Regulatory Note

Generic Development of Topical Dermatologic Products, Part II: Quality by Design for Topical Semisolid Products

Rong-Kun Chang,^{1,2} Andre Raw,¹ Robert Lionberger,¹ and Lawrence Yu¹

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Abstract. The emergence of quality by design as a relatively new systematic science and risk-based approach has added a new dimension to pharmaceutical development and manufacturing. This review attempts to discuss the quality by design elements and concepts applied for topical semisolid products. Quality by design begins with defining a quality target product profile as well as critical quality attributes. Subsequently, this is followed by risk identification/risk analysis/risk evaluation to recognize critical material attributes and critical process parameters, in conjunction with design of experiments or other appropriate methods to establish control strategies for the drug product. Several design-of-experiment examples are included as practical strategies for the development and optimization of formulation and process for topical drug products.

KEY WORDS: dermatologic product; generic; quality by design; semisolid; topical product.

INTRODUCTION

In recent years, the Food and Drug Administration (FDA) has emphasized “Quality by Design” (QbD) as a current Good Manufacturing Practices (cGMP) initiative for the twenty-first century. Despite numerous presentations and publications by FDA officials and leading pharmaceutical researchers (1–10), several pilot programs (11,12), and the adoption of QbD by the International Conference on Harmonization, misunderstanding about QbD is still prevalent throughout pharmaceutical, biotechnology, and medical device industries. This article points out the basic components of QbD and application of QbD concepts to develop formulations and optimize manufacturing processes for topical dermatologic products.

The opinions expressed in this review by the authors do not necessarily reflect the views or policies of the Food and Drug Administration (FDA).

¹ Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 7500 Standish Place, Rockville, Maryland 20855, USA.

² To whom correspondence should be addressed. (e-mail: richard.chang@fda.hhs.gov)

ABBREVIATIONS: Q1, Same components as the reference-listed drug; Q2, Same components in same concentration as the reference-listed drug; Q3, Same components in same concentration with the same arrangement of matter (microstructure) as the reference-listed drug; RLD, Reference-listed drug; QbD, Quality by design; QbT, Quality by testing; CMA, Critical material attribute; CPP, Critical process parameter; DoE, Design of experiments; QTPP, Quality target product profile; CQA, Critical quality attribute; FMECA, Failure mode effects criticality analysis; FMEA, Failure mode effects analysis.

The basic premise of QbD is that a product cannot be tested or inspected into a quality product and quality attributes should be designed *via* the thorough understanding of raw materials, formulation, and manufacturing process into a drug product. Additionally, under quality by testing (QbT), the sample size for each stage of testing is generally insufficient to ensure acceptable quality attributes for an entire batch. Hence, under QbD, testing confirms acceptable quality attributes, without extensive sampling. Specifications from raw materials, active ingredients, in-process testing, and drug product are only part of the quality control strategy. The quality needs to be designed into a drug product based upon a systematic understanding of how critical material attributes (CMAs) of drug substance and excipients, and critical process parameters (CPPs) used during manufacturing affect critical quality attributes of the drug product. This type of understanding can be achieved using various QbD tools including the use of risk assessment, design of experiments (DoE), and process analytical technologies (PAT) and subsequently, based on this understanding, control strategy as a set of control can be adopted for drug product quality assurance. The International Conference on Harmonization (ICH) guidelines: Pharmaceutical Development (Q8), Quality Risk Management (Q9), and Pharmaceutical Quality System (Q10) are the corner stone of QbD. The emergence of QbD as a relatively new systematic science and risk-based approach has added a new dimension to pharmaceutical development and manufacturing. Since pharmaceutical sciences are multidisciplinary, many scientific disciplines, such as medicine, pharmacy, chemistry, engineering, biology, mathematics, and statistics can all contribute to product development, process optimization, and quality improvement. Likewise, it takes a well-organized team to have a successful drug product development using the QbD concept.

