Opportunities and Challenges to The Implementation of New Technologies and Innovation in Pharmaceutical Manufacturing

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Goals

- Lay the framework for the discussions over the next 3 days
- Provide some provocative thoughts/ideas for your consideration and stimulate discussion
- Provide an opinion on hurdles to innovation within the pharmaceutical industry

In every hurdle/challenge lies an opportunity that can be capitalized
Discussion Topics

- Introduction
- Setting the Stage – Provocative Thoughts
- Challenges with Biological Products – A flavor
- From concept to reality - development and implementation timeframes
- Factors to consider during Implementation of New Technology
- Challenges and Opportunities during the Implementation of New Technologies
- Conclusions
Introduction

“Innovation”

- What does this mean to someone in the Pharmaceutical Industry?
  - Is it just the Introduction of new technologies?
    • Product Innovation
    • Process Innovation

- What is the driver for Innovation?
  - Understanding variability = greater assurance of quality = lower costs

- Who should innovation focused on?
  - The customer = patient = begin with the end in mind
New Technology –
- What do we mean when we say new technologies?
- Does it apply only to manufacturing?
- How about emphasis on patient?
  - For e.g.: delivery mechanisms
    - Important for the patient, assures patient compliance (from a dosing perspective)
- How about technologies to tackle counterfeiting?
- Scope of this talk – Includes everything (not just new technology as it pertains to manufacturing)
Proteins – Examples of Product Innovation

- Hemophilia Treatments
  - Factor VIII and Factor IX deficiency
    - Originally only plasma derived products were available
      • Disadvantage: Led to a number of patients contracting AIDS
    - Innovation –
      • Step 1: Development of recombinant products
      • Step 2: Eliminate all sources of animal derived material in process/formulation
      • Step 3: Improve delivery route of material (convenience)

Innovation in this case is focused on patient
Setting the Stage – Provocative thoughts
Factors influencing Innovation

- Complexity (or Simplicity) of Delivery Systems

- Solutions Suspensions
- Solid Dosage Products – Tablets, Capsules
- Biological Products Monoclonal antibodies, Vaccines, Proteins, Injectables
- Devices or Combination Products – Stents

Low

Complexity

Variability

Patient Risk

High
Innovative Concepts in Pharmaceutical Manufacturing

- Innovative technologies/concepts in pharmaceutical manufacturing
  - Continuous manufacturing (API and Drug Product)
  - Real Time Release testing
  - Quality by Design
  - Process Analytical Technology FF-FB
  - Micro reactors
  - Bench top Manufacturing - Combining the API and DP process to minimize steps and cycle times
  - Biotech- Disposable bioreactor approach

- What is the common theme?
Where is the current focus?

What about these areas? Is there a concerted effort to be more holistic?*

Raw Materials Including API

Product Design

Process Design

Areas of current emphasis

Continuous Improvement

Direct Compression Process

Blending

Compression

Coating

Packaging

Storage and Distribution

Maintenance – Commercial Stability. Complaint Handling etc.
Where is our Focus Today?

Solid Dosage Products – Tablets, Capsules

Biological Products
Monoclonal antibodies, Vaccines, Proteins

Devices or Combination Products – Stents

1. Most of the emphasis is on solid dosage products.
2. Amount of knowledge in solid dosage manufacture is considerable (most manufacturing platforms are standard and have been used extensively resulting in considerable knowledge).
3. Industry playing in familiar territory and acquiring knowledge that can be extrapolated to complex dosage forms – taking baby steps
4. Is this approach acceptable? Why not?

Is this approach Innovative enough? Are we stretching our capabilities? Is this the right business model? Is this reflective of the future of the pharmaceutical Industry? Are we thinking big enough?
Pfizer acquires Wyeth in October 2010

According to Reuters the deal would help Pfizer diversify into vaccines and injectable biologic medicines by adding Wyeth's big-selling Prevnar vaccine for childhood infections and Enbrel rheumatoid arthritis treatment, and Pfizer would also realize major cost savings by streamlining areas that overlap.

Pfizer’s goal is to be the # 1 biopharmaceutical company
What is the Industry moving towards?

- Merck Acquires Schering Plough and announces its foray into biogenerics
- Roche acquires Genentech
- J&J acquires stake in Elan (for a piece of the Alzheimer’s therapy) and Novacell (Vaccines)
- General trend is for the industry to move towards biopharmaceuticals

Does this trend necessitate the need to focus innovation on biopharmaceuticals?
Challenges with Biological Products – a flavor
Challenges with Biopharmaceuticals

- Complexity of molecules – Heterogeneous in nature
- Complexity increases as we move towards vaccines
- Biologics are relatively early in their development cycle (as compared to small molecules)
  - Prior knowledge is limited
  - Definition of critical quality attributes is still not clear and therefore where and what to control is often a subject of debate
  - Immunogenicity – assessing impact of modifications is a challenge
Challenges with Biopharmaceuticals

