Cultivate Your Vision for a Comprehensive Validation Procedure

Asmita Khanolkar, CeQur
CeQur Background

• CeQur was established in 2008
• Headquarters in Horw, Switzerland with Operations in Marlborough, Massachusetts.
• CeQur is dedicated to helping people with Type 2 diabetes
• PaQ is a wearable insulin delivery device that delivers both basal and bolus insulin for 3 days.
Asmita Khanolkar

- Manager, CeQur, Manufacturing Engineering & Operations
- Earned her Master’s degree in Material Science & Engineering from Worcester Polytechnic Institute, Worcester, MA
- Over 20 years of manufacturing and automation scale-up experience, specializing in the Medical Device industry
- Managed device projects starting from concept to high volume manufacturing launches
- Product portfolio includes devices in diabetes management, surgical devices, orthopedics, respiratory, cardiovascular, patient safety, and health monitoring devices, biomedical and cell regeneration devices, drug delivery, sports regenerative surgery, blood collection, pharmaceutical, diagnostics, needle protection, and airway products
- Presents, chairs, and participates in panel discussions at various medical device conferences
- Volunteering activities include FRC Robotics Team Mentor, STEM for Girls, Women in Engineering, Future Healthcare Professionals, Global Outreach STEM initiative for underprivileged kids
Overview

Develop an understanding of the medical device lifecycle as it relates to validation through a cross-functional approach

• Medical Device Life Cycle
• Product Realization Process and Standards
• Understanding the “Validation Challenge”
• Concurrent Engineering
• Cross Functional approach
• Key Elements of Verification and Validation
• A Comprehensive Master Validation Plan
• Example – Creating the Checklist for the Specific Application
• Tomorrow’s Technologies
Medical Device Life Cycle

Feasibility
- Concept
- Prototyping
- Preliminary testing
- Sourcing & manufacturing assessment

Bridge
- Alpha, Beta Builds
- System/Sub-system architecture
- Mechanical, Electrical & 3D Assembly design
- Supplier finalization
- Cost model

Pilot Manufacturing
- Part Fabrication
- Tool & fixture design
- Process validation
- Limited Launch

Production
- Lean Manufacturing
- Automated cells
- Efficient Capacity Planning
- In line Device testing

Sustaining Engineering
- Continuous Improvement
- Product Modifications
- Reduce COGS
- Additional Production Lines

Invention or Discovery

Concept

Design

Development

Clinical Testing

Mfg Scale - Up

Market

Commercially viable product
Medical Device Regulations and Standards

Quality Management System
- ISO13485

Regulatory Requirements
- FDA Title 21 CFR Part 11, Part 820

Risk Management
- ISO 14971

Medical Device Product Standards
- IEC 60601-1, 2
- IEC 61010-1
- IEC 62304

Software Standards
Understanding The “Validation Challenge” - The Big Picture

• Convergence of Technologies
• Evolving Markets and Consumerization
• Innovation and Speed to Market
• Changing Face of Manufacturing and Automation
• Need for Concurrent Engineering
• Emerging Global Markets, Supply Chain & Risks
• Regulatory Scrutiny, Changes & Harmonization
• Increased focus on costs and reimbursements
• Acquisitions and Mergers
Convergence of Science, Technology and Manufacturing

**Science**
- Bio materials
- Drug- Device-Biologic
- Gene therapy
- Microfluidics
- Miniaturization & MEMS
- Nanotechnology
- Precision Medicine

**Technology**
- Interoperability
- Tech Convergence
- Connectivity
- Flexible electronics
- Advanced sensors
- Power Management
- Data Handling
- Digital Security

**Manufacturing**
- Rapid Prototyping
- Novel Additive, Subtractive & Joining process
- New Coatings
- Surface treatments
- Micro manufacturing
- Automation
- Test Systems
Evolving Device Market

