



Science For A Better Life



Outsourcing biologics development and manufacturing: when, who, and how?

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Outsourcing biologics development and manufacturing: When, who, and how?

- Short introduction to Bayer Pharmaceuticals and its biotech products
- The mix of internal or external manufacturing strategies
- Best practices for selecting and managing your external partner
- Relationship management to ensure supply and quality
- Success factors to establish efficient partnerships
- Summary



116,482 employees*

Full year sales: €46.3 billion**

307 subsidiaries

R&D expenses: €4.3 billion***

As of December 31, 2015 (including Covestro) / Employees: as of March 31, 2016 (including Covestro)

* excluding Covestro: 100,742 employees (in full-time equivalents)

** excluding Covestro: €34.3 billion *** excluding Covestro: €4.0 billion

Our Business Areas



Pharmaceuticals

- Prescription drugs



Consumer Health

- Over-the-counter medicines, dietary supplements, dermatology products, foot care and sunscreen



Crop Science

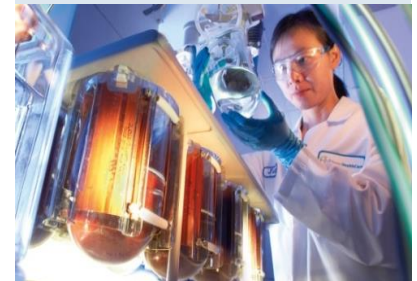
- Innovative crop protection and seeds

Pharmaceuticals Division

One of the leading innovative companies in the healthcare industry















- **Largest division** of Bayer in terms of sales
- One of the fastest **growing pharma companies** worldwide
- **Sales of 13.7 billion Euro**
- **Pro forma sales** of 15.3 billion Euro in 2015 *
- Global headquarter in Berlin, Germany
- **40,500 employees** worldwide in 2015 **
- **Largest German** pharma company
- Focus on **prescription products**, especially for cardiology, oncology, hematology, women's healthcare, and ophthalmology
- Also markets contrast-enhanced **diagnostic imaging** equipment together with contrast agents



Pharmaceuticals Division




Top 12 Products – Demonstrate the Value of Biologics



Product [sales in € million]		2015
 Xarelto™ <small>rivaroxaban</small>		2,252
 Eylea™ <small>(anti-VEGF solution for injection)</small>		1,228
 Kogenate™ <small>Koagulationsmittel (Kogementsubstitut) (Antihämostatikum)</small>		1,155
 Mirena™ product family		968
 Nexavar™ <small>(sorafenib) tablets</small>		892
 Betaferon™ / Betaseron™ <small>INTERFERON BETA-1b</small>		824
 YAZ™ / Yasmin™ / Yasminelle™		706
 Adalat™		633
 Aspirin™ Cardio		524
 Glucobay™		523
 Ultravist™ <small>Iopromide</small>		318
 Gadovist™ / Gadavist™ <small>Gadobutrol</small>		290

Bayer Pharmaceuticals' Biologics



Product	Betaferon® /Betaseron®	Kogenate®	Eylea®
			
Indication	Multiple sclerosis	Hemophilia A	Diverse ophthalmology indications
Market	Worldwide	Worldwide	Ex-US
Product presentation	Lyo-vial in kit	Lyo-vial in kit	Liquid-vial
Volume	High (double digit million vials)	Medium (one digit million vials)	Medium / Growing (one digit million vials)
Sales 2015	824 Mio€	1,155 Mio€	1,228 Mio€
Manufacture	External	In-house	External

Bayer's Commitment to Contract Manufacturing



Bayer to outsource Betaferon production

Tuesday May 31, 2011 03:46:21 AM GMT



REUTERS News



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BAYER/BETAFERON

FRANKFURT, May 30 (Reuters) - Bayer <BAYGn.DE> will outsource production of its blockbuster drug Betaferon to its rival Boehringer Ingelheim, Financial Times Deutschland said in an advance copy of its Tuesday edition.

Production in Emeryville will be shut down in 2013, resulting in the loss of around 540 jobs, the report said, citing the company.

