Purification: a Challenge for Bio-Based Chemicals

San Diego, January 2013
What is needed industrially!

- Furfural, HMF, Organic acids, Salts

- Feed material
- Side products
- Salts
- Proteins
- Biomass

Transforming the Biomass into an Intermediate
Which technologies for purification?

New raw materials
New production routes
Mixtures / broths

Distillation and crystallization are not fully applicable!

Only Advanced Purification Technologies can do the job!

C5 Sugars

Organic acids

C6 Sugars

Diols & Glycols

Combining the right technologies into a complete process is the key to be competitive
We develop processes and market equipment, to solve purification challenges, by using advanced technologies, since 45+ years
Our Markets

Biopharma
- Recombinant Proteins
- Vaccines
- mAbs - ADC
- Blood Fractionation
- Biomass Extracts
- Cell Therapy

Food Ingredients
- Sucrose
- Starch and derivatives
- Milk

Functional Ingredients
- Polyphenols
- Anthocyanes
- Oligosaccharides
- HI Sweeteners

Bio-Industries
- Bio Based Chemicals
- Organic Acids
- Aminoacids
- Antibiotics
- Vitamins
Novasep Process Sales: **120 M€**
Employees: **430**

**Process Development**
- # 20 purification processes per year in Industrial Biotechnology
- # 30 purification processes per year in Biopharma

**Equipment and Systems**
- More than 2,000 units installed worldwide

**Design and Engineering Offices**
- Shanghai, Philadelphia, Lyon and Nancy

**Sales by Segment**
- Industrial Biotech: 50%
- Pharma: 40%
- Biopharma: 10%
An Unparalleled Breadth of Key Unit Operations

**Biobased Chemicals Purification**

- **Continuous chromatography**
  - Applexion® SSMB
  - Separation of fractions
  - Purification

- **Membrane filtration**
  - Ceramic & Organic
  - Clarification
  - Concentration

- **Evaporation Crystallization**
  - Plate or tubular
  - Multiple effect
  - MVR

- **Electrodialysis**
  - Demineralization
  - Salt Conversion

- **Adsorption/IEX**
  - Salt conversion
  - Demineralization
  - Decolorization
  - Batch or Continuous
Membranes, Chromatography, IEX, Electrodialysis

= Efficient, cost-effective, reliable and industrial technologies
Allowing to reach high degrees of purity
& Relying on the use of various physico-chemical properties:

- pKa
- Molar mass
- Hydrogen bonds
- Solvatation size
- Isoelectric point
- Hydrophobic/hydrophilic interactions
- Polar/non polar interactions
- Molecular Geometry configuration
How to use these tools?

By selecting among competing technologies depending on local conditions,

By designing **optimized** and **integrated** process routes,

Novasep Process provides **Efficient, Cost-effective and Reliable** processes:

applied industrially in units working **350 days/year on a 24/7 basis**

**With typical capacities of 100 kT / year**

yielding products which **market prices are typically < 2€/kg**

- Lactic Acid
- Arabinose
- Succinic acid
- Glucaric acid
- 1,4 BDO
- Glucose
- Citric Acid
- 1,3 PDO
- Fructose
- Xylose
- Sorbitol
- Gluconic acid
- Xylose
Novasep Process Technology: Membranes
Clarification with Kerasep® ceramic membranes

- Removal of solids, bugs, colloids, proteins
- Industrial References:
  - PDO broth clarification in China, 2011
  - Organic acids broths clarification since 1995: succinic, lactic and citric acids
  - Other brothes since 1983

- 24/7 operation
- Carrousel operations with CIP/SIP
- Up to 6 years lifetime guarantee
- Installed Base > 50 000 m²
Novasep Process Technology: Ion-exchange
Ion Exchange and Adsorption

- Batch and continuous ion exchange: (> 150 units designed by Novasep)
- Adsorption on resins and activated carbon
- Applications: decolourization, desalting, purification and salt conversion
- IEX: Cyclic behaviour operated in columns:

<table>
<thead>
<tr>
<th>LOADING</th>
<th>FEED DISPLACEMENT</th>
<th>STRIPPING</th>
<th>REGENERANT DISPLACEMENT</th>
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<tbody>
<tr>
<td>Feed</td>
<td>H₂O</td>
<td>Regenerant</td>
<td>H₂O</td>
</tr>
<tr>
<td>Exhastted Solution</td>
<td>Back to Feed</td>
<td>Recovered Products</td>
<td>Recovered Regenerant</td>
</tr>
</tbody>
</table>
From IEX to continuous IEX

**Batch IEX**
- Loading
  - Top layer fully loaded, waiting to be eluted
  - Partially loaded
  - Lower layer not loaded

**Resin is NOT used at its maximum capacity**

**CIEX**
- Loading
  - Fully loaded, ready to be eluted
  - Partially loaded, and ready to be fully loaded
  - Not yet fully loaded, ready to be loaded

**Resin is used at its maximum capacity**

- Higher productivity
- Recovery up to 99.8%
- Less resin
- Strongly reduced water and chemicals consumptions
- In-line water and regenerant recycling
- Higher fractions concentrations
Industrial References of CIEX in Demineralization mode:

- Demin. of Biomass sugars: pilot stage
- Glycols desalting: Europe
Applexion® Continuous IEX Capture Mode

**Industrial References** of CIEX in “Capture” mode

- Lysin and nucleic acids: USA, Brazil, China, Indonesia
- Organic acids conversion
  - Succinic: USA, China: pilot stage
  - Gluconic: Europe
Novasep Process Technology: Chromatography
Chromatography

The Lab HPLC Equipment!
Applexion® SSMB Chromatography

The Industrial Process!

