



Pharmaceutical Industry Trends

Approaches to Process Validation and Risk Management

(Quality Systems and cGMPs)

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Process Validation

Guidance for Industry Process Validation: General Principles and Practices

January 2011 (CGMP) Revision 1



Statutory and Regulatory Requirements for Process Validation

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B))

Validation General Principles and Practices Process Validation General Stages 1, 2 and 3:

- **Stage1** Process Design development and scale up activities
- **Stage2** Process Qualification process design is confirmed capable of reproducible commercial manufacturing
- **Stage3** Continued Process Verification ongoing assurance assuring that your process remains in a state of control

Gain information during R&D and continue throughout the lifecycle of the product gaining additional knowledge and driving process improvement and better product

Stage 1,2,3 (Validation Protocols and Final Reports)

- Description of the process
- Prospective Validation Study
- Risk Assessment for the Process

Stage 1,2,3 (Validation Protocols and Final Reports)

- Risk assessment for DQ, IQ, OQ and PQ and risk assessment for testing
- List of Critical Equipment and Critical Utilities (WFI, Compressed Air, Steam)
- Process Flow Diagrams

Stage 1,2,3 (Validation Protocols and Final Reports)

- Number of Batches and Size of Each Batch
- Predetermined Process Parameters
- Qualification Study for Homogeneity and Reproducibility
- Risk assessment when revalidation is needed

Stage 1,2,3 (Validation Protocols and Final Reports)

- **Define the Critical Process Parameters** (Risk analysis, tools Fish Bone diagrams, Failure Mode and Effects Analysis-FMEA)
- Some examples of CPP (sterile filtering, mixing, wet granulation, tablet compression, coating etc.)

Stage 1,2,3 (Validation Protocols and Final Reports)

- Define the **In-process Critical Quality Attribute** and **finished product Critical Quality Attribute** (in-process and finished testing)
- Cleaning Validation Study and Cleaning SOPs: Swab testing, residual solvents, rinse studies, toxicity studies, recovery studies.
- Analytical Method Validation Studies (completed) and Tech Transfer Reports Completed
- Statically Sound Sampling plan (RSD), blend studies and hold studies

cGMP's 211 Trends for Process Validation

CGMP regulations require that manufacturing processes be *designed and controlled* assuring in-process materials and the finished product meet predetermined quality, consistently and reliably.

cGMP's 211 Trends for Process Validation

- **§ 211.100(a)**, which states that “[t]here shall be written procedures for production and process control *designed to assure* that the drug products have the identity, strength, quality, and purity they purport or are represented to possess...”
- **§ 211.110(a)** *Sampling and testing of in-process materials and drug products*, requires that control procedures “. . . be established to monitor the output and *to validate* the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” (in-process controls) for final product quality.”
-
- **§ 211.160(b)(3)** the CGMP regulations regarding sampling set forth a number of requirements for validation.

cGMP's 211 Trends for Process Validation

- **§ 211.165(c) and (d)** samples must represent the batch under analysis the sampling plan must result in statistical confidence.
- **§ 211.165(a)** the batch must meet its predetermined specifications and control batch-to-batch variability.
- **§211.180(e)** requires that information and data about product quality and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product quality and process performance is an essential feature of process maintenance. **(life cycle approaches)**

cGMP's 211 trends for Process Validation

- **§ 211.42** CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations.
- **§ 211.63** Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use.
- **§211.68** Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance.

What is Quality Risk Management?

Quality Risk Management System Should Be Patient Focused?

Quality risk management builds a strong foundation for regulatory operations, management of facilities and quality products.

Linking patient, process and validation

Quality Risk Management

- **Principle One:** Evaluation of risk should be based on science and link to patient safety
- **Principle Two:** Effort and documentation should commensurate with the level of risk
- **Core:** QRM should work in teams. Diverse team of leaders from various departments (QCU, Production, R&D, Statistics, clinical and Regulatory Affairs)

Quality Risk Management (Risk Assessment)

Risk Assessment (4 fundamental questions)

Q1. What might go wrong (identification of the hazard)?

Q2. What is the likelihood (probability) it will go wrong? Probability of Recurrence matrix score

Q3. What are the consequences (severity)? Impact on Quality (patient safety) matrix score

Q4. What is the probability the hazard be detected? Probability of detectability matrix score

Quality Risk Management Risk Assessment

- **Risk Identification** : What might go wrong and identify the possible consequences
- **Risk Analysis**: Estimation of the risk associated with the hazard. Qualitative (particles, smells, cloudy injectable, fungus) and quantitative (failed assay, dissolution failure, stability failure) links the likelihood of the occurrence (will it occur a lot) and severity of harm (can it cause death or grave illness to patient). Also the detectability of the harm also factors into the estimation of risk (is it easy to detect for example a contaminated bioreactor).
- **Risk evaluation**: Risk evaluations look at the strength of the evidence of all four fundamental questions.

Quality Risk Management

Risk Control

- **Risk control:** Includes the decision making to reduce and or accept risks. Is risk above acceptable level? How can you eliminate the risks? Do you have enough resources? Are new risks introduced from your controls?
- **Risk reduction:** Company actions taken to lessen the probability of occurrence of harm and the severity of that harm.
- **Risk Acceptance:** The decision to accept risk, what is acceptable and what is not.

Quality Risk Management (communication and review)

- **Risk Communication** Sharing information about risk and risk management between decision makers this committee should be defined.
- **Risk Review** An ongoing part of Risk Management process. Results of internal audits, change controls, CAPA and failure investigations. Reviewing and evaluating of the outputs and results.

Industry Trends Applying Quality Risk Management for Day to Day Operations (Quality Systems)

Quality Risk Management and Quality Systems

- **Quality Defects** suspected quality defect, complaint, trend, deviation, investigation, out of specification result (e.g., recall).
- **Auditing/Inspection** to define the frequency and scope of audits, both internal and external. What needs to be addressed Risk Assessments.
- **Periodic review** to select, evaluate, and interpret trend results of data within the product quality review. To interpret monitoring data (e.g., revalidation or changes in sampling).

