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QUALITY BY DESIGN (QBD) IS NOVEL APPROACH FOR RISK ASSESSMENT OF ORAL LIQUID FORMULATIONS

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ABSTRACT

Quality by design (QbD) is employed to develop generic formulations that are therapeutically equivalent to the reference product. The initial formulation quality target product profile (QTPP) was established by considering the properties of the drug substance, conducting a literature survey, characterizing the reference product, and taking into account the reference product label and the intended patient population. The identification of critical quality attributes (CQA's) was determined by considering the safety and efficacy of the product. Our research during the development of pharmaceuticals focused on the CQA's that could be affected by a realistic alteration to the drug product formulation or manufacturing process. For the test product, these CQA's included appearance, pH, viscosity, sedimentation rate, dissolution, uniformity of dosage units, related substances, assay and preservative content for liquid oral formulations. Risk assessment is employed throughout the development process to identify variables that may pose a high risk to the formulation and process. This helps determine the required studies to gain a comprehensive understanding of the product and process, enabling the development of an effective control strategy. Each risk assessment is revised after development to capture the decreased level of risk due to our enhanced product and process understanding. This new approach to drug development offers flexibility and efficiency, providing important benefits from a business perspective throughout the entire product's life cycle. By implementing quality by design (QbD), continual improvement can be achieved as it provides a systematic approach to product and process development.

KEYWORDS: Quality by design (QbD), Quality target product profile (QTPP), Critical quality attributes (CQA), Risk assessment, Control strategy, One factor at time (OFAT).

INTRODUCTION

Introduction

What is the concept of quality by design (QbD)?

It is a systematic approach to development that starts with clearly defined goals and focuses on understanding products and processes, as well as implementing effective control measures, all while ensuring scientific rigor and quality risk management. By adopting this approach to development, sponsors can effectively showcase the knowledge acquired during the process, while also leveraging their existing understanding of the product and process to demonstrate and document their comprehension.

To assure the quality of the product, a comprehensive approach provided by QbD should be embraced. QbD is defined in the ICH Q8 guideline as a systematic approach to development that starts with clearly defined objectives and places emphasis on understanding both the product and the process, as well as implementing effective quality risk management.[1] Quality by design (QbD) not only ensures the safety and effectiveness of drug supply for consumers but also holds the potential to greatly enhance manufacturing quality performance.

Advantages of QbD

Benefits for industry

1. Better understanding of the process.
2. Fewer batch failures.
3. Enhanced innovation due to the capability to enhance processes.
4. More streamlined and productive management of change.
5. Return on investment / cost savings.

6. An enhanced quality by design (QbD) approach to pharmaceutical development offers possibilities for more adaptable regulatory frameworks.
7. Any modifications made to the approved design within the specified boundaries would not require additional regulatory scrutiny.
8. The number of submissions made after approval was decreased.
9. For the consumer, greater product consistency.
10. Increased product accessibility and decreased rejections/ Failures.
11. Fewer investigations, improved yields, lower lost, reduced testing etc.
12. The time to market reductions have been significant, with some companies achieving a reduction from 12 to 6 years.
13. First time correct: asset management.
14. Improved technology transfer to manufacturing.
15. Less stringent regulatory oversight and fewer post-approval submissions.
16. Throughout the entire product life cycle, there should be a continuous effort to improve and maintain control over the variability, with the guidance of the patients.
17. Absence of design freeze (no variation issues).
18. Lower validation burden.
19. Time-sensitive controls (fewer batch controls).
20. Pragmatic risk perceptions.
21. Plays a significant role in achieving the goals of better, more affordable and safer transportation.

Elements of pharmaceutical development

Quality target product profile **(QTPP)**

The quality target product profile (QTPP) is a comprehensive overview of the quality attributes of a drug product, aiming to achieve the desired quality while considering safety and efficacy.

The QTPP is an essential part of a QbD approach and serves as the foundation for designing the generic product. For ANDAs, the target should be identified early in development based on the characterization of the drug substance, properties of the drug product and consideration of the drug label and the intended patient population.[8]

The QTPP encompasses all product attributes that are necessary to ensure equivalent safety and efficacy to the RLD.

The QTPP guides assist formulation scientists in developing formulation strategies and maintaining a focused and efficient formulation process. QTPP is related to identity, dosage form, assay, purity, and stability in the label. For example, a typical QTPP of an immediate release solid oral dosage form would consist of.

- Oral syrup, solution/suspension, or tablet Characteristics
- Identity
- Purity/impurity
- Assay and uniformity
- Stability, and
- Disintegration.

The quantity of a generic drug can be easily calculated from the reference listed drugs (RLD). In addition to other available information from scientific literature and possibly the pharmacopeia, the QTPP can be utilized to establish product specifications to some extent even before the product is developed. Having well-defined and top-notch product specifications enhances the objectivity and efficiency of the product and process design and development. Based on the clinical and pharmacokinetic (PK) characteristics as well as the in vitro dissolution and physicochemical characteristics of the RLD, A quality target product profile (QTPP) was defined for model drug oral solution/suspension, 1mg/ml as described in table.[9]

Table No. 1: Quality Target Product Profile (QTPP) for Model drug oral solution/Suspension.

