PharmaBlock

Innovative chemistry for a better future

PharmaBlock Sciences (Nanjing), Inc.
Address: 81 Huasheng Road, Jiangbei New District
Nanjing, Jiangsu 210032, China
Tel: +86-400 025 5188
Fax: +86-25 8691 8232
E-mail: sales@pharmablock.com

PharmaBlock (USA), Inc.
Address: 777 Schwab Rd, Unit D
Hatfield, PA 19440, USA
Tel: +1(877)678-5226 / +1(267)649-7271
Fax: +1(267)222-7551
E-mail: salesusa@pharmablock.com

PharmaBlock Pharmaceuticals (Zhejiang) Co., Ltd.
Address: 11 Weiqi Road, Hangzhou Bay Shangyu Economic and Technological Development Area, Shaoxing, Zhejiang, China

PharmaBlock Pharmaceuticals (Shandong) Co., Ltd.
Address: Renhe Road, Economic Development District, Pingyuan County, Dezhou City, Shandong, China

Technology Innovation

To Enable Greener and Low-carbon Pharmaceutical Development & Manufacturing

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**CONTENTS**

1. **Flow Chemistry**  
   - 1. Reaction Types  
   - 2. Reactor Types  
   - 3. Cases  

2. **Micropacked Bed Technology**  
   - 1. Technical Advantages  
   - 2. Reaction Types  
   - 3. Cases  
   - 4. Integrated Solutions  

3. **Catalysis**  
   - 1. Heterogeneous Catalysis  
   - 2. Biocatalysis  
   - 3. Cases  

4. **Innovative Equipment**  
   - 1. Customized Service  
   - 2. Equipment Design  
   - 3. Quality Control  
   - 4. Equipment Cases  

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**OUR VISION**

To provide better products and services through innovation of chemistry and low carbon technology in R&D and manufacturing.
### Flow Chemistry

<table>
<thead>
<tr>
<th>400+ projects</th>
<th>40+ reaction types</th>
<th>kilo to metric ton scale</th>
</tr>
</thead>
</table>

#### 2023 ACS GCI CMO Excellence in Green Chemistry Award Winner

The award-winning project implemented innovative continuous flow process.

### Application in safer, more stable, higher-yield processes

- High temperature/pressure
- Highly energetic
- Cryogenic
- Highly reactive and air-sensitive
- Toxic and/or stinky agents
- Unstable intermediates
- Oxidation and/or ozonization
- Sulfonation
- Esterification
- Halogenation
- Reduction

### Reactors

- Single-tube
- Static mixer
- Dynamic tubular reactor
- Photo-flow reactor
- Multi-tube
- Fixed/micropacked bed
- Electrochemistry reactor
- CSTR

### Cases

#### Cryogenic reaction

![Cryogenic reaction](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility of scaling up</td>
<td>x</td>
</tr>
<tr>
<td>Temperature</td>
<td>-70 to -60°C</td>
</tr>
<tr>
<td>Yield</td>
<td>N/A</td>
</tr>
<tr>
<td>Scaling-up risk</td>
<td>High</td>
</tr>
</tbody>
</table>

Completed 260 kg product with 240 mL continuous flow reactor in 30 hours

#### Diazotization

![Diazotization](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility of scaling up</td>
<td>x</td>
</tr>
<tr>
<td>Temperature</td>
<td>N/A</td>
</tr>
<tr>
<td>Yield</td>
<td>N/A</td>
</tr>
<tr>
<td>Scaling-up risk</td>
<td>High</td>
</tr>
</tbody>
</table>

Completed 200 kg product with a set of 100 mL continuous flow reactor in 2-3 days

### Nitration

![Nitration](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility of scaling up</td>
<td>x</td>
</tr>
<tr>
<td>Temperature</td>
<td>20 - 30 °C</td>
</tr>
<tr>
<td>Yield</td>
<td>N/A</td>
</tr>
<tr>
<td>Scaling-up risk</td>
<td>High</td>
</tr>
<tr>
<td>Automatic leve</td>
<td>Low</td>
</tr>
</tbody>
</table>