Industry Trends Applying Quality Risk Management for Day to Day Operations (Quality Systems)

- **Change management and change control** evaluate the impact of the changes on the product quality and availability of the final product and need for revalidation.
- **Continual improvement** to facilitate continual improvement in processes throughout the product lifecycle.

Industry Trends Applying Quality Risk Management for Day to Day Operations (Regulatory)

- **Quality Risk Management as Part of Regulatory** evaluate the significance of, for example, quality defects, potential recalls, and inspectional findings.

How to Apply Quality Risk Management for Day to Day Operations (Development)

Quality Risk Management as Part of Development

- To design a quality product and its manufacturing process.
- Can your process perform over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties, processing options, and process parameters).
- Assess the critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, APIs, excipients, or packaging materials.

Quality Risk Management as Part of Development

- Establish appropriate specifications, identify critical process parameters, and establish manufacturing controls (e.g., using information from pharmaceutical development studies and the ability to control variations during processing).
- Can you link to patient safety? For example content uniformity, dissolution and bioavailability.

Industry Trends Applying Quality Risk Management as Part of Development

- To decrease variability of quality attributes
- To reduce product and material defects
- To reduce manufacturing defects
- To make use of the *design space* concept

Industry Trends Applying Quality Risk Management as Part of Production Systems

- **Validation** approaches to verification, qualification, and validation activities (e.g. analytical methods, processes, equipment, and cleaning methods). Distinguish between critical and noncritical process steps to facilitate design of a validation study.
- **In-process sampling & testing** well defined in-process control testing and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

Industry Trends Quality Risk Management as Part of Laboratory System and Stability Studies

- **Out of specification results** identify potential root causes and corrective actions during the investigation of out of specification results.

Industry Trends Life Cycle Approach

Applying Product Lifecycle

- All phases of the life of the products, from development, marketing and discontinuation.
- Continual Improvement of Process Performance and Product Quality.

Life Cycle Approach (4 elements)

Four specific pharmaceutical quality system elements for Life Cycle Approaches

1. Process performance and product quality monitoring system
2. Corrective action and preventive action (CAPA) system; deviations risks assessment (level 1, level 2 or level 3)
3. Change management system; (risk assessment level 1, 2, and 3)
4. Management review of process performance and product quality (critical failures, recalls, adverse events and medical complaints, low sales and legal)

These 4 elements support product lifecycle stages

Life Cycle Approach (Lifecycle Stage Goals)

- i) Pharmaceutical Development** is designing a product and its manufacturing process to consistently deliver a safe drug that works.
- ii) Technology Transfer** is transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to make a safe drug that works.
- iii) Manufacturing** is maintaining a state of control and facilitating continual improvement. With a robust pharmaceutical quality system and exceeding the cGMPs.
- iv) Product Discontinuation** The goal of product discontinuation activities is to effectively manage the terminal stage of the product lifecycle.

Process Validation and Product Life Cycle

- Process validation activities should align with **Product Life Cycle** concepts
- Lifecycle concepts links the product with the process development, qualification of the commercial manufacturing process and maintains the process in a ***State Of Control***
- Lifecycle concepts include using modern manufacturing principals, driving process improvement, innovation and ***Sound Science***