SYNOPSIS OF QUALITY BY DESIGN

QbD begins with defining a quality target product profile (QTPP) as well as critical quality attributes (CQAs). This is followed by risk identification of the proposed formulation and manufacturing process on drug product critical quality attributes and risk assessment to identify putative critical material attributes and critical process parameters that need to be investigated. Screening DoE can be used as a tool to identify CMAs and CPPs. Then response surface DoE can be applied to explore formulation and process spaces for these CMAs and CPPs. Knowledge gained from DoE studies inform a control strategy that implements the optimized manufacturing process within an acceptable range/design space to consistently deliver a high-quality drug product. This approach also encourages the use of process analytical technology tools to monitor and adjust the process to compensate for raw material or process variability. An appropriate combination of some or all of the QbD tools may be applicable to formulation optimization, single-unit operation optimization, or to the entire manufacturing process to ensure process intermediate and end-product quality assurance. Finally, in the commercial production stage, QbD calls for continual improvement, *i.e.*, tracking, trending, and adjusting of process operations and statistical process control, as well as models and design space maintenance/update.

QUALITY TARGET PRODUCT PROFILE AND CRITICAL QUALITY ATTRIBUTES

The physicochemical characterization of the reference-listed drug (RLD), its packaging insert, and labeling provides the foundation to define the quality target product profile of the generic drug product, which in turn forms a development goal with specific elements and justifications. Having the same components (Q1), in same concentration (Q2), with the same arrangement of matter (microstructure) (Q3), the RLD is the most rational approach to formulate a generic dermatological product (13). However, topical products are not generally required to have a formulation that is qualitatively and quantitatively (Q1/Q2) the same as the RLD for Abbreviated New Drug Application (ANDA) filing. For various reasons, the generic firm may choose to formulate the generic product with a different excipient composition to the brand product. In these cases, it may be necessary to perform formulation optimization using experimental designs, depending on the extent of deviation from the RLD formula. In addition to formulation optimization, process development studies may also be needed to achieve a similar arrangement of matter as the RLD, which provides assurance of similar critical quality attributes to those of the RLD. Microstructure sameness includes similar rheology, type of emulsion (O/W emulsion, W/O emulsion, globule size), state of drug in semisolid system (drug form, solubilized drug *vs.* dispersed solid drug, and particle size of drug particles) compared to those of the RLD.

Table I provides an example of QTPP and CQAs for Flurouracil Cream, USP 5%. CQAs, which are a subset of the QTPP that have the potential to be altered by formulation and process variables, are essential attributes that need to be

closely monitored to gain assurance of Q3 microstructure similarity to the RLD. These CQAs may include rheological behavior, drug particle size, comparative flux, and type of emulsion. These CQAs can affect the permeation of the drug through skin, skin retention of cream, and patient acceptability. Based upon the QTPP and CQAs at the end of development, meaningful drug product specifications based on clinical performance can be achieved and an acceptable control strategy can be implemented to ensure equivalent safety and efficacy to the RLD.

RISK ASSESSMENT AND RISK CONTROL

Many risk assessment methods mentioned in ICH guideline Q9 can be considered in pharmaceutical development and manufacturing. For example, a failure mode effects criticality analysis (FMECA) model can be developed to screen process risks due to raw material variability. The model examines the various potential failure risks (*e.g.*, particle size, morphology, and polymorph of active ingredient; acid value, viscosity, and gelling property of associated excipients) and associated potential failure effects (*e.g.*, failure to meet content uniformity, drug product viscosity, and impurity level requirements). Based on development data and prior knowledge, the severity of impact of each failure along with the probability of occurrence needs to be evaluated and action plans can be developed to address significant factors related to raw material variations, *i.e.*, critical material attributes (CMAs) to mitigate these risk factors. Table II gives an example summarizing the risks identified through such an assessment with the action plans to reduce the impact of raw material variability on drug product critical quality attributes. Similarly, other risk assessment methods, such as Ishikawa diagram, Failure Mode Effects Analysis (FMEA), what if analysis, fault tree analysis, process map and flow chart, may be applied to identify the risk factor(s) for the proposed manufacturing process. In general, the failure modes involved in the manufacturing process for topical dosage forms may include the following:

- Failure of assay test
- Lack of homogeneity of the drug product
- Undesirable rheological properties
- Undesirable globule size (emulsion type preparation only)
- Undesirable drug particle size (drug dispersion type preparation only)
- Undesirable *in vitro* drug release rate
- Physical instability, which may include coalescence of globules, phase separation, and growth of drug particles
- Chemical instability of the drug and excipients
- Microbiological contamination

