Manufacturing

Dr. Ashley J. Stevens President



With thanks to:

Parika Petaipimol



Manufacturing

- □ How does a start-up company manufacture its products?
 - □ How do you raise the money to build capacity before product launch?
 - Should you build capacity before product launch?
 - □ Should you ever build capacity?
- What are the options?



Manufacturing Strategies

- More likely than not, you do not have internal manufacturing capabilities.
- Your options:
 - Build in-house manufacturing capabilities
 - Outsource manufacturing
 - Partner with a company that has manufacturing capabilities or has an existing relationship with a contract manufacturer
 - License your product
 - Get acquired





Manufacturing for Start-Ups

- Lt's easier than ever for a start-up to manufacture its products
- Supply chains have become so disaggregated that there are suppliers for every step in the chain
- Contract manufacturing is now a massive business
 - Some major corporations have permanently outsources part r all of their production
 - Apple
 - Lego





- Started with IBM PC in 1981
 - Product was developed and manufactured outside of IBM's bureaucracy
 - Generation Skunk works" in Boca Raton, FL
- Has sprea
 - Valmet
 - MagnaRapide
 - Flextror



the Porsch Boxster rcedes, Aston Martin





Some contract manufacturers are massive

Foxconn, Taiwan

Biggest exporter from PRC

□ iPad, iPhone, Kindle, PlayStation, Xbox 360

□ Flextronic, Singapore

□ First US company to offshore manufacturing

Now Singapore domiciled

Zune, Xbox, Xbox 360, LEGO



Frequently buy surplus plants from OEM's

- Magna Steyr spun off from Daimler Group and bought a Daimler plant
- □ Solectron bought plants from:

IBM

Hewlett-Packard

Phillips

Apple

Celestica:

- IBM Canada manufacturing division
- □ Standalone company in 1994
- □ Sold off in 1996
- Bought plants from:



H-P

Contract Manufacturers

- Increasingly do more than manufacture
 - Design
 - Development
 - Ensure easy manufacturability



Benefits:

- Avoidance of capital cost
- Avoidance of headcount
- Speed
- Cost
- Issues:
 - Risk of leakage of IP
 - □ Are you setting up a competitor



Levels of Engagement

Type of Relationship	Characteristics	Level of Commitment/Cost Control
Market Agreement	One time	Low
Framework Agreement	Several models in a given time period payments based on units produced or space utilized in manufacturing facility	Moderate-High
Strategic Alliance	Long term agreement; open sharing of processes and IP; frequent reciprocal communication	High



Prototyping

- Also getting easier
- Three Dimensional Printing aka Additive Manufacturing aka Digital Manufacturing
 - Very cheap to manufacture "looks like" prototypes
 - Economically feasible for early, low volume/high value production





Prototyping

Design companies can produce prototypes

- IDEO world leader
 - Palo Alto, CA!
 - Apple's first mouse
 - Microsoft's second mouse
 - Palm V PDA
 - Steelcase's Leap chair
- Fraunhofer GmbH, Germany
 - Non-profit
 - 60 Institutes in Germany
 - Seven Institutes in US
 - One at BU
 - Office for Process Engineering of Functional Materials and Robotics, Osaka



Very good at going from alpha to beta





Printing a blood vessel:



Photo by Sandy Huffaker for The Wall Street Journal

The Wall Street Journal



Sources: University of Houston; University of Missouri; WSJ reporting

Pilot Scale Production

Shared facilities

- Sematech model
- Obama plan for 16 Manufacturing Research Institutes
 - Photovoltaic Manufacturing Consortium, Halfmoon, NY
 - National Additive Manufacturing Innovation Institute, Youngstown, OH



Manufacturing in Life Sciences



Why Manufacturing Matters

- You need product for pre-clinical and clinical trials and/or regulatory enabling studies:
 - Pharmacodynamics/pharmacokinetics
 - Safety/efficacy
 - Dosage/frequency
 - Proof-of-concept and tolerance
- You need product to make money
 - Need product to sell to your markets



Regulations





When do you have to think about manufacturing?

Preclinical and clinical trials – stability data, safety data for patients prior for IND





19

When do you have to think about manufacturing?

