Importance of Quality by Design elements in the Pharmaceutical Manufacturing

Andiappan Murugan

Imagine . Innovate

Indian Pharmaceutical Industry

- Pharmacy of the world
- Provide High Quality Medicines at Affordable price
- Serving billions of people across the world everyday
- Saved millions of lives during Pandemic
- Nearly half of all ANDAs filed in US are from India
- Largest number of USFDA approved plant outside US

- 483s & Warning Letters
- Product contamination incidents
- Product recalls
- Failure to launch
- Cost Pressure

Reason: Poor product understanding, Non-robust processes and inconsistent quality and output

Quality by Design

Quality by Design is a **systematic approach to development** that begins with the predefined objectives and emphasizes on:

- product and process understanding
- process control
- based on sound science and quality risk management.

- Thoroughly define product and process parameters, materials, and quality attributes.
- Sufficient empirical testing and multivariate statistical analysis upfront to understand material and process interdependencies.
- Optimize production to tolerate natural variance and mitigate anticipated risks.
- Engage in ongoing post-approval improvement of products and processes.

Elements of Quality by Design

1. **QTTP/CQA:** A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product.

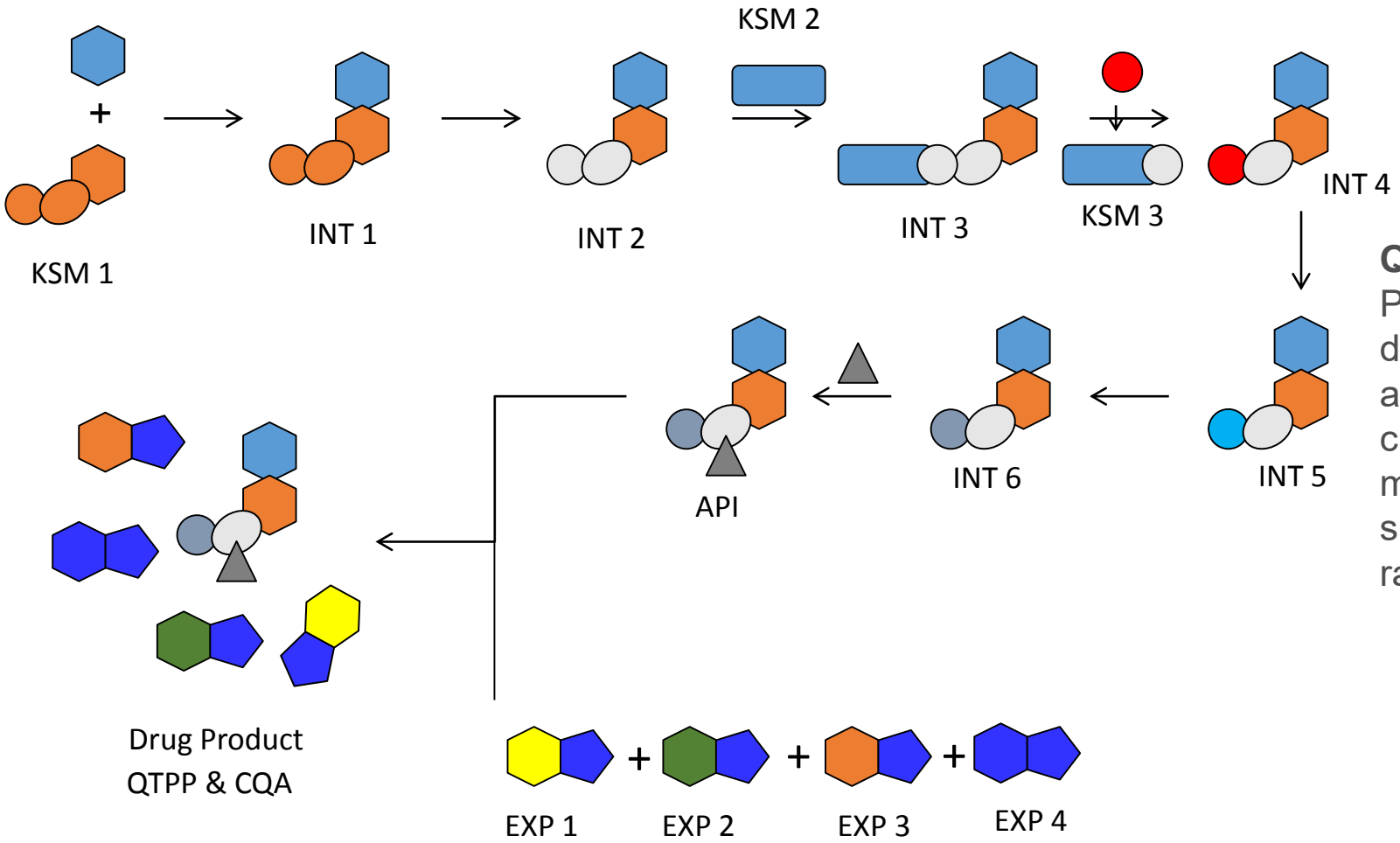
2. **CMA:** Product design and understanding including the identification of critical material attributes (CMAs)

3. **CPP:** Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs

4. **Control strategy** that includes specifications for the drug substance(s), intermediates, excipient(s), and drug product as well as controls for each step of the manufacturing process

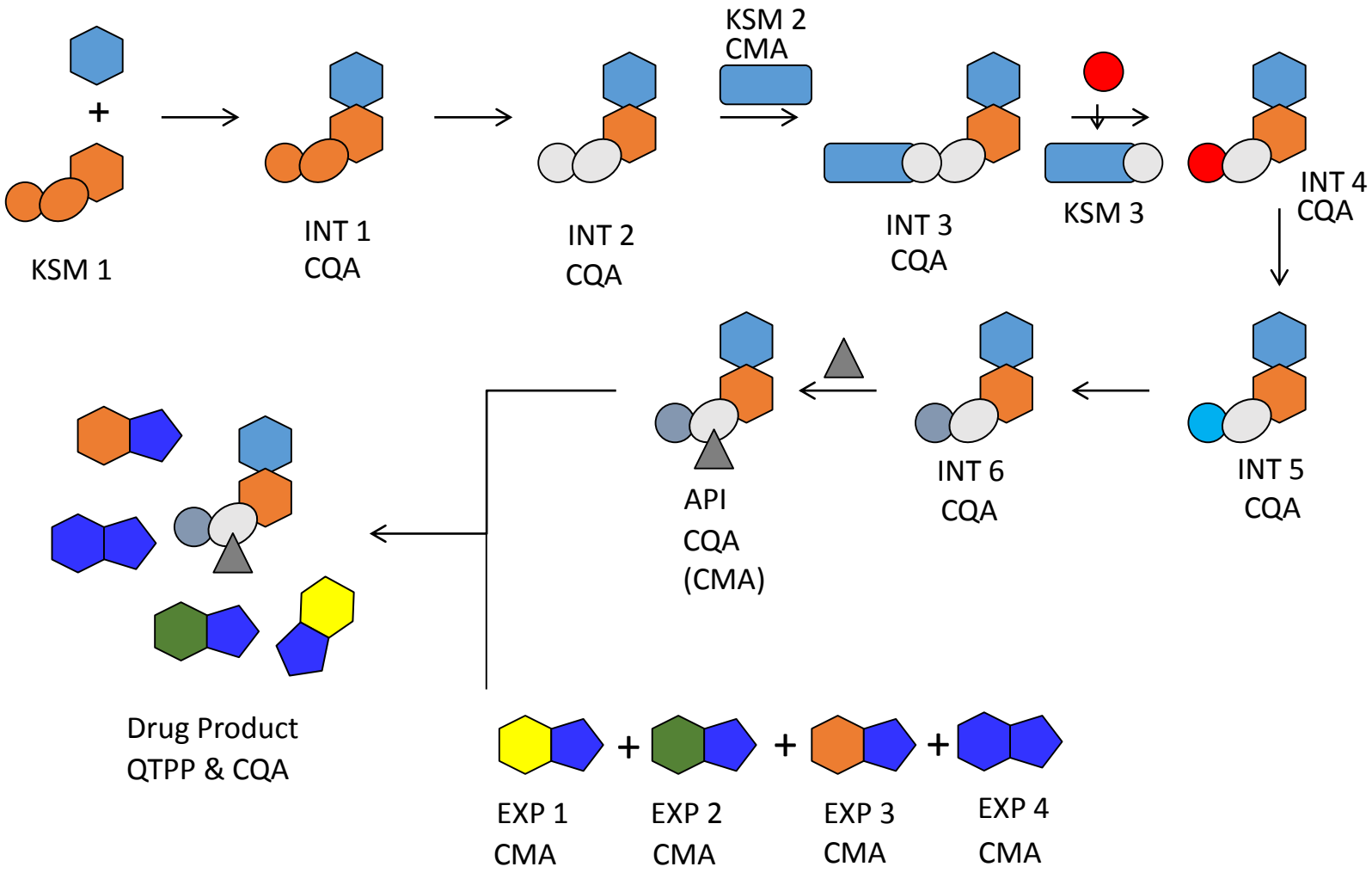
5. **Continuous Improvement:** Process capability and continual improvement