FDA 21st Century Initiative Risk

*PHARMACEUTICAL CGMPs
FOR THE 21ST CENTURY —
A RISK-BASED APPROACH*

FINAL REPORT

Department of Health and Human Services
U.S. Food and Drug Administration

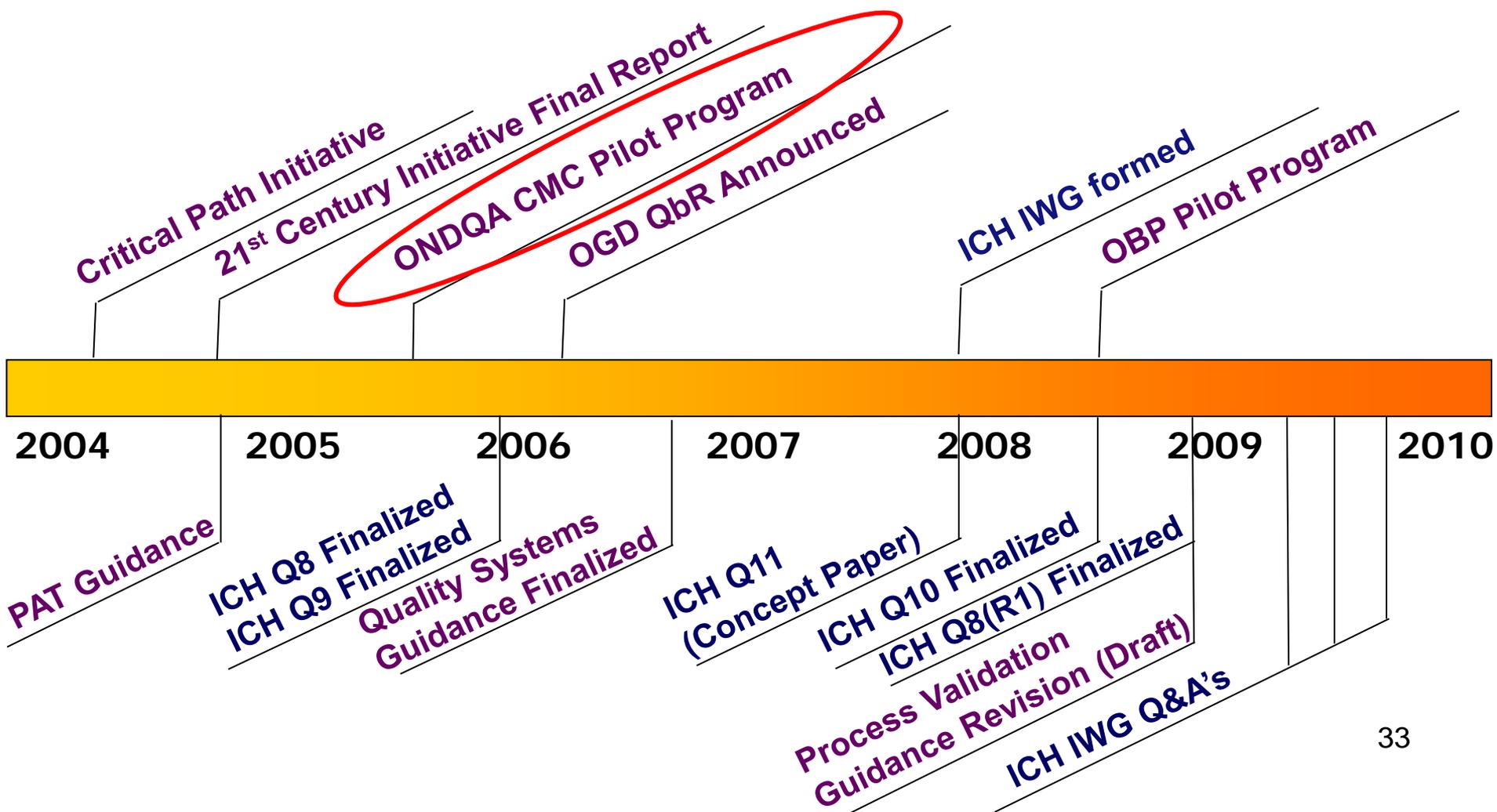
September 2004

September 2004

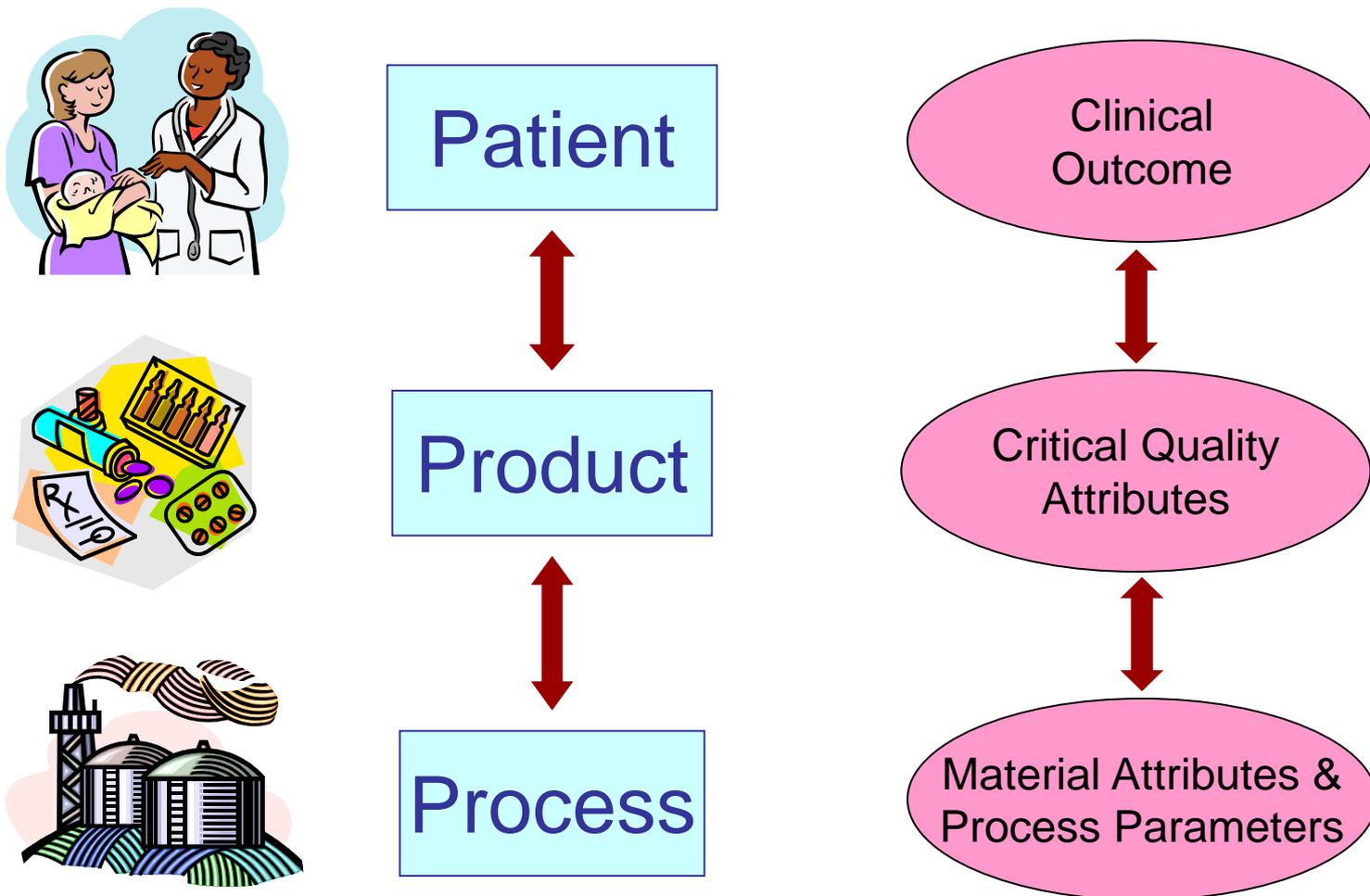
Objectives:

- ✓ Encourage the early adoption of new technological advances by the pharmaceutical industry
- ✓ Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches
- ✓ Encourage implementation of risk-based approaches
- ✓ Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- ✓ Enhance the consistency and coordination of FDA's drug quality regulatory programs