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Bayer's Commitment to In-house Manufacturing



FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

NEWS TOPICS ANALYSIS FEATURE

Bayer to invest more than 500 million Euros for the manufacturing of hemophilia A products currently in development

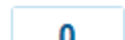
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Leverkusen, March 11, 2014 – With an investment of more than 500 million Euros at its sites in Wuppertal and Leverkusen, Germany, Bayer will establish additional capacities for the manufacturing of the recombinant factor VIII (rFVIII) hemophilia products that are currently in development. The investigational therapy options for hemophilia patients – a plasma protein-free rFVIII (BAY 81-8973) and a long-acting rFVIII (BAY 94-9027) – are both currently in Phase III clinical trials. In February 2014, Bayer HealthCare announced positive results

- **Strategy:**
 - A combination of in-house manufacturing and strategic outsourcing provides the best competitive position

Contract Manufacturing for Biologics



- High number of biologics at various stages of development
- At the same time, many first-generation biopharmaceuticals are maturing

- Many companies outsource part of their clinical and/or commercial manufacturing
- Major biopharmaceutical companies outsource manufacturing to CMOs to be able to focus on next-generation products
- Companies look towards CMOs as a strategic option

The Make or Buy Decision – Building Capacity or Outsourcing



- **In determining which strategy best suits its needs, a company must decide between building internal capacity and outsourcing**
- **Complexity of Influencing Factors**
 - Required process technology
 - Available in-house capabilities
 - Defined core and non-core technology
 - Project pipeline / product portfolio
 - Time to market
 - Contractual situation, IP, process ownership
 - Cost analysis, required investments
 - Risk considerations

Some Key Considerations



Capital investments ...

- ... are high for biotechnology manufacturing facilities
- ... might compete with simultaneous needs to finance expensive clinical studies or marketing activities

Operational expenses / Existing capacities

- As biotech facilities trend to have high fixed costs, capacity available in-house is a factor to keep the product within the company
- In order to make in-house manufacturing profitable, expected demand should be high enough to achieve adequate capacity utilization

Existing (or not existing) technologies

- Technology constitutes an entry barrier for manufacturing
- Non-core technologies are more likely to be outsourced

Reason for a Company to...



Outsource Manufacture:

- Lacking manufacturing capacity or expertise
- Low availability of capital
- Low revenue expectation
- High product risk
- Focus on development rather than manufacturing

Manufacture in-house:

- Manufacturing capability
- Capital available
- High revenue expectation
- Low risk product (e.g. life-cycle management project)
- Technology
- IP related issues

The Make-or-Buy Decision Criteria

- **Financial considerations:**
 - Cost comparison
 - NPV calculation for different scenarios
 - Cash flow
- **Strategic considerations:**
 - Importance / desire to have own manufacturing capability
 - Core vs. non-core technology
 - Expertise, experience, capacity etc.
- **Time to market**

Make it a standardized process !

- Request for quotation to internal production sites and CMO's
- Evaluation of quotes and assessment of suppliers

The Benefits and Challenges of Contract Manufacturing



Potential Advantages

- Use of existing facilities and know-how of CMO
- Reduced up-front investment
- Avoidance of investment at risk
- Higher speed to market - Building capacity takes time
- Variable instead of fixed costs
- Higher flexibility

Challenges

- Managing the interaction with the external partner - Communication is key
- In-house expertise is needed to effectively manage CMO activities
- Drafting contracts to avoid pitfalls
- Ensuring quality oversight
- Protecting your know-how and IP

Choosing between long-term Partnership and Project-by-Project Approach



Strategic Partnership – Preferred Partner – Case by Case

Strategic Partnership Partnership involving several projects	Best Fit Case by case selection of CMO
Pro's: <ul style="list-style-type: none"> ▪ Partner well known, contract in place, collaboration established ▪ Use of reserved capacity by several projects ▪ Benefit from technology platform ▪ Reduction of complexity 	Pro's: <ul style="list-style-type: none"> ▪ Full flexibility, selection of best partner per project ▪ Easy access to technology as needed for project ▪ Taking advantage of competition among CMOs
Con's: <ul style="list-style-type: none"> ▪ Only small advantage if different processes / products needed ▪ Possible disadvantage in pricing negotiations ▪ Often not possible for in-licensed products 	Con's: <ul style="list-style-type: none"> ▪ Higher complexity in supplier management ▪ No jump start possible (collaboration and contract to be established) ▪ No synergies between different projects

There is nothing wrong being tactical !