QTPP Elements	Target	Justification
Physical Attributes		
Dosage Form	Solution/Suspension	Pharmaceutical equivalence requirement: Dosage form same as per reference product.
Dosage Design	Oral, Aqueous Solution/Suspension	
Dosage Strength	1mg/ml	Pharmaceutical equivalence requirement: required to match reference product strengths.
Appearance	For Oral Solution/Suspension: A White to off white colored aqueous, homogenous Solution/Suspension with an Tutti-fruiti flavor.	To ensure patient compliance and maintain physical similarity.
	For Packaged Drug Product: 150ml of drug product filled in amber polyethylene terephthalate (PET) bottle with cap and liner.	
Odor	Tutti-fruiti flavor	Similar to reference product; to

		ensure patient acceptability and maintain physical similarity.
Deliverable Volume	The average volume of liquid obtained from the 10 containers is not less than 120 mL, and the volume of no container is less than 114 mL	Should deliver the required volume of the dose that is declared on the label of the reference product.
pH	Between 4.0 and 6.0	To ensure patient compliance and maintain physical similarity.
Viscosity of formulation (cps)	Between 50and 150 centipoise	
Sedimentation rate only for suspension	Not more than 1ml of clear liquid is found	
Chemical Attributes		
Identification	**By HPLC :**The retention time of the Principal peak in the chromatogram of the sample preparation should correspond to that of Active drug peak in the chromatogram of the standard preparation as obtained in the test of Assay. **By HPLC for Preservative contents:** In the Assay, the preservative peak in the chromatogram obtained with sample solution shows a peak with the same retention time as the preservative peak in the chromatogram obtained with standard solution.	To ensure clinical effectiveness and safety
Assay	Not less than 90.0% and Not more than 110.0% of the labelled amount of Active drug.	
Related Substances		
Any other individual impurity	Not More Than 0.2%	
Total impurities	Not More Than 1.5%	
Preservative Content	NLT 80.0 % and NMT 110.0 % w/w of the labelled amount of Preservative content.	
Dissolution in 0.1 N HCl, Paddle, 50rpm, 900ml	Not less than 80% (Q) of the labelled amount is dissolved in 30minutes.	To ensure clinical effectiveness and safety and need to ensure batch to batch consistency.
Uniformity of dosage units (Content uniformity) (By HPLC)	Criteria 1 : Acceptance value NMT 15.0 when determined on 10 dosage units Criteria 2 : Acceptance value NMT 15.0 when determined on 30 dosage units and No dosage units is less than 0.75M and more than 1.25M	To ensure clinical effectiveness and safety.
Polymorphism	The initial polymorphic form of the drug substance in finish product should be intact throughout shelf life.	
Packaging and Storage		
Container closure system	**PET Bottle Description:** 120ml (28mm) Amber PET Bottle **Cap Description:** 28mm CRC closure (Foam liner)	To achieve target shelf life.
Label claim	Each ml Solution/Suspension contains 1 mg active drug.	Pharmaceutical equivalence requirement

Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Neurogenic detrusor over activity in pediatrics.	Pharmaceutical equivalence requirement: same indication
Administration/concurrence with labeling	Should be administered on an empty stomach. Shake well before use.	Pharmaceutical equivalence requirement: same indication
Stability	At least 24 month shelf life at room temperature.	Needed to ensure stability during shelf life. Equivalent to or better than reference product shelf life

Critical quality attributes (CQA)

Critical quality attribute (CQA) as outlined by ICH 8 (R2) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are commonly linked to raw materials (drug substance, excipients), intermediates (in-process materials), and the final drug product. The characteristics of a drug product that are crucial for its performance, including quality, safety, and efficacy, are known as CQAs.[7]

The identification of CQA can be done by utilizing previous knowledge and/or quality risk management (QRM). Previous knowledge can be gained through literature review, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event reports, and recalls. Quality risk management, on the other hand, utilizes different tools to identify and prioritize potential risks.[3]

The quality of liquid oral dosage forms is primarily influenced by factors such as purity, strength, drug release, and stability. CQAs for other delivery systems can additionally include lot of product specific aspects, corresponding to aerodynamic properties for inhaled products, sterility for parenteral, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (eg., particle size distribution, bulk density) that affect drug product CQAs.

Potential drug product CQAs derived from the quality target product profile and/or previous knowledge is used to guide the product and process development. The list of potential CQAs will be changed once the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be employed to determine the order of potential CQAs for further analysis. Relevant CQAS can be identified by an iterative process of quality risk management and experimentation that assesses the extent to that their variation will have an impact on the quality of the drug product.[1]

Table summarizes the quality attributes of model drug oral solution/suspension and indicates that attributes were classified as drug product critical quality attributes (CQAs). For this product, assay, content uniformity (CU), dissolution and degradation products are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, are going to be investigated and discussed in detail in subsequent formulation and process development studies. On the other hand, CQAs including residual solvents, identity, and microbial limits which are unlikely to be impacted by formulation and/or process variables will not be mentioned well within the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.[9]

The quality attributes of generic active drug oral solution/suspension 1mg/ml and indicates which attributes were classified as drug product CQAs. For this product description, pH, viscosity, dissolution, uniformity of dosage units, related substances, palatability, stereo chemical impurity, assay and preservative content were identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, will be investigated and discussed in detail in subsequent formulation and process development studies.