Over 300 kg of product completed with an integrated continuous tubing reactor

### High temperature

![High temperature](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility of scaling up</td>
<td>x</td>
</tr>
<tr>
<td>Temperature</td>
<td>200 °C</td>
</tr>
<tr>
<td>Yield</td>
<td>N/A</td>
</tr>
<tr>
<td>Scaling-up risk</td>
<td>High</td>
</tr>
<tr>
<td>Automatic leve</td>
<td>Diphenyl ether (BP: 258 °C)</td>
</tr>
</tbody>
</table>

Over 100 kg of product completed

### Oxidation

![Oxidation](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMI</td>
<td>15</td>
</tr>
<tr>
<td>Time</td>
<td>&gt; 4 h</td>
</tr>
<tr>
<td>Yield</td>
<td>88 - 90%</td>
</tr>
<tr>
<td>Complexity of work-up</td>
<td>High</td>
</tr>
</tbody>
</table>

Over 100 kg of product completed

### Photocatalytic reaction

![Photocatalytic reaction](image)

**Comparison**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility of scaling up</td>
<td>x</td>
</tr>
<tr>
<td>Time</td>
<td>30 h</td>
</tr>
<tr>
<td>Light source</td>
<td>Medium pressure mercury lamp</td>
</tr>
<tr>
<td>Scaling-up risk</td>
<td>High</td>
</tr>
</tbody>
</table>