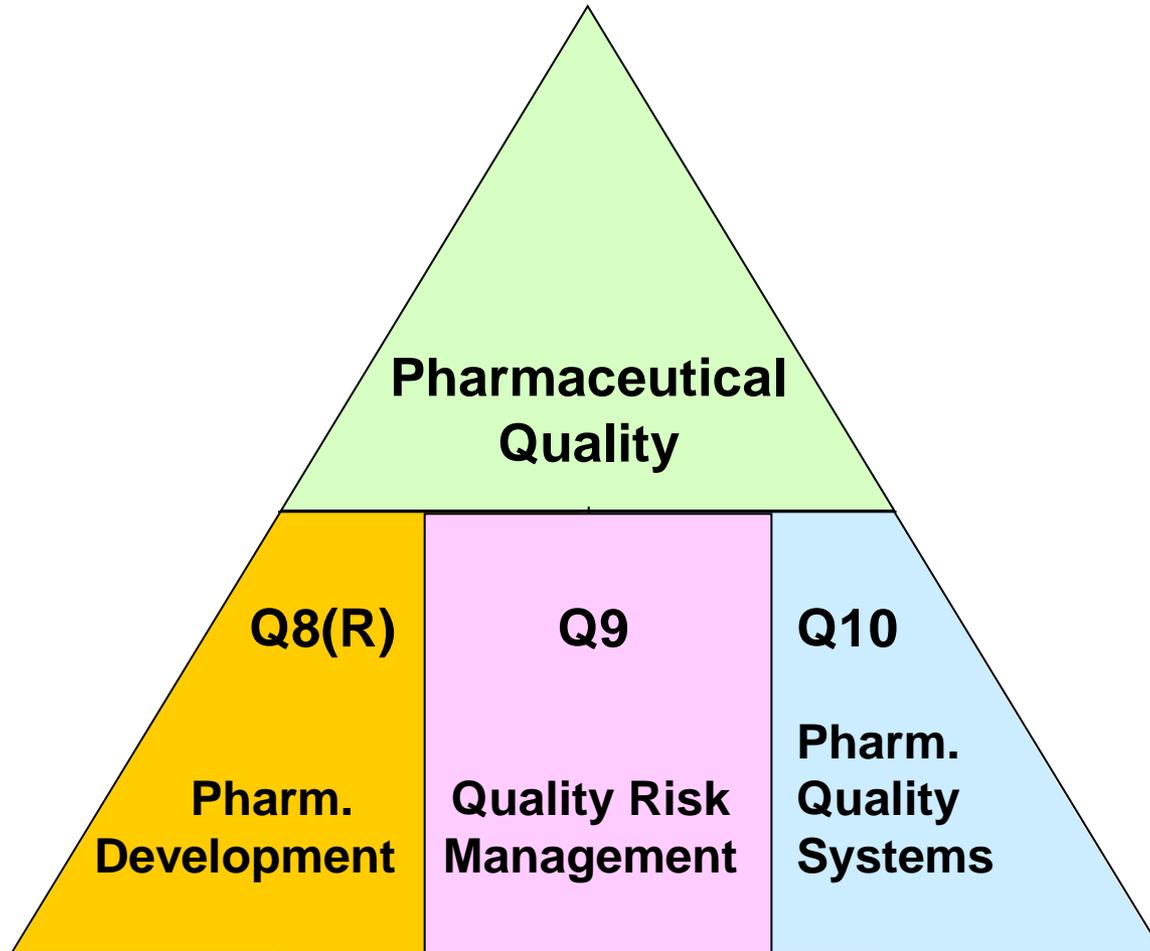
Quality Related Guidance and Initiatives



Linking Patient - Product - Process

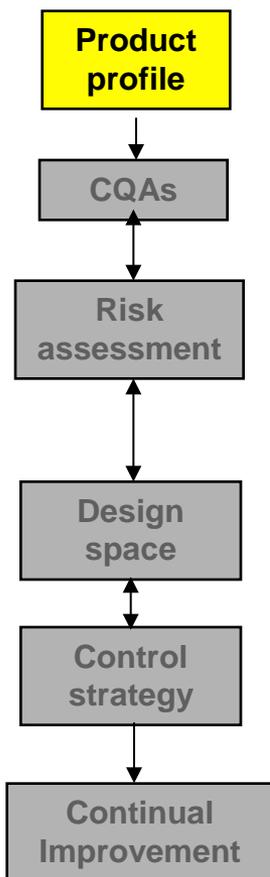


Integration of Pharmaceutical Quality

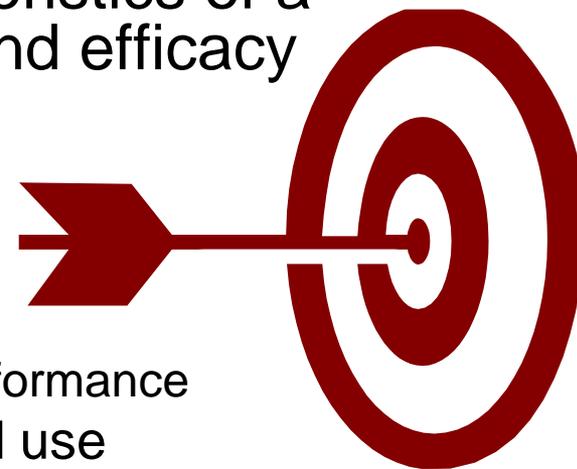


Quality Target Product Profile

“Begin with the end in mind”

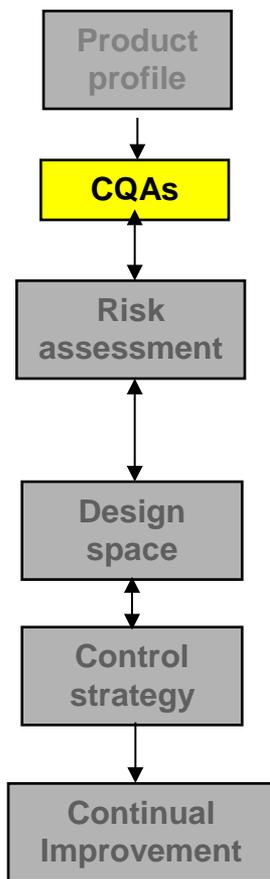


- Summary of the quality characteristics of a drug product to ensure safety and efficacy
- Includes, but not limited to:
 - Dosage form
 - Route of administration
 - Pharmacokinetic characteristics
 - e.g., dissolution, aerodynamic performance
 - Quality characteristics for intended use
 - e.g., sterility, purity
 - Patient needs – elderly, children
 - Amount of drug per dose
 - Desired dosing schedule
 - Route of administration
 - Safety requirements