On the other hand, CQAs including identification, elemental impurities, residual solvents, deliverable volume, sedimentation rate and polymorphism identification which are unlikely to be impacted by formulation and/or process variables will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.

Table No. 2: Critical Quality Attributes (CQAs) of Model drug Oral Solution/Suspension.

Quality Attributes of the Drug product	Target	Is this a CQA?	Justification
Physical Attributes			
Dosage Form	Solution/Suspension	No	General product requirement
Dosage Design	Oral, Aqueous Solution/Suspension	No	
Dosage Strength	1mg/ml	No	
Appearance	For Oral Solution/Suspension: A White to off white coloured aqueous, homogenous Solution/Suspension with Tutti-fruiti flavor. For Packaged Drug Product: 100ml of drug product filled in amber polyethylene terephthalate (PET) bottle with cap and liner.	No	To ensure patient compliance, maintain physical similarity to ideal Solution/Suspension and patient acceptability
Odor	Tutti-fruiti flavor	No	
Deliverable Volume	The average volume of liquid obtained from the 10 containers is not less than 120mL, and the volume of no container is less than 124 mL.	Yes	Should deliver the required volume of the dose that is declared on the label of the reference product.
pH	Between 4.0 and 6.0	Yes	To ensure patient compliance and maintain physical, chemical & drug product stability.
Viscosity of formulation (cps)	Between 100 and 200 centipoise	Yes	
Sedimentation rate only for suspension	Not more than 1ml of clear liquid is found	No	
Chemical Attributes			
Identification	**By HPLC:** The retention time of the Principal peak in the chromatogram of the sample preparation should correspond to that of Solifenacin peak in the chromatogram of the standard preparation as obtained in the test of Assay. **By HPLC with diode array detector:** UV spectra of the Solifenacin peak of sample solution and the Solifenacin peak of Standard solution should match and exhibit maxima at the same wavelengths. **By HPLC for Sodium benzoate:** In the Assay, the Sodium benzoate peak in the chromatogram obtained with sample solution shows a peak with the same retention time as the Sodium benzoate peak in the chromatogram obtained with standard solution.	Yes*	To ensure clinical effectiveness and safety
Assay	Not less than 90.0% and Not more than 110.0% of the labelled amount of Model drug.	Yes	
Related Substances			
Any other individual impurity	Not More Than 0.2%		General product requirement, Related substances can impact safety and must be controlled based on ICH to limit patient exposure and Preservative content may be critical for safety and efficacy of the drug product.
Total impurities	Not More Than 1.5%		
Preservative Content	NLT 80.0 % and NMT 110.0 % w/w of the labelled amount of Sodium benzoate.	Yes	
Dissolution in 0.1 N HCl, Paddle, 50rpm, 900ml	Not less than 80% (Q) of the labeled amount is dissolved in 30minutes.	Yes	Need to ensure batch to batch consistency with respect to quality

Uniformity of dosage units (Content uniformity) (By HPLC)	Criteria 1 : Acceptance value NMT 15.0 when determined on 10 dosage units Criteria 2 : Acceptance value NMT 15.0 when determined on 30 dosage units and No dosage units is less than 0.75M and more than 1.25M	Yes	To ensure clinical effectiveness and safety.
Microbiological Attributes			
Microbiological Examination of Non-Sterile Products	A) Microbial Enumeration Tests: Total aerobic microbial counts: Not more than 102 cfu per ml Total yeasts and molds counts: Not more than 101cfu per ml B) Test for specified Micro-Organisms: E. coli : Absent/ml	Yes*	Non-compliance with microbial limits will impact patient safety. However as long as raw materials comply with compendia microbial requirements, the formulation and process variables are unlikely to impact this CQA. However the final product will be tested to ensure that the drug product does not support microbial growth.
Antimicrobial effectiveness test	Bacterial count: Not less than 1.0 log reduction from the initial count at 14 days and no increase from the 14 days at 28 days. Yeast and Molds count: No increase from the initial calculated count at 14 and 28 days.	Yes*	Non-compliance with antimicrobial effective test will impact patient safety.
Packaging and Storage			
Container closure system	PET Bottle Description: 120ml (28mm) Amber PET Bottle Cap Description:28mm CRC closure (Foam liner)	No	To achieve target shelf life.
Label claim	Each ml Solution/Suspension contains 1 mg of Model drug.	No	General product requirement.
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Neurogenic detrusor over activity in paediatrics.	No	General product requirement: same indication
Administration/concurrence with labeling	Should be administered on an empty stomach. Shake well before use.	No	General product requirement: same indication
Stability	At least 24-month shelf life at room temperature.	Yes	Needed to ensure stability during shelf life.

*Formulation and process variables are unlikely to impact the CQAs. Therefore, the CQA will not be investigated and discussed in details in subsequent risk assessment and pharmaceutical development. However, the CQAs remains at target element of the drug product profile and should be addressed accordingly.

