Quality by Design (QbD) for Topical Dermatologic Products

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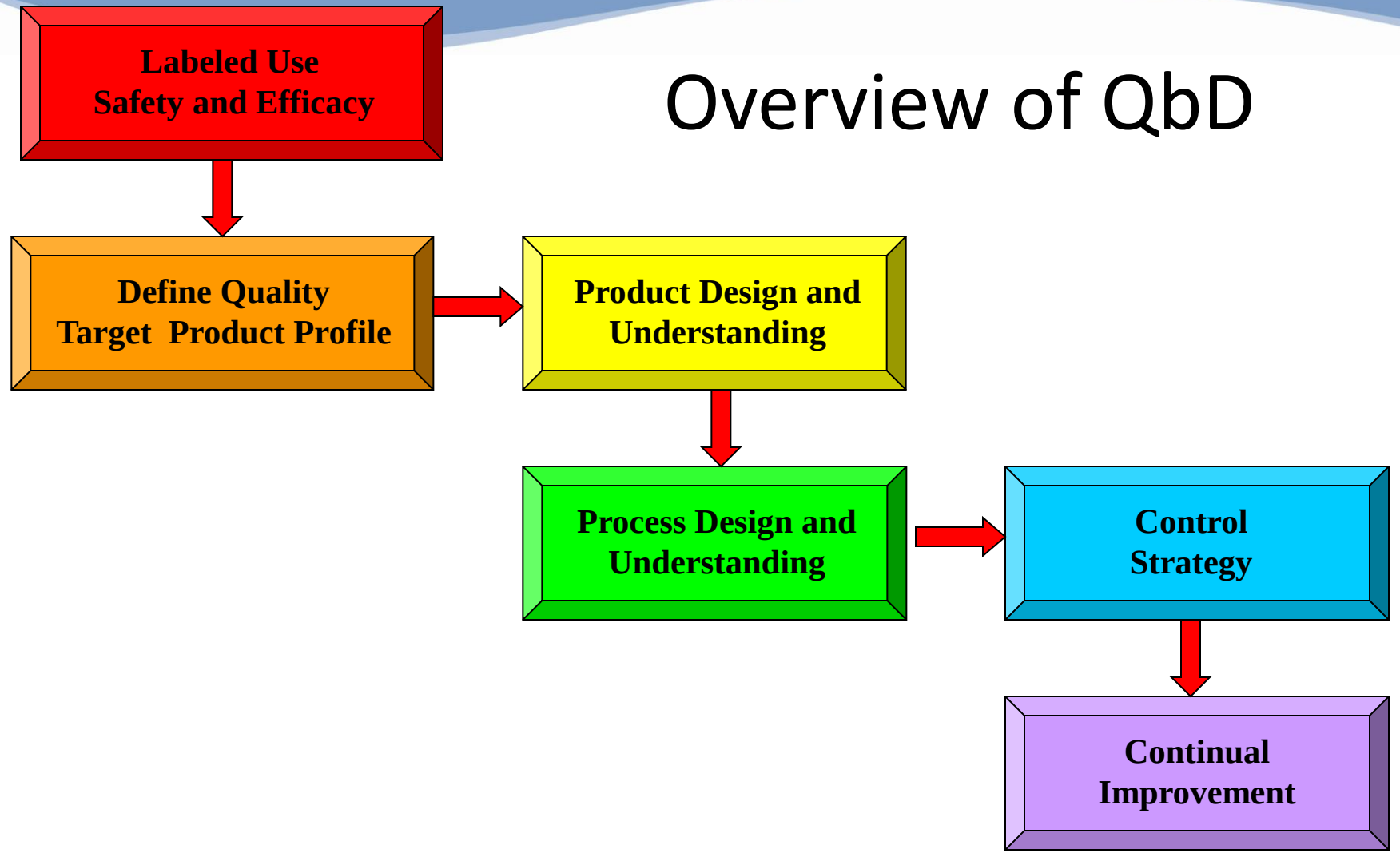
*Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

Quality by Design (QbD)

- ICH Q8(R2) Definition
  - a systematic approach to development
  - begins with predefined objectives
  - emphasizes product and process understanding and process control,
  - based on sound science and quality risk management

Pharmaceutical Quality = f (Drug substance, excipients, manufacturing, and packaging)

Overview of QbD



TARGET → **DESIGN and UNDERSTANDING** → **IMPLEMENTATION**

Topical Products

TABLE 1 Typical Sites of Action and Dosage Forms for Various Topical Routes of Administration

Route of administration	Site of action	Dosage form
Skin	Local or systemic	Aerosols Creams Emulsions Gels Irrigations Lotions Ointments Strips Pastes Powders Solutions Tinctures Suppositories Suspensions Transdermal systems
Eye (ophthalmic)	Local	Emulsions Ointments Solutions Suspensions Strips
Ear (otic)	Local	Emulsions Ointments Solutions Suspensions
Nose (nasal)	Local or systemic	Inhalations Powders Solutions Suspensions
Mouth–(oral respiratory)	Local or systemic	Inhalations
Anus (rectal)	Local or systemic	Aerosols (two-phase, three-phase, and foam) Creams Gels Irrigations Ointments Solutions Suppositories Suspensions
Vagina (vaginal)	Local	Aerosols (two-phase, three-phase, and foam) Creams Gels Ointments Suppositories/pessaries Suspensions Tablets or inserts