Pharmaceutical Manufacturing process



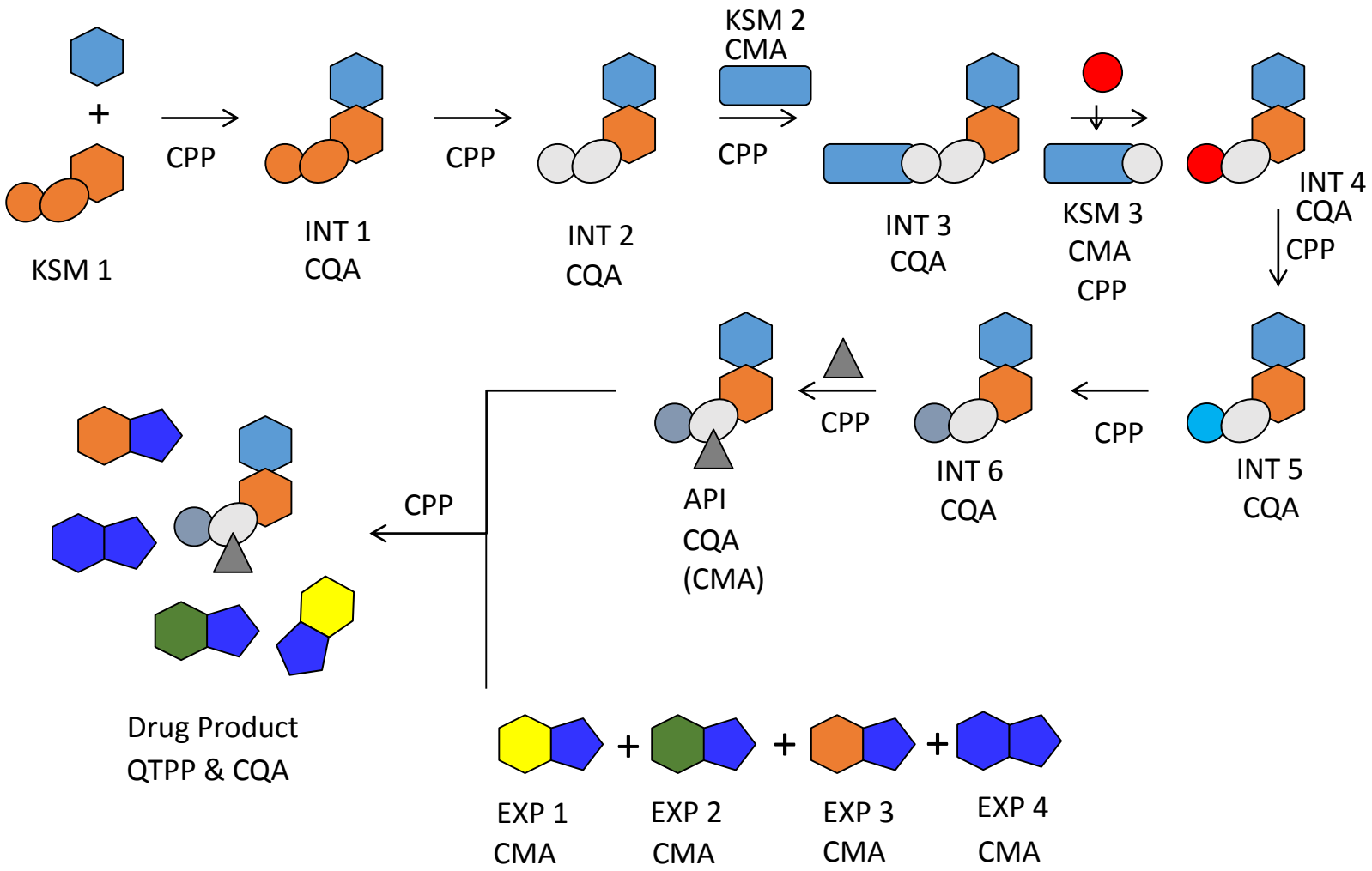
Quality (QTPP + CQA). The Quality Target Product Profile (QTPP) is a summary of the desired quality of the end product, taking into account safety and efficacy. It includes a list of critical quality attributes (CQAs) of any output material, such as uniformity, degradation, size, shape, and color, within an appropriate limit, range, or distribution.

Pharmaceutical Manufacturing process



Product (CMA): Understanding the critical material attributes (CMAs) of all input material within an acceptable limit, range, or distribution to ensure the desired QTPP.
RoS of individual materials are evaluated to arrive at a suitable CMA.

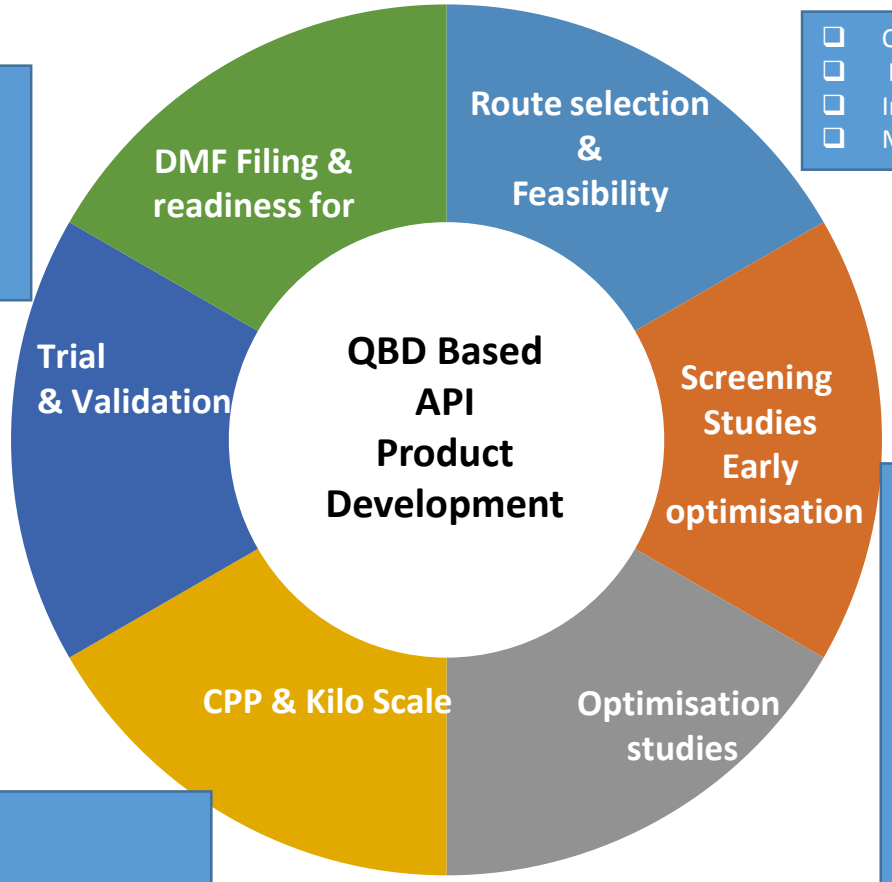
Pharmaceutical Manufacturing process



Process (CPP). The process understanding includes the identification of critical process parameters (CPPs), which by definition have a significant influence on the final product; Establish links between CMAs, CPPs and CQAs; and a thorough understanding of scale-up principles.

