PDA/FDA Joint Regulatory Conference

Evolution of the Global Regulatory Environment: A Practical Approach to Change

September 24, 2007

Implementing Quality by Design

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Focus

- Why quality by design?
- Where are we in preparing for quality by design in CMC review programs (implementation an industry activity)
- Opportunities and challenges

State of Pharmaceutical Manufacturing

- In many cases, not state-of-art as compared to other industries
- Able to achieve reasonable product quality – but 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 on final product
- Inability to analyze or understand reasons for manufacturing failures
- Globally fragmented

Consequences

- High cost for products due to
  - Low efficiencies in manufacturing
  - Waste
  - Manufacturing time requirements based on testing, etc.
- Drug shortages due to manufacturing problems
- Lack of improvements based on new technologies
- Slowed development/access for investigational drugs
- Need for intensive regulatory oversight

State of Regulatory Quality Review Processes

- Oversight increased – reviewed every change made – increased number of application supplements
- Focused on chemistry but not on other important areas (e.g., engineering)
- 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

- Too much work
- Not enough staff
- More and more information from sponsors required (not always relevant)
- No flexibility in regulatory process
- Impossible to ensure consistency
- Discouraged innovation on part of manufacturer because of need for supplements
- Assumed all responsibility for product quality

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

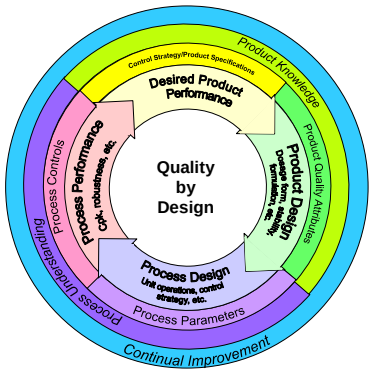
A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

Janet Woodcock, M.D.

Answer to Desired State for CMC Review – Quality by Design

- QbD is:
  - Scientific, risk-based, holistic and proactive approach to pharmaceutical development
  - Deliberate design effort from product conception through commercialization
  - Full understanding of how product attributes and process relate to product performance
- QbD information and conclusions should be share with FDA

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

Quality by Design (QbD) – A Comprehensive Systematic Approach to Pharmaceutical Development and Manufacturing

Aspects	Traditional	QbD
Pharmaceutical Development	**Empirical**; typically univariate experiments	**Systematic**; multivariate experiments
Manufacturing Process	**Fixed**	**Adjustable** within design space; opportunities for innovation **(PAT)**
Process Control	In-process testing for go/no-go; offline analysis w/ slow response	**PAT utilized** for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance (safety and efficacy)
Control Strategy	Mainly by intermediate and end product testing	**Risk-based**; controls shifted upstream; real-time release
Lifecycle Management	**Reactive to problems** & 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 Drugs
- 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 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!

Opportunities

- “Efficient, agile, flexible” system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management approach

Challenges

- Need agreement on terminology (e.g., design space)
- Need to determine what relevant data is needed in applications
- Need to determine next steps for global implementation
- Need to determine how best to handle legacy products in line with those products issued under QbD
- Need a “regulatory agreement” or postmarket management plan
- Need to continue to ensure collaboration and coordination between inspectors, compliance and review
- Need training, training, training – both internal and external

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 for moving forward for implementation
- 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
- 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