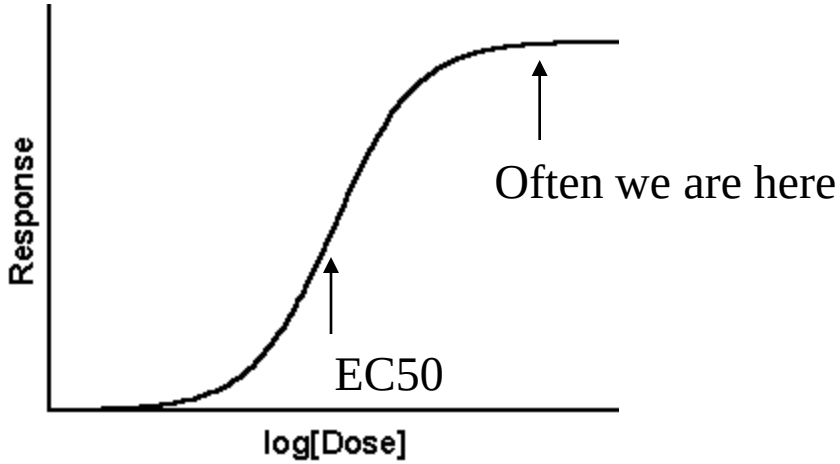
Chapter 3: Topical Drug Products--Development, Manufacture and Regulatory Issues, in *Generic Drug Product Development: Specialty Dosage Forms*, Informa 2010, New York, NY

The Challenges

Generally we account for Formulation Differences to Ensure Equivalent Safety and Effectiveness via Comparative Pharmacodynamic Endpoint (Topical Steroids) or Clinical Endpoint (Most Other Topicals)

However

21 CFR 320.34 Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. <u>This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.</u>



Paradigm Shift

Traditional Approach

ANDA Formulation/Process Submitted Without Context

Claimed to be Acceptable Based Upon a Passing BE study to the RLD

"Equivalence by Testing"

QbD Approach

QTPP/CQA: predefined target

Asks Sponsors How They Systemically Arrived at a Pharmaceutical Equivalent & Bioequivalent Drug Product

"Equivalence by Design"

QTPP for Generic Topical Products

- **Analysis of the reference listed drug (RLD) product**
  - **RLD labeling**
    - **Dosage form, Strength, Route of administration**
    - **Clinical Pharmacology**
    - **Indication and Usage**
    - **Precautions/ Adverse Reactions**
    - **Dosage and Administration**
    - **How supplied (container closure system and storage)**
  - **Comprehensive testing**
    - **Physical Attributes: appearance, color, odor, pH, rheological behavior (consistency, viscosity), drug particle size, oil globule size, spreadability etc.**
    - **Identification of inactive ingredients including preservative and antioxidant etc.**
    - **Assay, homogeneity, and tube uniformity**
    - **Impurity profile: RLD near expiration**
    - **In Vitro Release Test (Flux assay using porcine ear/synthetic membrane/cadaver skin)**
- **Other resources**
  - **Scientific literature/Patents**
  - **FOI requests**
  - **FDA database for dissolution / bioequivalence recommendation**
- **Begin with the end in mind: pharmaceutical equivalence and bioequivalence**

Example Quality Target Product Profile (QTPP) for X Cream USP, N%

QTPP Element	Target	Justification
Dosage form	Cream	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Topical	Pharmaceutical equivalence requirement: Same route administration
Dosage strength	N% w/w	Pharmaceutical equivalence requirement: Same strength
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life, pharmaceutical equivalence requirement.
Drug product quality attributes	Physical Attributes: rheological behavior, drug particle size, oil globule size	Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)
	Identification	
	Assay	
	Homogeneity and Tube Uniformity	
	Degradation products/Residual Solvent	
	Preservatives Content	
	Microbial Limits	
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
Administration	Concurrence with RLD labeling	Information provided in the RLD labeling

Example Critical Quality Attributes (CQA) for X Cream USP, N%

CQA	Target	Justification
Identification	Positive for Active	Needed for clinical effectiveness
Assay	90 – 110%	Needed for clinical effectiveness
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
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
Physical Attributes Rheological behavior particle size Oil globule size	Match RLD	Needed for clinical effectiveness and patient acceptability To demonstrate similar arrangement of matter to RLD (Q3)
In Vitro Release Test	Match RLD	In-vitro Surrogate used to guide BE
Microbial Limits	Meet USP <61>	Needed for safety
Residual Solvents*	Meet USP <467>	Needed for safety