QbD Based Product Development Framework

Imagine . Innovate



- QTPP/CQA
- Literature survey and route selection
- Innovation targets
- Material safety

- Reagent and Solvent screen
- Attainment of maxima yield
- Calorometric studies (Safety & QA)
- Brainstorming to Parameter selection
- CQAs & CMAs
- Linking intermediate QA , CMA with product CQA (Matrix diagrams)
- Kinetics studies (HPLC, GC, Run charts)
- Automation tools (Avoid variality of DOE experiments)
- PAT (functional transformation, drying studies, cake washings etc.)
- Impurity tracker (Defining key, critical, non-critical, GTA, cutt-off imp's)
- Process map
- Lab validation
- What-ifs and holding studies
- Stability studies
- PMI tracker

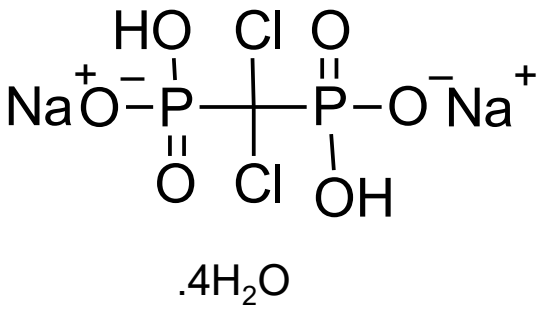
- Scale dependent and independent parameters
- Scale up FMEA
- Simulation Studies
- Specifications (NOR, PAR, Process capability)
- Control Strategy (Process, equipment, Inprocess)
- CPP, CMA, CQA representation through matrix diagram
- Design space verification
- Stability Prediction (Regression analysis)

- Inprocess and Spec trend analysis
- Scale dependent parameters
- Current operating conditions, future operating conditions, Knowledge space representation in DS
- Continuous Improvement

Quality by Design Process Development

- Identify all possible known input material attributes that could impact the performance of the product
- Use risk assessment and scientific knowledge to identify potentially high risk attributes
- Establish levels or ranges of these potentially high-risk material attributes
- Design and conduct experiments, using DoE when appropriate
- Analyze the experimental data and, when possible, apply first principle models to determine if an attribute is critical
- Develop a control strategy. For critical material attributes, define acceptable ranges.

Clodronate Disodium Tetrahydrate: Product Profile



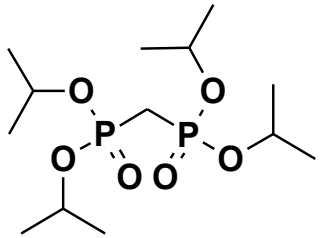
Clodronic acid tetrahydrate is used to treat bone problems, such as osteoporosis, bone pain, and high calcium levels in the blood.

Dosage: Injectable, multi grams

Target API Specifications (EP)

S.No.	TESTS	LIMITS
1	Description	White or almost white, crystalline powder
2	Solubility	freely soluble in water, practically insoluble in ethanol (96 per cent),
3	Identification	
	A) By IR	Should match with standard
	B) Test for Sodium	Should comply the reaction
4	Water content	Not less than 18.5 and Not more than 21%
5	pH	3.0 to 4.5
6	Assay	99.0 per cent to 101.0 per cent (anhydrous substance).
7	Related substance	
	(A) Impurity A+B	Not more than 0.2%
	(B) Any other individual impurity*	Not more than 0.05%
	(C) Total impurities	Not more than 0.3%

Route of Synthesis

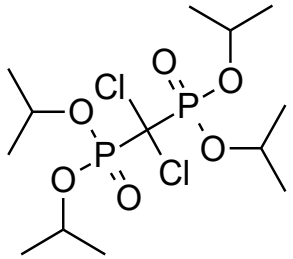


M.Wt.-344.32

Tetraisopropylmethylene diphosphonate

(KSM)

NaOCl Solution

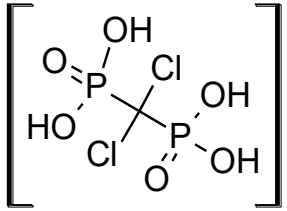


M.Wt.-413.21

(Stage-01)

Tetra isopropyl dichloromethylene diphosphonate

Conc. HCl

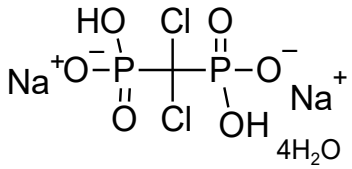


M.Wt.- 244.89

(Stage-02)

Clodronic acid

NaOH

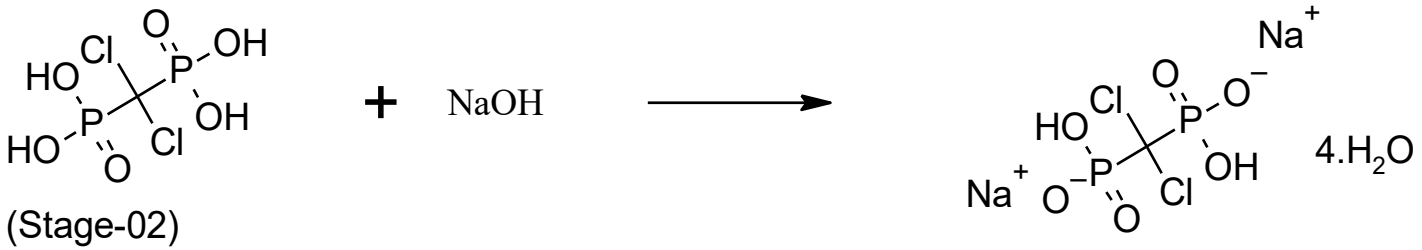


M.Wt.- 360.9

(Stage-03)

Clodronic acid disodium, API

Synthetic Scheme: Stage-3 (API)



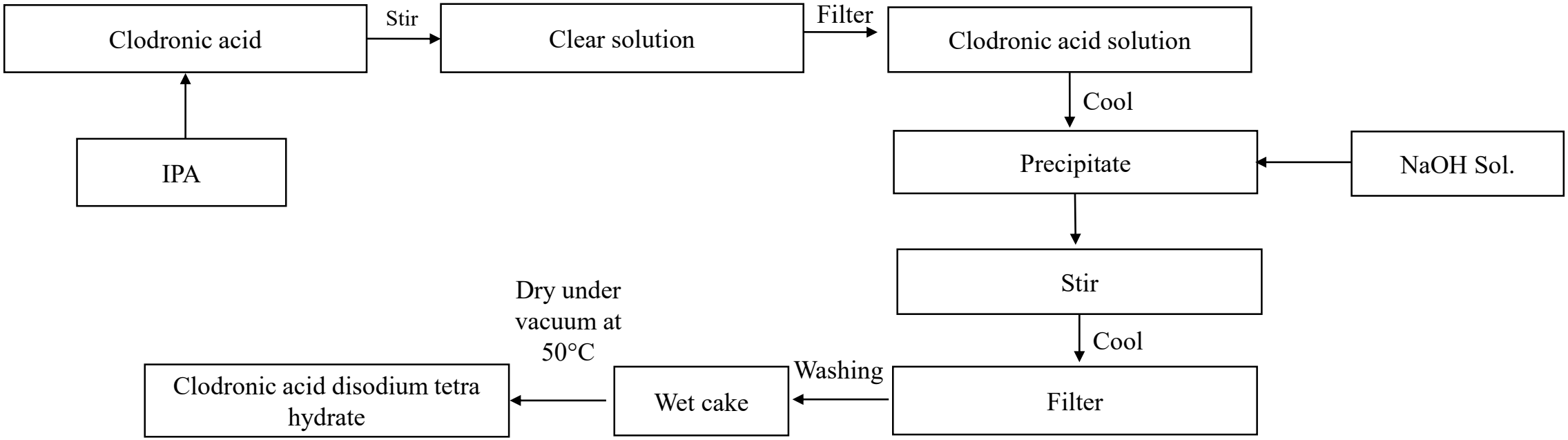
(Stage-02)

M.Wt.-244.89

(Stage-03)

M.Wt.-360.89

Process Flow diagram of Stage-3



List of Material: Stage-3

1. Clodronic acid
2. Sodium hydroxide
3. Purified water
4. Isopropanol

Critical Quality Attribute of API

Critical Quality Attribute for Qbd analysis			
Sr. No.	**QA**	**Sub-Quality Attribute**	**Remark**
1.	Description	-	White or almost white, crystalline powder
2	Solubility	in water	Freely soluble
		in ethanol (96%)	Practically insoluble
		in methanol	Slightly soluble
3	Identification	By IR	Should match with standard
		Test for Sodium	Should comply the reaction
4	Water content	-	Not less than 18.5 and Not more than 21%
5	pH	-	3.0 to 4.5
6	Assay	-	99.0% - 101.0 % (anhydrous substance).
7	Related Substance	Impurity A	Not more than 0.2%
		Impurity B	
		Impurity D	Not more than 0.05%
		Phosphate ion	-
		Phosphite ion	-
		SMUI	Not more than 0.05%
		Total unknown	-
		Total impurities	Not more than 0.3%
8	Organic Volatile Imp.	Isopropyl chloride	-
		Ethanol	Not more than 5000 ppm
		IPA	
		Benzene	Not more than 2 ppm
9	Yield	-	-

Mapping of St-03 CQA with CMA of Stage-02 (Risk Assessment -Qualitative)