- Wearable portable devices
- Telemedicine / Tele health
- Combination drug delivery devices
- Smart drug delivery devices
- Precision localized Medicine/Triggered release
- Drug coated devices
- Point of Care diagnostic devices
- Biomarkers / Proteomics
- Personalized Scaffold tissue generation
- Spinal fusion and fixation
- 3D Imaging and diagnostics
Manufacturing Processes & Concurrent Engineering

Prototype
- 3D printing
- Stereo Lithography
- Powder Bed Laser Sintering
- Inkjet Deposition
- E beam melting
- Ultrasonic Consolidation
- Fused Deposition Modeling
- Etching
- Laser cutting
- Hot Embossing
- Precision Machining

Bridge
- 3D printed molds
- Aluminum molds
- Low cavitation Molds
- Micro molding
- Assembly fit
- Pressure laminating
- Ultrasonic welding
- Heat staking
- Laser etching/welding
- Clean room environments
- Flexible Automation
- Packaging

Production
- High cavitation molds
- Finished assembly cells
- Soft Electronic Packaging
- Flexible Automation
- Aseptic Manufacturing
- Custom packaging Form, Fill and Sealing
- Fluid handling and dispensing equipment
- Powder handling and dispensing systems
- Coating, spraying and dosing equipment
- Web handling and converting
- Automated test
- Vision inspection systems
### Key Elements of Verification and Validation

#### Product / Design V&V

<table>
<thead>
<tr>
<th>Tests</th>
<th>Usability Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Performance, Biocompatibility, Bioburden, Package, Environmental, Shelf</td>
<td>Formative, Summative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection</th>
<th>System Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Article Inspection, Metrology, Visual</td>
<td>Product Software, Connectivity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMEA, FEA, Thermal, Computational Fluid Dynamics, Tolerance stack, Worst Case</td>
<td>Human Studies, Clinical Protocol and Reports</td>
</tr>
</tbody>
</table>

#### Process / Equipment V&V

<table>
<thead>
<tr>
<th>Design Qualification</th>
<th>Installation Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>URS, FAT, SAT, Layout and specification of the equipment design, pFMEA</td>
<td>Utilities, Auxiliary equipment install, Safety and Environmental check</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement System</th>
<th>Operational Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis Gage R&amp;R</td>
<td>Key Process variables, DOE, Limits, Controls</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Software Verification and Validation</th>
<th>Performance Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process or equipment software validation</td>
<td>Capability and Consistency over multiple PQ runs (PPQ - 3 stage approach for process design, process validation and continuous verification)</td>
</tr>
</tbody>
</table>
Design/ Product V&V

*Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.  
(Can I make the product right?)  
List how the output will be verified to assure output meets input requirements  
- Inspections; SOPs; Chart review

*Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.  
(Can I make the right product?)  
How the design will be validated to ensure it meets user/needs  
- Animal Study; Clinical Study
§820.30 Design Control Guidance Methodology


Verification

Clinical Studies ➔ Formative User Studies

Validation

User Needs ➔ User Needs

Review Requirements

Design Input

Review Specifications

Design Process

Review Design

Design Output

Review Product

Design Transfer

Medical Device

Validation

CeQur
Cross Functional Approach – “Device meets User Requirements”

- **Marketing Unmet Need**
  - URS
  - Focus groups
  - Surveys
  - Market Research

- **QA/Regulatory Requirements**
  - Device Specification
  - DMR
  - Total finished design

- **R&D Product Knowledge**
  - Design V&V
  - Process V&V
  - Usability Trial
  - Clinical Report
  - Risk Analysis

- **Manufacturing Process Knowledge**
  - Quality Plan, SOP
  - Supplier Review
  - Equipment
  - Regulatory Submission

- **Clinical Patient Studies**
  - Market Launch
  - Distribution
  - Regulatory Release

**RISK MANAGEMENT**
Process Verification and Validation

• Commissioning
  A process that will ensure installed equipment or systems perform in conformity with their intended design.