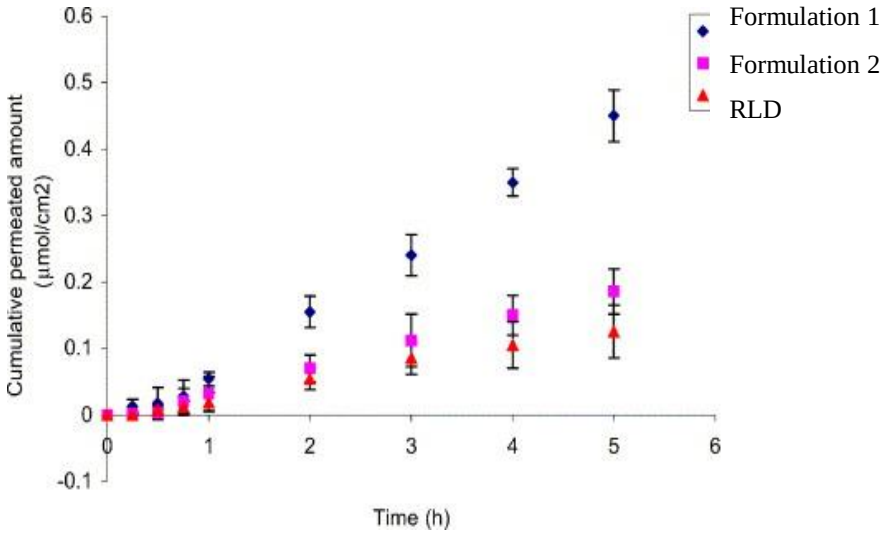
Implications of QTPP Design Target

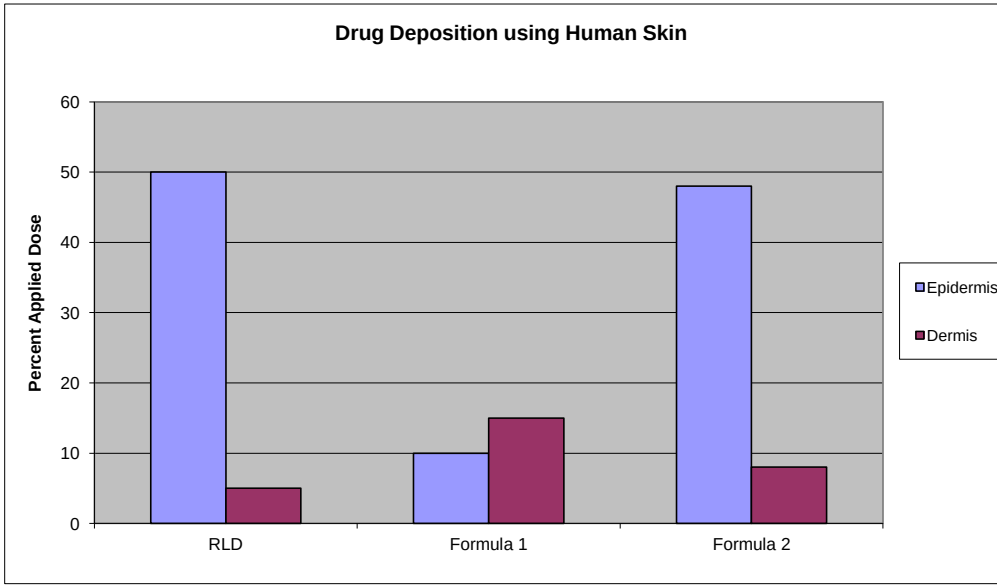
Generic		RLD	
Ingredient	Amount % w/w	Ingredient	% (w/w)
Active Ingredient	1.0	Active	1.0
--	--	EXCIPIENT A	3.0
Excipient B	20.0	EXCIPIENT B	20.0
Excipient C	1.9	--	--
Excipient D	1.1	Excipient D	--
Preservative A	1.0	Preservative B	2.0
Purified Water, USP	72	Purified Water	72

Dichotomy: The RLD uses excipient A which are "purported" to have functionality (e.g. retentive properties on the epidermis) and the generic uses excipients C/D which have no evidence of retentive properties. With these formulation differences, how can we ensure equivalent effectiveness, given the insensitivity of clinical BE studies?

Implications of QTPP Design Target

Understanding how the sponsor systematically arrived in their development program at their formulation based upon in vitro flux studies in skin to mimic those of excipient A would be informative toward ensuring equivalence





Sponsors are strongly encouraged to provide this development information in the context of their QTPP/CQA to avoid more questions from the FDA regarding their formulation design