Initial risk assessment for critical material attributes of drug substance

A thorough evaluation of the drug substance attributes was conducted to assess their influence on the drug product CQAs. The level of risk associated with each attribute was categorized as high, medium, or low. The high-risk attributes necessitated additional investigation, while the low-risk attributes did not require any further investigation. The level of risk is deemed acceptable given the existing information. Additional investigation may be required for medium-risk situations to minimize the risk. The same ranking system was applied consistently throughout the process of developing new medications. Based upon the physicochemical and biological properties of the drug substance, the initial risk assessment of drug substance attributes on drug product CQAs is shown in below table.[6]

Table No. 3: ***Overview of relative risk ranking system.***

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

Table No. 4: Initial risk assessment of drug substance attributes.

Drug Product CQA	Drug substance attributes						
	Solubility	Assay	Water content	Related substances	Polymorphic Identification	Particle Size Distribution	Residual Solvents
Description	Low	Low	Low	Low	Low	Low	Low
Assay of Model drug	Low	Medium	Low	Low	Low	Medium	Low
Assay of Sodium benzoate	Low	Low	Low	Low	Low	Low	Low
Dissolution	Medium	Low	Low	Low	Medium	Medium	Low
Related substance	Low	Low	Low	High	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low
Viscosity	Low	Low	Low	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low	Low	Low	Low
Palatability	Low	Low	Low	Low	Low	Low	Low

Table No. 5: Justification for the initial risk assessment of the drug substance.

Drug Substance Attributes	Drug Product CQA's	Initial Risk Assessment	Justification
Solubility	Description	Low	API is BCS class I hence solubility does not affect description, since the drug substance is uniformly dispersed during manufacturing of Solution/Suspension. Therefore, risk is assigned as low.
	Assay of Model drug	Low	This attribute is unrelated to the Assay of model drug, Assay of Sodium benzoate in the drug product. Hence risk is rated as Low.
	Assay of Sodium benzoate		
	Dissolution	Medium	As a result, the solubility of the model drug will not affect the dissolution process. However, during manufacturing of drug product model drug is complexed with beta-cyclodextrin to mask bitter taste of drug substance. Consequently, the dissolution of drug-B- cyclodextrin complexes should be carefully observed. Therefore, the level of risk is considered to be Medium.
	Related Substances	Low	Solubility of Model drug API is unrelated to Related substances, pH, Viscosity, Content uniformity and palatability of finished product. Therefore, risk is Low.
	pH		
	Viscosity		
	Content Uniformity		
	Palatability		
Assay	Description	Low	This attribute is not related to the Description of the drug product. Therefore, risk is rated as low.
	Assay of Model drug	Medium	Assay of model drug medium variation in the assay of input drug substance will affect the final product assay Before the drug substance is given to patients, assay compensation is performed. However, it is necessary to assess the initial and long-term stability of the drug product through assay testing. Therefore, risk is rated as medium.
	Assay of Sodium benzoate	Low	This attribute is unrelated to the assay of sodium benzoate, dissolution, related substances, pH, viscosity, content uniformity, impurity and palatability of the drug product. Therefore, risk is rated as low.
	Dissolution		
	Related Substances		

	pH Viscosity Content Uniformity Palatability		
Water content	Description	Low	This attribute is not related to the description of the drug product. Therefore, risk is rated as low.
	Assay of Model drug Assay of benzoate Dissolution Related Substances pH Viscosity Content Uniformity Palatability	Low	The water content of the drug substance is controlled within the specified limit of NMT 0.5%. This specification will not affect the experiment. Additionally, it is important to assess compensation before dispensing based on the water content of the API to guarantee that the input API meets the label claim. Therefore, risk is rated as low.
Related Substances	Description Assay of Model drug Assay of Sodium benzoate Dissolution pH Viscosity	Low	This attribute is not related to the description, assay of API, assay of sodium benzoate, pH, viscosity and dissolution of the drug product. Therefore, risk is rated as low.
	Related Substances	High	Model drug API is susceptible to oxidative degradation; hence stability may impact the related substances of API in finished product. Therefore, risk is High.
	Content Uniformity Palatability	Low	This attribute is unrelated to the Content uniformity and palatability of finished product. Therefore, risk is Low.
Polymorphic Identification	Description Assay of Model drug Assay of Sodium benzoate	Low	This attribute is not related to the description, assay of API, assay of sodium benzoate in the drug product. Therefore, risk is rated as low
	Dissolution	Medium	Different solubility profile and having different dissolution profile Drug manufacturers consistently provide the crystalline API throughout the development process, Hence, risk is assigned as medium.
	Related Substances pH Viscosity Content Uniformity Palatability	Low	This attribute is unrelated to the Related substances, pH, Viscosity, Content uniformity and palatability of the drug product. Hence risk is assigned as low.
Particle Size Distribution	Description	Low	This attribute is unrelated to the Description in the drug product. Hence risk is assigned as low.
	Assay of Model drug	Medium	Higher particle size of Model drug may have impact on solubility and complexation with B-cyclodextrin which may impact on assay of drug product. Model drug exhibits high solubility across the physiological pH range including water. Hence the solubility of Model drug will not have any impact on the Assay. However, need to be evaluated on finished product. Thus, risk considered is Medium.
	Assay of Sodium benzoate	Low	This attribute is unrelated to the Assay of Sodium benzoate in the drug product. Hence risk is assigned as low.
	Dissolution	Medium	Model drug exhibits high solubility across the physiological pH range including water. Hence the solubility of Model drug will not have any impact on the Dissolution. However, it is complexed with B-cyclodextrin. Hence need to be evaluated on finished product. Thus, risk considered is Medium.