• Qualification
  The process of insuring equipment or system are properly installed or properly operating or properly performing a process.

• Verification
  Evidence that establishes or confirms the accuracy or truth of something at a single point in time.

• Validation
  Validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.
§820.75 Process Validation Methodology – “V-Model”

Manufacturing Equipment

Test Equipment/Software

CLR / Facilities monitoring

Raw material Supplier

Contract Manufacturer

Sterilization Vendor

Process Control / Monitoring
# Validation Types

<table>
<thead>
<tr>
<th>Systems</th>
<th>Examples</th>
<th>Validation Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Systems</td>
<td>Leak tests, Dose testing</td>
<td>Measurement System Analysis</td>
</tr>
<tr>
<td>Computerized Systems, non equipment</td>
<td>Supervisory data monitoring &amp; management systems</td>
<td>IOQ and Performance Verification</td>
</tr>
<tr>
<td>Computerized Systems, manufacturing equipment</td>
<td>Semi – automated and automated equipment</td>
<td>IO, OQ and Performance Verification</td>
</tr>
<tr>
<td>Computerized Systems, instruments</td>
<td>UV Spectrophotometer</td>
<td>IOQ and Performance Verification</td>
</tr>
<tr>
<td>Non computerized equipment</td>
<td>Manual equipment</td>
<td>IOQ and Performance Verification</td>
</tr>
<tr>
<td>Non computerized instruments</td>
<td>Instruments with firmware</td>
<td>IOQ</td>
</tr>
<tr>
<td>Manufacturing processes</td>
<td>Molding, Assembly, Welding, Staking, Bonding</td>
<td>Process Validation (IQ,OQ,PQ)</td>
</tr>
<tr>
<td>Lot/Batch workflows</td>
<td>Process flow</td>
<td>Process Validation (DQ, IQ,OQ,PQ)</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Ultrasonic , Wash systems</td>
<td>Process Validation (IQ,OQ,PQ)</td>
</tr>
<tr>
<td>Sterilization</td>
<td>EtO, Gamma, Autoclave, e-beam</td>
<td>Process Validation (IQ,OQ,PQ)</td>
</tr>
</tbody>
</table>
## A Comprehensive Master Validation Plan

<table>
<thead>
<tr>
<th>Item</th>
<th>Type</th>
<th>Description</th>
<th>Materials &amp; Equipment</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchased Components</td>
<td>Verification</td>
<td>Supplier to develop process &amp; produce parts, verify specifications are met.</td>
<td>Raw Materials, Processing Equipment</td>
<td>Supplier</td>
</tr>
<tr>
<td>Mold Qualification</td>
<td>IQ/OQ</td>
<td>Mold installation &amp; operational qualification Mold factory acceptance</td>
<td>Raw Materials, Molding Machine Auxiliary Equipment</td>
<td>Molder</td>
</tr>
<tr>
<td>Test Method validation</td>
<td>MSA</td>
<td>Testing will be developed and validated – gage R&amp;R, capability, establish correlation.</td>
<td>Force Tester, Leak and Flow tester, Vision test system, Dose Accuracy Tests</td>
<td>OEM</td>
</tr>
<tr>
<td>Assembly Process (Product Build)</td>
<td>IQ/OQ/PQ</td>
<td>Develop process window for each process and conduct IQ, OQ and PQ protocol. Each PQ, 3 lots build, product and package testing</td>
<td>Assembly Raw Materials &amp; Process/Test Equipment</td>
<td>CMO</td>
</tr>
<tr>
<td>Sterilization Validation</td>
<td>PQ</td>
<td>Dose mapping and Sterilization PQ on 3 lots followed by testing</td>
<td>Sterilization equipment</td>
<td>Sterilizer</td>
</tr>
<tr>
<td>Accelerated aging product and package stability testing</td>
<td>PQ</td>
<td>3, 6,12,18,24 months accelerated age testing. Package seal strength and integrity testing Product tests</td>
<td>Product conditioned and tested</td>
<td>OEM</td>
</tr>
<tr>
<td>Real Time Aging product and package stability testing</td>
<td>PQ</td>
<td>0,3,6,9,12,18,24 months real time aging. Package seal strength and integrity testing. Product tests</td>
<td>Product conditioned and tested</td>
<td>OEM</td>
</tr>
<tr>
<td>Final Report</td>
<td>Verification</td>
<td>Complete Report</td>
<td>Documents</td>
<td>OEM</td>
</tr>
</tbody>
</table>

