Challenges in API manufacturing

Dr. Hendrik Baumann, Commercial Director
First of all ....

... CONGRATULATIONS to the 5th anniversary of Rapid Pharma Development

and best wishes for the future from the whole team of CU Chemie Uetikon GmbH
Our areas of activity

- **Custom Synthesis** - for all clinical phases of pharmaceutical development - from development through production to registration

- **API's** with (proprietary) Drug Master Files (DMF) or Certificate of Suitability (CEP) in Full compliance with international quality standards like cGMP, ISO 9001:2000

- **Special Intermediates** of high purity and **High Performance Chemicals** for the Electronic Industry, Cosmetics or Nutrition
About us: CU Chemie Uetikon GmbH

- CU Chemie Uetikon GmbH - a German CMO with long presence and excellent reputation in the market
- Located in Lahr, southwest Germany, directly linked to the major hubs of the Pharmaceutical and Chemical Industries
- Easy access by train, car and through major airports like Frankfurt, Paris, Basel or Zurich

- 1941: Start of chemical operation by the predecessor of Uetikon in Lahr
- 1987: First successful FDA inspection
- 1994: First certification according to ISO 9001
- 1997: Initial operation of a thermal waste gas treatment plant
- 1998: Acquisition of the business activities by CPH Group
- 2000: Erection and start operation of the GMP kilo-lab and upgrading of further laboratory infrastructure in Lahr
- 2002: Start operation of a state-of-the-art GMP production plant (MPA P3) with initially 2 production trains
- 2009: Extension of the GMP kilo-lab with a Cryoreactor
- 2010: Successful inspection by COFEPRIS (Mexico)
- 2011: Acquisititon of 90% of CU Chemie Uetikon GmbH by Barclays Private Equity (since 2012 Equistone Switzerland). Management holds 10% of the company shares
- 2008: Completion and operational start of two additional production trains in the MPA P3 plant, one equipped with a cryogenic reactor (-90°C).
- 2009: GMP-inspection by German authorities and GMP certification
- 2010: Purchase of additional land reserves (about 2,500 m²)
- 2011: Most recent successful FDA inspection
- 2011: Successful re-certification according to ISO 9001:2008
- 2011: Extension of the GMP kilo-lab with a Cryoreactor
- 2012: Successful inspection by COFEPRIS (Mexico)
- 2012: Successful re-certification according to ISO 9001:2008
- 2011: Extension of the GMP kilo-lab with a Cryoreactor
- 2012: Purchase of additional land reserves (about 2,500 m²)
Key Financials

- **Key figures 2011:** 108 employees and a capacity of 91,5 m³ reactor volume

- **Turnover 2011:** 32,3 MEUR

- **Project success rate:**
  - > 200 inquiries ("Paperevaluation")
  - 175 registered projects with sample
  - 31 projects in pilot production and/or commercialisation
  - Turnover with new projects in 2011 >10%
Business Model: Custom Synthesis

- The API manufacturing is a highly regulated business.
- Key for success is the smart combination of modern technologies with efficient processes development and implementation.

Worldmarket

- Pharma: 790 Mrd. $*)
- Outsourcing Pharma: 168 Mrd. $**) 
- Chem. API/Adv. Intermediates: 12 Mrd. $**) 

- 55% of the current APIs or key intermediates are outsourced to CMO's *)

*) IMS Health 2008
**) Frost & Sullivan
Business Model: Custom Synthesis

- "This is a business model where you are guaranteed to lose your entire orderbook of business every 8 years."

- "Speed, Endurance und Experience" are key for success and excellent customer relationship the basis for a sustainable business.

- Number of competitors worldwide >1000; nobody has more than 3% of market share.