Appropriate application of risk assessment principles to the proposed manufacturing process can be helpful in prioritizing and focusing the pharmaceutical development to enhance product quality attributes (*e.g.*, satisfactory content uniformity, assay value close to 100% label claim, desired rheological properties, desired drug particle size

Table I. QTPP and CQA for Fluorouracil Cream USP, 5%

Elements	Target	Justification	CQA items
Dosage form	Cream	Pharmaceutical equivalent requirement	
Route of administration	Topical	Pharmaceutical equivalent requirement	
Dosage strength	5% w/w	Pharmaceutical equivalent requirement	
Dosage design	Oil in water emulsion cream with fluorouracil dispersed in the cream base	Match RLD	
Appearance	White smooth cream with dispersed fluorouracil API	Match RLD and for patient acceptability	
Identification	Positive for fluorouracil	Needed for clinical effectiveness	CQA ^c
Assay	90–110%	Needed for clinical effectiveness	CQA
Impurities	Impurity A: NMT 0.2% Impurity B: NMT 0.2% Any individual unknown: NMT 0.2% Total impurities: NMT 0.5%	Needed for safety	CQA
Homogeneity and tube uniformity	Top, middle and bottom of three containers Nine assay values should be within 90.0% to 110.0% label claim and RSD is not more than 5%.	Needed for clinical effectiveness	CQA
Physical attributes ^a	Match RLD	Needed for clinical effectiveness and patient acceptability	CQA
Rheological behavior		Required to demonstrate Q3	
Fluorouracil particle size			
Oil globule size			
<i>In vitro</i> release test ^b	Match RLD	Required to demonstrate Q3	CQA
Preservatives content	Methyl Paraben: 80.0–110.0% label claim Propyl Paraben: 80.0–110.0%	Needed for ensuring antimicrobial effectiveness	
Microbial limits	Meet USP <61>	Needed for safety	CQA ^c
Residual solvents	Meet USP <467>	Needed for safety	CQA ^c
Container closure system	Identical primary packaging to RLD	Match RLD and for patient acceptability	
Package integrity	No failure	Needed for stability, clinical effectiveness and safety	
Stability	No less than 24-month expiration dating period	Match the shelf life of RLD	

Note that generic drug products should meet pharmaceutical equivalence, bioequivalence, safety and commercial requirements

^a Physical Attributes may include the following: appearance, odor/irritant, rheological attributes (particle size, viscosity, specific gravity, globule size, spreadability) and pH as applicable

^b Flux assay using either porcine ear or synthetic membrane or cadaver skin

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

and globule size, and desired flux rate) and apply control strategies to mitigate risks. For example, the risk of microbiological contamination can be mitigated by microbial testing of the finished product and by monitoring the preservative content to ensure that the preservative level is higher than the established minimum limit. This risk can be further minimized by microbial testing of all raw materials and by an environmental monitoring program for the manufacturing and packaging areas. If generic firms put their efforts toward developing the aforementioned mitigation strategies for these risks and there is no trend and no evidence of failure in these CQAs there may be less need to implement a control strategy in batch release to monitor microbiological attributes in the finished drug product.

In another example, if a proposed manufacturing process calls for the emulsification of aqueous and oil phases to form a cream base and subsequent dispersion of the drug substance into the cream base through powder eduction and a rotor-stator type homogenizer,

the drug powder addition rate, rotor stator gap, rotor speed and homogenization time are relatively critical factors (*i.e.*, CPPs) that may impact the homogeneity of the drug product. Initial risk assessment for process development is displayed in Table III showing the potential for each unit operation to affect various CQAs. Table IV gives an example of risk assessment for assay failure and lack of homogeneity using FMECA which is a more quantitative analysis of how each parameter would affect these CQAs and ranks these upon the severity, probability, and detectability. In using this approach, it is essential to quantitatively evaluate each risk thoroughly to identify the risk factors associated with the manufacturing process.