Confidential
Example - Personalized Monitoring Device

- **Systems Integration**
- **Personal area network via wireless connectivity**
- **Data transfer & Security via cellular or Ethernet**

**Wearable Medical Device**

**Design V&V Challenges**
Technology Convergence, Sensor, Expandable network, Data management & Security

**Process V&V Challenges**
Hermetic Packaging, Joining methods, Wafer & Die attach, Supplier Sourcing and scalability planning
## Manufacturing Process V&V Flow

### Sensor Preparation
- ESD handling, deionizing
- Flex circuits
- Sensor calibration

### System Assembly
- Soldering, wire bonding, adhesive curing
- Adding system components to housing
- Power on, software check

### Component Manufacturing
- Micro molding
- Insert & conventional molding
- Tooling
- Automation

### Final Assembly
- Component assembly
- Joining methods, Hermetic seal
- Automation cells

### Device Testing
- Integrity
- Calibration
- Function

### Packaging & Sterilization
- Product handling, IFU, label
- Pouch or tray sealing Fill, form and seal
- ETO, Gamma, E beam sterilization

---

### Table:

<table>
<thead>
<tr>
<th>Sensor Preparation</th>
<th>System Assembly</th>
<th>Component Manufacturing</th>
<th>Final Assembly</th>
<th>Device Testing</th>
<th>Packaging &amp; Sterilization</th>
</tr>
</thead>
</table>
| ESD handling, deionizing | Soldering, wire bonding, adhesive curing | Micro molding
Insert & conventional molding
LIM & LSR
Two shot | Component assembly | Integrity | Product handling, IFU, label |
| Flex circuits | Adding system components to housing | Tooling | Joining methods, Hermetic seal | Calibration | Pouch or tray sealing Fill, form and seal |
| Sensor calibration | Power on, software check | Automation | Automation cells | Function | ETO, Gamma, E beam sterilization |
Creating “The Checklist” for the Specific Application

<table>
<thead>
<tr>
<th>Design V&amp;V</th>
<th>Process V&amp;V</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hardware and Software verification</td>
<td>• Identification Requirements for validation</td>
</tr>
<tr>
<td>• Product Reliability Testing</td>
<td>• Process Flow</td>
</tr>
<tr>
<td>• Product Design Validation</td>
<td>• Master Validation Plan</td>
</tr>
<tr>
<td>• Product Usability validation</td>
<td>• Validation Protocols</td>
</tr>
<tr>
<td>• Test Automation</td>
<td>• IQ,OQ,PQ</td>
</tr>
<tr>
<td>• Interoperability Testing</td>
<td>• Monitoring</td>
</tr>
<tr>
<td></td>
<td>• Controls</td>
</tr>
</tbody>
</table>
Emerging Technologies- Tomorrow’s devices

- **Artificial Intelligence**: Hardware/Software that can learn and think as humans.
- **Biochips**: Computer chip that can perform thousands of biological reactions.
- **Human Augmentation**: Creating cognitive and physical human enhancements.
- **3D Bio printing**: Using living cells to print organs, prosthetics or devices.
- **Brain Computer Interfaces**: Manipulate device with brain.
- **Digital Security**: Electronic digital safety.
- **Smart Robot**: Hardware/Software that can learn and think as humans.
THANK YOU