Asymmetric Hydrogenation: A Sustainable Technology for Pharmaceutical Manufacture

Presentation for the RSC Symposium 2016: Survival in the Speciality Chemicals Industry

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Outline of the Presentation

- Short Introduction to Chiral Quest
- Asymmetric Hydrogenation Background
- Asymmetric Hydrogenation: A Sustainable Technology?
- Chiral Quest’s Examples of Asymmetric Hydrogenation
  - Manufacture of Phenylalanines
  - Manufacture of Chiral Alcohols
  - Applications to Generic Pharmaceuticals
- Conclusions
Background of Chiral Quest

- 2000: Founded by Professor Xumu Zhang
- 2003: Chiral Quest’s NJ R&D Lab (near Princeton) established
- 2005: Scale-up facilities, Chiral Quest Jiashan (near Shanghai)
- 2008: Chiral Quest Receives Series B Financing of $13 m
- 2009: New Chiral Quest pilot plant opened May 2009 in Suzhou, Biobay
- 2012: Purchase of Jiang Xi Long Life Biopharmaceuticals Co. Ltd
- 2013: New R&D Laboratories in Suzhou opened and Series C Financing completed - $23 Million
- 2013: Chiral Quest files a US DMF for Duloxetine and Sitagliptin Ints.
- 2014: New workshops complete and the current plant capacity is >310 KL.
- 2014: REACH registration for (S)-MMAA completed
- 2015: Chinese Drug Manufacture Permit obtained
Management Team

Dr James Wu, CEO
PhD Organic Chemist, SIOC. 10 years with GSK in Senior Management roles, 7 years with other Chinese companies (GM and CTO). Founder of Jiang Xi Long Life

Dr. Ian Lennon, Senior Vice President, Global Business Development
More than 27 years pharmaceutical industry experience, in process chemistry and business development, with Merck, Parke Davis, Chirotech, DowPharma and Dr Reddy’s

Dr. Wenge Li, Vice President, Research & Development
Wenge has been with Chiral Quest since 2002 and has extensive experience in the application and development of asymmetric hydrogenation

Dr. Wenjun Tang, Senior Consultant
Research professor at SIOC, specialized in catalysis, synthesis and processes, 6 years pharmaceutical industry experience with Boehringer Ingelheim in process chemistry.
Commercial Manufacturing Facility

- Jiang Xi Long Life, located in Jiangxi Province, P.R. China.
- Wholly owned by Chiral Quest and has 208 employees
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New Chiral Quest Manufacturing Facility

- Jiang Xi Long Life, located in Jiangxi Province, P.R. China
- >170 reaction Vessels (>310,000 L volume capacity )
- New workshop will open in March 2016 with 40 more vessels
- High pressure vessels (1 x 100 L, 2 x 500 L, 4 x 1000 L, 2 x 2000 L), up to 100 atm
- Temperature range from -80°C to 300°C (10 vessels for -80°C, 50-2,000 L)
- 4 distillation column towers (to 0.1mmHg)
- Licenses for Toxic chemicals including: - NaCN, Cl₂, POCl₃, Cl-SO₃H, CICOOC₂H₅ and CH₃SO₂Cl
- Long Life has Chinese High Tech Certification
- In 2015 Chinese Drug Manufacture Permit granted, by the CFDA
- This was a hardware and software audit that determined that the plant is capable of cGMP manufacture
Expertise in Asymmetric Hydrogenation

11 Hydrogenation reactors with high pressure capability (100 L to 2000 L)

- 2 x 2,300 L, 1 x 1,300L, 3 x 1000 L, 2 x 500 L and 1 x 100 L stainless steel hydrogenation reactors (maximum rating 100 atm)
- 1 x 1000 L and 1 x 100 L glass lined hydrogenation reactor (10 atm)
- Our own proprietary catalysts

Catalysts:
- Rh-TangPhos Complex
- Rh-DuanPhos Complex
- Rh-Binapine Complex
- Rh-Binaphane Complex
- Ru-C3-TunePhos Complex
Chiral Quest Suzhou – Headquarters

Headquarters

- Chiral Quest has its HQ on the Suzhou Industrial Park
- The new R&D center and HQ houses 31 employees and was opened in July 2013

- R&D, Administration, Finance, HR, QA/QC and business development functions are located at the new Suzhou HQ
- Chiral Quest employs 3 PhD, 5 MS and 6 BS level chemists and 5 analysts
- Chiral Quest has a total of 240 employees
Chiral Quest Suzhou – R&D Centre

Research & Development

– All R&D is carried out in the new Suzhou R&D Centre
– Modern and well equipped chemical Laboratories for >40 chemists

– Glove boxes for handling air-sensitive compounds
– Analytical equipment, including HPLC’s, GC’s and LCMS
Over 70% of commercial asymmetric catalytic processes involve asymmetric hydrogenation.

