



Challenges and Opportunities for Biologics Manufacturing

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Purpose

Stimulate your thinking about by presenting some broader issues facing the biologics manufacturing industry.

I hope that you reflect on these challenges and opportunities as you listen and learn from the speakers which follow who will each address different aspects of the biologic drug development and/or manufacturing process.

Disclaimer: This is my personal perspective from where I work as a technical expert at a manufacturing site for a large biopharmaceutical corporation. I am obviously influenced by where I work, but this is my personal perspective, not a GSK perspective.

Outline

- External Pressures
- Internal Pressures
- Opportunities

Simplified Biologics Manufacturing Process (vial to vial)

Cell Bank

Seed Propagation

Production Culture

Cell Removal

Separation Steps

Formulation

Fill and Finish

Development and construction of the manufacturing process is expensive and involves the coordination of work of multiple disciplines

Expensive as this manufacturing effort is, it typically is less than the pre-clinical and clinical development costs.

Manufacturing remains a significant cost component in drug pricing.

Challenges: External Pressures on the Pharmaceutical Industry

- General economic uncertainty
- Healthcare costs
- Public perception of the pharma industry
- Industry's perception of regulatory expectations
- Cost to Consumer (or Payer) in various markets
- Raw material adulteration
- Environmental responsibility
- Competition for employees

Uncertainty

- Uncertainty tends to drive short term thinking and discourage long term investment. Public companies are particularly vulnerable to this pressure from investors.
- Health care costs, including reimbursement for drug costs, are estimated at 17% of the GDP and are the subject of much debate in the USA. Roughly 10% of health care expenditures are for drugs. Because the USA represents a large fraction (roughly 50%) of world wide sales this adds uncertainty as to the outcome of investment in pharmaceuticals. High priced BioPharmaceuticals are particularly under public scrutiny adding downward pressure to Biological costs.
- Evidenced based medicine (EBM) or Comparative Effectiveness Research (CER) is an increasingly important field of study which attempts to understand how to reduce health care costs with minimum impact to patient health. However, today in its early phases CER adds uncertainty in that some fear payers may use the outcome of CER to determine reimbursement for accepted treatment practices and therefore limit physician and patient choices



Public Perception

- The BioPharmaceutical Industry holds a trust with the general public that enables the industry to perform our business and provide value to patients
- Groups such as the press, politicians, interest groups and some law groups are able to influence public opinion and challenge our industry. Sometimes this is good and other times it is because public groups do not have the whole story to permit them to view all the facts.
- The speed of communications continues to accelerate.
- Pharma costs continue to rise, yet some other high technology industries such as electronics have reduced costs.

Regulatory Compliance

- International harmonization efforts such as the ICH have been very successful to date.
- Despite tremendous progress, harmonization is not complete and pharmaceutical developers and manufacturers are still working with multiple agencies which naturally raise different concerns. Industry's attempts to anticipate these concerns is not perfect.
- There is constant public pressure on regulatory agencies to do more, yet funding for these same agencies continues to be insufficient.

Balancing Patient Risk between Quality and Cost

- The risk to patients from safety is often discussed. Industry and government have evolved regulations and procedures to capture our collective learning and guide us in our future activities.
- There is also a health risk to patients world wide from lack of affordability. There is less guidance for our industry on how to reduce cost without affecting safety.
- The path forward is not clear, but there is desire to improve.
 - For example, on 9FEB10, The NY Times quoted GSK CEO Andrew Witty regarding healthcare delivery...
“I’m in charge of an organization that can actually make a difference for people in the third world, and I am not going to be the person who, after X years, sits back and says, ‘Oh, I wish I’d done more.’ ”

Raw Material Adulteration

- Reports of adulteration and/or counterfeiting of drugs remind us that the unethical people can adversely affect patients through their actions. For example, glycerine, heparin and epogen issues have occurred in recent history. Food adulteration incidents add to the drug industry concerns.
- Manufacturers must protect their patients by protecting their supply chains.

Environmental Responsibility

Pharmaceutical processes including biologics are low yielding processes compared to other industrial manufacturing processes. To be fair one must note that active pharmaceutical ingredients are typically very potent and only small amounts are consumed by each patient.