Critical Quality Attributes (CQAs)

A measurable property of the drug substance or drug product that is critical to ensuring patient safety and efficacy

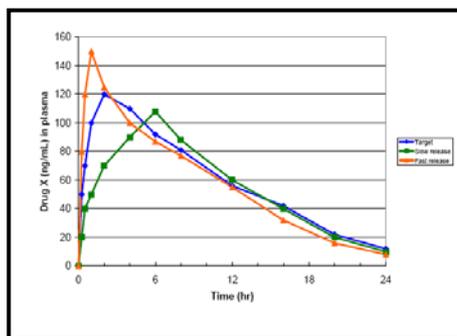


Defining CQAs Example: In Vitro – In Vivo Correlations

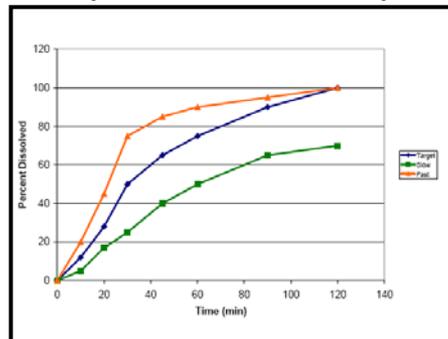
Formulation and
Manufacturing Process



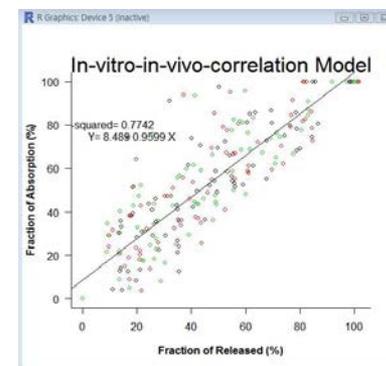
**In Vivo Response
(Plasma Conc. Profile)**



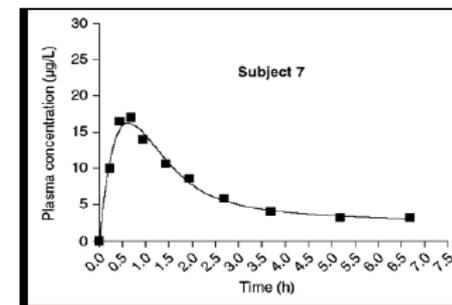
**In Vitro Release
(Dissolution Profile)**



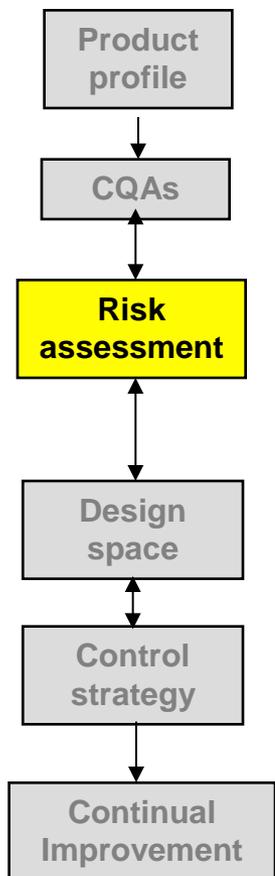
In Vitro/In Vivo Correlation



Predictive Model



Risk Management (ICH Q9)

