Generics Embracing QbD / PAT Globally

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Adnan Sabir, Dr. Reddy’s Laboratories
Vice President, COE-FST, IPDO, Hyderabad, India

Yashwant Pathak, University of South Florida, College of Pharm
Tampa, Florida, USA
Facts - Demanding Changes in DDP

- According to Times magazine, the US spends $200 billion dollars a year on prescription drugs with the growing rate of 12 percent a year
- The pharmaceutical industry is a big part of the cost and spending
- Today, close to 69% of all prescriptions in the US are generics
Facts...... *Contd.*

- The generic industry has come a long way since 1984 when the Hatch-Waxman or Drug Price Competition and Patent Term Restoration Act allowed for industry to sale and produce generic drugs.
- The FDA’s Orange Book lists over 12,751 drugs of those, more that 10,072 or 79% of the products have generic version available.
- According to IMS Health, the generic drugs industry is expanding at a growth rate of 7.8%, which is faster than the world’s market for pharmaceuticals
Facts ............Contd.

• Furthermore, the average cost of $1,500 a year for each drug, and a senior who takes six different prescription drugs would have to spend $9,000 out of pocket.

• A new economic analysis conducted by IMS Health and the Commissioned by Generic Pharmaceutical Industry Association (GPhA) reveals generic medications saves the US Health Care system $734 billions over the last decade (1999-20008).
Generics: A $90 Billion Opportunity

- Western Europe: $17bn
- Eastern Europe & Russia: $10bn
- China: $3bn
- Japan: $4bn
- Rest of World: $4bn
- Total World Pharmaceutical Sales: $600bn

Source: TS Research, IMS Health, VCI PharmaHandbook
Cost Savings by Therapeutic Area

Generic products for nervous system and cardiovascular treatments account for 57% of cost savings.

Generics Cost Savings by TA (over all ten years)

- Nervous System: 34%
- Cardiovascular: 23%
- Metabolism: 10%
- Anti-Infectives: 9%
- Systemic Hormones: 6%
- Musculo-Skeletal: 6%
- GU system: 5%
- Respiratory: 3%
- Cancer: 1%
- Sensory Organs: 1%
- Blood Disorders: 1%
- Other: 0%
- Parasitology: 0%

Generic versions of nervous system and cardiovascular drugs account for about $420 billion in cost savings for the U.S. over the past decade.

Source: IMS Midas Data
Note: Yearly data is MAT Sep. Ex-mfg
So, here comes Quality by Design (QbD) and Process Analytical Technology (PAT)

These are two promising tools for developing affordable medicines for the public health
Innovation

• **QbD** - Product and Process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches

• **PAT** - A system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality
What QbD/PAT can do?

• Essentially saving money for the US Healthcare system and allowing affordable medicines for the average and senior citizens

• How can QbD & PAT help save money for the pharmaceutical industry’s manufacturing process
  – In general, but specifically for generics

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What QbD/PAT can do?

• PAT will design manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible products quality and performance throughout a product’s shelf life.

• The Good Manufacturing Practices for Pharmaceuticals 6th edition noted the analytical in PAT is viewed broadly to include chemical, physical, microbiological, and mathematical and risk analysis conducted in an integrated manner.
What QbD/PAT can do?

• Ultimately, PAT will allow manufacturers to positively identify complications in the manufacturing process to ensure positive outcomes of the products and thus, an economical savings in production process.

• PAT is a novel opportunity; which can give quality and economic benefits to the generic industry and can assimilate them into existing business.

• Consultation with the FDA is available prior to implementation including marketing applications, amendments, or supplements to application process
Applying Fundamentals of QbD/PAT

• Initiatives are to drive the scale-up of your innovative generics manufacturing process globally including outsourcing
• Understanding how QbD/PAT can enhance the development of generics
• Ensuring process robustness through the use of DOE (Design of Experiments)
• When DOE is required (or not) – A decision tree
• Innovation in scalability – from lab to commercial
Levels of Innovation

- **Incremental innovation** - new dosage forms and new formulations
- **Stepwise innovation** – different molecules of one chemical family offering some differences in properties, e.g. indications, side effects, and drug metabolism
- **Breakthrough innovation** - real new approach to a disease / New Chemical Entity (NCE)
- **Breakthrough innovation in Process Development** - New approach for building Quality into product proactively through QbD approach
QbD/PAT for Outsourcing - why?