CMA of Stage-02	CQA of Stage-03									Justification
	Description	Identification	Solubility			Assay	Water	pH	Yield	
			Water	Ethanol	Methanol					
Description										Colour of Stage-02 may affect colour of Stage-03
Identification by IR										Stage 2 Identification will impact API Identification
Stage-01										Unreacted stage-1 will have impact on assay and yield
Impurity-A (monoisopropyl)										Imp.-A in St-02 will impact assay, yield and solubility.
Impurity-D (mono Chloro)										Imp.-D in St-02 will impact assay, yield and solubility.
Imp. B (Phosphoric acid)										Imp.-B in St-02 will impact assay, yield and solubility.
Single Max unknown (SMUI)										SMUI in St-02 will impact assay, yield and solubility.
Total unknown (TU)										Total unknown (TU) may have impact on Assay, yield and solubility.
Assay										Assay of stage 2 will impact assay and yield of the product
Water										Water in St-02 may affect the yield
pH										pH may affect solubility and yield
Isopropyl Chloride										Isopropyl Chloride content may affect yield of St-03

	High Risk
	Medium Risk
	Low risk

Mapping of St-03 CQA with CMA of Stage-02 (Risk Assessment -Qualitative)

Material Attribute of Stage-2	Critical Quality Attributes of Stage-03												Justification
	Related Substance								Organic Volatile Imp.				
	Imp.-A	Imp.-B	Imp.-D	SMUI	Total unknown (TU)	Total Impurity	Phosphate Ion	Phosphite Ion	Isopropyl chloride	IPA	Ethanol	Benzene	
Description													Description will not have direct effect on impurities
Identification by IR													IR identification will not have direct effect on impurities
Impurity-A mono-isopropyl													It will affect on impurity-A and total impurity.
Impurity-D (mono Chloro)													It will affect on impurity-D and total impurity.
Imp.B (Phosphoric acid)													Impurity-B of St-02 will impact on impurity-B, total impurity impurity Phosphate Ion
Single Max unknown (SMUI)													SMUI of St-02 may affect the SMUI,TU,total imp. and Phosphite ion of St-03
Total unknown (TU)													Total unknown will impact on total unknown, total impurity of St-03
Assay													Low assay of St-02 may affect yield and purity
Water(KF)													Water will not impact on these quality attributes
pH (HCl content)													Due to HCl, NaCl will form, which is detectable in IC of St-03
Isopropyl Chloride													Residual IPCl, will release Cl anion in basic condition, Cl^- is detectable in IC of St-03

	High Risk
	Medium Risk
	Low risk

Mapping St-03 CQA with CMA of NaOH

Material Attribute of NaOH	Critical Quality Attributes of Stage-03									
	Description	Identification	Solubility			Assay	Water	pH	Yield	**Justification**
			Water	Ethanol	Methanol					
Identification										Identification of NaOH may impact the identification of stage-3.
Assay										Assay will impact on Solubility, assay, pH and yield
Carbonate (Na_2CO_3)										Carbonate is a inorganic part so it will impact on Solubility, Assay, pH and yield.
Chloride (Cl										Free chlorine will impact the assay and pH
Sulphate (SO_4)										SO_4 will impact the assay and pH of NaOH and hence may impact solubility, pH and assay of stage-3
Iron (Fe)										Iron will impact on Solubility, assay and yield
Heavy metals (Pb)										Heavy metals will impact on solubility and assay it may also impact on yield

	High Risk
	Medium Risk
	Low risk

Mapping St-03 CQA with CMA of NaOH

Material Attribute of NaOH	Critical Quality Attributes of Stage-03												
	Related Substance								Organic Volatile Imp.				Justification
	Impurity-A	Impurity-B	Impurity-D	SMUI	Total unknown	Total Impurity	Phosphate Ion	Phosphite Ion	Isopropyl chloride	IPA	Ethanol	Benzene	
Identification													Identification of NaOH only impact on identification only.
Assay													Assay will impact SMUI, total unknown, total impurity, phosphate ion and phosphite ion
Carbonate (Na_2CO_3)													Carbonate it can impact on will impact on Solubility, SMUI, total unknown, total impurity.
Chloride (Cl													Free chloride will impact the assay and pH
Sulphate (SO_4)													SO_4 will impact SMUI, Total unknown, total impurity, phosphate ion and phosphite ion
Iron (Fe)													Iron will not impact on related substance and organic volatile impurities
Heavy metals (Pb)													Heavy metals (Pb) will not impact on related substance and organic volatile impurities

	High Risk
	Medium Risk
	Low risk

Mapping St-03 CQA with CMA of IPA

Material Attribute of IPA	Critical Quality Attributes of Stage-03											
	Description	Identification	Solubility	Impurity-A+B	Impurity-D	Single Max unknown (SMUI)	Total Impurity (TI)	Assay	Water	pH	Yield	**Justification**
Description												Description of IPA may impact the Description of stage-3.
Solubility												Insolubility may impact on solubility, Single Max unknown (SMUI), and Total impurity (TI) and assay.
Purity by GC%												GC Purity % of IPA may impact on Single Max unknown (SMUI), and Total impurity (TI) and Assay
Water content												Water content will not impact on any factor

	High Risk
	Medium Risk
	Low risk

Mapping Stage-03 CQA with Unit operations

Unit Operation	Experimental factors	Critical Quality Attributes of Stage-03									Justification
		Description	Identification	Solubility			Assay	Water	pH	Yield	
				Water	Ethanol	Methanol					
Addition of RM	Solvent Qty										-Solvent quantity may affect description. -May affect pH -May affect yield -May affect purity which indirectly affect solubility and assay
	Water Qty										-May affect colour -May affect assay -May affect yield -May affect pH due to improper wash -May affect purity which indirectly affect solubility and assay
Dissolution	Time										-Dissolution time may impact the yield, assay and purity.
	Temperature										-Dissolution temperature may impact the yield, assay and purity.
Filtration	Pore size										-Due to improper filtration fine particle will appear in product and may affect solubility
Preparation of NaOH solution	Water Qty										-May affect the filtration -May affect the assay
	NaOH Qty										-May affect the product formation and thus affect identification, Assay, pH and yield
	Pore size										-Due to improper filtration fine particle may appear in product and may affect solubility
Addition of NaOH	Time										-With less time temperature may increase due exothermicirty which may increase degradation and thus affect description, yield and assay
	Temperature										-higher temp.may increase degradation and thus affect description, yield and assay

Mapping Stage-03 CQA with Unit operations

Unit Operation	Experimental factors	Critical Quality Attributes of Stage-03									
		Description	Identification	Solubility			Assay	Water	pH	Yield	Justification
				Water	Ethanol	Methanol					
Reaction Maintenance (salt formation)	Temperature										-Temperature may affect reaction completion and thus affect Assay, pH and yield -Temperature may affect degradation and can affect description
	Time										-Time may affect reaction completion and thus affect Assay, pH and yield -Time may affect degradation and can affect description
Crystalli-zation	Temperature										-Temp. may affect purge out of impurities and thus affect solubility, Assay and pH -Higher Temp. may affect product loss and yield
	Time										-Crystallization time may affect the precipitation and thus affect yield
Washing	Solvent Qty										-Solvent qty may affect washing of impurities and thus affect description and pH. Higher qty may affect product loss and thus affect yield
	Ratio										-Water solvent ratio may affect description, pH and yield
	Temperature										Washing temperature may affect product loss and thus affect yield
Drying	Time										-Drying time may affect degradation and thus affect description and assay, -Drying time will affect water content
	Temp										-Drying temp. may affect degradation and thus affect description and assay -Drying temp. will affect water content
	Vacuum										-Magnitude of vacuum may affect water removal.
Storage	Temp										-Storage temp. may affect degradation and thus affect description and assay
	Humidity										-Humidity may affect degradation and thus affect description -May affect water due to hygroscopicity
	Light										-Light may affect degradation and thus affect description and assay

Mapping Stage-03 CQA with Unit operations

Unit Operation	Experimental factors	Critical Quality Attributes of Stage-03												Justification
		Related Substance								Organic Volatile Imp.				
		Imp.-A	Imp.-B	Imp.-D	SMUI	Total unknown	Total Impurity	Phosphate Ion	Phosphite Ion	Isopropyl chloride	IPA	Ethanol	Benzene	
Addition of RM	Solvent Qty													-Solvent quantity may affect the purging out of impurities
	Water Qty													-water quantity may affect the purging out of impurities
Dissolution	Time													- Will have no impact on impurities
	Temperature													
Filtration	Pore size													- Will have no impact on impurities
Preparation of Sodium hydroxide solution	Water Qty													- Will have no impact on impurities
	NaOH Qty													- May have impact on inorganic impurities
	Pore size													- Will have no impact on impurities
Addtion of NaOH	Time													-Faster addition may increase exothermicity and thus induce degradation
	Temp.													-Higher temp. may increase degradation
Salt formation	Time													-Longer time may induce degradation
	Temp.													-higher temp. may increase degradation and degradation may increase unknown impurities and phosphate ions