<table>
<thead>
<tr>
<th>Examples</th>
<th>Product price</th>
<th>Installed capacity</th>
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<tr>
<td>Fructose HFCS</td>
<td>0,7 €/kg</td>
<td>1710 kT / y</td>
</tr>
<tr>
<td>Citric acid</td>
<td>0,8 €/kg</td>
<td>135 kT / y</td>
</tr>
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Novasep Process Industrial Biotech
Low pressure chromatography installed capacity

- Tons TS/day
- Year

Graph showing installed capacity from 1990 to 2010.
Batch Chromatography Principle

Low pressure liquid chromatography allows to separate two components by using their difference of affinity with a solid adsorbent phase (generally ion-exchange resins). No regeneration is required.

Example of butane-diol / salt separation by batch chromatography at 65°C (BDO boiling point : 235°C)

Two fractions are recovered: Raffinate (low affinity) & Extract (high affinity)
Inside SSMB PROCESS

- **Affinity chromatography:**
  - Xylose / Arabinose / Glucose separation
  - Glucose / Mannose
  - Polyols separation
  - Mono & di- Organic acids separation

- **Ion exclusion:**
  - Sugar and salt separation
  - Polyol demineralization
  - Organic acids / salts & esters separation

- **Size exclusion:**
  - Oligosaccharides / Monomers separation

- High purity fractions
- Low water usage
- No chemical consumption
Example 1 : Chemical Polyol Purification

- Separation of a polyol (Teb > 280° C) and salts by Applexion® SSMB, on ion exclusion principle, at 65° C
- Capacity : 20 kT / y
- Concentration by reverse osmosis
- Separation at 65° C of polyol and sugar by Applexion® SSMB, on affinity principle : recovery of both pure streams
Example 2: Separation of organic acids

Gluconic acid (monoacid)
- \( pK_a = 3.86 \)
- Molar Mass: 196 Da
- Boiling Point: 674 °C at 760 mmHg

Saccharic acid (diacid)
- \( pK_a = 2.99 - 5 \)
- Molar Mass: 210 Da
- Boiling Point: 766 °C (760 mmHg)

- Separation of the two acids by low-pressure chromatography, applied at ambient T° and with no mineral salt addition
- > 90% purity achievable (not possible by direct crystallization)
- Direct recycling of gluconic stream without crystallization

Intermediate for further chemical transformation

Target capacity (1 unit): 200 kT / y
Novasep Process Technology: Electrodialysis
Electrodialysis

- **ED**: transport salts from one solution through ion exchange membranes to another solution, thanks to electrical current
- **EDBM**: Bipolar Membrane Electrodialysis: water splitting used for salt conversion into acid and base
- Applications: lactose desalting, purification of sugars, organic acids

- High desalting efficiency
- No chemicals consumption
- But electricity consumption
- By construction, suitable for high conductivity and rather low capacity jobs
Succinic Acid Purification

- Succinic acid is produced by fermentation under its salt form: conversion into acid form (by capturing the counter cation) and purification are needed.

- The process:
  - Clarification by Kerasep® membrane filtration
  - 2 different conversion routes, depending on local conditions:
    - Applexion® CIEX
    - Novasep – Mega® Electrodialysis
  - Nanofiltration: colour removal

- 1st industrial Bio Succinic Acid plant worldwide started in 2009, with Capacity 3,000 t/year.

![Molar mass]: 118.09 g mol⁻¹
**Boiling point**: 235 °C
**Solubility** in water: 58 g/L (20 °C)
Different Process Routes for Organic Acids

- **Broth**
  - Clarification
  - Batch Ion Exchange Demineralization
  - Continuous Ion Exchange Salt Conversion
  - Batch Ion Exch. Softening
  - Batch Ion Exch. Polishing
  - Batch Ion Exch. Polishing
  - Evaporation
  - Continuous Chromatography
  - Continuous Chromatography

- **Glucose**
  - Oxidation
  - Continuous Ion Exchange or Continuous Chromatography

- All types of fermentation broth
- Organic acids produced as salts
- Lactic acid, Succinic acid
- Organic acids produced as acids
- Citric acid, Succinic acid
- Gluconic acid, Glucuronic acid, Mono/Di acids separation
How to perform?

- Selecting the right technologies for your specific case
- Sequencing correctly the operations
- Building an integrated process

is the key to **BEST-IN-CLASS ECONOMICS!!**
Thank you for your attention!

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