- Manufacturing – Aseptic conditions

- Dosing typically in syringes – Innovative approaches (pre-filled syringes, Lyoject etc) increase need for better understanding of glass/syringe barrel manufacturing and impact on fill/finish process as well as supply chain, distribution and dosing practices.
Challenges with Vaccines - Example

- **Complexity of Manufacturing process**
  - Vaccine manufacturing includes several manufacturing steps
  - Complexity due to several serotypes
  - Variability of final product encompasses variability in the manufacture of each of the conjugates

- **Complexity of the Supply Chain**
  - Cold chain product

- **Variability of the final product encompasses the variability in each of these steps.**

What does this mean for us?
FROM CONCEPT TO REALITY... Development and implementation timeframes
Timeline for ICH implementation

- PAT guidance draft – 1999
- ICH Q8, Q9 and Q10 – First discussed in early part of this century
  • Guidances finalized over the past few years
- Achievements:
  • QbD applications approved,
  • RTRt implemented at least by a few companies over the last few years
- Topics Still being discussed (examples)
  • Procedures for model maintenance,
  • Sampling for PAT
  • What do we need to do to move this forward?
- ICH applies to only 3 regions: What about the ROW?
  • What about Emerging Markets?

Are we moving fast enough? If not what can we do to improve the model?
Current model for Collaboration on New Approaches – QbD as an example

Guidelines ICH Q8, Q9 and Q10

Interpretation by Regulators and Industry

Expectations of Industry and Regulators

- ICH working groups
- PQLI – ISPE
- CASSS
- PDA
- ASTM
- ERC
- CPAC
- CAMP

- Position Papers
- Consensus Standards
- Mock case Studies
- Publications

Should we enhance the model?
Factors to consider during Implementation of New Technology
Example 1: Sampling during Real Time Release Testing

- Sampling: What is the appropriate number of samples for analysis?

- Large “N” approach for content uniformity sampling
  - Approach is sound
    - Focus on Operating Characteristic similarity to current compendial UDU test – Specification
    - Provocative thought: Why can’t we move the test to the in process section and develop tighter OC curves?
      - This would be along the lines of process control principles
      - Need better understanding of control limits versus specifications
Example 2: Implementation of Chemometric Models in Manufacturing

- Spectroscopic Techniques have been used for polymorphism and moisture analysis in the pharmaceutical industry (used in petrochemical and food industry longer).

- Question: What changes to chemometric models should be reported and why?
  - No consensus within the industry (and with the regulators).
  - Are we not learning from industries such as the petrochemical industry?
  - Are we using the information (MVDA) as part of feedback control? If not why? Shouldn’t this be the primary focus to minimize variability?
Example 3: Telescopyng of API and Drug Product Manufacturing

- Synergies and efficiencies can be obtained by directly feeding output of API manufacturing into DP process (without isolation)
  - Can we treat API as an intermediate?
  - Need to collaborate with regulators to think of approaches to accommodate such innovative thinking
Challenges and Opportunities during the Implementation of New Technologies
Elements For Success

Innovation and Compliance

People

Science

Systems
Challenges and Opportunities while Implementing New Technologies - People

Multidisciplinary and cross-functional teams collaborating is a key to successfully implementing new technologies.
Challenges and Opportunities while Implementing New Technologies - 1

- **Resources**
  - Cross-functional / multi-disciplinary team necessary collaborating to develop robust systems is critical for innovation
  - Personnel with different skill sets necessary may be necessary to implement innovative approaches
  - Culture/mindset challenges (proactive versus reactive quality)
  - Initial capital commitment may be needed for implementation of new technologies
Challenges and Opportunities while Implementing New Technologies - 2

- Quality Systems Development
  - Robust change management systems necessary
  - Quality risk management
    - e.g. Need systems to assess the impact of failure of the technology and develop proactive plans to mitigate risk
  - Impact to QP/ Q release person
    - Understand control strategy, quality systems etc.
Challenges and Opportunities while Implementing New Technologies - 3

- Regulatory challenges
  - Global acceptance of Innovative Technologies
  - Are we ready to learn together?
- Benefits
  - Increased assurance of quality for our patients
  - Faster cycle times
  - Lower manufacturing costs
    - Improved yields
    - Fewer deviations and/or rejects
    - Reduced QC resources
Conclusions
Conclusions

- Partnership between regulators, academia and industry
- Implementation of New Technologies (and Innovation) is a marathon not a sprint
  - Need constant re-evaluation of where we are and need to redirect ourselves
  - May need some bold steps – Need to prepare ourselves to take it
- Focus not only on Small Molecules but also Proteins and Vaccines
- Mechanism to involve China/India and other regions may provide further incentive to implement novel technologies
- Focus on areas where the needs will be greatest in the future like complex delivery systems or treatments