SCREENING DESIGN EXPERIMENT TO IDENTIFY CRITICAL FACTORS

Following the initial risk assessment, a screening design experiment, such as fractional factorial designs (*i.e.*,

Table II. Raw Material Risk Assessment and Action Plans

Formulation component	Potential risk	Potential impact on drug product CQAs	Action plan
Drug substance	Particle size or morphology change	Shift in content uniformity, drug release and dermal distribution of the drug	Micronized drug substance with identical solid state form to the RLD from a qualified source is used for the drug product manufacturing and particle size is measured as part of drug substance release testing with a tight limit of D90 of not more than 10 μ m Drug concentration in the cream preparation needs to be monitored to ensure homogeneity of drug distribution in the drug product matrix
White petrolatum	Viscosity variation	Shift in viscosity	White petrolatum from a qualified source is used for the drug product manufacturing. Consistency is measured as part of every white petrolatum lot <i>via</i> release testing using more stringent limits than USP limits (consistency value 100 to 200 vs. USP limits 100 to 300) to ensure product viscosity closely matching that of the RLD.
Propylene Glycol	Unidentified	—	—
stearyl alcohol	Variation in stearyl alcohol content	Shift in viscosity	Each lot of stearyl alcohol should contain not less than 90.0% of stearyl alcohol. Monitor and trend viscosity of the product.
Polysorbate 60	Unidentified	—	—
Methyl and propyl Paraben	Possible chemical instability of preservatives in the cream	Shift in preservative content in the cream	The antimicrobial properties of the drug product are studied during the product development stage through antimicrobial effectiveness test. Based on the results from these microbial studies, set an adequate lower limit of preservative content for drug product release and stability specifications to reduce the risk of microbial contamination.
Purified water	Increased water activity and bacteria growth potential	Drug product microbial limit	Quality system, cGMP

resolution III and IV), Plackett–Burman designs, or Taguchi orthogonal arrays can be used to evaluate the relative importance of the process variables. The following is a hypothetical six-factor problem concerning a cream product using a 12-run Plackett–Burman design. The variables for the experiments along with actual two-level experiment conditions and code are listed as follows: mixer speed (100 rpm (–1) and 300 rpm (+1)), mixing time (10 min (–1) and 20 min (+1)), rotor–stator gap (10 mm (–1) and 20 mm (+1)), powder eduction rate (slowest machine setting (–1) and fastest machine setting (+1)), rotor speed (1,000 rpm (–1) and 2,000 rpm (+1)), and homogenization time (10 min (–1) and 30 min (+1)). Various responses (*e.g.*, content uniformity, viscosity, globule size, and drug particle size) can be measured after each randomized experiment is carried out. Table V illustrates a factor effect computation for this 12-run Plackett–Burman screening design to rank the relative importance of various input process parameters on bulk uniformity (defined as %RSD, calculated by the standard deviation of 10 assay values divided by mean assay value). When analyzing this data, a 95% confidence interval for a factor effect including zero means that the factor effect is essentially zero and not significant statistically. Such results are suggestive of only three important factor

effects (*i.e.*, powder eduction rate, rotor speed, and homogenization time) that affect blend uniformity and need further investigation.

When invoking these screening designs, several DoE software packages, such as Statgraphics, Design Expert, Design-Ease, and JMP, can simplify complicated problem solving and interpretation of the results. For example, the factor effect analysis *via* JMP-9 software similarly reports that powder eduction rate, rotor/stator gap and homogenization time are three significant factor effects through the statistics table, Pareto chart, and half normal chart (14). By invoking this computation, the process parameters that show strong relationships to CQAs (*i.e.*, %RSD) are likely CPPs and should become a key focus point of a thorough study during process optimization. Other CQAs such as viscosity and globule size can be similarly evaluated through the same procedure and it was found that there is no significant factor effect for these responses. This is suggestive that unlike bulk uniformity, these CQAs are not significantly impacted by the process parameters investigated within the range of the studies. It should be pointed out that although other screening designs such as a fractional factorial design can be used, Plackett–Burman designs have been mentioned here because they are available in more convenient sizes (*e.g.*,

Table III. Initial Risk Assessment for Process Development

Drug product CQA	Manufacturing operation				
	Pharmacy	Aqueous phase	Oil phase	Emulsification	Drug powder eduction phase
Appearance	Low	Low	Low	Medium	Medium
Assay	High	Low	Low	Low	Low
Impurities	Low	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low	High
Drug particle size	Low	Low	Low	Low	High
Viscosity	Low	Low	Low	Medium	High

Note for relative risk ranking system: *Low* broadly acceptable risk; no further investigation is needed. *Medium* risk is accepted; further investigation may be needed in order to reduce the risk. *High* risk is unacceptable; further investigation is needed to reduce the risk

12-, 20-, 24-, 28-, 36-, and 24-run foldover design, *etc.*) and generally allow the experimenters to efficiently screen a large number of variables in a small number of trials. One should be aware that there is a major drawback associated with these designs, *i.e.*, all interactions are confounded with main effects.