	High Risk
	Medium Risk
	Low risk

Mapping Stage-03 CQA with Unit operations

Unit Operation	Experimental factors	Critical Quality Attributes of Stage-03												Justification
		Related Substance								Organic Volatile Imp.				
		Imp.-A	Imp.-B	Imp.-D	SMUI	Total unknown	Total Impurity	Phosphate Ion	Phosphite Ion	Isopropyl chloride	IPA	Ethanol	Benzene	
Crystallisation	Time													-Time for crystallization may affect impurities removal
	Temp.													-Time for crystallization may affect impurities removal
Washing	Ratio													-water solvent ratio may affect impurities removal
	Solvent qty													-Solvent qty may affect impurities removal
	Temp.													- temp. of solvent may affect impurities removal
Drying	Time													-Drying Time, and Temp. may affect degradation and thus affect unknown impurities -Drying time, temp. and vacuum may affect residual solvent
	Temp.													
	Vacuum													
Storage	Temp.													-Storage temp. may affect unknown impurities through degradation
	Humidity													-Humidity may affect degradation
	Light													-Light may affect degradation and thus affect unknown impurities

	High Risk
	Medium Risk
	Low risk

Selection of Experimental Factor for DOE

S. No.	Experimental Factors	Linked CQA of St-03	Consideration of factor for DOE/OFAT	Justification
1	IPA quantity	Description, pH, Yield, impurities	DOE	These factors may have correlation
2	Water qty with solvent	Description, Assay, pH, Yield, impurities	DOE	
3	Dissolution time	Assay, pH, yield	OFAT	These factors may be optimized
4	Dissolution Temp.	Assay, pH, yield	OFAT	
5	Filtration Pore Size	Solubility, Impurities	OFAT	
6	Water for NaOH	Assay, pH	OFAT	Water qty can be optimized for suitability of filtration and exothermicity during addition
7	NaOH Qty	Identification, assay, pH and yield.	DOE	These factors may have correlation with other factors
8	NaOH addition time	Description, Assay, Impurities and Yield	OFAT	Addition time will not have correlation with any other factor and can be controlled
9	NaOH addition temp.	Description, Assay, Impurities and Yield	DOE	These factors may have correlation with other factors

Selection of Experimental Factors for DOE

S. No.	Experimental Factors	Linked CQA of St-03	Consideration of factor for DOE/OFAT	Justification
10	Reaction Time	Description, Assay,pH, Yield	DOE	These factors may have correlation
11	Reaction temperature	Description, Assay,pH, Yield	DOE	
12	Crystallisation Temp.	Solubility, Assay, pH, Yield, Impurities	DOE	
13	Crystallisation Time	Yield, Impurities	DOE	
14	Washing solvent qty	Description, pH, Yield and impurities	DOE	
15	Washing solvent ratio	Description, pH, Yield and Impurities	DOE	
16	Washing solvent temp.	Impurities, pH and Yield	OFAT	This factor can be optimized with couple of experiments
17	Drying time	Description, Assay, Water, Residual solvent, impurities	OFAT	These factors have no correlation with other factors
18	Drying temp.	Description, Assay, Water, Residual solvent, Impurities	OFAT	
19	Drying vacuum	Water, Residual solvent	OFAT	
20	Storage Temp.	Description, Assay	OFAT	These factors have no correlation with other factors
21	Storage humidity	Description, water	OFAT	
22	Storage Light	Description, Assay	OFAT	

Factorial Experimental Design

Design Summary

Factors:	10	Base Design:	10, 32	Resolution:	IV
Runs:	33	Replicates:	1	Fraction:	1/32
Blocks:	1	Center pts (total):	1		

Factorial Experimental Design

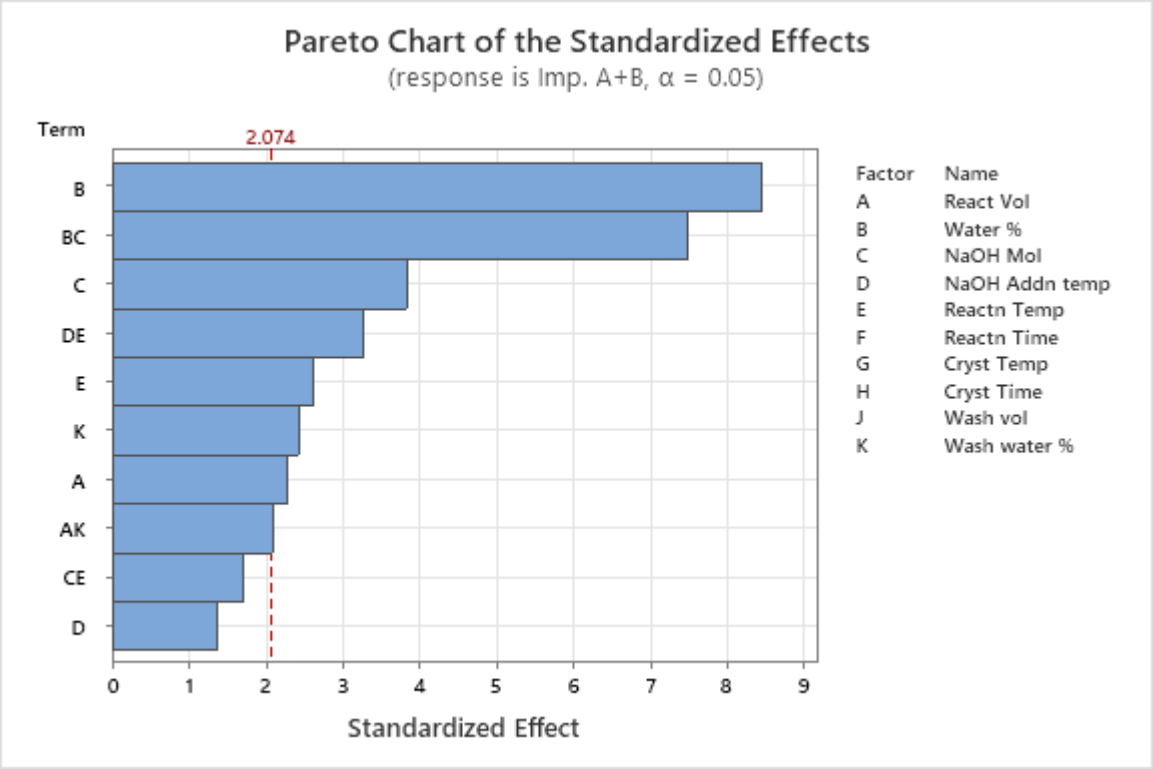
StdOrder	RunOrder	CenterPt	Blocks	React Vol	Water %	NaOH Mo	NaOH Add	Reactn Te	Reactn Tir	Cryst Tem	Cryst Time	Wash vol	Wash wat	Imp. A+B	Imp.-D	0.22RRT	Chloride	0.51 RRT	TU-Cl	pH	Mol.Yield
1	1	1	1	5	10	2	10	10	8	30	4	4	40	0.355	0.004	0.027	0.034	0	0.039	4.92	105.09%
13	2	1	1	5	10	3	30	10	8	0	1	4	40	0.431	0.006	0.027	0.028	0.056	0.092	7.41	93.42%
19	3	1	1	5	40	2	10	40	2	30	4	2	40	0.185	0	0.032	0.017	0	0.037	3.55	87.69%
18	4	1	1	10	10	2	10	40	2	30	4	4	10	0.207	0	0.017	0	0	0.029	3.59	92.59%
33	5	0	1	7.5	25	2.5	20	25	5	15	2.5	3	25	0.19	0.003	0.019	0.017	0	0.024	5.78	93.44%
24	6	1	1	10	40	3	10	40	2	30	1	2	10	0.042	0.007	0.016	0.019	0	0.026	7.4	97.93%
15	7	1	1	5	40	3	30	10	2	30	4	4	10	0.016	0.002	0.035	0.029	0.044	0.084	6.95	100.67%
16	8	1	1	10	40	3	30	10	8	0	1	2	10	0.055	0.004	0.013	0.083	0.044	0.061	7.33	112.63%
30	9	1	1	10	10	3	30	40	2	0	1	4	10	0.71	0.019	0.046	0.019	0.018	0.087	6.4	102.35%
22	10	1	1	10	10	3	10	40	8	0	4	2	40	0.315	0.01	0.042	0.031	0.031	0.09	7.41	100.72%
11	11	1	1	5	40	2	30	10	8	0	4	2	40	0.24	0.002	0.02	0	0	0.02	4.83	86.03%
27	12	1	1	5	40	2	30	40	8	30	1	4	10	0.037	0	0.006	0	0	0.006	3.53	83.15%
32	13	1	1	10	40	3	30	40	8	30	4	4	40	0	0	0.012	0	0	0.012	6.67	92.27%
28	14	1	1	10	40	2	30	40	2	0	4	2	10	0.059	0.001	0.008	0	0	0.008	4.47	88.23%
6	15	1	1	10	10	3	10	10	8	30	1	4	10	0.599	0.02	0	0.056	0	0.021	6.89	91.48%
17	16	1	1	5	10	2	10	40	8	0	1	2	10	0.13	0	0	0.013	0	0.008	3.54	95.56%
5	17	1	1	5	10	3	10	10	2	0	4	2	10	0.649	0.021	0.026	0	0	0.039	6.1	117.30%
10	18	1	1	10	10	2	30	10	8	0	4	4	10	0.188	0.006	0	0.005	0	0.009	3.54	94.57%
3	19	1	1	5	40	2	10	10	2	0	1	4	10	0.418	0.007	0.037	0	0	0.047	4.63	83.40%
21	20	1	1	5	10	3	10	40	2	30	1	4	40	0.361	0.026	0.025	0	0	0.034	6.58	104.48%
2	21	1	1	10	10	2	10	10	2	0	1	2	40	0.192	0.009	0.026	0	0	0.037	3.63	80.80%
4	22	1	1	10	40	2	10	10	8	30	4	2	10	0.215	0	0	0.075	0	0.043	3.57	87.19%
29	23	1	1	5	10	3	30	40	8	30	4	2	10	0.659	0.024	0	0.024	0	0.021	6.2	105.56%
9	24	1	1	5	10	2	30	10	2	30	1	2	10	0.157	0.006	0.021	0	0	0.032	3.51	91.25%
20	25	1	1	10	40	2	10	40	8	0	1	4	40	0	0	0	0.027	0	0	6.88	89.87%
14	26	1	1	10	10	3	30	10	2	30	4	2	40	0.388	0.035	0.018	0	0	0.018	7.34	106.73%
23	27	1	1	5	40	3	10	40	8	0	4	4	10	0.051	0.007	0	0.55	0	0.177	6.81	98.33%
25	28	1	1	5	10	2	30	40	2	0	4	4	40	0.25	0.018	0.024	0	0	0.031	4.86	92.21%
7	29	1	1	5	40	3	10	10	8	30	1	2	40	0.201	0	0	0.057	0	0.008	3.55	84.25%
8	30	1	1	10	40	3	10	10	2	0	4	4	40	0.027	0.015	0.024	0	0	0.024	6.77	90.00%
26	31	1	1	10	10	2	30	40	8	30	1	2	40	0	0	0	0.014	0	0.009	3.47	87.36%
12	32	1	1	10	40	2	30	10	2	30	1	4	40	0.104	0.004	0.028	0	0	0.028	3.86	82.09%
31	33	1	1	5	40	3	30	40	2	0	1	2	40	0.015	0.019	0.035	0	0.057	0.092	7.09	102.66%