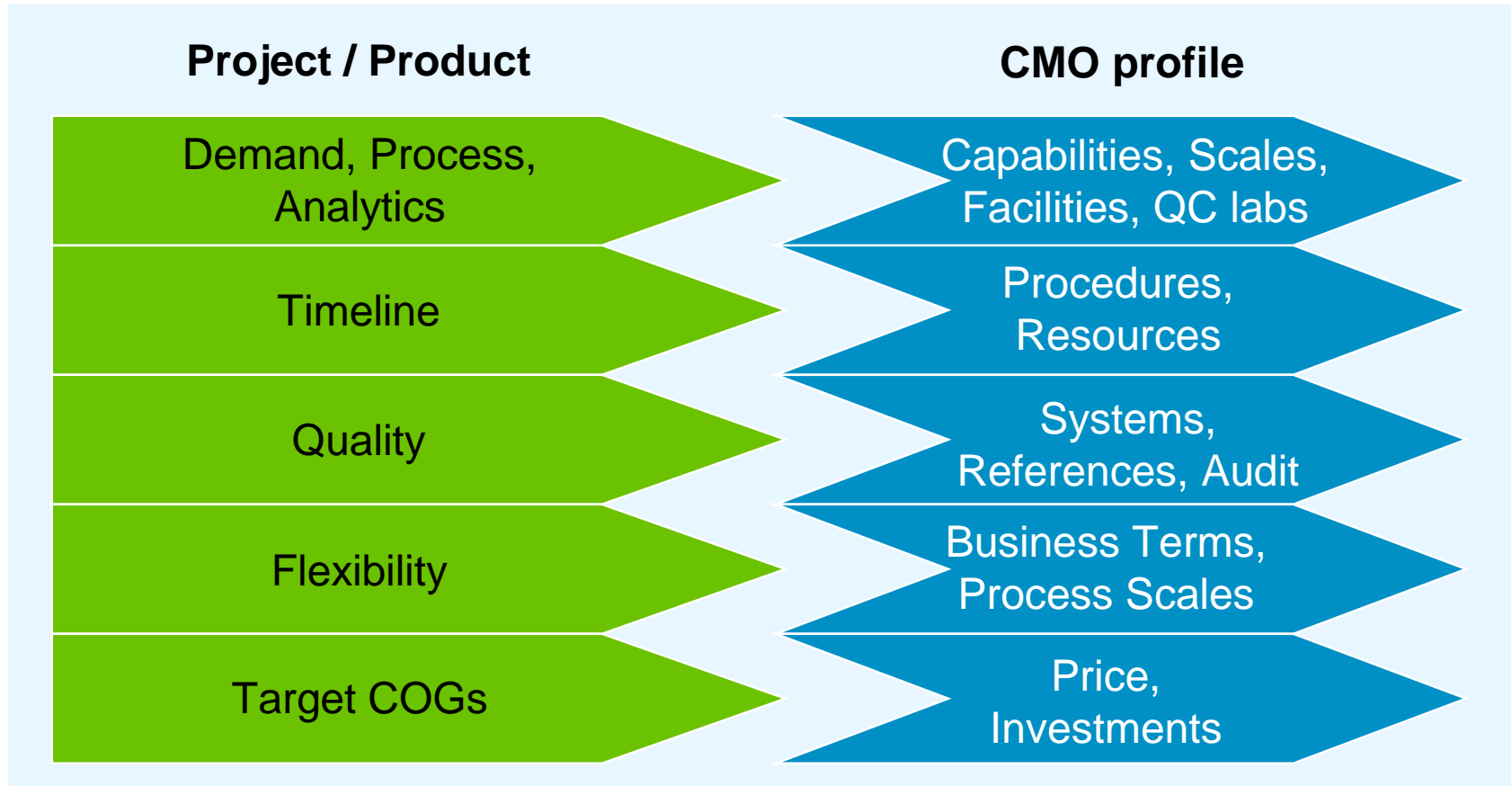
**Strategic outsourcing means a long term
commitment of both parties !**

At the moment of choice, all CMOs will try to look most beautiful !