RESPONSE SURFACE OPTIMIZATION, DESIGN SPACE, AND CONTROL STRATEGY

Subsequently, QbD calls for response surface optimization using identified significant process variables from screening experiments. Many response surface designs, such as central composite and Box–Behnken designs can be utilized to find the optimum process conditions for drug product. In general, central composite and Box–Behnken designs are efficient, compared to three-level factorial designs. When deciding upon a particular DOE design, it is important to have an understanding of critical design issues (*e.g.*, variables and levels, center points, randomization, blocking, replication, responses, and transformations) and an understanding of advantages and drawbacks to each approach. Central composite designs are usually preferred because many types of central composite designs can be selected, the quadratic effects are much better estimated, the designs are more robust against missing data, and it is possible to use the corner and center point trials from previous conducted factorial experiments. Box–Behnken design can simplify execution of the experiments due to its three levels of each factor and its missing corner may be useful when the experimenter should avoid combined factor extremes. One should be aware that larger number of center points are necessary for uniform precision and face-center designs and a single missing data point may lead to the inability to estimate an interaction for Box–Behnken design (15–17).

The following is a hypothetical three-variable central composite design to explore the effects of powder eduction rate, rotor speed, and homogenization time on blend uniformity. Table VI shows a JMP-9 face-center cube central composite design with three center points along with %RSD response values; Fig. 1 shows parameter estimates by JMP-9 software along with the prediction equation and contour plots for the study. These plots can be used to guide the selection of process parameters

(and ranges) to avoid failure of blend uniformity and to achieve the optimized %RSD for the drug product. The design space at the batch scale for DoE can be defined in this case as the three-dimensional combination and interaction of these process parameters that have been demonstrated to provide assurance of product quality, *e.g.*, blend uniformity % RSD less than 5. As a consequence, any process falling within the design space should be acceptable and gain regulatory flexibility, provided QbD experimentation is carried out at the manufacturing scale. Furthermore, the developed mathematic model would need to be verified and validated using an independent data set to gain assurance of the multivariate predictive properties. For optimization of multiple responses, trade-offs are often necessary to find a set of independent variable levels that yield the best set of responses. Table VII displays the application of control strategies based upon the identified design space to reduce the identified risks in process parameters.

In accordance with QbD principles, sponsors should have a mechanistic understanding of the major degradation pathways of the API in their formulation. The forced degradation studies carried out during the method validation activities for the related substances are useful to pinpoint the degradation pathway. Based upon this understanding, sponsors should take appropriate steps to limit this degradation with appropriate excipient control, formulation design, manufacturing process, and container/closure choices, especially given that stability problems are significantly exacerbated when dealing with topical drug products. The need to control pH, add a chelating agent, incorporate an antioxidant, and provide protection from light *via* container/closure selection in the RLD, give a hint of instability of the drug in the formulation matrix. Other than the formulation strategies used for the RLD, it is prudent to put special attention to the grade of excipients, including possible reactive residues of excipients (*e.g.*, peroxides) and extractables/leachables of container/closure system, because these minor differences may trigger significant chemical degradation. Furthermore, variation of raw materials, for example acid value variation of excipients, may shift the chemical stability of drug product. When chemical stability is a concern DoE can be utilized as a tool during formulation optimization. The following is a hypothetical 2^2 factorial design to investigate the effect of acid value variation for two

Table IV. Risk Assessment Using Failure Mode Effects Criticality Analysis for Lack of Homogeneity