DoE Analysis

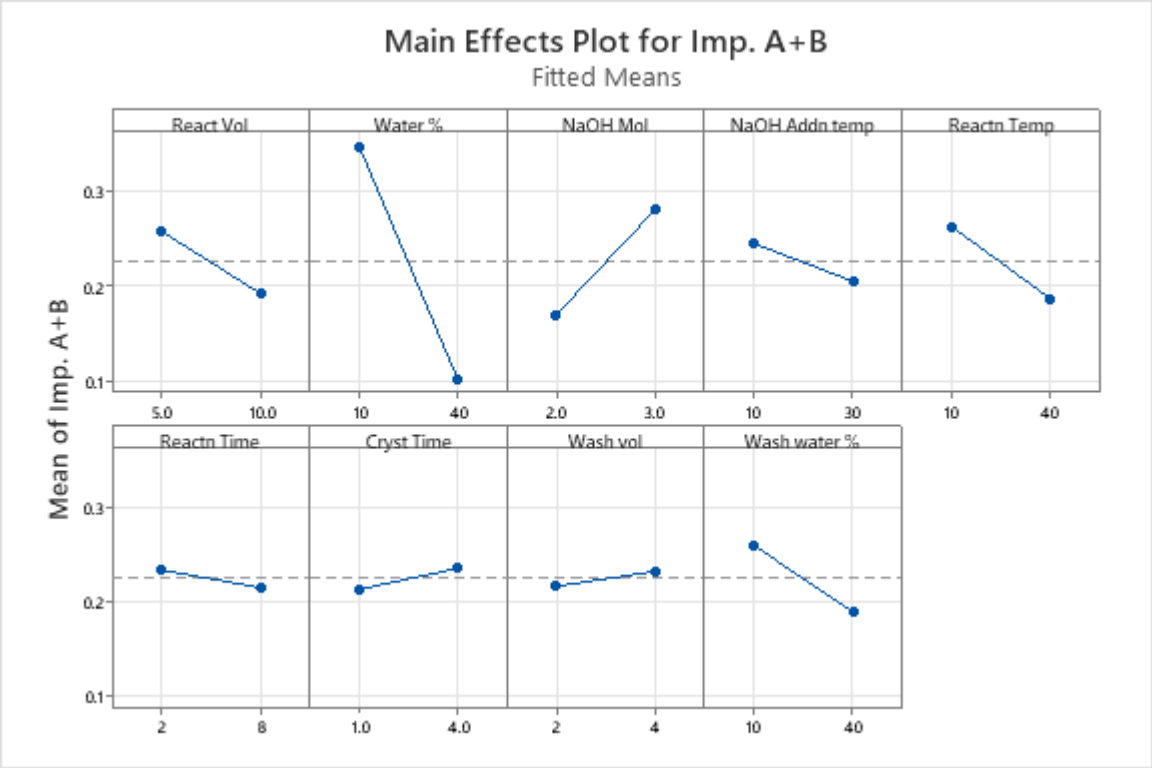
Factorial Regression: Imp. A+B versus React Vol, Water %, NaOH Mol, NaOH Addn temp, Reactn Temp, Reactn Time, Cryst Temp, Cryst Time, Wash vol, Wash water %, CenterPt

Model Summary

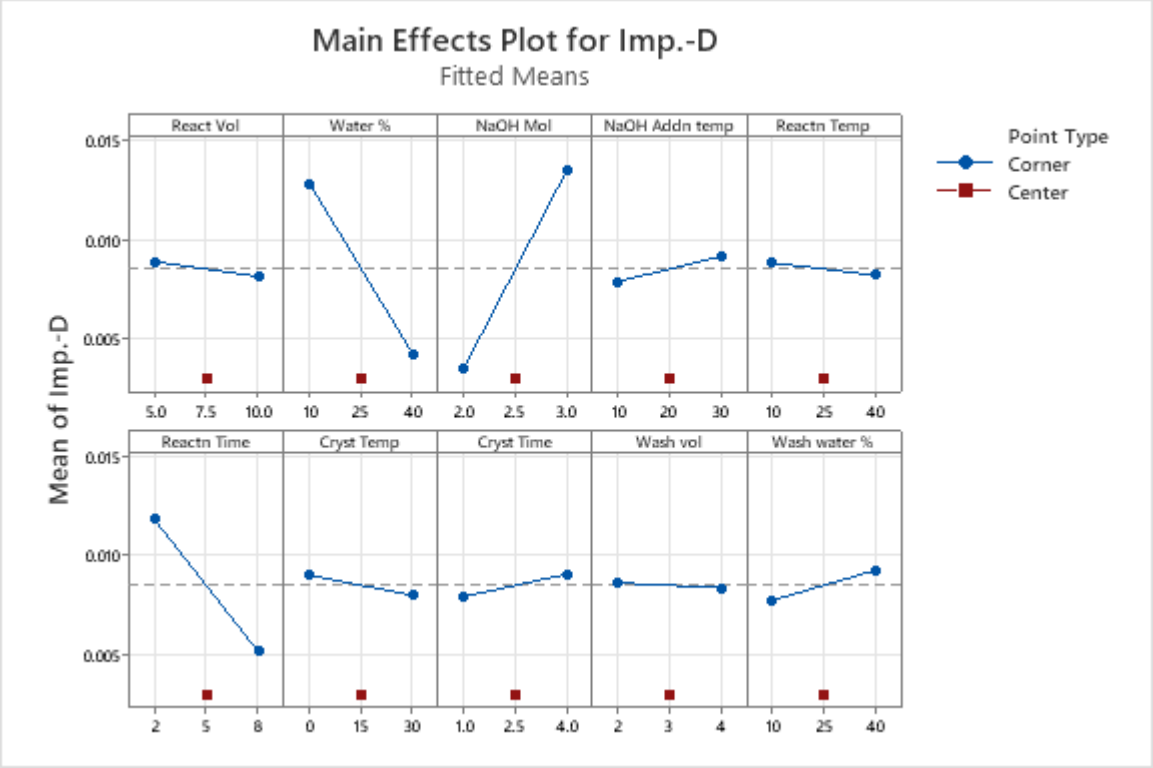
S	R-sq	R-sq(adj)	R-sq(pred)
0.0822160	89.09%	84.13%	74.85%