Selection process for biomanufacturing

CMO looks for the best fit

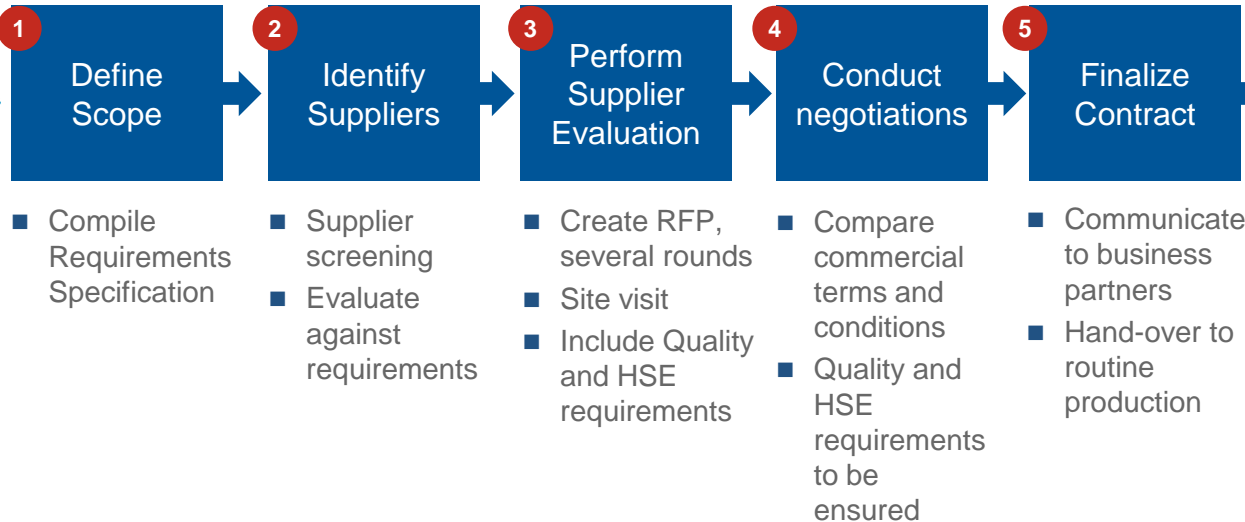


CMO Evaluation/Selection Process



Manufacturing / Sourcing Strategy

Supplier selection process



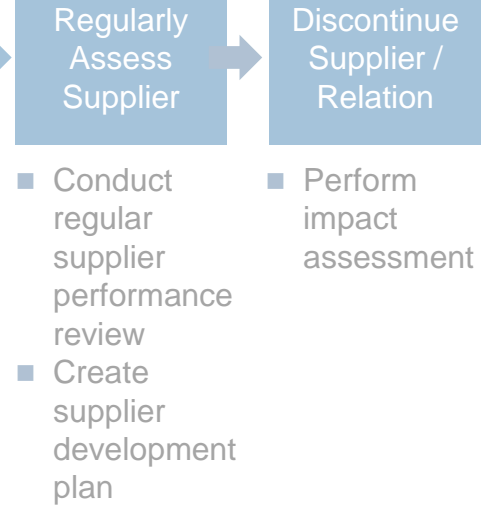
Quality gate 1

Define qualification approach/strategy

Quality gate 2

Provide compliance assessment

Supplier mgmt process



Selection process for the right outsourcing partner



- Is a key process!
- Supplier evaluation must be performed professionally
- Prepare well – pre-defined selection criteria, checklists!
- Have knowledgeable people
- Check the data and track records
- Technical know how – where is the expertise? Risk of losing?
- Development status – lab, pilot plant, commercial scale?
- Technology and equipment available?
- IP protection ensured?