Category ^a	Process parameter	Mode of failure	Cause of failure	Effect of failure	S ^b (1–5)	P ^c (1–5)	D ^d (1–5)	RPN ^e SxPxD	C ^f rank
Lack of homogeneity	Raw material weighing	Weighing error of material	Lack of cGMP training	Wrong amount of material in the batch manufacturing	5	1	1	5	8
	Temperature for mixing aqueous and non-aqueous phases ^g	Temperature out of the range	Lack of process monitoring	Temperature higher than the range may cause instability of materials; temperature lower than the range may cause to form a non-homogeneous mixture.	3	2	1	6	7
	Mixing speed	Mixing speed out of the range	Lack of process monitoring	Mixing speed higher than the range may cause excessive air entrapment; mixing speed lower than the range may cause a non-homogeneous mixture.	3	2	1	6	6
	Mixing time	Mixing time out of the range	Lack of process monitoring	Mixing time higher than the range may cause excessive air entrapment and instability of materials; mixing time lower than the range may cause a non-homogeneous mixture.	3	2	2	12	5
	Powder eduction rate	Powder eduction rate out of the range	Lack of process monitoring	Potential impact on content uniformity of the drug	4	2	2	16	3
Rotor stator gap	Rotor stator gap	Rotor stator gap out of the range	Lack of process monitoring	Impact on content uniformity of the drug	3	2	2	12	4
	Rotor speed	Rotor speed out of the range	Lack of process monitoring	Potential impact on content uniformity of the drug	4	3	2	24	2
	Homogenization time	Homogeni-zation time out of the range	Lack of process monitoring	Potential impact on content uniformity of the drug	4	4	2	32	1

Note that temperature for mixing aqueous and non-aqueous phases is based on the melting points for the raw materials to ensure all the ingredients are in solution or molten state (*i.e.*, in the current case, temperature range is targeted at 75°C). The cream base is cooled to 25°C to 30°C, before dispersion of the drug substance to the cream base

^a Need to expand to other categories, for example, viscosity and particle size

^b Severity (in the 1–5 scale, 1 means the least severe case and 5 means the most severe case)

^c Probability (in the 1–5 scale, 1 means the case with the least probability and 5 means the case with the most probability)

^d Detectability (in the 1–5 scale, 1 means the case with lowest detectability and 5 means the case with highest detectability)

^e Risk priority number (risk priority number is a product of severity, probability, and detectability. High RPN suggests the criticality of the process parameter on CQA, lack of homogeneity.)

^f Criticality rank

^g Note that temperature for mixing aqueous and non-aqueous phases is based on the melting points for the raw materials to ensure all the ingredients are in solution or molten state (*i.e.*, in the current case, temperature range is targeted at 75 °C). The cream base is cooled to 25 °C to 30 °C, before dispersion of the drug substance to the cream base.

Table V. Factor Effect Computation for 12-Run Plackett–Burman Design

Trial #	Mean	Mixing speed	Mixing time	Rotor stator gap	Eduction rate	Rotor speed	H. time	Unassigned factors					Response (%RSD)
		X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	
1	+	+	+	+	+	+	+	+	+	+	+	+	4.5
2	+	–	+	–	+	+	+	–	–	–	+	–	5.1
3	+	–	–	+	–	+	+	+	–	–	–	+	4.2
4	+	+	–	–	+	–	+	+	+	–	–	–	4.8
5	+	–	+	–	–	+	–	+	+	+	–	–	5.9
6	+	–	–	+	–	–	+	–	+	+	+	–	1.2
7	+	–	–	–	+	–	–	+	–	+	+	+	6.9
8	+	+	–	–	–	+	–	–	+	–	+	+	6.2
9	+	+	+	–	–	–	+	–	–	+	–	+	2.5
10	+	+	+	+	–	–	–	+	–	–	+	–	3.8
11	+	–	+	+	+	–	–	–	+	–	–	+	6.2
12	+	+	–	+	+	+	–	–	–	+	–	–	7.2
Sum +	58.5	29.0	28.0	27.1	34.7	33.1	22.3	30.1	22.6	28.2	27.7	30.5	
Sum –	0	29.5	30.5	31.4	23.8	25.4	36.2	28.4	35.9	30.3	30.8	28.0	
Check Sum	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	
Difference	58.5	–0.5	–2.5	–4.3	10.9	7.7	–13.9	1.70	–0.7	–2.1	3.1	2.5	
Effect	4.99	–0.08	–0.42	–0.71	1.82 ^a	1.28 ^a	–2.32 ^a	0.28	–0.12	0.35	0.52	0.42	
Lower CL		–1.01	–1.34	–1.50	1.25	1.28	–3.01	–0.65	–1.05	–3.03	–0.41	–0.51	
Upper CL		0.85	0.51	0.22	2.45	2.48	–1.81	1.21	0.81	1.28	1.45	1.35	