	Related Substances	Low	Model drug is solubilized in water and complexed with B-cyclodextrin thus API particle size does not have any impact on Related substances, pH, Viscosity, Content uniformity and palatability of the drug product. Therefore, risk is assigned as low.
	pH		
	Viscosity		
	Content Uniformity		
	Palatability		
Residual Solvents	Description	Low	API residual solvent does not have any impact on Description, Assay of API, Assay of Sodium benzoate, Dissolution, Related substances, pH, Viscosity, Content uniformity and palatability. Therefore, risk is assigned as low.
	Assay of Model drug		
	Assay of Sodium benzoate		
	Dissolution		
	Related Substances		
	pH		
	Viscosity		
	Content Uniformity		
	Palatability		

Table No. 6: Updated risk assessment of the drug substance.

Drug Product CQA	**Drug Substance Attributes**						
	Solubility	**Assay**	**Water content**	**Related substances**	**Polymorphic Identification**	**Particle Size Distribution**	**Residual Solvents**
Description	Low	Low	Low	Low	Low	Low	Low
Assay of Model drug	Low	Low*	Low	Low	Low	Low*	Low
Assay of Sodium benzoate	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low*	Low	Low	Low	Low*	Low*	Low
Related substance	Low	Low	Low	Low*	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low
Viscosity	Low	Low	Low	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low	Low	Low	Low
Palatability	Low	Low	Low	Low	Low	Low	Low

***** The initial level of risk is reduced to Low

Table No. 7: Justification for the updated risk assessment of the drug substance.

Drug Substance Attributes	**Drug Product CQA's**	**Initial Risk Assessment**	**Updated Risk Assessment**	**Justification**
Solubility	Dissolution	Medium	Low	Risk of solubility of Active drug associated with the dissolution is reduced by solubilization of API in water and then complexation with B- cyclodextrin throughout the development. Dissolution profile of finished product, release more than 80 % drug in 30 minutes. Hence, risk is reduced from medium to low.
ssay	Assay of Active drug	Medium	Low	Sodium vapor lamp is used during dispensing and manufacturing of complexation part of Active drug. Assay compensation is done before dispensing of API. Assay is evaluated in initial and stability specification of finish product and found to be passing as per defined specification. Hence risk reduced from medium to low.

Drug Substance Attributes	Drug Product CQA's	Initial Risk Assessment	Updated Risk Assessment	Justification
Related substance	Related substance	High	Low	As per stability data on development batch, the total impurities are well within defined specification. Hence, risk is reduced from high to low.
Polymorphic identification	Dissolution	Medium	Low	During manufacturing of Solution/Suspension, active drug is solubilized in water and then complexed with B- cyclodextrin under stirring. Dissolution profile on initial and stability of development batch meets defined specification. Hence risk reduced form medium to low.
Particle Size Distribution	Assay of Active drug	Medium	Low	During manufacturing of batches particle size of D(90) NMT 140microns is used. However active drug is solubilized in water during manufacturing. Assay and dissolution of finished product meets the defined specifications hence risk reduces to low.
	Dissolution	Medium		

Risk assessment of formulation component attributes

Initial risk assessment for formulation variables

Initial risk assessment was done based on the literature, characteristic of API and prior knowledge of formulation development on liquid oral dosage forms. Initial risk assessment for formulation variables is mentioned in the below table.

Table No. 8: Initial risk assessment of formulation component attributes.

Drug Product CQA's	Formulations Variables										
	Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose	Xantun Gum	Sodium benzoate	Xylitol	Sucralose	B- cyclodextrin	Simethicone Emulsion 30%	Citric Acid monohydrate	Taste masking agent	Tutti-fruiti flavour	Purified Water
Description	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Assay of Model drug	Low	Low	Low	Low	Low	Low	Low	Medium	Low	Low	Low
Assay of Sodium benzoate	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Medium	Medium	Low	Low	Low	Medium	Low	Low	Low	Low	Low
Related Substances	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low

Viscosity	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Medium	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low
Palatability	Low	Low	Low	Medium	Medium	High	Low	Low	Medium	Medium	Low

Table No. 9: Justification for the initial risk assessment of formulation component attributes.

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Justification
Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose	Description	Low	Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose is used as suspending agent in the formulation and quantity of Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose will not impact Description, Assay of API, Assay of sodium benzoate of finished product. Therefore, risk is considered as low
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Medium	Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose is used as suspending agent in the formulation. Being used as suspending agent it imparts viscosity in formulation hence used quantity may impact dissolution of finished product. Hence risk is considered as medium.
	Related Substances	Low	Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose is used as suspending agent in the formulation and quantity of Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose will not impact Related substances and pH of finished product. Hence risk is considered as low.
	pH	Low	
	Viscosity	High	Being used as suspending agent in the formulation quantity of Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose will impact the Viscosity and Uniformity of dosage units in finished product. Hence, risk is considered as high for Viscosity and medium for Uniformity of dosage units.
	Content Uniformity	Medium	
	Palatability	Low	Palatability, stereochemical impurity and will not impact formulation material attribute hence risk assigned is low.
Xantun Gum	Description	Low	Xantun Gum is used as viscosity building agent in the formulation and quantity of Xantun Gum will not impact Description, Assay of API, Assay of sodium benzoate of finished product. Hence risk is considered as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Medium	Xantun Gum is used as viscosity building agent in the formulation which may delay API solubility in dissolution media and quantity of Xantun Gum will impact dissolution of finished product. Hence risk is considered as Medium.
	Related Substances	Low	Xantun Gum is used as viscosity building agent in the formulation and quantity of Xantun Gum will not impact Related substances and pH of finished product. Hence risk is considered as low.
	pH	Low	
	Viscosity	High	Xantun Gum is used as suspending agent in the formulation, and level of Xantun Gum impacts the Viscosity and Uniformity of dosage units in finished product. Hence, risk is considered as high for
	Content Uniformity	Medium	