DoE Analysis

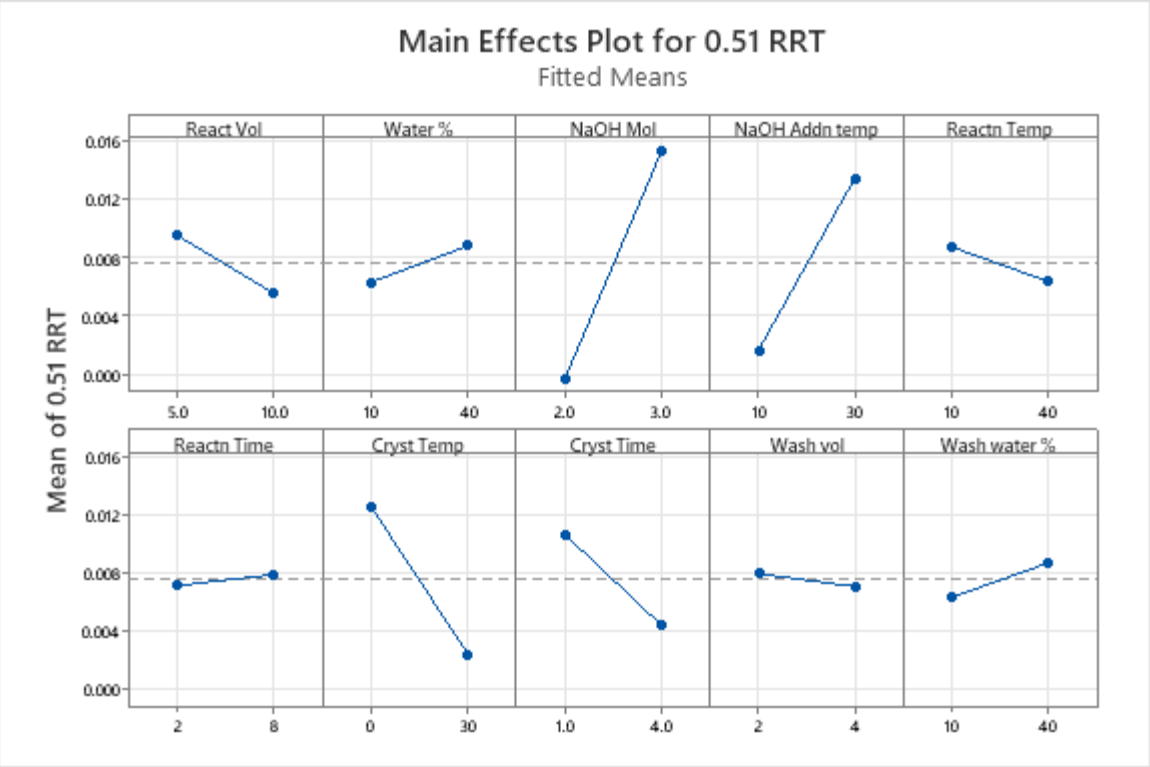


DoE Analysis

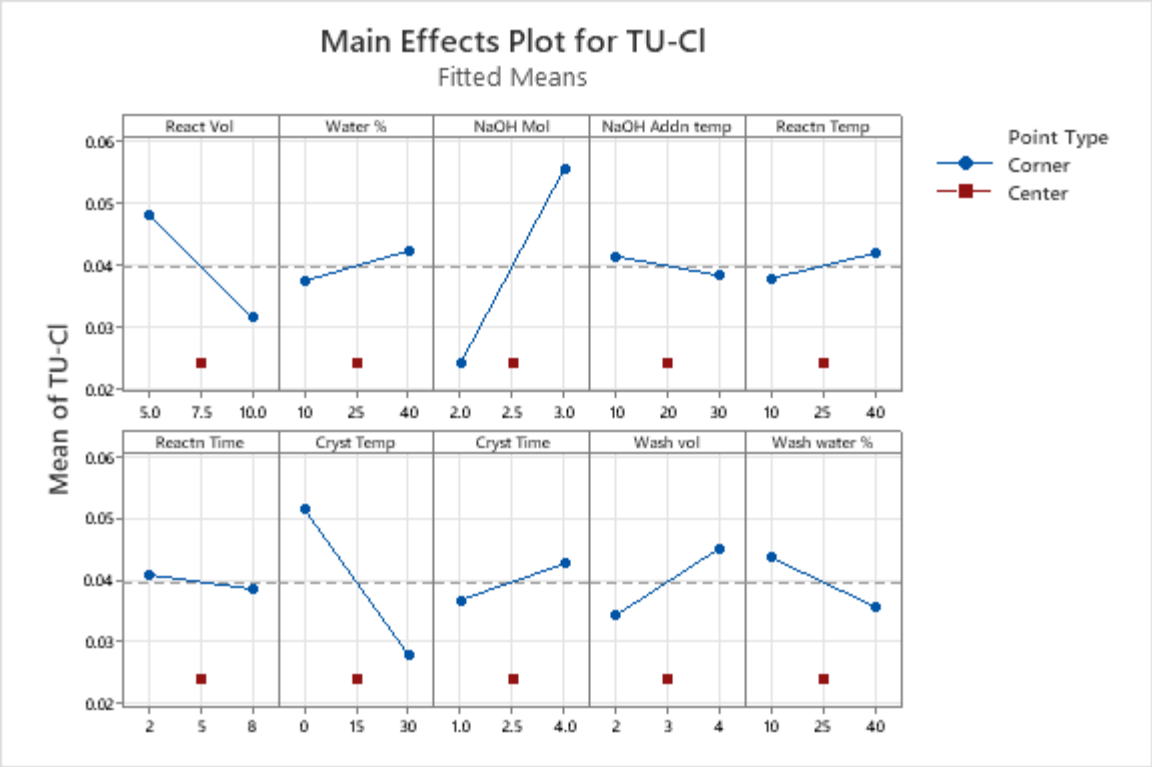


DoE Analysis

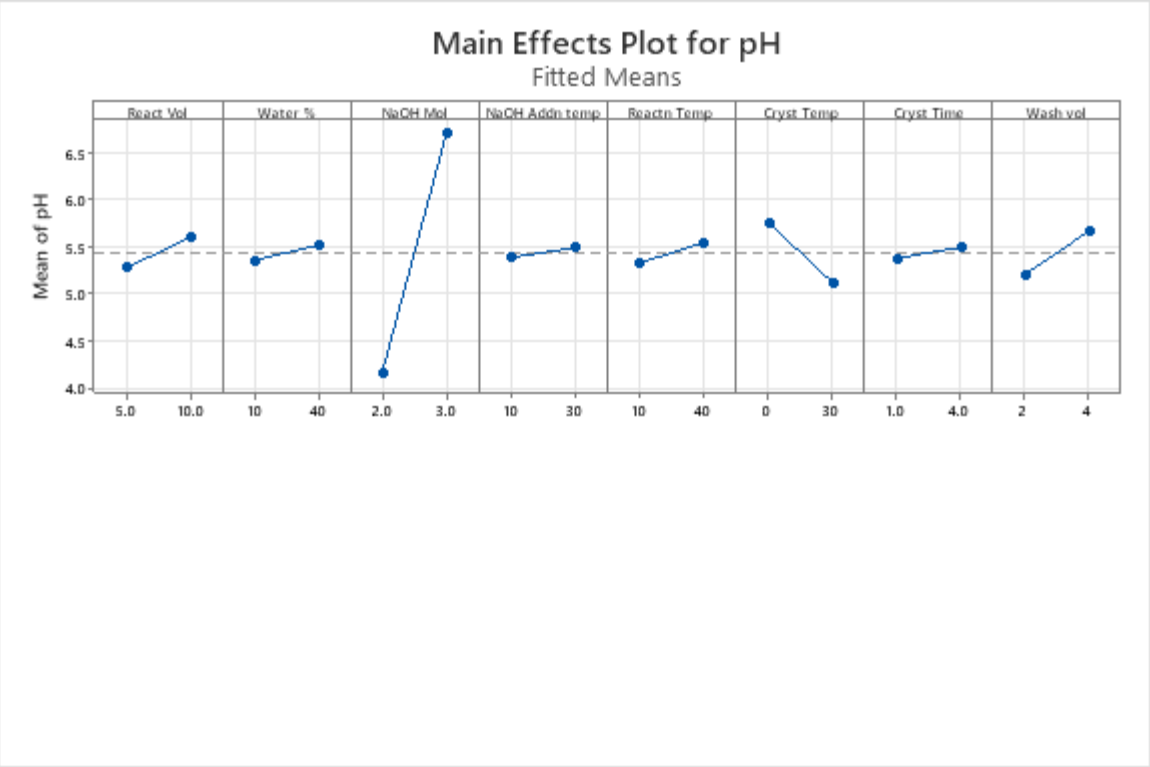
DoE Analysis



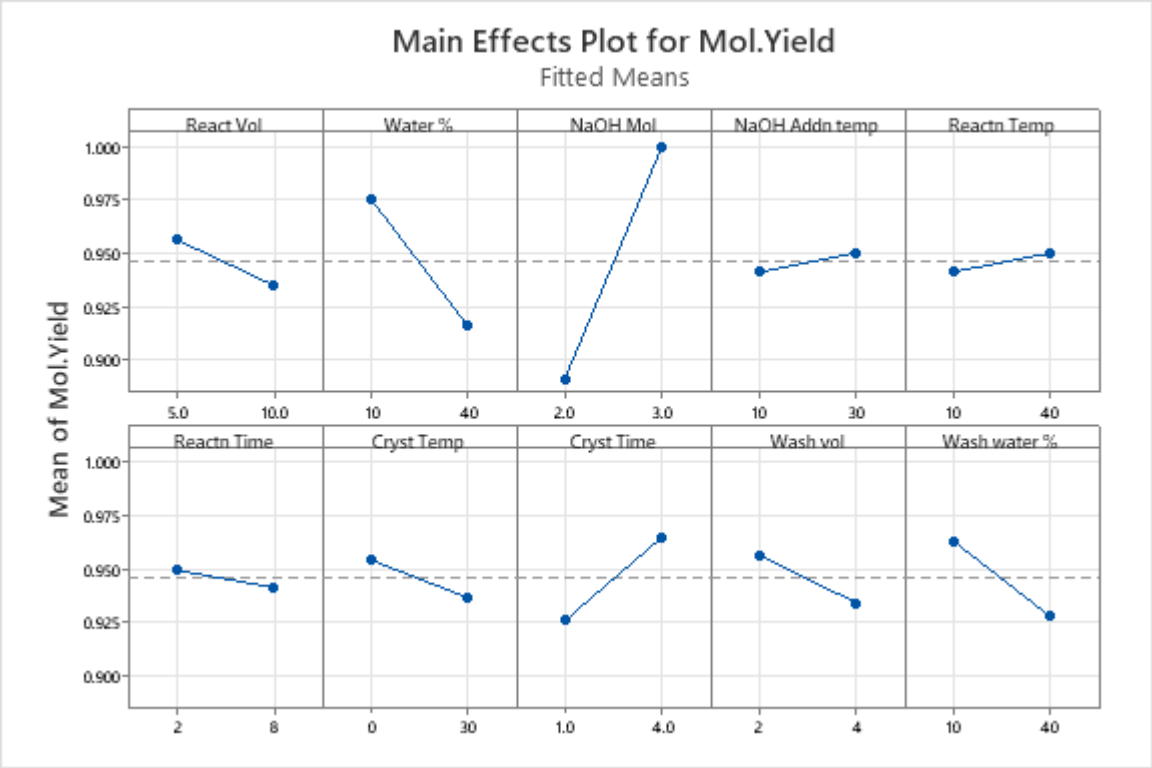
DoE Analysis



DoE Analysis



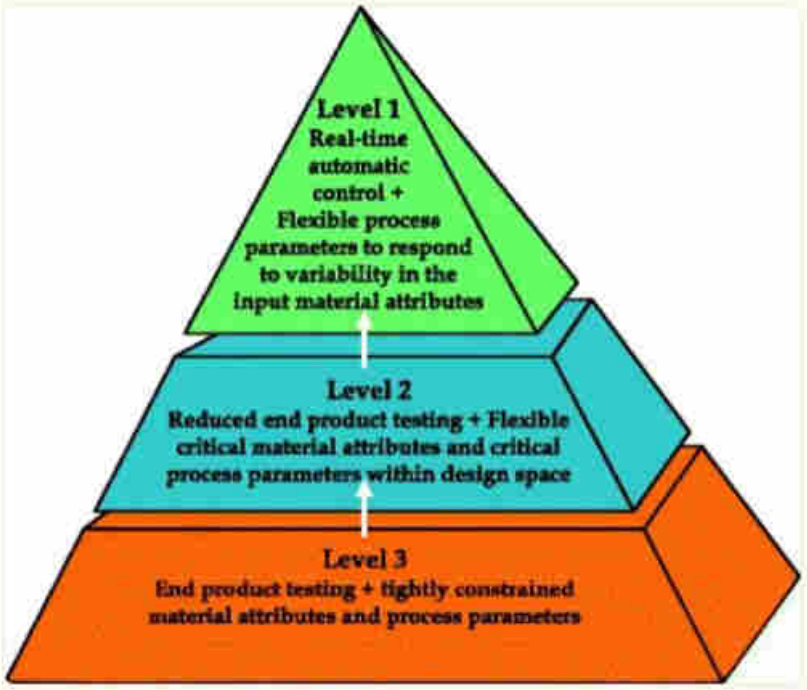
DoE Analysis



Control Strategy

- Control of input material attributes (*e.g.*, Starting materials, Intermediates, drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or product quality
- In-process or real-time release testing in lieu of end-product testing (*e.g.*, measurement and control of CQAs during processing)
- A monitoring program (*e.g.*, full product testing at regular intervals) for verifying multivariate prediction models

Control Strategy



Level 1 utilizes automatic engineering control to monitor the CQAs of the output materials in real time. This level of control is the most adaptive. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs consistently conform to the established acceptance criteria.

Level 2 consists of pharmaceutical control with reduced end-product testing and flexible material attributes and process parameters within the established design space.

Level 3 This control strategy relies on extensive end-product testing and tightly constrained material attributes and process parameters

Process Capability and Continuous Improvement

- Define the problem and the project goals, specifically
- Measure key aspects of the current process and collect relevant data
- Analyze the data to investigate and verify cause-and-effect relationships.
- Improve or optimize the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

Traditional Vs QbD Approach

troikaa
Imagine . Innovate

Aspect	Traditional Approach	QbD Approach
Overall Pharmaceutical Development	• Empirical • Process development using OFAT • Know-Hows	• Systematic • Process developed using multivariate approach • Design Space
Manufacturing Process	• Fixed; often run on suboptimal parameters or at the edge of failure • Focused on optimization and reproducibility	• Adjustable within the Design Space • Focus on control strategy and Robustness
Process Controls	• In-process testing (Go/NoGo) • Offline analysis	• PAT tools are used to feed back and process parameter controls