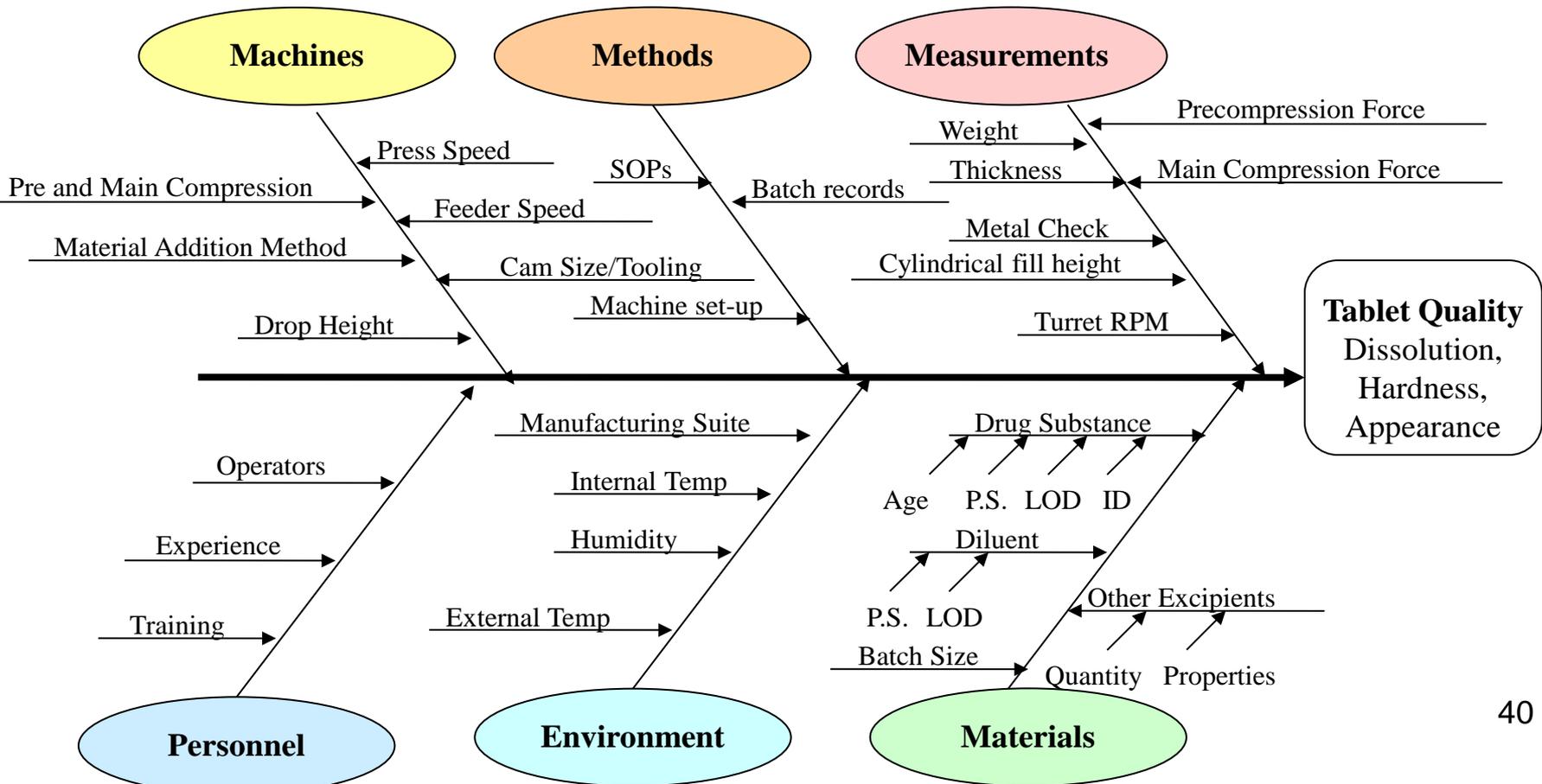


- A systematic process for the assessment, control, communication and review of risks to the quality of the drug product
- Evaluation of risk to quality should:
 - be based on scientific knowledge
 - link to the protection of the patient
 - Extend over the lifecycle of the product
- Typically conducted with an integrated group of experts, including development and manufacturing

Risk Assessment Example #1

Ishikawa Diagram

Tablet Compression





Risk Assessment Example #2

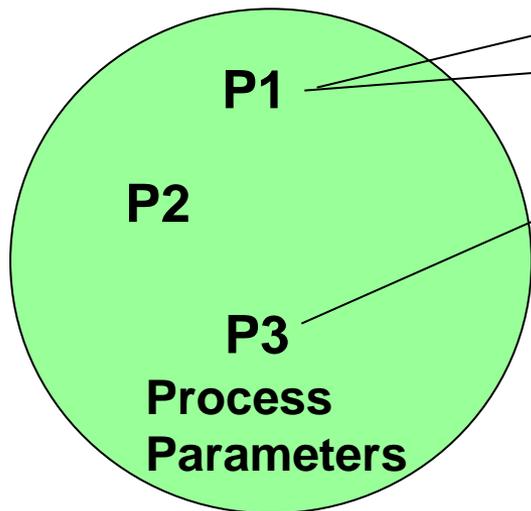
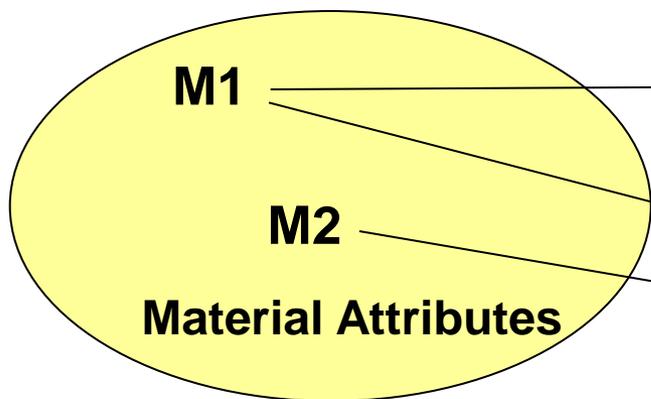
Failure Mode and Effects Analysis

Humidity Sensitive Crystalline Product

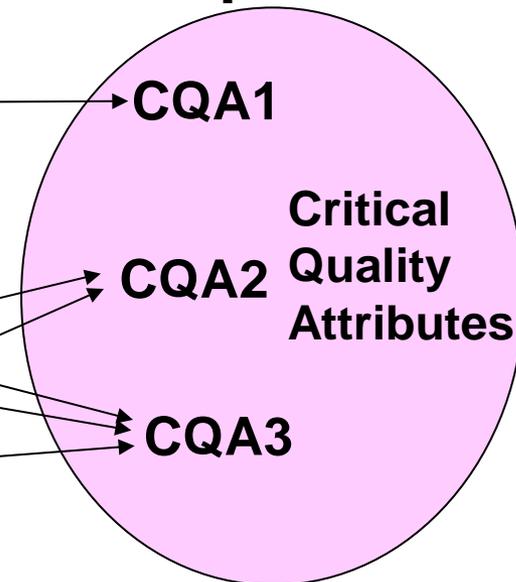
Category	Process Parameter	Severity S (1-5)	Occurrence O (1-5)	Detection D (1-5)	Risk priority number S*O*D	Criticality rank
Crystalliztn	Residual solvent	5	4	3	60	1
	Induction time	4	3	2	24	6
	Anti-solvent addition time	5	3	2	30	4
	Mixing	2	2	1	4	11
Isolation/ drying	Temperature during crystal drying	4	4	2	32	3
	Solids transfers	3	1	1	3	13
	Washing effectiveness	2	1	1	2	15
Handling/ storage	Relative humidity	5	3	3	45	2
	Inerting	4	2	3	24	6

Mapping the Linkage

Inputs:

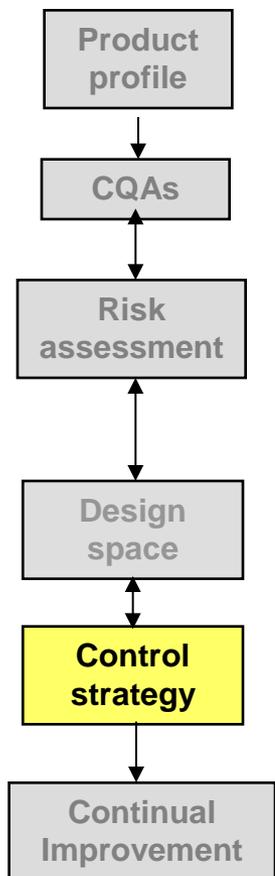


Outputs:



