROVED the EFFICIENCY of the RAPTOR
- NEXT STEP: DOWNSTREAM 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

Raptor # 5

Separation - Washing
## CONTINUOUS VS BATCH

<table>
<thead>
<tr>
<th></th>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual production</td>
<td>60 MT</td>
<td></td>
</tr>
<tr>
<td>Equipment used</td>
<td>Vessel (6 rm³) + tanks</td>
<td>Raptor (0,001rm³) + tanks</td>
</tr>
<tr>
<td>Duration of Production</td>
<td>25 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Productivity</td>
<td>42 kg/h</td>
<td>100 kg/h</td>
</tr>
<tr>
<td>Productivity x week</td>
<td>2,4 MT</td>
<td>6 MT</td>
</tr>
<tr>
<td>Reaction temperature</td>
<td>10 – 15°C</td>
<td>45°C</td>
</tr>
<tr>
<td>Toluene</td>
<td>3,5 vol</td>
<td>1,75 vol</td>
</tr>
<tr>
<td>Water (washing)</td>
<td>4 vol</td>
<td>2 vol</td>
</tr>
<tr>
<td>Excess CMS &amp; TEA</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Product Quality</td>
<td>Orange (purification step needed)</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>Disposal</td>
<td>6,2 kg /kg</td>
<td>3kg / kg</td>
</tr>
</tbody>
</table>
RAPTOR SUMMARY

- 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

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