Global Biomanufacturing Trends, Capacity and Technology Drivers

Industry Biomanufacturing Capacity Overview

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Introduction

• Current global biopharmaceutical capacity landscape
  – Production technologies
  – Product types and phases of development
  – Geographical distribution
  – Supply forecasts
  – Balance of demand and supply

• Future trends affecting capacity
Current and Future Biopharmaceutical Market

• Biopharmaceuticals have become an increasing percentage of overall pharma sales

• Sales of top 6 selling MAb products were nearly $52B in 2014*

• CAGR for MAb products for 2003-2014 was 21%; slowing to high teens in coming years

• Of the over 900 biopharm products in clinical development in US and EU, ~70% are MAb products

• Approximately 95% of these biopharma products are produced in mammalian cell culture

Sources: bioTRAK™ database, EvaluatePharma 2014
*2015 Data collection in process
bioTRAK® Database

• Over the past decade, BPTC has built the proprietary bioTRAK® database to track
  – **Biopharmaceutical products** in development (Preclinical to Phase 3),
    awaiting approval (BLA, MAA, NDA) and products approved for commercial
    sale in the US and EU markets
  – **Manufacturing capacity** (Clinical and Commercial) required to manufacture
    these biopharmaceuticals for the US and EU markets
• All data within bioTRAK is obtained from public sources with a referable citation
  – No confidential or proprietary information is included in the database
• Applications include
  – **Forecasting future supply and demand for manufacturing capacity**
  – Assessing the demand and market potential for technologies and services
    and perform competitive analyses
  – Strategic facility life cycle management
  – Identifying secondary suppliers

MAMMALIAN CAPACITY ANALYSIS
2014-2020
Distribution of Products by Production Technology

- Market: 62% (Mammalian), 38% (Microbial), <1% (Other)
- BLA/MAA/NDA: <1%
- Phase 3: <1%
- Phase 2: <1%
- Phase 1: 199 (Mammalian), <1% (Microbial), <1% (Other)

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Distribution of Mammalian Products by Product Type & Phase

Percent of Products

- Antibody
- Blood Protein
- Cytokine
- Enzyme
- Fusion Protein
- Hormone
- Protein

Phases:
- Market
- BLA/MAA/NDA
- Phase 3
- Phase 2
- Phase 1

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Forecast Bulk Kg Product Requirements

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Quantity (Kg/Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>13</td>
</tr>
<tr>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>40</td>
</tr>
</tbody>
</table>

- **Commercial**
- **BLA/MAA/NDA**
- **Phase 3**
- **Phase 2**
- **Phase 1**
- **Clinical**
Forecast Volumetric Product Requirements

- 2014: ~1,400
- 2015: ~1,400
- 2016: ~1,400
- 2017: ~1,400
- 2018: ~1,400
- 2019: ~1,400
- 2020: ~3,000

**Legend:**
- Commercial
- BLA/MAA/NDA
- Phase 3
- Phase 2
- Phase 1
- Clinical
Current Mammalian Supply

- Installed Capacity (1,000s L)
- 2014: ~3,600
- 2015: ~3,600
- 2016: ~3,600
- 2017: ~3,600
- 2018: ~3,600
- 2019: ~3,600
- 2020: ~3,600
- 2021: ~5,600

Legend:
- CMO
- Excess
- Product

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Geographic Distribution of Capacity

- Asia: ~16%
- Europe: ~32%
- North America: ~52%

Installed Capacity (1,000t)

Distribution of Clinical and Commercial Capacity

- **Clinical**
- **Commercial**

<table>
<thead>
<tr>
<th>Year</th>
<th>Clinical Capacity</th>
<th>Commercial Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>0</td>
<td>3,400,000</td>
</tr>
<tr>
<td>2016</td>
<td>0</td>
<td>3,400,000</td>
</tr>
<tr>
<td>2017</td>
<td>0</td>
<td>3,400,000</td>
</tr>
<tr>
<td>2018</td>
<td>0</td>
<td>3,400,000</td>
</tr>
<tr>
<td>2019</td>
<td>0</td>
<td>4,250,000</td>
</tr>
<tr>
<td>2020</td>
<td>0</td>
<td>4,250,000</td>
</tr>
<tr>
<td>2021</td>
<td>0</td>
<td>5,100,000</td>
</tr>
</tbody>
</table>
## Capacity Control