Contains Nonbinding Recommendations

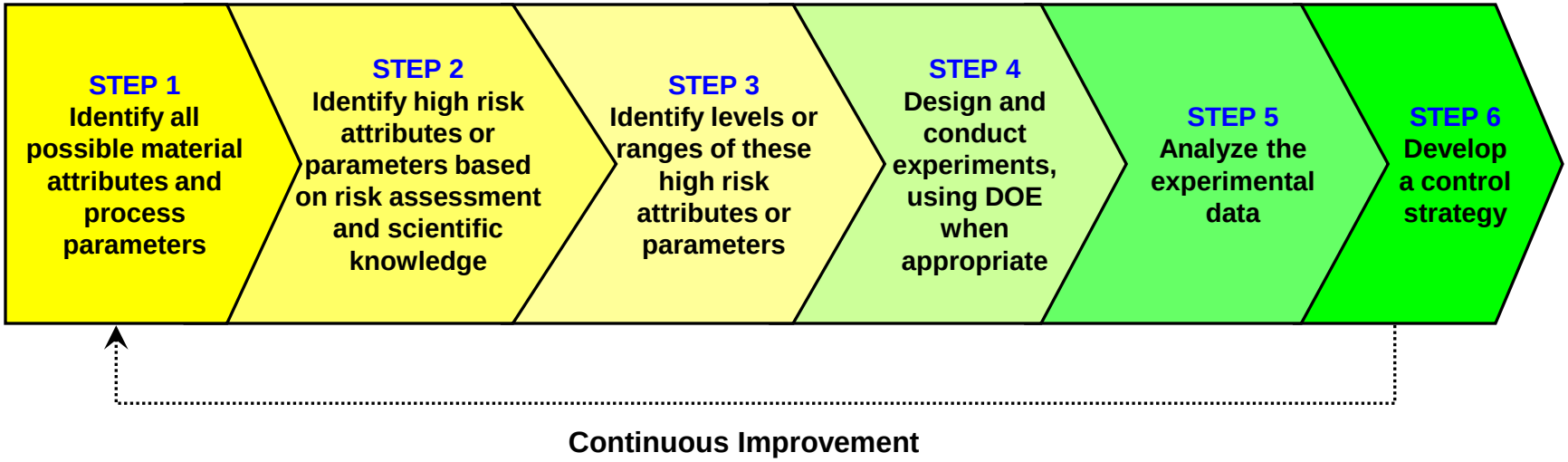
Draft Guidance on Tretinoin

Active ingredient: Tretinoin (NDA 020475)
Form/Route: Gel/Topical

Pharmaceutical Equivalence:

If a proposed generic drug product does not use microsphere technology, or if the formulation contains microspheres that are substantially different from that of the reference listed drug (RLD), then a drug stability test in presence of benzoyl peroxide (BPO) and UV light exposure **and a comparative in vitro release test should be performed to support pharmaceutical equivalence**. We recommend you conduct the in vitro release test using a diffusion cell system with excised human skin, a non-occlusive system in the donor cell, a finite dosing technique, and aqueous media at physiological pH in the receptor cell. The model should be adequately validated. We recommend…

Product & Process Understanding



Product Understanding

Past/Present Paradigm

Single Batch Manufacturable at Exhibit (Biobatch) Scale and Placed on Stability

↓

Does this Ensure Sponsor has Developed a Robust Formulation and with Adequate Stability Characteristics?

Has Sponsor Identified Critical Attributers of Active or Excipients that Need Control???

QbD Paradigm

↓ **Risk Assessment**

Identification of Active/Excipient Attributes Having High Likelihood to Affect DP CQAs

↓ **Experimentation (as Needed) To Determine Impact on Active/Excipient Attributes On Drug Product CQAs**

Adoption of a Control Strategy on Active/Excipients CMA's To Mitigate Risk of CQA failures

Risk Assessment for Formulation Component

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 µm. 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 via release testing using more stringent limits than USP limits to ensure product viscosity closely matching that of the RLD.
Propylene Glycol	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

An Example: Excipient CMA Identification and Control

- 2^2 factorial design is used to investigate the effect of acid value variation for two excipients (cetyl ester wax and glyceryl monostearate) used in a cream formulation on chemical stability of a drug
- % impurity A detected for stability samples stored at 40°C/75% RH for six months as the response

Process Optimization

Past/Present Paradigm

Exhibit (Biobatch) Production Record

No Data to Classify CPPs versus non-CPPs

10 x Scale-Up Same Equipment/ Operating Principle

Full Production Batches
(Not Reviewed by OGD)

Can Sponsor Reliably Manufacture at Commercial Production Scale (or Even at the Same Scale)?

QbD Paradigm

Risk Assessment
+
Design of Experiments

Classify CPPs versus non-CPPs in the unit Operation

Define Design Process Space for CPPs At Pilot Scale (Bioequivalence Batch)

Increased Likelihood of a Successful Commercial-Scale Process

Manufacturing Process Development Example

- 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.

Example 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

Potentially High Risk Process Variables

- Powder Eduction Rate
- Rotor Speed
- Rotor/Stator Gap
- Mixing time
- Mixing Speed
- Homogenization time

Screening DOE to Identify Critical Process Parameters

- Following the initial risk assessment, a screening design experiment is used to evaluate the relative importance of the process variables.
- Screening DOE options
  - Plackett-Burman designs
  - Fractional factorial designs (Resolution III or IV)
  - Taguchi orthogonal arrays

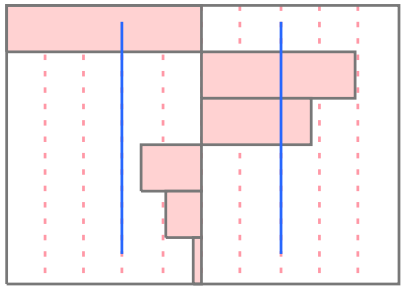
Parameter Estimates and Half-Normal Plot for 12-run Plackett-Burman Design Generated by JMP-9 Software Tool (Response: %RSD)

