Manufacturing Technical Panel

Facilitated Session Results

October 22, 2008

Manufacturing: Future Characteristics/ Vision/Goals

- Understanding of structure-function relationship (and correlation with performance and properties)
  - Raw materials and impacts
  - Quality
  - Each stage of manufacturing
  - Performance correlated to properties
  - Design based on knowledge
- Faster product/process modification in development and manufacture of licensed products.
- Personalized biotherapeutics (design, development, delivery); customization of niche products for personalized medicine
- Flexible continuous manufacturing with short turnaround

Manufacturing: Future Characteristics/ Vision/Goals

- Transparent process and product endpoints (know what you made)
- In-line/in process real time representative sampling.
- Consider (include) more complex manufacturing scenarios:
  - Integrated (combination or hybrid) products, e.g. biologics-devices
  - Cell based products: e.g. differentiated stem cells into cellular, tissue, or organ based regenerative therapies
- Controlling and understanding variations in order to deliver quality for "P_4 medicine" markets.

Manufacturing: Highlights of Broad Challenges and Barriers

- Drivers for Innovation
  - Biologics manufacturing is a fundamentally *lousy* manufacturing process: poor/limited understanding of manufacturing science
  - R&D costs associated with technology solutions
  - Negative environment (lack of education and research, static regulatory structure, capacity/or lack of, size of challenge, and competing global efforts) begs solutions
  - Inability to communicate value of innovative concepts
- Knowledge
  - Inadequate systems biology knowledge
  - Lack of manufacturing science knowledge
  - Variability and relevance of material attributes
  - Trained bioengineers and Interdisciplinary communications

Manufacturing: Highlights of Broad Challenges and Barriers

- Enabling Technologies
  - Lack of measurements for functionality, in-process and end-products
  - Lack of relevance of measurements in production to predict product performance, as in a clinical trial (no system similar to engineered products)
- Other
  - Lack of *continuous* improvement models in current manufacturing paradigm
  - Zero-risk demands – and inadequate tools to assess risk

Manufacturing: What We Need to Measure and Why

- Cell Manufacturing (Process/Platform)
  - Genotypic and phenotypic drift of the platform organism – leading to product drift.
  - Rapid glycol-profiling of therapeutic proteins
  - In process assessment (bioreactor environment, e.g. nutrients, wastes, pH, O_2/CO_2, etc)
  - Scale-up: transfer of measurements from lab to larger scale
- Raw Material Inputs
  - Raw (starting) material components, impurities, etc.
  - Acceptable limits of variability (starting materials, product)
  - Feed stock characteristics, impact on organism growth
  - Feed streams for purity, concentration to increase control

Manufacturing: What We Need to Measure and Why

- Biopharmaceutical Production/Product
  - Adoption of consensus standards of product definition (which ones?, how many are enough ?)
  - Physiochemical attributes, biophysical and biological attributes, material attributes.
  - Protein identification (specific protein, concentration, purity/safety, contaminants etc.)
  - In-line product potency evaluation, immunogenicity, etc.
  - Acceptable limits of variability (starting materials, product)
  - Efficiency of purification and effect of such on the product properties.

Manufacturing: Selected Priority Measurement & Standards Barriers

- Process
  - Not clear how to use the data to improve the process.
  - Specific measurements in complex matrices – interference in in-process environments
  - Cross platform compatibility, comparable methodology.
  - Getting representative samples online
- Product
  - Inadequate understanding of sources of product variability
  - Bioassays (potency) in face of inherent variability
  - Mimicking complex systems in simpler ways. (e.g. immune system assay)

Manufacturing: Selected Priority Measurement & Standards Barriers

- Tools/Methods
  - Alternatives to MS as a measurement tool for protein/biomarker in complex fluids
  - Sensitivity, specificity, objectivity of measurement
  - Lack of generally applicable data pre-processing tools to incorporate more info into models.
- Fundamental Knowledge
  - Safety and efficacy is determined by different processes and procedures – not necessarily matched to criteria of acceptability within the manufacturing process. Thus risk analysis is not rational (e.g. drug related or physician error).

Manufacturing: Approaches to Selected Priority Measurement & Standards Barriers

- Systems Biology of Production Platforms
  - Objectives: Commonly available, fully described set of cell culture and production/product reference systems
  - Rationale: Allows us to assess relevance and risk associated with new measurement tools/technologies, and enables identification of sources and effects of variability; leads to better predictive outcomes
  - Impacts: Accelerates innovation (high), provides "U_L" concept for biomanufacturing, increases speed of process, lowers cost of development and production; increase production efficiencies (and reduces waste and contaminants, etc)

Manufacturing: Approaches to Selected Priority Measurement & Standards Barriers

- Optimal Sampling Methods
  - Objectives: Design criteria, such as representative sample size, sterility requirements, utility and disposal considerations, sample preservation; characterization of reactor performance.
  - Rationale: Enables quality assurance, optimization which provided flexibility, and better control
  - Impacts: Accelerates innovation (high) in process development; enhances competitiveness (high) if data used for optimization.

Manufacturing: Approaches to Selected Priority Measurement & Standards Barriers

- Standards for Improving Biomanufacturing
  - Objectives: Standards to improve processes which accelerate delivery of good medical products to end users (reduces measurement uncertainty – reduces manufacturing costs, lead to high product consistency, better manufacturing predictability.
  - Rationale: Lean, mean and green – enhances predictable biomanufacturing processes, delivery, and costs and end user benefits
  - Impacts: Accelerates innovation (high), provides better medicines faster,

Manufacturing: Approaches to Selected Priority Measurement & Standards Barriers

- Next Generation Tools for Biomanufacturing
  - Objectives: Orthogonal methodology for glycosylation, aggregation, oxidation, folding, and other aspects; assessing or establishing comparability of methods, determining what to measure; capability for data analysis, multi-variant analysis for performance
  - Rationale: Enables predictive biotechnology, understanding of structure/function relationships, enhances quality and consistency, safe and effective products, with high yields
  - Impacts: Accelerates innovation and competitiveness (high), societal benefits via safer more effective products