<table>
<thead>
<tr>
<th>2016 Rank</th>
<th>2021 Rank</th>
<th>Company</th>
<th>2016 Volume (1,000s L)</th>
<th>2021 Volume (1,000s L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Roche</td>
<td>673</td>
<td>909</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>Lonza</td>
<td>261</td>
<td>281</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Johnson &amp; Johnson</td>
<td>230</td>
<td>230</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>Sanofi</td>
<td>223</td>
<td>243</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Boehringer Ingelheim</td>
<td>205</td>
<td>338</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>Amgen</td>
<td>204</td>
<td>225</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>Biogen</td>
<td>196</td>
<td>316</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Pfizer</td>
<td>149</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>Celltrion</td>
<td>140</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>Lilly</td>
<td>137</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>Samsung</td>
<td>-</td>
<td>362</td>
</tr>
<tr>
<td>-</td>
<td>7</td>
<td>Bristol-Myers Squibb</td>
<td>-</td>
<td>237</td>
</tr>
<tr>
<td>-</td>
<td>10</td>
<td>Novartis</td>
<td>-</td>
<td>205</td>
</tr>
<tr>
<td>All Others (120/128)</td>
<td></td>
<td>1,214 (33%)</td>
<td>2,106 (39%)</td>
<td></td>
</tr>
</tbody>
</table>
Select Manufacturing Events

- Future builds coming on line by 2021
- Nearly 70% of capacity coming on line is Product based, 25% is CMO based and 17% is Excess based

- Alexion: (~80kL) New in Ireland
- AstraZeneca: (~45kL)
  - Acquired facility from Amgen in CO
  - Expanding MD Facility
- Biogen: (~120kL) New in Switzerland
- Boehringer Ingelheim: (~160kL)
  - Continue build out of China Facility
  - Expanding Germany
  - Installing Mammalian in Austria
- Bristol-Myers Squibb: (~105kL)
  - Expanding MA facility
  - New in Ireland
- Novartis: (~80kL) New in Singapore
- Regeneron: (~100kL)
  - Expanding NY Facility
  - New in Ireland
- Roche: (~236kL)
  - Expanding Chugai in Japan
  - CA facility back online
- Samsung: (~330kL) Expanding South Korea
- Takeda: (~40kL) Acquired from Baxalta in MN
### Overall Industry Supply/Demand Balance

- **Baseline Utilization Rate**
  - 2014: 50%
  - 2015: 55%
  - 2016: 62%
  - 2017: 62%
  - 2018: 63%
  - 2019: 68%
  - 2020: 73%

**Assumes:**
- 18 batches / BRX / yr
- Demand for capacity is 1yr ahead of product demand
- Demand is based on sales (actual and forecast)

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**Legend:**
- Commercial
- BLA/MAA/NDA
- Phase 3
- Phase 2
- Phase 1
- Clinical
- Available Capacity
Comment on Utilization and Variance Drivers to Demand

• A utilization rate of 50% may give the appearance that the industry is not operating at “full utilization”. However manufacturers often consider “full utilization” in the range of 75-80% (or lower) rather than 100%
  – Manufacturers often take a proactive approach in protecting unused capacity - product demand increases and additional indication approvals for a product can cause increases in manufacturing capacity required

• There is a high probability that many products currently in clinical trials will fail to be approved
  – Forecasts for the quantity of product required in future years is probability weighted based on the assumption that products will succeed or fail in the clinic

• Certain indications (i.e. Alzheimer’s disease, PDL/PDL-1 cancers) with large patient populations may increase manufacturing demands should these products be approved and covered by Pharmacy Benefit Managers
Manufacturing Trends: Smaller, More Diverse Markets

- Increased focus on orphan drugs and personalized medicine
- Shift from full length naked MAbs to alternative formats and more potent products (i.e., ADCs) requiring lower doses which may alter demand for manufacturing capacity
- 2014 kg requirements for each of the top 6 selling MAbs ≥0.75 metric tons (total 8.5 MT)
  - Demand for all other MAbs combined ~4 MT
- Anticipated demand for ~70% of new MAb products approved between 2016 and 2020 is expected to be <100kg per year per product
  - Exceptions: Alzheimer's, PD-1/PDL-1 asthma, PCSK-9

Future commercial manufacturing needs for 50% of products in development today can be met with a 5,000L bioreactor or smaller per product

<table>
<thead>
<tr>
<th># Products in Phase 2 and 3 Trials</th>
<th># Reactors</th>
<th>&lt; 2,000L Bioreactor</th>
<th>5,000L Bioreactor</th>
<th>10,000L Bioreactor</th>
<th>&gt; 10,000L Bioreactor</th>
</tr>
</thead>
<tbody>
<tr>
<td>285</td>
<td>1</td>
<td>118 (41%)</td>
<td>25 (9%)</td>
<td>32 (11%)</td>
<td>110 (39%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>139 (49%)</td>
<td>36 (13%)</td>
<td>23 (8%)</td>
<td>87 (31%)</td>
</tr>
</tbody>
</table>
Thanks to

- Dawn Ecker, Consultant
- Tom Ransohoff, Principal Consultant