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	4.875	0.18246	26.72	<.0001 *	4.4059715	5.3440285
Mixer Speed(100,300)	-0.041667	0.18246	-0.23	0.8284	-0.510695	0.4273618
Mixing Time(10,20)	-0.208333	0.18246	-1.14	0.3053	-0.677362	0.2606951
Rotor/Stator Gap(10,18)	-0.358333	0.18246	-1.96	0.1068	-0.827362	0.1106951
Powder Eduction Rate	0.9083333	0.18246	4.98	0.0042 *	0.4393049	1.3773618
Rotor Speed(1000,2000)	0.6416667	0.18246	3.52	0.0170 *	0.1726382	1.1106951
Homogenization Time(10,30)	-1.158333	0.18246	-6.35	0.0014 *	-1.627362	-0.689305

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Homogenization Time(10,30)	-1.158333	0.18246	-6.35	0.0014 *
Powder Eduction Rate	0.9083333	0.18246	4.98	0.0042 *
Rotor Speed(1000,2000)	0.6416667	0.18246	3.52	0.0170 *
Rotor/Stator Gap(10,18)	-0.358333	0.18246	-1.96	0.1068
Mixing Time(10,20)	-0.208333	0.18246	-1.14	0.3053
Mixer Speed(100,300)	-0.041667	0.18246	-0.23	0.8284