Residual pharmaceuticals in the environment are another emerging environmental issue.

The industry is committed to make positive efforts to reduce environmental impact. In many, if not most cases, cost savings may be realized from reducing manufacturing waste.



Competition for Employees

- Biologics are growing in market share.
- Bioenergy and Biochemicals are also predicted to grow and require technical manufacturing staff with similar training.
- Demand for Biologics manufacturing personnel should remain strong.
- Companies will continue to compete for the best talent.

Internal Challenges within BioPharmaceutical Organizations

The challenges within our industry include:

- Long drug development timelines and high drug development costs
- High drug development risks because clinical studies are long and difficult and success is unknown
- High capital investment for manufacturing must typically be made at risk before the clinical outcomes are known
- IP protection is often uncertain and delays to market may further shorten useful patent life
- Post marketing side effects may emerge limiting a drug's patient population
- Competition from other drugs in the same class, biosimilars and next generation therapies cannot be accurately predicted

Internal Challenges within BioPharmaceutical Organizations

- Projected manufacturing capacity needs are driven by uncertain projections of both market size and dose/frequency. Projections often change after a commitment is made for either internal or external commercial manufacturing capacity.
- Because the cost of lost sales from having too little capacity typically exceeds the cost of building too much capacity, the pharmaceutical industry tends to have excess manufacturing capacity. (Ransohoff, 2004, Amer Pharm Outsourcing)

Responses / Opportunities

Focus on the customers

#1) the Patient for Quality, Efficacy and Safety

These cannot be compromised

#2) the Payer for Cost.

Maintain or build public trust

Provide safe, effective products of value.

Improve means to effectively communicate with the public about the high business risks that our industry faces.

Responses / Opportunities (cont.)

- Industry and government must work together and **apply science to determine what really impacts product quality and what does not** to enable lower cost production of quality drugs. This is more challenging in practice than it may sound.
- A key is to find and eliminate non-value added activities.
- Quality by Design (ICH Q8) and Risk Management (ICH Q9) provide a **practical risk based scientific approach** and tools to enable this effort. www.ich.org
- A key challenge in the application of QbD to biologics development and manufacturing is that ranges for the Critical Quality Attributes are challenging to define during the drug development process when both clinical knowledge and commercial process knowledge are low. Use of **platform manufacturing technologies** increases this knowledge.

Biologic API candidate selection

Current process development practices now consider the stability and 'developability' of candidate Active Pharmaceutical Ingredients (APIs) using criteria such as:

- removal of proteolysis sites
- removal of deamidation sites
- removal of oxidation sites
- solubility
- expression levels
- half life In Vivo
- potential delivery mode

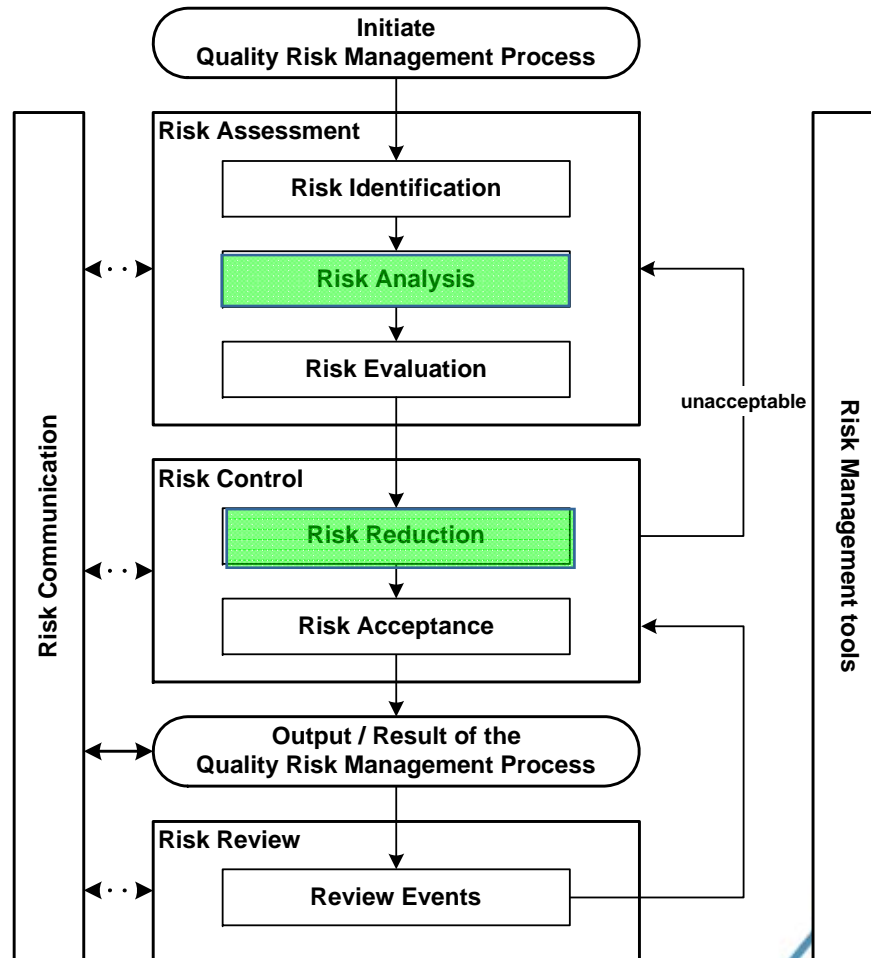
Understanding the fate of the API molecules in the body is also recognized to be important for candidate selection.