^a Statistically significant factor effectStandard error of a factor effect, $S_{FE} = ((UFE_1^2 + UFE_2^2 + UFE_3^2 + UFE_4^2 + UFE_5^2)/q)^{1/2} = \{[(0.28)^2 + (-0.12)^2 + (0.35)^2 + (0.52)^2 + (0.42)^2]/5\}^{1/2} = 0.364$, where UFE is unassigned factor effect and q is number of unassigned factors

t value for 95% confidence and 5 degree of freedom=2.57

Plus or minus part of CL (95%)=0.364×2.57=0.93; lower CL=factor effect –0.93 and upper CL=factor effect +0.93

Table VI. Central Composite Design for Investigating Three Process Variables to Minimize %RSD

	Design pattern	Homogenization time (X_1)	Powder eduction rate (X_2)	Rotor speed (X_3)	% RSD (Y) ^a
1	+--	30	-1	1,000	3.6
2	000	20	0	1,500	2.0
3	a00	10	0	1,500	5.8
4	+--+	30	-1	2,000	1.0
5	0A0	20	1	1,500	3.2
6	00a	20	0	1,000	2.6
7	--+	10	1	2,000	7.2
8 ^b	---	10	-1	1,000	5.3
9	000	20	0	1,500	1.6
10	---+	10	-1	2,000	5.9
11	000	20	0	1,500	1.1
12	00A	20	0	2,000	0.9
13	++-	30	1	1,000	5.4
14	0a0	20	-1	1,500	2.2
15	-+-	10	1	1,000	7.5
16 ^b	+++	30	1	2,000	4.5
17	A00	30	0	1,500	2.8

^a Other response values, such as viscosity and API particle size should be evaluated in the same study. The objective of the present study is to minimize %RSD and the acceptable range for %RSD is NMT 5%^b During the outlier checking using Cook's distance test, these points are identified to be suspicious from a statistical perspective. The regression both with and without these outliers is performed. It is determined that there is no significant influence on the results. Therefore, the regression with these data points is presented here

excipients (cetyl ester wax and glyceryl monostearate) used in a cream formulation on chemical stability of a drug. Table VIII shows a 2² factorial design based upon variations in these two excipients along with percent impurity A detected for stability samples stored at 40°C/75% relative humidity (RH) for 6 months. Estimates of factor effects by computation and JMP-9 software are in agreement that acid values for both excipients are statistically significant and interaction of these two factors can be ignored. Figure 2 shows the contour plot of percent impurity A after 6-month storage at 40°C/75% RH versus acid value of cetyl ester wax and acid value of glyceryl monostearate. These studies indicate that a movement toward a region with low acid value of cetyl ester wax and glyceryl monostearate lots is critical to ensure the end product having the level of impurity A below the specification limit of not more than 1% for 6-month samples stored at accelerated conditions. Such studies set the foundation for informing a control strategy on input excipients to ensure acceptable product stability.

Finally, at scale up and commercial batch production, it may be necessary to verify and compare the studies used in development in terms of manufacturing processes, e.g., assessment of equipment used at development stage vs. commercial equipment, as well as the adjustments needed for previously defined process parameters at commercial scale, to inform whether experimentation is needed for conformation or exploration of design space. In other words, the design space and understanding of

Fig. 1. Contour plot of %RSD versus homogenization time, powder eduction rate, and rotor speed along with parameter estimates and the prediction equation

process sensitivities developed in the R&D stage form the foundation for scale-up and production batch manufacturing process development. If projected process parameters are within the design space obtained in the R&D stage (i.e., for situations as the scale-up factor is very low with no equipment change or manufacturing unit operation is

not batch size related), confirmation run(s) is/are needed to verify the validity of the design space at commercial scale. On the other hand, if projected process parameters are far off from the design space generated from R&D batches, experimentation to scrutinize the process parameter effect is encouraged to create a design space for

Table VII. Application of Control Strategy to Mitigate Identified Risks in Process Parameters