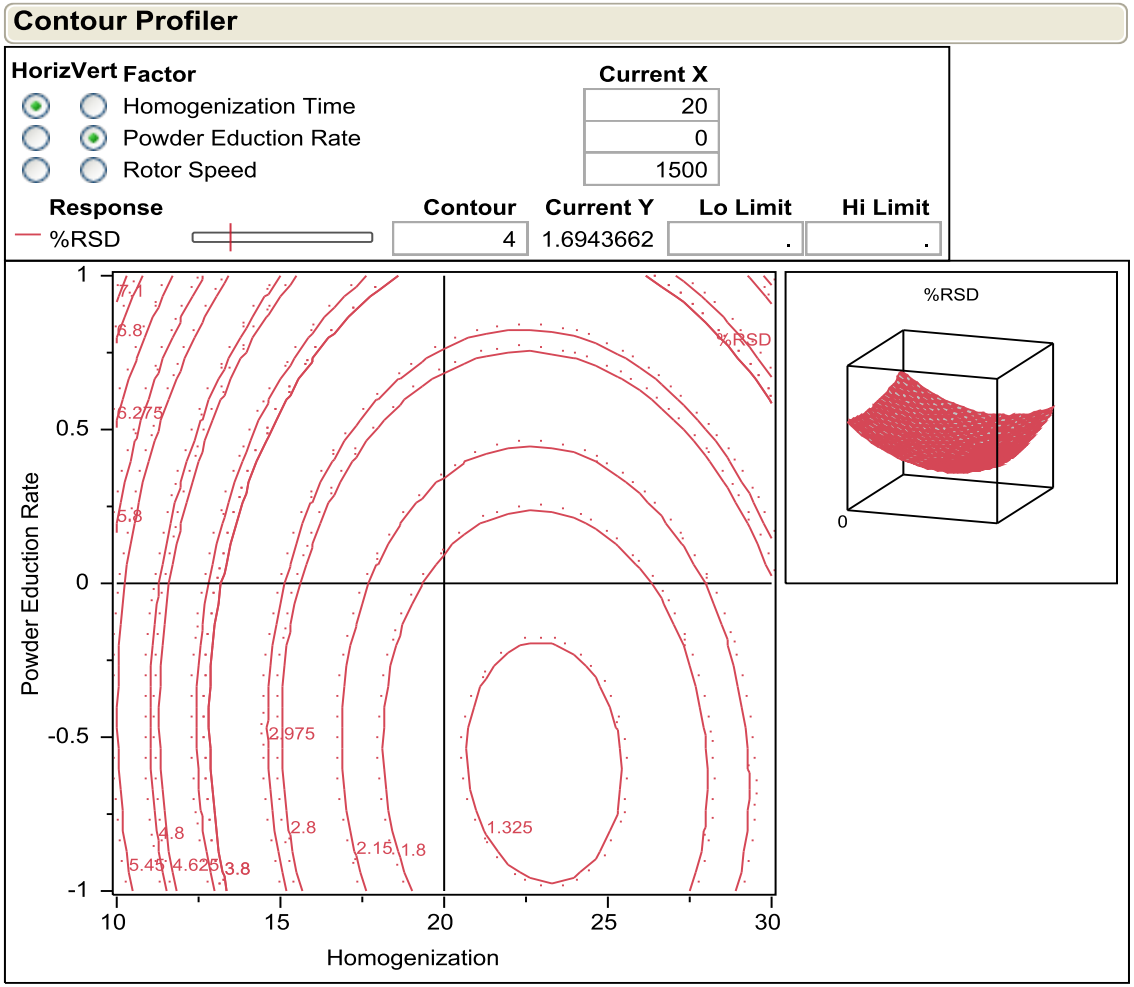


Response Surface Designs for Process Optimization

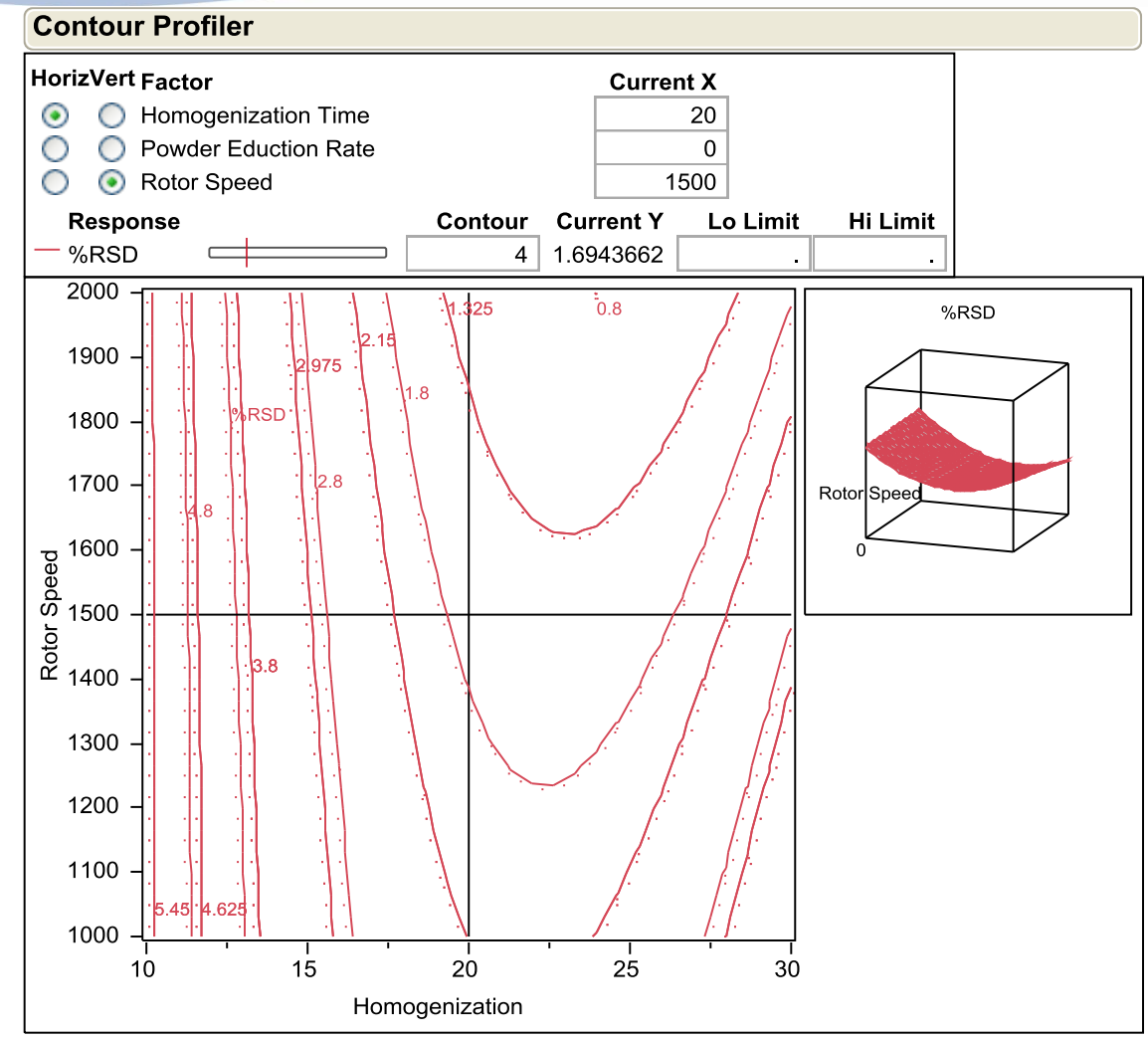
- A response surface DOE is used to further optimize the identified significant process variables from screening DOE experiments.
- Response Surface Designs
  - Central composite design
  - Box-Behnken design
  - 3-level full factorial design