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Justification
			Viscosity and medium for Uniformity of dosage units.
	Palatability	Low	Palatability, Stereochemical Impurity and will not impact formulation material attribute hence risk assigned is low.
Assay of Sodium benzoate	Description	Low	Sodium benzoate content in the formulation is very less, and it will not impact the Description and Assay of API in finished product, hence risk is assessed as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	High	Suboptimal quantity of Sodium benzoate leads to microbial contamination in the formulation, and it will impact the Assay of Sodium benzoate in the finished product. Hence risk is assessed as high.
	Dissolution	Low	Sodium benzoate content in the formulation is only relevant to the control of microbial growth in the formulation. It is also compatible with the other excipients in the formulation and hence will not impact the Dissolution, Related substances, pH, Viscosity, Content Uniformity, palatability and Stereochemical impurity of the finished product as the level in the finished product is very less; hence risk is assessed as low.
	Related Substances	Low	
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Low	
Xylitol And Sucralose	Description	Low	Xylitol and Sucralose in the formulation are used as sweetener and will not impact the description, assay of API, Assay of Sodium benzoate Dissolution, Related substances, pH, Viscosity, content Uniformity and stereochemical impurity of the finished product, hence risk is assessed as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Low	
	Related Substances	Low	
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Medium	Sweetness being a parameter for palatability needs to be evaluated. Hence risk assigned as Medium.
Beta cyclodextrin	Description	Low	Model drug is bitter in taste. Beta cyclodextrin is added as taste masking agent in the formulation, hence level will not impact Description, Assay of API, Assay of sodium benzoate of the finished product. Hence risk is considered as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Medium	Beta cyclodextrin being a taste masking agent it forms complexation with Model drug which may impact on dissolution. Hence risk assigned as medium.
	Related Substances	Low	Model drug is bitter in taste. Beta cyclodextrin is added as taste masking agent in the formulation, hence level will not impact Related substance, pH, viscosity and content uniformity and stereochemical impurity of the finished product. Hence risk is considered as low.
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	High	Bitterness of API is a parameter for palatability need to be evaluated. Hence risk assigned as High.
Simethicone Emulsion 30%	Description	Low	Simethicone Emulsion 30% is added as anti-foaming agent in the formulation, hence Simethicone Emulsion 30% level will not impact Description, Assay API, Assay of Sodium benzoate, Dissolution, Related substances, pH, Viscosity, Content Uniformity, palatability and stereochemical impurity
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Low	

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Justification
	Related Substances	Low	of finished product. Hence risk is considered as low.
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Low	
Citric Acid Monohydrate	Assay of Model drug	Medium	Citric acid is used to adjust pH of final Solution/Suspension. The level of citric acid in the formulation will have impact on impurities which will impact on assay of finished product, hence risk is assessed as Medium.
	Description	Low	Citric acid is used to adjust pH of final Solution/Suspension. The level of citric acid in the formulation will not impact the Description, Assay of Sodium benzoate and dissolution of finished product, hence risk is assessed as low.
	Assay of Sodium benzoate	Low	
	Dissolution	Low	
	Related Substances	High	Citric acid being a pH modifier may impact Related substances in the finished product, hence risk is assessed as High.
	pH	High	Citric acid is used as pH modifier in the formulation; the suboptimal concentration leads to impact on the pH of the finished product; hence risk is assessed as high.
	Viscosity	Low	As the level of citric acid in the formulation will not impact the Viscosity, Content Uniformity, palatability and Stereochemical impurity and of the finished product, hence risk is Low.
	Content Uniformity	Low	
	Palatability	Low	
Taste masking agent	Description	Low	Taste masking agent is added as reducing bitterness in the formulation, hence taste masking agent level will not impact Description, Assay of API, Assay of Sodium benzoate, Dissolution, Related substances, pH, Viscosity, Content Uniformity and stereochemical impurity of the finished product. Hence risk is considered as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Low	
	Related Substances	Low	
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Medium	Quantity of taste masking agent used in Solution/Suspension is a parameter for palatability and need to be evaluated. Hence risk assigned as Medium.
Tutti-fruti Flavour	Description	Low	Tutti-fruti Flavour is added as flavouring agent in the formulation, hence Tutti-fruti Flavour level will not impact Description, Assay of API, Assay of Sodium benzoate, Dissolution, Related substances, pH, Viscosity, Content Uniformity and stereochemical impurity of the finished product. Hence risk is considered as low.
	Assay of Model drug	Low	
	Assay of Sodium benzoate	Low	
	Dissolution	Low	
	Related Substances	Low	
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Medium	Quantity of Tutti-fruti Flavour used in Solution/Suspension is a parameter for palatability and need to be evaluated. Hence risk assigned as Medium.
Purified Water	Description	Low	These product CQAs are unaffected by purified water since it is used merely as a vehicle for the ingredients of the formulation, hence risk is assessed
	Assay of Model drug	Low	
	Assay of Sodium	Low	