Manufacturing operation					
Drug product CQA	Pharmacy	Aqueous phase: RT mixing and heating to 75°C	Oil phase: heating to 75°C and mixing	Emulsification phase: emulsification and cool down	Drug powder eduction phase
Appearance	Low	Low	Low	Low	Low ^a
Assay	Controlled by cGMP training of dispensing personnel and manufacturing workers	Low	Low	Low	Low
Impurities	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Controlled by eduction rate, rotor speed and homogenization time ^b
Drug Particle Size	Low	Low	Low	Low	Low ^a
Viscosity	Low	Low	Low	Low	Low ^a

Note that temperature for mixing aqueous and non-aqueous phases is based on the melting points for the raw materials to ensure all the ingredients are in solution or molten state (i.e., in the current case, temperature range is targeted at 75°C). The cream base is cooled to 25°C to 30°C, before dispersion of the drug substance to the cream base

^a Based on experience and knowledge obtained during process development, risk rating was changed to low risk

^b Response surface optimization was used to provide guidance for the manufacturing parameters to mitigate risk

Table VIII. 2^2 Factorial Design to Investigate the Effect of Acid Value Variation for Cetyl Ester Wax and Glyceryl Monostearate Used in a Cream Formulation on Chemical Stability of a Drug

Run	Design		Observations ^a		Y: average (% impurity A)
	X_1	X_2	Replicate 1	Replicate 2	
1	-1 (1.0) ^b	-1 (1.0) ^c	0.15	0.12	0.135
2	+1 (5.0)	-1 (1.0)	0.95	0.98	0.965
3	-1 (1.0)	+1 (6.0)	1.89	1.95	1.92
4	+1 (5.0)	+1 (6.0)	2.64	2.54	2.59

^a The percent level of Impurity A detected for stability samples stored at 40°C/75% RH for six months

^b Coded X_1 (acid value of cetyl ester wax used in the experiment)

^c Coded X_2 (acid value of glyceryl monostearate used in the experiment)

Coded X_1 =(acid value of cetyl ester wax -3)/2 and coded X_2 =(acid value of glyceryl monostearate-3.5)/2.5

Intercept=(0.135 + 0.965 + 1.92 + 2.59)/4 = 1.4025

Estimate of main effect of factor X_1 = [(0.965 - 0.135) + (2.59 - 1.92)]/2 = 0.75

Estimate of main effect of factor X_2 = [(1.92 - 0.135) + (2.59 - 0.965)]/2 = 1.71

Estimate of interaction effect=[(2.59 - 1.92) - (0.965 - 0.135)]/2 = -0.08

A 95% confidence interval for an effect, based on r replications of a 2^2 factorial design, is estimate effect $\pm (S^2_{\text{pooled}}/r)^{1/2} \times t_{0.025}$, where degree of freedom=4($r-1$) for $t_{0.025}$

The number of replicates is $r=2$ and consulting the t table for $df=4$, we find that $t_{0.025}=2.776$. Then, $(S^2_{\text{pooled}}/r)^{1/2} \times t_{0.025} = (0.001925/2)^{1/2} \times 2.776 = 0.086$, so that X_1 effect=0.75 $\pm$ 0.086, X_2 effect=1.71 $\pm$ 0.086, and interaction=0.08 $\pm$ 0.086. It can be concluded that both factor effects (*i.e.*, acid value for two excipients) seem to be real and the interaction term is not statistically significant. The prediction equation is $Y = 1.4025 + 0.375 X_1 + 0.8525 X_2 - 0.04 X_1 X_2$

scale-up and commercial product batch size to obtain the regulatory flexibility.

CONCLUSION

Across the pharmaceutical industry, the emphasis is on QbD and enhanced knowledge from raw materials (*e.g.*, CMAs) to manufacturing processes (*e.g.*, CPPs),

from QTPP to CQAs, and from risk management to DoE. These new endeavors aim to boost productivity and product quality in the end. The understanding of the myriad roles that QbD plays has pharmaceutical companies looking at drug product development and manufacturing issues in a way they simply could not a few decades ago. This systematic science and risk-based approach will lead to the development of control strate-

Fig. 2. Contour plot of percent impurity A for samples after 6-month storage at 40°C/75% RH versus acid value of cetyl ester wax and acid value of glyceryl monostearate

gies that reliably produce generic drug products with a high quality.

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