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

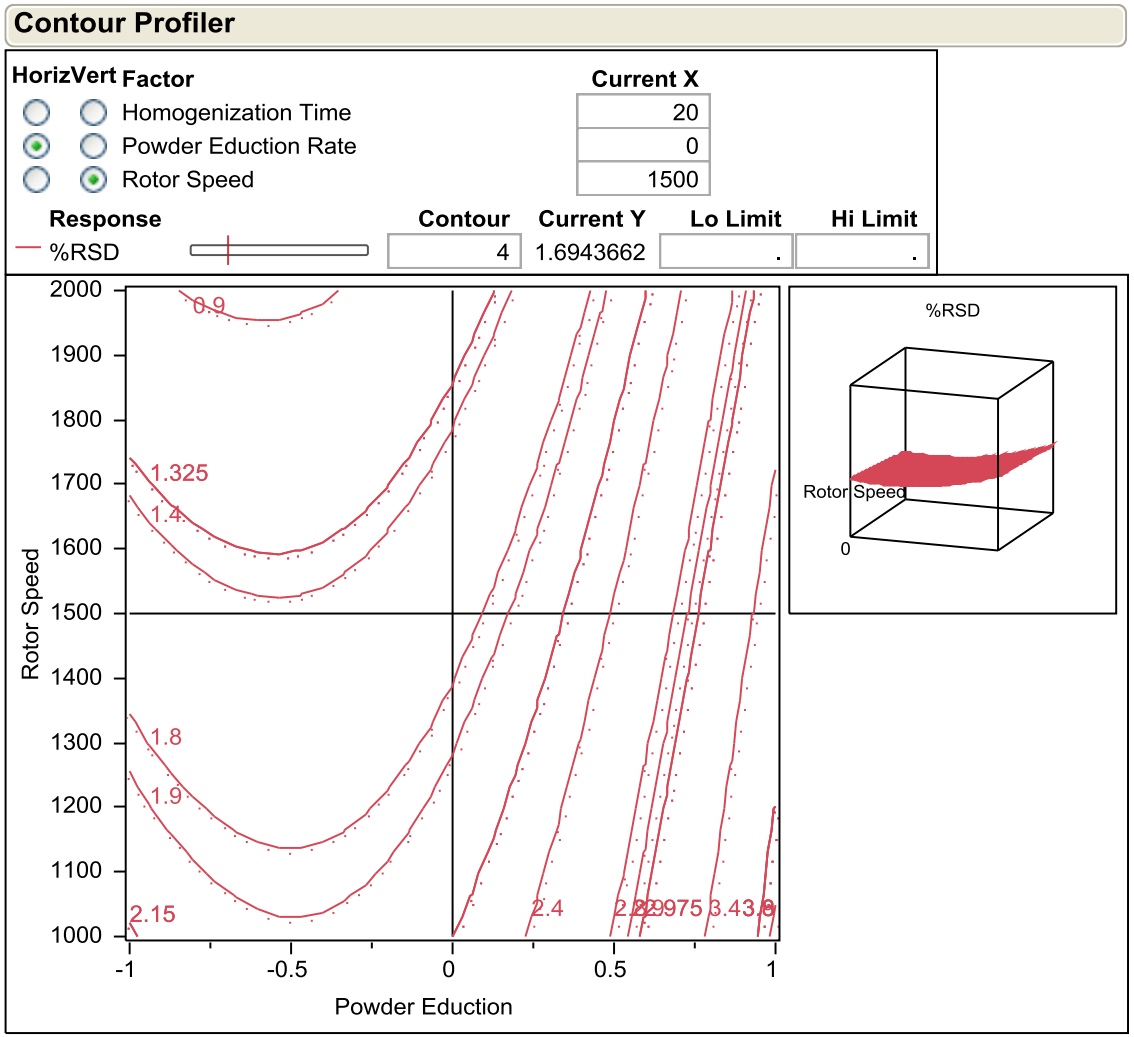
	Pattern	Homogenization Time (X_1)	Powder Eduction Rate (X_2)	Rotor Speed (X_3)	% RSD (Y)
1	+−−	30	-1	1000	3.6
2	000	20	0	1500	2.0
3	a00	10	0	1500	5.8
4	+−+	30	-1	2000	1.0
5	0A0	20	1	1500	3.2
6	00a	20	0	1000	2.6
7	−++	10	1	2000	7.2
8	−−−	10	-1	1000	5.3
9	000	20	0	1500	1.6
10	−−+	10	-1	2000	5.9
11	000	20	0	1500	1.1
12	00A	20	0	2000	0.9
13	++−	30	1	1000	5.4
14	0a0	20	-1	1500	2.2
15	−+−	10	1	1000	7.5
16	+++	30	1	2000	4.5
17	A00	30	0	1500	2.8