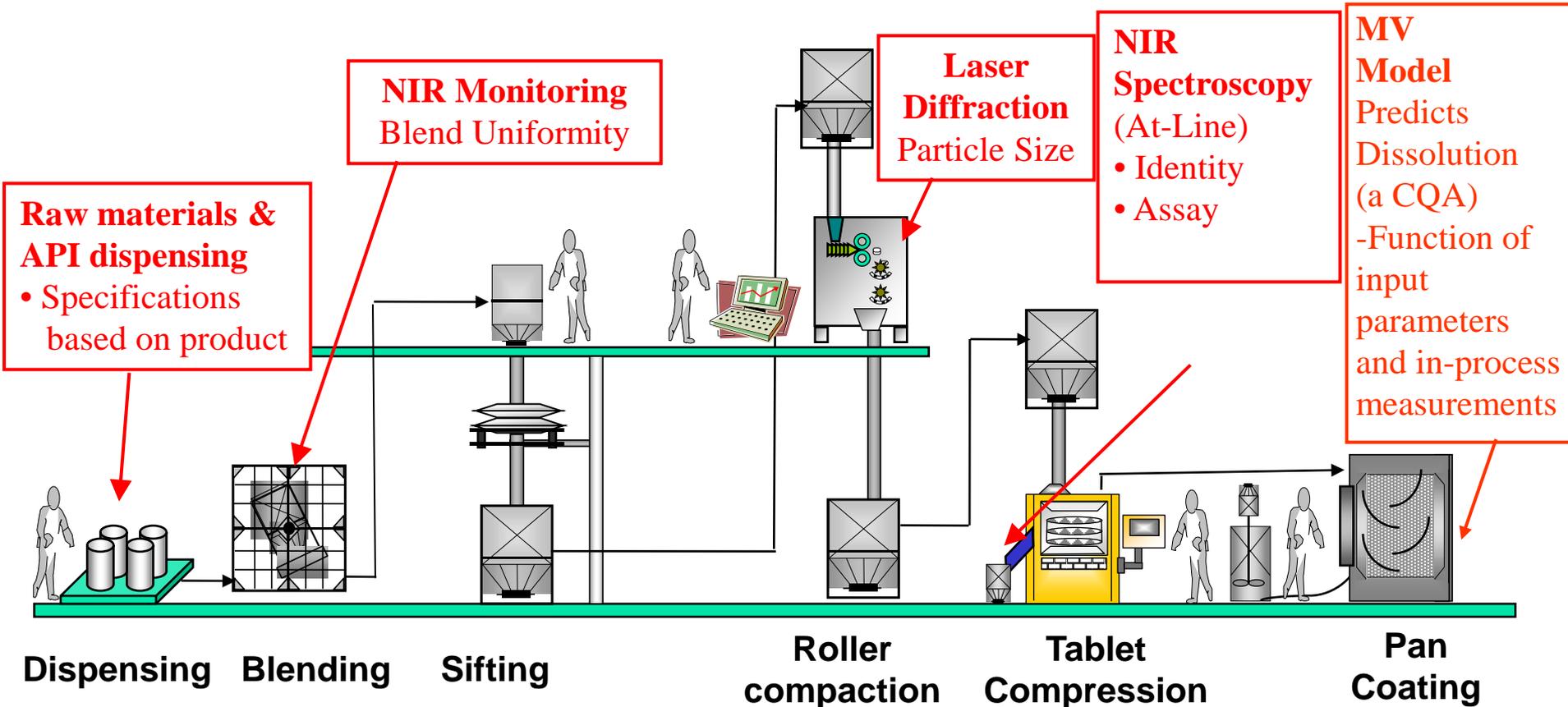
Relationships:
 CQA1 = function (M1)
 CQA2 = function (P1, P3)
 CQA3 = function (M1, M2, P1)

Control Strategy



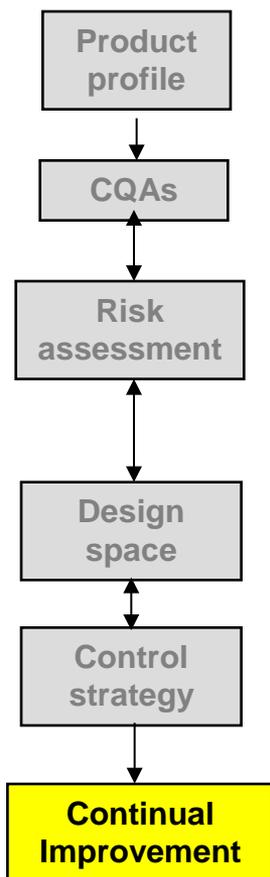
- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality (ICH Q10)
- Control strategy can include
 - parameters and attributes related to drug substance and drug product materials and components
 - facility and equipment operating conditions
 - in-process controls
 - finished product specifications
 - associated methods and frequency of monitoring and control

Control Strategy Example – Real Time Release



Continual Improvement

- Lifecycle risk management
 - Use development information as starting point
 - Update as experience gained
- Process tracking and trending
 - Statistical process control
 - Adjust trends before they become problems
- Knowledge management
- Model maintenance and updating