- The successful players are small-midsized companies (SME's) or departments of big companies (BASF-Orgamol for example)
Overview: API supply chain

- Discovery: mg - g
- Preclinical: 1-20 kg
- Clinical: 100-500 kg
- Launch: > 500 kg

CMC for clinical trials
IND*

CMC for Launch
NDA**
Process Development: TCQ triangle

API supply

- Time
- Medchem Supply
- Early Phase or Clinical Phase Supply
- Cost
- Quality

Launch and Late Phase Supply
Challenge 1: Reduction of complexity

- Heat reactants, cool down and filter off the crystals
- How to get there?
- Start at the end of the process

Reaction in DMF
- Quench into Water
- Filter and Dry
- Suspend in EtOAc
- Filter
- Crystallize from THF/Heptane
- Filter and Dry
- Crystalline API yield 70-75%

Reaction in THF
- Add Heptane and Crystallize
- Filter and Dry
- Crystalline API yield 83-87%

Challenge 2: Plant utilisation

- Multipurpose plants are more expensive than dedicated plants. As more dedicated products are available, as lower the COG are.

- For an SME it is important to have a "base load" of repeating products to cover costs and to guarantee an average utilisation of >50%.

- "Ideal" plant size for CMO's is between 80 – 160m$^3$ of capacity with vessels of max. 6m$^3$.

- There must be a mix of new projects (small volume, small batch size), with established projects (medium volume, max. batch size) and proprietary products (medium-high volume, ideal batch size).
Challenge 2: Plant utilisation

<table>
<thead>
<tr>
<th>Firma</th>
<th>Sales (Mill. EUR)</th>
<th>Mitarbeiter</th>
<th>Kesselvol. (m³)</th>
<th>Umsatz pro MA (TEUR)</th>
<th>Umsatz pro m³ (TEUR)</th>
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<td>300</td>
<td>225</td>
<td>315</td>
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</table>

- The most of the successful CMO's have an average turnover per employee of >250 TEUR/MA and an average turnover of >300 TEUR/m³ per reactor volume.

- Backward integration (to Asia) and foreward integration (to FDF) are strategic questions for future success of CMO's.
Challenge 3: "simple" Hydrogenation

- **Target:** Reduction of the Carbonyl group without reduction of the aromatic system.

- **Result of the development:**
  - More or less no literature available, if available "exotic" conditions like loop reactor, FeCoCr-catalysts etc.
  - Catalyst producers offering standard portfolio only.
Challenge 3: "simple" Hydrogenation

- We have tested more than 50 different catalyst systems.
- Always reduction of the aromatic systems or no reduction or masses of impurities.
- Brainstorming results: Back to old school
- Solution: Reduction in HCl/Fe or Zn yields perfect product and a competitive process.
- A simple system which is easy applicable in the current production, no additional equipment necessary and product quality is sufficient.
Challenge 4: "green" Chemistry

- Due to increasing legislation and environmental protection many of the good old "recipes" are not longer applicable or the limits in the end product are extremely low (LOD).

- Examples: Halogenated solvents, Oxidation with Chromium or Permanganate, heavy metals as catalysts, alkylation agents etc.
Challenge 4: "green" Chemistry

Literature Route #1

Expensive

<table>
<thead>
<tr>
<th>Chemical Transformation</th>
<th>Reagents</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{NaBH}_4$ to $\text{NaH}$</td>
<td>MeOH, DMF</td>
<td>91%</td>
</tr>
</tbody>
</table>

Literature Route #2

$\text{H}_2$, Rh/$\text{Al}_2\text{O}_3$ to $\text{K}_2\text{Cr}_2\text{O}_7$ in $\text{H}_2\text{SO}_4$

**MEHQ** - hydroquinone monomethyl ether

www.uetikon.com
Challenge 4: "green" Chemistry

1. Use of a catalytic reduction step
2. Using cheap MEHQ as starting material
3. Use of a mild oxidation reagent, no chromium salt!

Bleach and TEMPO are versatile „green“ reagents for Oxidation reactions

yield: 95%

yield: 60%

yield: 87%
Summary

- Custom Synthesis is and was a challenging business. "Speed, Endurance und Experience" are key for success and excellent customer relationship is the basis for a sustainable business.

- Big is not beautiful.

- The CM market is more or less saturated and the CAGR in Pharma is estimated with 3,6% for 2012-2015. That means gaining market share will only be possible by displacement of competitors.

- Technology is self understanding, customer intimacy is key for survival in that business.
Summary

A successful CMO is able to deliver all CMC services which are necessary for a successful launch of the API.

Don’t build a house without an architect