Device – consider manufacturing for prototyping

FDA Medical Device Approval Process



Some Examples of Manufacturing Processes



Biopharmceutical Manufacturing





Stent Manufacturing Process

- Laser cutting is a typical method for stent production
- Despite initial fabrication technique, most stents see a similar fabrication process



23



Building In-House Manufacturing

- To give you an idea of the cost to build or buy a manufacturing facility
 - 2001 Immunex breaks ground for a 500,000 ft² facility in West Greenwich, RI estimated cost of \$500M.
 - 2003 Biogen Idec starts Hillerod, DK construction for a 34000 m² (366000 ft²) manufacturing facility which was completed in 2007. Total cost was approximately \$600M.
 - 2005 Genentech purchased the Biogen Idec manufacturing facility in Oceanside, CA for \$408M cash.
 - 2008 Genmab buys PDL's manufacturing facility in Brooklyn Park, MN for \$240M cash.
 - □ 2011 Merck invests \$250M in Singapore for a MFG facility
 - Operational costs average for a 175,000 ft² between \$22.6M to \$30.7M annually.





Building In-House Manufacturing

- Depending on the complexity of the device a single prototype can range from hundreds to thousands of dollars.
- An Atlanta-based medical device start up invested approximately \$2M for an 11,000 ft² facility.
- Georgia Tech is currently building a modular facility (retrofitting an old warehouse) in order to manufacture medical devices. They have currently spent \$500K (small lots)

Bottom line is: building or buying in-house manufacturing capabilities can be very expensive and time consuming. As a start up, you may eventually aim to become a FIPCO, but it's not feasible to start out that way. For a medical device and potentially a diagnostic, costs may be reasonable, but you need to take into account lead times which could delay your regulatory filings.



25

Biologics Contract Manufacturers





- One stop shop: All manufacturing activities in one site (API, fill/finish, label/pack)
- Contract out to parts of your manufacturing process and product
 - May want to keep control of trade secrets, critical process steps, QC testing in house.
 - Manufacture API in one place, fill/finish in another manufacturing site, label/pack at another
 - Manufacture components in different sites and bring them in house for sterilization and assembly



- Advantages:
 - Cheaper than building, buying, or maintaining manufacturing capabilities.
 - Products get manufactured by people with expertise in manufacturing (GMP)
 - □ You have 100% ownership and responsibility of your product
- Disadvantages:
 - Coordination and project management. Relationship maintenance.
 - Dependent on someone else to manufacture your product. Some of the bigger contract manufacturers may not have any interest in doing small batches or may have a minimum order quantity. Relying on their schedule and may not have availability when you need it.



28

- More likely than not, start ups and small companies will only have one manufacturing site. If something happens to the manufacturing site will jeopardize your supply.
 - Formatech received a FDA warning letter in Feb 2011 due to their lack of compliance with cGMPs. They had a program called "Fillantropy Program" where they filled products for several small companies.
- Depending on where you manufacture, trade secrets may leak out and give rise to piracy.
 - China raided several pill manufacturers selling fake "Viagra". These pills were colored with blue printer ink and other items.



□ Things to keep in mind

- Location of your clinical trials. Different regulations in different countries of where you manufacture. There are different regulatory requirements for clinical trials taking place ex-US.
- Your clinical manufacturing process may be ok for small amounts needed for regulatory enabling studies, but not optimal for commercialization (either the facility does not have the capacity to produce the commercial demands or the process itself is inefficient and has a low yield).



30

Partner with another company

- Partner with a company that has manufacturing capabilities or has an existing relationship with a contract manufacturer. Negotiate manufacturing in the deal terms
 - Hanwha Chemical + Merck team up for an Enbrel biogeneric/biosimilar. Merck to take over development and manufacturing and marketing (\$720M deal)
 - Biocartis + J&J J&J, which participated in Biocartis' \$41 million B round, agreed to partner with Biocartis on developing tests for viral infections and neurological conditions.



Partner with another company

- □ Advantages:
 - May get an upfront payment of some sort for your product (equity or cash).
 - Cost sharing for R&D and manufacturing. May have access to ancillary resources such as development, regulatory, quality, and supply chain.
- Disadvantages:
 - May not have 100% control over your product or the development of your product (maybe 100% initially, but control may taper off as the product matures)
 - Smaller companies tend to be able to develop products faster and cheaper than bigger companies.



37

Other Considerations

- □ There are several things you need to keep in mind.
 - Quality! Make sure you have appropriate controls and specifications for a safe product for your patients.
 - You have to consider a supply chain to get your product to your patients/clinicians. Internal or external system. Consider the stability of the product and storage conditions
 - Be aware of different and changing regulations for clinical trials which vary country to country