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Justification
	benzoate		as low.
	Dissolution	Low	
	Related Substances	Low	
	pH	Low	
	Viscosity	Low	
	Content Uniformity	Low	
	Palatability	Low	

Update risk assessment of formulation

Table No. 10: Updated risk assessment of formulation component attributes.

Drug Product CQA's	Formulations Variables										
	Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose	Xantun Gum	Sodium benzoate	Xylitol	Sucralose	B- cyclodextrin	Simethicone Emulsion 30 %	Citric Acid monohydrate	Taste masking agent	Tutti-fruiti flavour	Purified Water
Description	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Assay of Model drug	Low	Low	Low	Low	Low	Low	Low	Low*	Low	Low	Low
Assay of Sodium benzoate	Low	Low	Low*	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low*	Low*	Low	Low	Low	Low*	Low	Low	Low	Low	Low
Related Substances	Low	Low	Low	Low	Low	Low	Low	Low*	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low	Low*	Low	Low	Low
Viscosity	Low*	Low*	Low	Low	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Low*	Low*	Low	Low	Low	Low	Low	Low	Low	Low	Low
Palatability	Low	Low	Low	Low*	Low*	Low*	Low	Low	Low*	Low*	Low

***** The initial level of risk is reduced to Low

Table No. 11: Justification for the updated risk assessment of formulation component attributes.

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Updated Risk Assessment	Justification
Microcrystalline Cellulose/ Sodium Carboxymethyl Cellulose	Dissolution	Medium	Low	The concentration of Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose was challenged in the formulation as presented in design of experiments or OFAT trials and were evaluated for dissolution, viscosity and uniformity of dosage unit and results were found to be within defined specification. Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose is compatible with Model drug in drug excipient compatibility study. Hence risk is reduced to low.
	Viscosity	High		
	Content Uniformity	Medium		
Xantun Gum	Dissolution	Medium	Low	The concentration of Xantun gum was challenged in the formulation as presented in design of experiments or OFAT trials and were evaluated for dissolution, viscosity and uniformity of dosage unit and found to be within defined specification. Xantun gum is compatible with Model drug in drug excipient compatibility study. Hence risk is reduced to low.
	Viscosity	High		
	Content Uniformity	Medium		
Sodium benzoate	Assay of Sodium benzoate	High	Low	The concentration ranging from 60%, 80%, 100% and 120% of Sodium benzoate was varied in the formulation was evaluated for assay of Sodium benzoate. It was found that Sodium benzoate with different concentration has no impact on preservative content as well as on microbial quality. Hence risk is reduced from high to low.
Xylitol	Palatability	Medium	Low	The concentration of Xylitol was challenged in the formulation as presented in design of experiments or OFAT trials and were evaluated for palatability, viscosity and uniformity of dosage unit and found to be within defined specification. Xylitol is compatible with Model drug in drug excipient compatibility study. Hence risk is reduced to low.
Sucralose	Palatability	Medium	Low	As mentioned in compatibility study sucralose is compatible with Model drug API. Sweetness being a parameter for palatability was evaluated on different concentration s of sucralose. However finished product analysis found to be within specification limits. Hence risk was reduced from medium to low.
Citric Acid Monohydrate	Assay of Model drug	Medium	Low	Citric acid monohydrate is compatible with Model drug API however there is no impact on assay, pH and related substance on finished product. The initial and stability results well within specification hence risk is reduced to low.
	Related Substances	High		

Formulation Component Attributes	Drug Product CQA	Initial Risk Assessment	Updated Risk Assessment	Justification
	pH	High		
B-Cyclodextrin	Dissolution	Medium	Low	The concentration of B-Cyclodextrin was varied in the formulation was evaluated for dissolution profile and found to be within specification limits. Hence risk is reduced from medium to low.
	Palatability	High	Low	B-cyclodextrin is compatibility with Model drug API. B-Cyclodextrin forms a complex with Model drug which helps in bitter taste masking of drug substance. Palatability of Solution/Suspension was evaluated on volunteers and found to be acceptable. Hence risk was reduced from high to low.
Taste masking agent	Palatability	Medium	Low	Taste masking agent is compatible with Model drug API. Palatability of Solution/Suspension was evaluated on volunteers and found to be acceptable. Hence risk was reduced from medium to low.
Tutti-fruti flavour	Palatability	Medium	Low	Tutti-fruti flavour is compatible with Model drug API. Palatability of Solution/Suspension was evaluated on volunteers and found to be acceptable. Hence risk was reduced from medium to low.