- Major generic production is being outsourced from USA, will help in monitoring the quality and reproducibility of production in compliance with FDA/MHRA etc.
- Innovation in the pharmaceutical sector can bring improvements to healthcare delivery
- Improvement in existing production processes resulting in improved quality
- Increased market competitiveness ($) due to health coverage regulations by underwriters
Quality by Design (QbD)
Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Continually monitor and update process to assure consistent quality

Identify and control sources of variability in material and process

Understand impact of material attributes and process parameters on product CQAs

FMEA or PHA - Risk assessment and risk control

BAC: Upfront agreements from Technical Personnel on Product & process design and development

QbD System: Application in Generics Development being Outsourced
FDA’s view on QbD
Moheb Nasr,
2006
Benefits of QbD when Applied for Outsourcing

- Consistently meet product Critical Quality Attributes (CQA)
- Knowledge on impact of formulation and process components
- Well controlled process leading to reduced variability and rapid development
- Meet patient requirements
- Can be implemented anywhere where the products have been outsourced or transferred to the site of manufacturing

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Design Space

- Definition of Design Space according to ICH Q8:
  “The multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality.”

- Translation – what combination(s) of input settings will meet the specifications for the output(s)?

- Multiple response optimization determines the optimum set of conditions to meet specs of 2 or more outputs simultaneously

- “Weighting "the outputs provides opportunity to allow for relative importance in “trade-off” situations"
Design Space Determination

- **Successive approximation**
  - One parameter at a time keeping all other parameters constant

- **Statistically designed experiments (DOEs)**
  - Efficient method for determining impact of multiple parameters and their interactions

- **Scale-up correlation**
  - A semi-empirical approach to translate operating conditions between different scales or pieces of equipment within scope of that particular unit operation
FMEA/PHA Methodology

- Knowledge available from literature
- Prior history
- Expertise available (SMEs)

<table>
<thead>
<tr>
<th>CPPs</th>
<th>Fluid uptake</th>
<th>Kneading time</th>
<th>Mill speed</th>
<th>Blending time</th>
<th>Tablet Hardness</th>
<th>Temperature</th>
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<tbody>
<tr>
<td>CQAs</td>
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<tr>
<td>Dissolution</td>
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</table>
DoE decision tree

3. Input parameters (CPP)

Interactions?

- Yes
- No

1. Risk factor

- Lo
- Med
- Hi

- No
- Subjective call
- Yes

2. Responses (CQA)

- Quantitative?
  - Yes
  - Qualitative?
    - No
Design of Experiments (DOE)
Design of Experiments

- Structured, organized method for determining the relationship between factors affecting a process and the response of that process
- Application of DOEs
  - Scope out initial formulation or process design
  - Optimize product or process
  - Determine design space, including multivariate relationships
DOE Methodology

(1) Choose experimental design (e.g., full factorial, d-optimal)

(2) Conduct randomized experiments

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Factor A</th>
<th>Factor B</th>
<th>Factor C</th>
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<tr>
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<td>4</td>
<td>+</td>
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</table>

(3) Analyze data

(4) Create multidimensional surface model (for optimization or control)
## Types of DoE Designs

<table>
<thead>
<tr>
<th>Screening Designs</th>
<th>Modeling Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Typically 6 – 11 factors</td>
<td>- Typically 2 – 5 factors</td>
</tr>
<tr>
<td>- Many factors in few runs</td>
<td>- Prediction equation (Transfer function)</td>
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<tr>
<td>- Narrow the focus</td>
<td>- 2 or 3 levels</td>
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<tr>
<td>- 2 or 3 levels</td>
<td>- Optimization, robust design, tolerance allocation</td>
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<tr>
<td><strong>Examples</strong></td>
<td></td>
</tr>
<tr>
<td>- Taguchi L12 (or PB12)</td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td>- Taguchi L18 (3 levels)</td>
<td>- Full / Fractional Factorial</td>
</tr>
<tr>
<td>- PB 20</td>
<td>- Central Composite Design</td>
</tr>
<tr>
<td>- Fractional Factorials</td>
<td>- Box Behnken</td>
</tr>
</tbody>
</table>

**Examples**

- Taguchi L12 (or PB12)
- Taguchi L18 (3 levels)
- PB 20
- Fractional Factorials

**Examples**

- Full / Fractional Factorial
- Central Composite Design
- Box Behnken
DOE Models

Central Composite

Box Behnken
Process Analytical Technology (PAT)
PAT

PAT provides an opportunity to move from the current “testing to document quality” paradigm to a “continuous quality assurance” paradigm that can improve our ability to ensure quality was “built-in” or was “by design” – ultimate realization of the true spirit of cGMP
Goals and Objectives

Using PAT as a model technological opportunity, develop a regulatory framework to facilitate introduction of new manufacturing technologies that enhance process efficiencies and understanding