Considerations for partner selection in outsourcing



- How dependent are you on the service provider?
- Any chance of second sourcing?
- If you want to change the service provider, will you be able to transfer the technology?
- Who is your partner of choice?
- What are the commercial interests of your service provider?
- Will the partner have competing interests?
- Particular expertise?
- Risk sharing?

Contract Drafting to Avoid Pitfalls (1 of 2)



- **Know what you are buying (or selling)**
 - Product specification
 - Manufacturing process and analytics
 - Capacity
 - Provided service, e.g. documents for regulatory filings
 - Other support needed, e.g. hosting of inspections
 - Clearly defined quality
- **Know what you are providing**
 - Clear forecasting and ordering mechanism
 - Where will raw materials be sourced and who will take the responsibility?

Contract Drafting to Avoid Pitfalls (2 of 2)



- **Know your price and payment terms**

- Is the product priced correctly, and how? Will the price increase over time, and how?
- Is payment required per batch or only on delivered product meeting specifications?
- Is payment required up front ?
- Cost of compliance to applicable GMP – who bears this?

- **Define liabilities / Indemnities**

- Failure to supply
- Liability for expensive raw materials

- **IP**

- Outright ownership or license
- Process/product improvements – Customer will need FTO, at least
- Service provider may require license-back

Managing the Relationship (1 of 2)



No simple "Buyer -/- Supplier" relationship !
No simple purchase of goods !

Working level: "Joint Operations or Technical Team"

- Clearly defined contacts at both partners
- Direct interaction between expert functions
- Periodic regular meetings (face-to-face or conference calls)

Other interactions and/or steering level

- Business Committee / Steering Committee
as escalation level / guidance for Joint Operations Team
- Key Account Management
Feedback from supplier performance evaluation

Implementing Project Management Expertise



Leveraging a Project/Product-dedicated Team

"Operations Team" responsible for day-to-day work and projects:

- Launch preparation, market supply, exception handling
- Change management, deviation management, complaints etc.
- Life cycle management
- Contract negotiations and modifications

Combines representatives of all relevant functions to assure complete overview of all activities

- Production, SCM, QA, QC, Regulatory Affairs, Procurement, Sites involved in supply network, Engineering etc.

Established early and remaining active over whole lifecycle of the product

Team leader, "Operations Manager", represents Production towards Development and Marketing

Managing the Relationship (2 of 2)



Effective Communication

- Frequent communication
- Periodic regular meetings
- Do not underestimate cultural and time differences!

Constructive Behaviour and Mind-set

- Biopharmaceutical company:
 - transparent, responsive, respectful
- Manufacturing partner / CMO:
 - reliable, proactive, flexible

If you outsource...



Consider critical factors in the selection of your manufacturing partner

- Capability and experience
- Customer service
- Quality
- Price
- Time to market
- Intellectual property

Ensure you have a good process to manage the interaction with your manufacturing partner

You are not alone. In 2016, nearly half of the biopharmaceutical companies outsource part of their biomanufacturing



Q&A Session

"Production outsourcing in biopharmaceuticals will continue to mature as it becomes an increasingly important element in the development strategies for most companies."

Do you agree to this statement ?

How does the make or buy decision process look like in your company?

Is the decision by your company to make or buy typically a tactical or a strategic decision?

"We are a virtual company. We can easily outsource our manufacturing requirements and do not need to invest in internal infrastructure."

Is this an accurate statement?

When should the Make or Buy decision process be started?

When is the last decision point?

How could the time to market affect the decision making?

As a big company, what aspects of your business would you clearly outsource? Why?

How would that answer differ for a smaller company with a few commercial products and a healthy pipeline of new ones?



Can a mixed strategy (outsourcing and in-house manufacture) be the most appropriate solution for certain products?

"For smaller companies, the most important characteristics sought in a contractor is its experience and reputation."

Is this an accurate statement?



Outsourcing to developing countries: When is this a viable option?

Can you share examples of where you decided to make product in-house, despite significant financial pressures? How were you able to manage the risk and the capital investment (and ultimately convince your Board of Directors)?



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Thank you!

Forward-Looking Statements



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