Asymmetric hydrogenation can be applied to make over 50% of all chiral moieties in pharma products.

Avoids wasteful production of 50% of the wrong isomer.

Catalytic Asymmetric Hydrogenation

Nobel Prize in Chemistry 2001

The most powerful Chemocatalysis method
Reactions Under Pressure!

WE CARRY OUT ALL OF OUR REACTIONS UNDER PRESSURE ...

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Some of the First Applied Phosphine Ligands

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% ee</th>
<th>Ligand</th>
<th>% ee</th>
<th>Ligand</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrPh·CH₃</td>
<td>28%</td>
<td>DIPAMP - 1974</td>
<td>95%</td>
<td>CHIRAPHOS - 1977</td>
<td>95%</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>CAMP - 1970</td>
<td>88%</td>
<td>Rhone-Poulenc - 1974</td>
<td>87%</td>
<td>BPPM - 1976</td>
<td>91%</td>
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<tr>
<td>DIOP - 1971</td>
<td>83%</td>
<td>Ph₄PF₄</td>
<td>94%</td>
<td>BPPFA - 1980</td>
<td>93%</td>
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</table>
Early Applications of Asymmetric Hydrogenation


**Monsanto L-DOPA process**

Some of the 3,000 Known Phosphine Ligands
Noyori’s Binap Complexes

Asymmetric Catalysis in Organic Synthesis, R. Noyori
John Wiley & Sons, 1994

[(R)-Ru-(Binap)Cl2]2.NEt3
Binap = 100% Conv.
98% ee, syn:anti =94:6
120 tonnes per year Carbapenem intermediate

[[(R)-Ru-(Binap)Cl2]2.NEt3
S/C 3,000
0.1 mol% HCl, MeOH
40 psi H2, 40°C
>98% ee

Largest Scale Industrial Asymmetric Hydrogenation

BASF Menthol Process

- Worldwide consumption of Menthol is 20,000 MT
- Takasago and Symrise manufacture 5,000 MT
- Rest comes from natural sources
- BASF capacity for Menthol is 3 – 5,000 MT, sells for $19/kg
- BASF back integrated into Geranial
Application of Asymmetric Hydrogenation to Drugs

Atorvastatin
Pfizer, 1997, Hyperlipidemia

Levetiracetam
UCB, 2000, Epilepsy
Rh-DuPhos

Pregabalin
Pfizer, 2004, Neuropathic pain
[(R,R)-Me-DuPhos Rh]

Solifenacin
Astellas, 2004, Overactive bladder

(S)-Duloxetine
Lilly, 2004, Depression

Tipranavir
Bl, 2005, HIV
[(R,R)-Me-DuPhos Rh]

Rozerem
Takeda, 2005, insomnia
BINAP-Ru

Sitagliptin
Merck, 2006, Diabetes
¹Bu-JosiPhos-Rh

Aliskiren
Novartis, 2007, Hypertension
MonoPhos-Rh, WalPhos-Rh

Eslicarbazepine acetate,
Eisai, 2009, Epilepsy
RuCl(S,S-TsDPEN(p-Cymene))
Merck’s Hydrogenation Route to Sitagliptin

- Hydrogenation is of an advanced imine intermediate, but catalyst loading high.
- Rh is recovered onto Ecosorb and sent for refining – 94% recovery
- First ever final stage asymmetric hydrogenation process for a API
- Probably the largest Scale Asymmetric Hydrogenation for an API -100-200 MT/year
- 2006 Presidential Green Chemistry Award!
Asymmetric Hydrogenation: A Sustainable Technology?

- Can achieve very good catalyst loadings (S/C >120,000/1)
- Single solvent, substrate, hydrogen and catalyst
- Provides pure product, single solvent and catalyst – Easy Work-up
- Metal is not destroyed and can be recovered!
- 30,000 kg of rhodium consumed worldwide in 2012
- 24,300 kg (81%) went into Catalytic Converters ($\frac{1}{3}$ recovered)
- 964 kg of rhodium was used in the glass industry
- 2,520 kg in the chemical industry (not Pharmaceuticals!)
- Pharmaceuticals comes behind Dentistry, Jewellery and electronics in Rh usage
- This technology meets many of the Principles of Green Chemistry
Catalysts made on a Kg scale for our manufacturing requirements
>30 kg of DuanPhos made to support manufacturing
### RSM’s Made Using Asymmetric Hydrogenation