- Identify and eliminate perceived/real regulatory hurdles
- A thorough understanding of process
- Minimize variations by eliminating subjectivity
- Develop a dynamic, team based, scientific approach for regulatory assessment of new technologies
PAT tools

- Near Infra Red technology for raw material identification, moisture measurement, blend uniformity, content uniformity of tablets
- Torque sensor for end point granulation
- Focused Beam Reflectance Measurement (FBRM) for particle size measurements
- Imaging systems for process controls and process monitoring in various applications
Innovation in Scalability

➢ With Scale Up models for unit operations like
  • RMG
  • Fluid bed granulation and coating
  • Pan coating

➢ With better process controls for unit operations like
  • Blending (NIR, Effusivity etc)
  • Compression (Strain gauges for compression and ejection forces, automatic sampling and rejection systems etc)
  • Capsule filling

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PAT in Outsourcing

Old Process

• Traditional way
• Emphasis on Outcome, Money and time line
• Reasons: Primarily Technology, Equipment, Capacity, Resources
• Quality is driven by CFR and SOPs
• Variability were taken granted as part of manufacturing

New Process

• Innovative way
• Primarily on quality (ICH Q8, Q9, and Q 10), others follow automatically
• Reasons: Skill set and Compliance are primary others are secondary
• Emerging evidence that focus on PAT improves quality
• Variability are identified, proactively, and Plan of Action put in place accordingly

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Benefits of QbD/PAT Implementation

- Greater control of product uniformity
  - Improved safety, quality compliance, unbiased
- Shorter cycle times, batch release times
  - Cost savings, supply chain stability
- Moves us towards parametric release
  - Cost savings, lower inventory
- Moves us towards continuous operations
  - Improved control, significant capital adjustment
Implement QbD & PAT Now, Because

• It is projected that in 2011, the generic industry will double its growth rate and will make up 20% of the total pharmaceuticals market.

• Therefore, time is now to implement and promote innovation in Manufacturing Process through QbD & PAT
Implement - Bc’s Support is Available

• FDA designates a special task force called FDA Process Analytical Technology Team to help with manufacturers who wish to implement PAT

• As Congress and the Obama administration is working toward reducing cost- there is a place for PAT in the generic industry

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Thank you
Transfer Functions

The transfer function is an equation which mathematically describes the relationship between the process inputs and outputs.

- This empirical model is extremely valuable knowledge:
  - Process optimization
  - "What if" scenarios
  - Robust design
  - Setting specifications

- 2 level designs: \( Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 \ldots \)
- 3 level designs: \( Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \ldots \)
Design Space Example

$Y_1 = \text{dissolution}$

$Y_2 = \text{dosage uniformity}$
Case Study: Product A

- Identify important factors and find critical few:
  - Fluid Uptake (54 – 60%)
  - Binder Addition time (2 min – 4 min)
  - Kneading time (1 min – 4 min)

- Identify Important Responses:
  - Dissolution: 10 min (%)
  - Dissolution: 30 min (%)
  - Dissolution: 45 min (%)

- Model Selected: Box–Behnken Design
# Software: Design Expert

<table>
<thead>
<tr>
<th>Select</th>
<th>Std</th>
<th>Run</th>
<th>Factor 1 A: Fluid Uptake %</th>
<th>Factor 2 B: Kneading min</th>
<th>Factor 3 C: Binder addition</th>
<th>Response 1 Dissolution (30%)</th>
<th>Response 2 Dissolution (10%)</th>
<th>Response 3 Dissolution (45%)</th>
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</table>
Final Equation in Terms of Coded Factors

Dissolution (10 min) = +42.54 (-7.13* A) (-6.75* B) (-1.87* C)

Dissolution (30 min) = +59.38 (-7.75* A) (-8.75* B) (-2.25* C)

Dissolution (45 min) = +65.23 (-7.50* A) (-9.00* B) (-2.50* C)
Optimization:
Feed the desired ranges of responses
Design Space

Design-Expert® Software

Desirability

X1 = A: Fluid Uptake
X2 = B: Kneading

Actual Factor
C: Binder addition time = 2.49
# DOE Confirmatory Batch

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<tr>
<th>Solutions</th>
<th>(Based on 13 Trials: F055 - F067)</th>
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<td>54.99</td>
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<tr>
<td>19</td>
<td>54.59</td>
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</table>
Conclusion

- Final Optimized Parameters:
  - Fluid Uptake - 55 %
  - Binder addition time - 3 min
  - Kneading time - 1 min

- Scale-up Batch also successfully taken in Pilot with the above optimized parameters