Over 1 MT of product completed
**Electrocatalytic reaction**

```
\[ \text{Entry General Process Electrochemical Process} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>General Process</th>
<th>Electrochemical Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Yield</td>
<td>45%</td>
<td>67%</td>
</tr>
<tr>
<td>PMI</td>
<td>135</td>
<td>73</td>
</tr>
<tr>
<td>Cost of Material</td>
<td>&gt; 30% cost reduction</td>
<td></td>
</tr>
</tbody>
</table>

Self-made equipment, Kg scale preparation

**Telescoped flow cases**

1. **cooling bath**
   - HCl solution
   - Yield: 86%
   - Kg production
   - 2 steps telescoped

2. **cooling bath**
   - Oxygen
   - Yield: ~100%
   - 100Kg production
   - 2 steps telescoped

**End-to-end solution**

- Manufacturing (1ton+)
- Lab scale (100~500g)
- In plan

Continuous Manufacturing GMP Workshop at PharmaBlock Zhejiang
Micropacked Bed Technology

450+ projects
kilo to metric ton scale
commercial and GMP projects

Technical advantages
- Safety, efficiency, consistency
  - Meet safety regulations
  - Increased productivity
  - No batch variation
  - Heavy metal < 10 ppm
- Superior selectivity
- Significant cost savings
  - Lower catalyst cost
  - Lower solvent usage
  - Shorter production time

Cases

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Batch</th>
<th>Micropacked Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalyst loading</td>
<td>3.3%</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Solvent</td>
<td>20V</td>
<td>10V</td>
</tr>
<tr>
<td>Product delivered</td>
<td>~</td>
<td>Hundred Kilo</td>
</tr>
</tbody>
</table>

Integrated solutions
- Proof of concept and bench-scale R&D of flow hydrogenation process
- Pilot-scale process research, design and operation
- Turnkey solution service for industrial-scale plant operation (including hydrogenation process, equipment and catalyst)
**Catalysis**

500+ heterogeneous catalysts

400+ biocatalysis projects

Kilo to hundred-kilo scale

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**Heterogeneous catalysis**

> 500 bead-supported fixed-bed hydrogenation catalysts (built in-house and purchased)

> 40 cats have been used in Kilo projects or larger

Various metals: Pd, Pt, Ru, Rh, Fe, Co, Ni, Cu

Consistent performance and releasing on real substrates

Catalysts characterization, design, screening, and continuous optimization

Contract research and customized catalysts

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**Biocatalysis**

Enzyme discovery and engineering

Fermentation

Enzymatic process

Screening and process development

Enzyme immobilization

**Benefits**

Significant cost savings

Safer process, better quality and shorter timeline

Continuous improvement enabled by continuous enzyme engineering

- > 500 enzymes in stock (commercial and in-house)
- Fermentation: up to 5 ton, using Various microbes
- Screening and process development
- Enzyme discovery and enzyme engineering

---

**Cases**

Semi-rational Design

Database, multiple sequence alignment, docking & scoring, MD simulation, DFT, AI, etc

Enzymatic selectivity/specificity: diastereo-selectivity, enantio-selectivity, asymmetric substrate's resolution

Activity improved >100 fold, E >300, >100 kg production

49% yield ee>99.0%

49% yield ee>99.0%
Innovative Equipment

Capabilities

- Equipment innovation
- Membrane tech
- Fluid simulation
- Engineering construction
- Process design
- Automation design

Rich experience and standardized process design.

Equipment Cases

Carry out innovation of equipment under the demand of research and production. Design various customized equipment demanding for different order of production.

**Microchannel reactor/mixer**

- Volume: 1-5 mL

**Membrane separation equipment**

- Volume: 10-100 mL

**Electrochemical equipment**

- Volume: 1-20 L
- Easy to multiply capacity

**Photo reaction**

- Kilo lab scale
- Manufacturing scale
  - Volume: 1-1,000 kg/day; GMP

**Continuous hydrogenation**

- Continuous hydrogenation reactor
  - (30-150 kg/day)
- Continuous nitrination reactor
  - (100-500 kg/day)
- Continuous high temperature reactor
  - (1,000-1,500 kg/day)

**Continuous special material manufacturing equipment**

**Equipment design capacity**

- Equipment material corrosion test
- Fluid simulation and verification
- Process design
- 3D modeling

**Customized service**

- Project evaluation
- Process validation
- Integrated design
- Equipment processing
- Installation
- Acceptance test
- Data delivery
- Equipment maintenance

**Quality control**

- Software validation
  - IQ
  - OQ
  - PQ
- Hardware validation
  - DQ
  - IQ
  - OQ
  - PQ

**Integration and assembly; on-site installation.**

- Independent programming and customized design of PLC control.
PharmaBlock (Stock Code: 300725.300725) is a global, fully integrated CRDMO in the pharmaceutical R&D and manufacturing industry. Its core businesses include a collection of rationally designed building blocks, supplying from discovery to development and commercialization; building block-enhanced hit generation and hit-to-lead optimization services and solutions; and development and manufacturing of RSMs, intermediates, APIs, and drug products for drug development and commercialization.

Throughout the product lifecycle, PharmaBlock integrates innovative and enabling technologies, such as flow chemistry, micropacked bed technology, chemo-catalysis, bio-catalysis, and equipment R&D, to proactively explore greener, safer, and more intelligent manufacturing and service models in the biopharmaceutical field, and promote the sustainable development of the industry.

Officially operated in 2008, PharmaBlock has partnered with almost all of the top 20 pharmaceutical companies, as well as hundreds of small to medium-sized biotech companies around the world. Its mission is to provide better products and services through innovation of chemistry and low-carbon technology in R&D and manufacturing, and help partners improve the efficiency of new drug discovery and development, and accelerate the project launch process at full speed.

About PharmaBlock

Teams

Our core management and technical teams have in-depth industry experience in leadership and R&D, previously spearheading drug discovery and CMC campaigns at Roche, GSK, Boehringer Ingelheim, Merck, Agios and other global pharmaceutical and biotech companies.

PhDs

Well-trained scientists

Employees

PhDs

Master’s & above

2,500+

1,500+

100+

40%+