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>Approx. Volume</th>
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<tbody>
<tr>
<td>FDA Approved</td>
<td>&gt;5 MT</td>
</tr>
<tr>
<td>FDA Approved</td>
<td>&gt;4 MT</td>
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<tr>
<td>FDA Approved – 3 products</td>
<td>100-200 kg</td>
</tr>
<tr>
<td>Pre-Registration</td>
<td>&gt;10 MT</td>
</tr>
<tr>
<td>PIII – 2 products</td>
<td>1 to &gt;3 MT</td>
</tr>
<tr>
<td>PII – 2 products</td>
<td>100 – 200 kg</td>
</tr>
<tr>
<td>PI – 3 products</td>
<td>50 – 100 kg</td>
</tr>
<tr>
<td>Pre-Clinical – 3 products</td>
<td>1-10 kg</td>
</tr>
</tbody>
</table>

- Chiral Quest applies Asymmetric Hydrogenation Technology for 16-20 products
- Many of these are now on MT scale
- We can manufacture 130-150 MT of products per year
Manufacture of $\alpha$-Amino Acids

$\text{R} \equiv \text{COOR}^1 \xrightarrow{\text{Rh-Ligand}*} \text{H}_2 (20 \text{ psi}), \text{MeOH, r.t.} \xrightarrow{\text{S/C} = >10,000}$

- $\text{NHAc}$
  - COOH
  - 99.9% ee

- $\text{F}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{MeO}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{MeO}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{COOMe}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{COOMe}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{Br}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{F}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- $\text{F}$
  - $\text{NHAc}$
  - COOH
  - > 99% ee

- Same Rh-DuanPhos catalyst can produce many Phenylalanine products
Manufacture of (S)-N-Boc-3,4-Difluorophenylalanine

Vantia therapeutics made a request for 15 kg of (S)-N-Boc-3,4-Difluorophenylalanine

The product was made, shipped and received by the customer in under 10 weeks from receipt of a purchase order

Conditions for the Rh-DuanPhos hydrogenation are mild and scaleable.
The Erlenmeyer route does not work for the sterically hindered aldehyde.

The Horner-Emmons reagent is routinely manufactured on a MT scale.

This reagent is now routinely used for \( \alpha \)-amino acid manufacture.
Chiral Quest has manufactured 5 and 50 kg lots of this product for CML Europe.

High enantiomeric excess (99.9%) and purity (99.5%) was achieved.
Chiral Quest Advantaged Chiral API’s and Intermediates

- Dorzolamide
- Aprepitant
- Linagliptin
- Duloxetine
- Sitagliptin
- Rasagiline

Examples of Active Pharmaceutical Ingredients that can be manufactured using Chiral Quest Technology
Asymmetric hydrogenation of methyl acetoacetate requires a Hastelloy reactor

Chiral Quest has a 1,000 L Hastelloy hydrogenation vessel

>5MT of this intermediate has been manufactured
Intermediate for Aprepitant

In excess of 10 MT of the chiral alcohol for Aprepitant has been manufactured.

Chiral Quest obtained a license for the ketone hydrogenation technology from the Japan Science & Technology Agency in December 2009.

Chemotherapy-induced nausea/vomiting
2012 sales, **$309 Million**, Patent Expiry 2013
Chiral Quest’s Approach to the Key Intermediate of Duloxetine

Process transferred to Jiang Xi Long Life and is in routine production.

>30,000 kg of MMAA has been manufactured, >99% ee, >99% purity

Chiral Quest has filed a US DMF for the MMAA process – Ref. Number 26862
REACH Registration completed – Registration No. 01-2120053179-54-0000
Traditional Routes to Duloxetine

- DMAA is made by resolution
- Methyl Chloride is the by-product of demethylation!
- An extra purification process by an oxalate salt is required

(S)-Duloxetine (Cymbalta™)

- DMAA is made by resolution
- Methyl Chloride is the by-product of demethylation!
- An extra purification process by an oxalate salt is required
Chiral Quest’s Route to Sitagliptin Intermediate

- Highly efficient asymmetric hydrogenation process, S/C = 5,000 (2,360/1 \text{ wt/wt})
- Three manufacturing campaigns completed >25,000 kg made.
- Chiral Quest has filed a US DMF for the Sitagliptin process – Ref. Number 27115

Diabetes type 2
2012 Sales $5.98 Billion, Patent Expiry 2022
Summary

- Many products are made annually using Asymmetric Hydrogenation
- The process is highly efficient, providing high enantiomer excess, high purity and producing very little waste.
- If volumes are high enough, then continuous flow plants can be built
- Unfortunately, this is rarely the case in Pharmaceuticals
- Chiral Quest offers the manufacture of a range of products on a commercial scale, such as Chiral Alcohols, $\alpha$- and $\beta$-Amino acids using this technology
A Recognized Leader in Chiral and Process Chemistry

Ian Lennon
ilennon@chiralquest.com

Please Visit Chiral Quest at Stand H10

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