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GMP Upgrade Projects to achieve FDA Approvability

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Objectives

- Improve Quality Standards
- Achieve full GMP Compliance
- To be “best in class” site
- Get FDA Approvability
- Supply most important market

GMP Upgrade Projects

- Define a GMP upgrade Project
- Get Management Support (Resources, Budget)
- Define a GMP Upgrade Team with members from:
  - IT
  - Production
  - QA/QC
  - Engineering
  - Supply Chain Management / Warehousing
  - Development
- Define Project Leader
- Define Roles and Responsibilities for all involved people
- Define realistic Timelines
- Define Project Milestones

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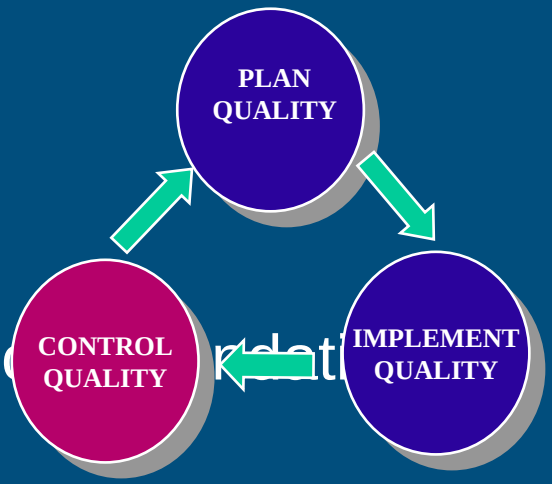
GMP Upgrade Projects

- Perform Baseline Mock Inspection to identify the needs
  - System Audit over the whole site
  - All departments should be covered by the Inspections
  - Focus: products shipped to the US
  - Multidisciplinary Audit team with required skills
- Detailed Report should be issued, including re[illegible] how to fix the issues
- Detailed Action Plan should be issued (responsibilities, timelines)
- Perform Audits to check progress, but focus only on the agreed actions. Don`t issue new findings !!!



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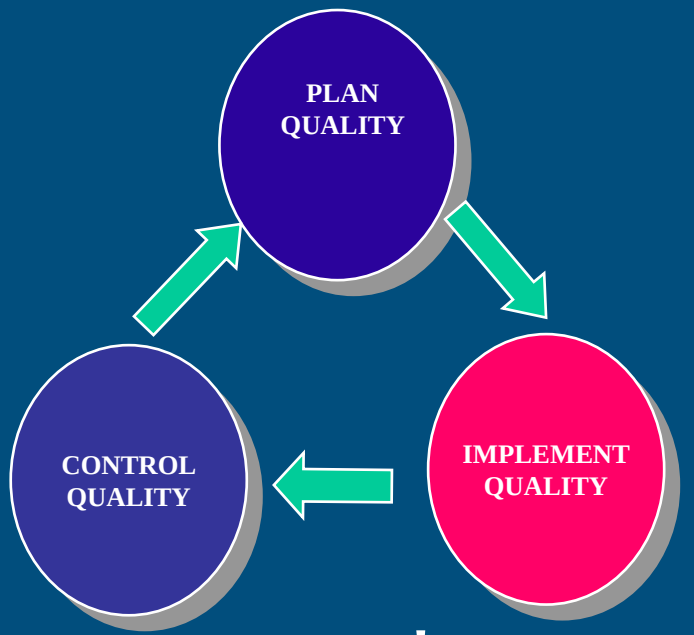
Areas to be Covered

Quality Systems

- Quality Manual, SOP`s, SOP System, Document Management System
- Complaint Handling (technical versus medical complaints)
- Deviation Management, OOS Handling
- Change Management
- Training
- Validation/Qualification
- Batch Record Review, Release
- Process Maps for key GMP-Processes
- Trending



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Areas to be Covered

Quality Control

- OOS / OOE – Management,
- Trending
- Documentation (pre-numbered worksheets)
- Lab-layout
- Equipment Qualification / Calibration, Method Validation
- Testing Methods
- Sampling
- Microbiological testing
- Computer System Validation / Part 11
- Statistical control of retention samples (yearly)

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Areas to be Covered

Manufacturing

- Cleanliness zone concept
- Risk for Cross Contamination
- Documentation
- Equipment Qualification and maintenance
- Process Validation
- Rejected batches, Deviations
- Annual Product Reviews
- Environmental Monitoring Data
- Traceability, Reconciliation

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Areas to be Covered

Engineering

- Engineering Drawings
- P&IDs
- Calibtation Program
- Calibration Documentation
- Preventative Maintenance Program
- Water System
- Infrastructure (N_2, CO_2)
- Qualification Approach
- Contractors

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Areas to be Covered

Warehousing

- Temperature Mapping
- Material status (released, quarantined, rejected)
- Cross Contamination
- Sampling
- Documentation
- Product Traceability
- Materials Management
- Computer System Validation / Part 11

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Areas to be Covered

Information Technology

- Data security
- Data integrity
- Archiving
- Overview about computer systems
- CSV Part 11
- Computer system validation
- Traceability

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Areas to be Covered

Development

- Development Reports
- Quality Risk Analysis to identify critical steps
- Validation Concept
- Technical Batches
- Upscaling
- Pivotal Batch
- Deviations
- Analytical Method Development / Validation
- Stability Data

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Pre-Operational Review with FDA for a sterile manufacturing site

Experience Report

Novartis Pharmaceutical Operations CH

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Meeting purpose

- Proactive relationship with FDA
- Achieve agreement on cGMP interpretation
- Prevent costly construction errors
- Increase efficiency and result in the timely processing of applications (site transfer)

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Cooperative project goals

- Basis: FMD No. 135
- constant project team (FDA and Novartis)
- avoid duplication of review
- co-ordination of reviews with project milestones
- co-ordination with regulatory affairs (FDA and Novartis)
- nomination of a project leader from FDA and Novartis

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Pre-operational Reviews

- at the end of detailed design - design review
- after equipment qualification documentation is finalized - review equipment qualification plans
- after equipment qualification is completed - review actual qualification & process validation plans
- 482 on site inspection

(Note that because of the scope and timing, there may be multiple reviews during each stage. For target dates please refer to the project plan)

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Experience

- Very good experience with this project
- Improved approval process with respect to timing
- Avoidance of costly reconstruction work
- Improved relationship with authorities
- No surprises for both sites
- Good model for the futures

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GMP Upgrade Projects

- Can be used as a model for all kinds of projects within the pharmaceutical environment.
  - EU
  - FDA
  - Japan (new regulations in 2005)

- Focused Approach
- Team Work

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