Consumer Healthcare Products Association

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Office of Pharmaceutical Science Program Updates

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Content of Presentation

- Where we came from
- Where we are
- Where we are going

State of Pharmaceutical Manufacturing at Beginning of 21st Century

- Not state-of-art as compared to other industries
- Able to achieve reasonable product quality – but often at a great effort and cost
- Little emphasis on manufacturing – mainly on development although manufacturing is approximately 25% of expenses
- For some products, waste as high as 50%
- Inability to predict effects of scale up
- Inability to analyze or understand reasons for manufacturing failures
- Globally fragmented

Consequences

- High cost for products due to
  - Low efficiencies in manufacturing
  - Manufacturing time requirements based on testing, etc.
  - Waste
- Drug shortages due to inability to manufacture because of manufacturing changes not approved or other problems
- Lack of improvements to products despite new technologies which could result in efficiencies
- Slowed development/access for investigational drugs
- Need for intensive regulatory oversight

State of Regulatory Quality Review Processes at Beginning of 21st Century

- Oversight increased – reviewed every change made – increased number of manufacturing change supplements
- Focused on chemistry but not on engineering and other relevant science
- Implemented numerous changes in process to facilitate increasing review requirements (SUPAC, BACPAC)
- Issued numerous “how to” guidances (prescriptive)
- All standards internally developed
- PDUFA requirements speed up review process
- More complex products along with new dosage forms
- Increased emphasis on focused issues such as counterterrorism, pandemic, counterfeiting

Consequences

- Increased workload
- Not enough staff
- More and more information from sponsors required and submitted (not always relevant)
- Very little flexibility
- Impossible to ensure consistency
- Discouraged innovation
- Assumed all responsibility for product quality
- Conservative

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

Janet Woodcock, M.D.

Characteristics of the Desired State

- Quality is controlled by industry
- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
  - Knowledge comes from product development, prior experience, studies, scientific and technical literature
  - Use that knowledge to understand product risk and risk mitigation
  - Use that knowledge to determine appropriateness to make manufacturing changes
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement
- FDA's role is to do initial verification and subsequently audit

Desired State = Quality by Design for CMC

- Just begun - laid the foundation -involves both industry and agency
- Evolution not a revolution
- Incorporation of critical factors of desired state
  - International harmonization
  - Pharmaceutical development information
  - Quality risk management
  - Quality systems
  - New technology
- Implementation of Quality by Design (QbD) in product review – all three CMC review offices

QbD System

Product & process design and development

Define desired product performance upfront; identify product CQAs

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Design formulation and process to meet product CQAs

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Understand impact of material attributes and process parameters on product CQAs

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Identify and control sources of variability in material and process

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Continually monitor and update process to assure consistent quality

Risk assessment and risk control

Differences in Approaches

Aspects	Traditional System	QbD System
Pharmaceutical development	Empirical, random, focus on optimization	Systematic; multivariate experiments; focus on control strategy and robustness
Manufacturing Process	Fixed; focus on optimization	Adjustable within design space; continuous verification within design space; managed by company's quality systems
Process Control	In-process testing; off-line analysis	PAT utilized; process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible
Life Cycle Management	Reactive to problems and to OOS; post-approval changes needed	Continual improvement enabled within design space

QbD in CMC Review Offices

- Three different CMC review offices in OPS
  - Office of New Drug Quality Assessment
  - Office of Generic Drugs
  - Office of Biotechnology Products
- Implementing Q8, Q9 and Q10
- Implementing at a different pace – reason being different products, different complexities, different focus
- All will end up at the same place

Office of New Drug Quality Assessment (ONDQA)

- Science-based assessment
- Restructured organization and reorganized staff – premarket staff and postmarket
- CMC Pilot
  - A number of applications submitted
  - Lessons learned
  - Evaluation of information
- Implementation of PMP

Office of Generic Drugs (OGD)

- Question-based Review (QbR)
  - QbR contains the important scientific and regulatory review questions
    - Evaluate whether a product is of high quality
    - Determine the level of risk associated with the manufacture and design of this product
- 416 applications received using QbR by June 2007
- Successful in ensuring that questions address issues regarding QbD

Office of Biotechnology Products (OBP)

- Have more complex products
- Already doing some aspects of QbD
- In process of preparing to accept applications using QbD
- Beginning a pilot for biotech products for QbD – using mainly comparability protocols
- Also implementing Q8, Q9 and Q10

Benefits of Implementing Quality by Design For FDA

1. Enhances scientific foundation for review
2. Provides for better coordination across review, compliance and inspection
3. Improves information in regulatory submissions
4. Provides for better consistency
5. Improves quality of review (establishing a QMS for CMC)
6. Provides for more flexibility in decision making
7. Ensures decisions made on science and not on empirical information
8. Involves various disciplines in decision making
9. Uses resources to address higher risks

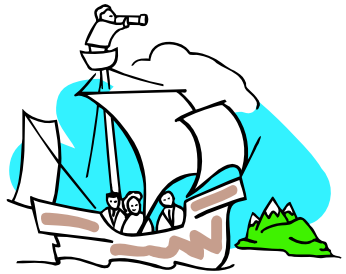
Benefits to Industry

1. Ensures better design of products with less problems in manufacturing
2. Reduces number of manufacturing supplements required for post market changes – rely on process and risk understanding and risk mitigation
3. Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
4. Allows for possible reduction in overall costs of manufacturing – less waste
5. Ensures less hassle during review – reduced deficiencies – quicker approvals
6. Improves interaction with FDA – deal on a science level instead of on a process level
7. Allows for continuous improvements in products and manufacturing process
8. Allows for better understanding of how APIs and excipients affect manufacturing
9. Relates manufacturing to clinical during design
10. Provides a better overall business model!

Where Do We Go From Here?

- Companies need to continue to implement QbD and FDA needs to continue to be prepared to accept applications in new paradigm
- Move toward CMC – PMP – this is important
  - Already prepared to reduce required manufacturing supplements based on risk
  - Revising 314.70 and related guidances
- Work with industry to determine what is relevant date to be included in applications
- Finalize definitions
- Evaluate the ONDQA pilot – lessons learned that we can share
- Implement the OBP pilot
- Evaluate the QbR process
- Continue harmonization efforts through ICH and other processes
- Develop case studies
- Hold additional workshops and strive toward better interactions between industry and regulators

Summary



- Have made tremendous process – still have a ways to go – again not a revolution
- Devil is in the details – still have many to work out
- If work together though can accomplish the desired state of a “maximally efficient, agile, flexible” pharmaceutical quality system which will advantage industry, regulators and most of all the public