Similar rationale applies to the selection of the host substrate and expression system.

ICH Q9 Quality Risk Management

Two Principles

- 1) The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- 2) The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.



Promotes positive inter-disciplinary dialogue

Responses / Opportunities (cont.)

- Increase yields and/or manufacturing throughput
 - Still the most powerful way to increase manufacturing capacity, reduce costs and lower environmental footprint.
 - Upstream improvements have often advanced more quickly than downstream improvements. Consequently, most facilities eventually become constrained by either downstream and/or utilities capacity.
 - Important to insure yield and capacity improvements do not adversely impact quality
- Minimize waste and develop robust processes.
- Use of standard industry manufacturing technologies enables the potential movement of production from one facility to another to adjust manufacturing capacity to market demand and make more effective use of our industry's collective manufacturing capacity.
- Use of newer technologies to reduce capital costs such as in-line dilution and disposable technologies. (New technologies have a special challenge in that they must bring benefits which outweigh the capacity flexibility provided by industry platform technologies)

Initiatives to improve the supply chain

Stronger regulatory agencies to prevent unscrupulous actions for short term gain. The Alliance for a Stronger FDA, founded in 2006, advocates for the FDA. The FDA oversees one quarter of the US economy using less than 0.1% of the federal budget. www.strengthenfda.org

Increased international coordination between regulatory agencies to make efficient use of resources. For example joint EMEA/FDA inspections announced in 2008.

In Feb 2010, FDA announced a new risk-based screening system for imports called PREDICT.

Increasing the available resources at regulatory agencies to permit more frequent contact with industry would be of benefit to development efforts and ultimately to patients.

Intra Industry Collaborations

There is also a trend toward increased coordination between Pharma companies, for example:

- Combine resources to more extensively and actively audit the supplier chain to avoid problems such as adulteration. www.rx-360.org
- Sharing of manufacturing capacity to adjust to changing market projections. Kamarck (2006) Nature Biotechnology, v 24, n5, p503.
- Contract Manufacturing
- Establishing industry standards through ASME, PDA and other professional organizations.
- Professional groups foster information exchange.

Summary: External Challenges

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Summary: Opportunities

Despite the looming uncertainty in both the economy and healthcare costs, there is great opportunity because biologics manufacturing is part of the solution for patients and payers.

Use of industry standards and platform manufacturing technology where appropriate increases knowledge from which we work to both enable a more effective QbD approach and provides more manufacturing options using existing facilities.

Application of QbD to the biologic candidate selection process

Increased coordination between companies and between regulatory bodies to combine resources to either do more and/or save effort and cost.

Apply scientific and TQM principles to understand the real root causes and develop & verify solutions. Eliminate waste on non-value added activities. Reduce costs to make our products accessible to more patients.