Modern Control Strategies

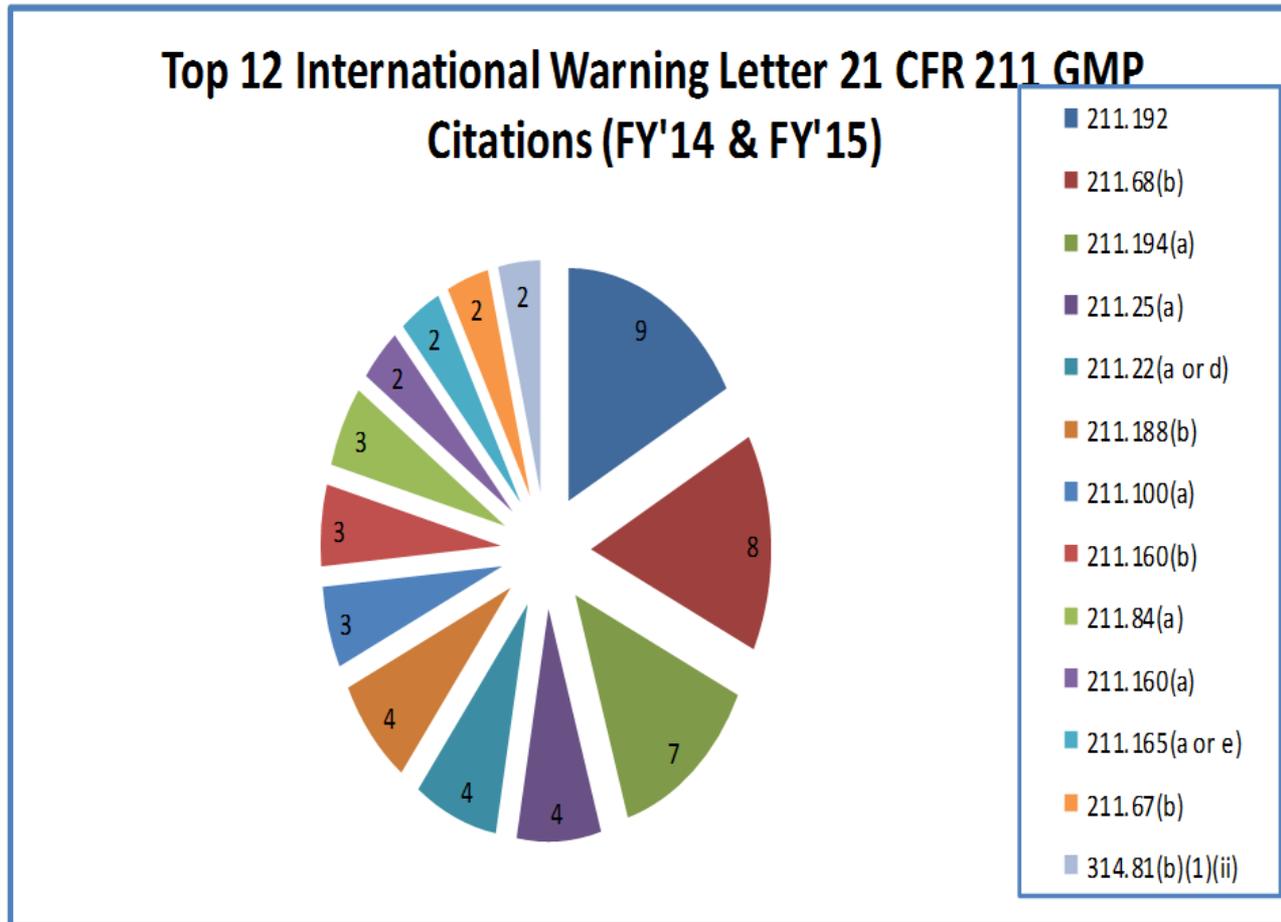
- Translating process understanding into effective controls
 - On-line and in-line measurement instruments
 - Effective sampling strategies
 - Feed-back and feed-forward control systems
- Modern manufacturing approaches
 - Lean manufacturing and real-time release testing
 - Continuous manufacturing
- Continual Improvement
 - Maintenance and update of process and analytical models
 - Utilization of process data to update control models (e.g., Multivariate statistical process control)
 - Knowledge retention and risk management updates

Cite ID	Count	Reference No.	Citation Text
1105	162	21 CFR 211.22(d)	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
3603	121	21 CFR 211.160(b)	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***
2027	111	21 CFR 211.192	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***
1361	100	21 CFR 211.100(a)	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***
1451	85	21 CFR 211.113(b)	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***



1883	83	21 CFR 211.165(a)	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically, ***
1213	76	21 CFR 211.67(a)	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, ***
1215	74	21 CFR 211.67(b)	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically, ***
3585	59	21 CFR 211.110(a)	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***
1434	58	21 CFR 211.42(c)(10)(iv)	Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically, ***

International Warning Letter GMPs



Quality System

Top Three International W/L GMP Citations FY'14 & FY'15

Cite

Details

#1 211.192

There is a failure to thoroughly review [any unexplained **discrepancy**] [the **failure** of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.

#2 211.25(a)

Employees are not given **training** in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations].

Quality System

Top Three International W/L GMP Citations FY'14 & FY'15

- #3 211.22(a or d)** a. There shall be a **quality control unit** that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The QCI shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
- d. The responsibilities and procedures applicable to the **quality control unit** shall be in writing; such written procedures shall be followed.

Laboratory Controls System

Top Four International W/L GMP Citations in FY'14 & FY'15

Cite

#1 211.194(a)

Details

Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays.

#2 211.160(b)

Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.

Laboratory Controls System

Top Four International W/L GMP Citations in FY'14 & FY'15

#3 211.160(a)

Deviations from written [specifications] [standards] [sampling plans] [test procedures] [laboratory mechanisms] are not [recorded] [justified]; Established [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] are not [followed] [documented at the time of performance]; The establishment of [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] including any changes thereto, are not [drafted by the appropriate organizational unit][reviewed and approved by the quality control unit].

#4 211.165(a or e)

- a. There shall be appropriate laboratory determination of satisfactory conformance to final specs of the drug product.
- e. The accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

Production System

Top Two International W/L GMP Citations FY'14 & FY'15

Cite

Details

#1 211.100(a)

There are no written procedures for production and process **controls** designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

#2 211.188(b)

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include: documentation that each significant step in the manufacture, processing, packing, or holding



Facilities & Equipment System

Top Two International W/L GMP Citation for FY'14 & FY'15

Cite

Details

#1 211.68(b)

Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from computer or related system of formulas or other records or data shall be checked for accuracy...A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that back data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

#2 211.67(b)

Written procedures shall be established and followed for cleaning and maintenance of equipment.



Material System

International W/L GMP Citation for FY'14 & FY'15

Cite

Details

211.84(a)

Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the [quality control unit](#).



My Information

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