Control strategy

The control strategy is described as a carefully planned set of controls, based on the current understanding of the product and process, which ensures that the process operates effectively and produces high-quality products. The control strategy within the QbD paradigm is determined through risk assessment, considering the importance of the CQA and the process capability. The control strategy will incorporate the following components: procedural controls, controls in the process, lot release testing, characterization testing, process monitoring, comparability testing, and stability testing. It is important to mention that the application of risk assessment in formulating the control strategy is limited to the QbD approach.[2]

A control strategy is created to guarantee that a product of required quality will be consistently manufactured. The elements of the control strategy ought to describe and justify however in-process controls and also the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on a thorough understanding of the product, formulation, and process, and should include, at a minimum, control of the critical process parameters and material attributes.

By adopting a comprehensive pharmaceutical development approach, the process and product understanding will be enhanced, and potential sources of variability will be identified. It is important to identify and understand the sources of variability that can affect the quality of a product, and then take steps to control them. Recognizing the sources of variability and their influence on downstream processes, in-process materials, and drug product quality will provide an opportunity to shift controls upstream, thereby reducing the need for end product testing. By combining knowledge of products and processes with quality risk management, it is possible to control the process in a way that compensates for variations in raw materials, ensuring consistent product quality.

This understanding of the process can lead to a new way of manufacturing where the variability of the materials used can be less restricted. Instead, it will be feasible to create an adaptive process step (a step that adjusts based on the input materials) with effective process control to ensure consistent product quality.

A deeper comprehension of the product's performance will provide sufficient evidence to support the adoption of alternative methods to verify that the material is fulfilling its quality requirements. The utilization of these alternatives could potentially facilitate real-time release testing. Real-time release testing will replace end product testing, but it does not replace the review and quality control steps required under GMP to release the batch. A control strategy will encompass, but is not limited to, the following:

i. The control of input material attributes, such as drug substances, excipients, and primary packaging

materials, is based on an understanding of their influence on the process ability or product quality.

ii. Product specification(s)

iii. Controls for unit operations that can affect downstream processing or product quality (e.g., the impact of drying on degradation, the particle size distribution of the granulate on dissolution).

iv. Instead of conducting end-product testing, in-process or real-time release testing can be used to measure and control CQAs during the processing stage.

v. A monitoring program, such as regular product testing, is implemented to verify the accuracy of multivariate prediction models. (1)

The control strategy for active drug oral solution/suspension is based on the results of comprehensive product and process studies. These studies examined the critical control points (CPPs) and critical manufacturing aspects (CMAs) that were identified as high-risk factors during the initial risk assessment of the drug product. In certain instances, variables that were considered to be of medium risk were also examined. By conducting thorough research and analysis, the CMAs and CPPs were identified, and the acceptable operating ranges were determined. All variables identified as high risk in the initial risk assessment are incorporated into the control strategy since the outcome of the experiments relied on the specific ranges examined. As a result, the control strategy is a comprehensive overview of how quality is ensured by considering the current process and product knowledge. The proposed control strategy for the batches of active drug oral solution/suspension 1mg/ml is outlined and explained in the table below. The control strategy encompasses the high-risk process parameter ranges that were examined during development and scale-up, the observed operating ranges during exhibit batches, and the proposed operating ranges for commercial batches.

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REFERENCES

1. US Food and Drug Administration. Guidance for industry: Q8(R2) pharmaceutical development. US Department of Health and Human Service (FDA, Rockville, MD, 2009.
2. Sandipan Roy, Quality by design: A holistic concept of building quality in pharmaceuticals, Int J Pharm Biomed Res, 2012; 3(2): 100-108.
3. Shashank Jain, Quality By Design (Qbd): A Comprehensive Understanding Of Implementation And Challenges In Pharmaceuticals Development, Int J Pharm Pharm Sci, 2014; 6(1): 29-35.
4. Dr. Bhusnure O.G et al., Formulation & Evaluation of Fast Dissolving Tablet Montelukast Sodium By Using QbD Approach, Indo American Journal of Pharm Research, 2015; 5(03): 1092-1104.
5. ANNEX C: Guidance For Quality by Design as An Alternative Approach to Process Validation.
6. Sonam Ranga et al, A Review On Design Of Experiments (DoE), International Journal of Research and Reviews in Pharmacy and Applied science, 2013; 3(6): 867-882.
7. Chaudhari Rakesh et al., Quality By Design (QbD): An Emerging Paradigm For Development Of Pharmaceuticals, International Journal of Pharmacy, 2014; 4(2): 138-146.
8. Roy Connolly, Vaishali Ketkar, consideration for strategic partnering with CRO/CMOs: Incorporating QbD In Product Development is key to success, Pharmaceutical online the magazine.
9. Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms, Food and Drug Administration.www.GenericDrugs@fda.hhs.gov.
10. Lawrence X. Yu, Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control, Pharmaceutical Research, 2008; 25(4): 781-79.
11. Amit S. Patil, Anil M. Pethe, Quality by Design (QbD): A new concept for development of quality pharmaceuticals, International Journal of Pharmaceutical Quality Assurance, 4(2): 13-19.1. 1.
12. Gibson, M., Product Optimization: Pharmaceutical Pre-formulation and Formulation. Taylor & Francis, New York, 2001.
13. V. S. Chopra, Mayank Nagar, A study over effects of process parameters on quality attributes of a tablet by applying quality by design, Scholars Research Library- Der Pharmacia Letter, 2010; 2(2): 370-392.