Product Specification	• Primary means of control • Based on batch data	• Based on overall quality strategy • Based on desired product performance
Control Strategy	• Intermediate and end product testing	• Product quality is ensured by risk based control strategy • Quality controls shifted upstream
Lifecycle Management	• Reactive problem solving • Investigation and CAPA based on personal experience	• Statistical data based investigation • Continuous improvement

Advantages of Quality by Design in Pharmaceutical Manufacturing

- Better understanding of the process and the product
- Better understanding of risks involved & mitigation
- Minimizing variations to achieve consistency in manufacturing quality.
- More flexible regulatory approaches for example: Manufacturing changes within the approved design space can be without regulatory review or approval.
- Timely launch of products
- Right first time & every time concept
- Reduction of post-approval submission
- Greater regulator confidence of robust products
- Less recalls from market.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Continuous improvement over the total product life cycle
- Real time Release thru PAT implementation.
- Better return on investment / cost savings.
- More efficient technology transfers

Quality Culture

troikaa
Imagine . Innovate

Quality Culture is the foundation to implement QbD successfully

- Commitment to quality: Including establishing effective pharmaceutical quality systems & maintaining, modernizing as needed, equipment and facilities.
- Adopt a “Quality Culture”: Stress importance of product quality from the top down. Decision making with end-user / patient in mind
- Proactively monitoring products and processes: Using risk- based approaches and modern analytical methods
- Invest in quality and continuous improvement: Quality can pay for itself!
- Need for conviction from Leadership and Management team
- Training and re-training of technical teams; QbD should start from the R&D
- Do away with market specific product strategy. Harmonize and produce the best quality product that serve all markets.

  High quality products are not always expensive.
- Need to continually upgrade our manufacturing and quality systems

THANK YOU