Contour Plots of %RSD versus Powder Edution Rate and Homogenization Time

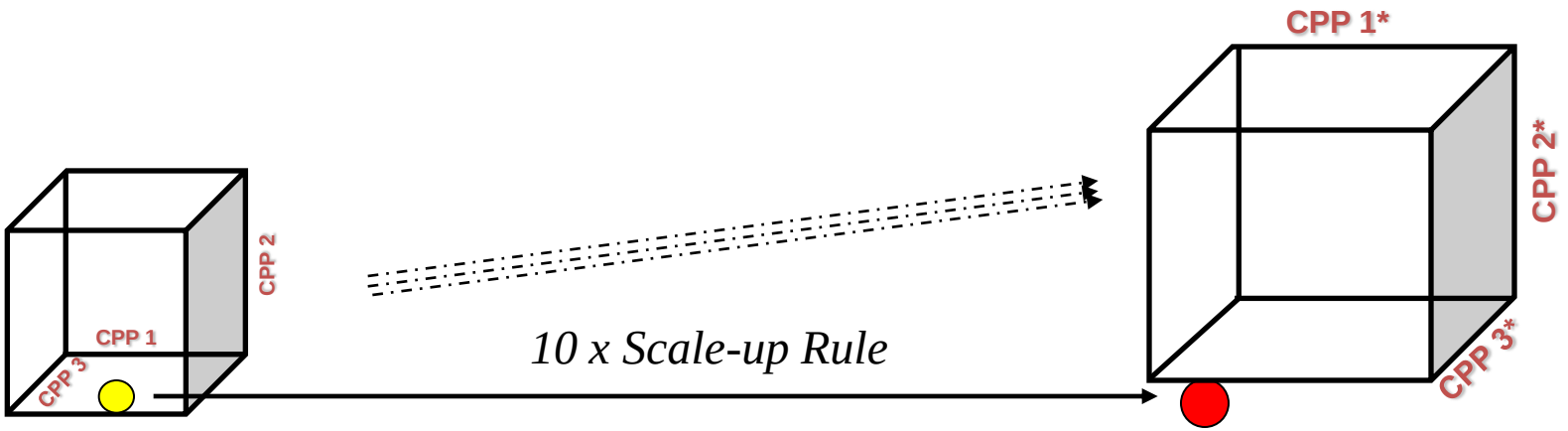


Contour Plots of %RSD versus Rotor Speed and Homogenization Time



Contour Plots of %RSD versus Rotor Speed and Powder Eduction Time

Historical Paradigm for Scale-Up In ANDAs

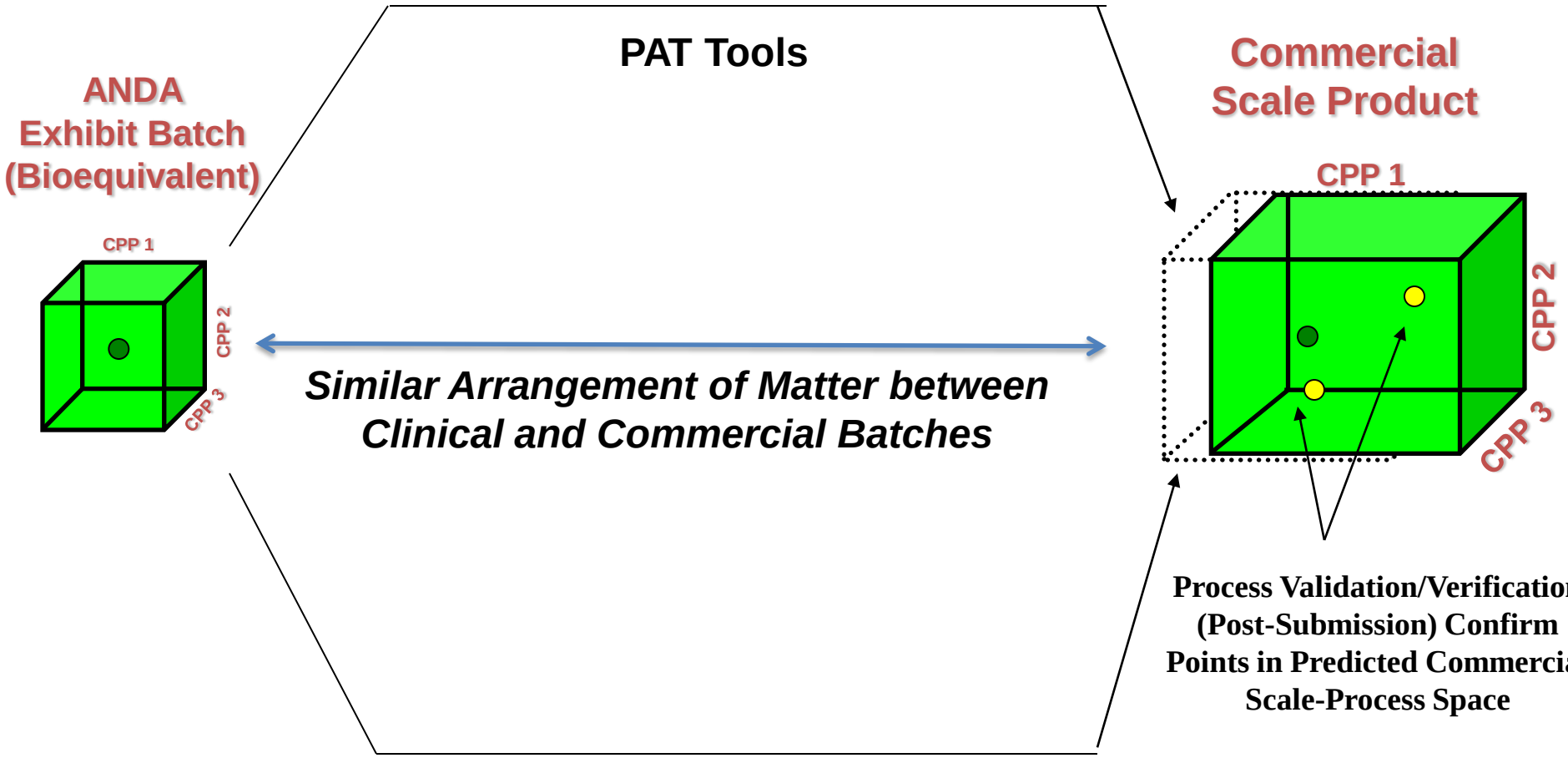


ANDA Exhibit Batch

Commercial Batch

Is Commercial Scale Drug Product Equivalent to the ANDA Exhibit Batch (Is the arrangement of matter Q3 (e.g. emulsion droplet size, API particle size) the same as the pivotal ANDA Clinical Batch used to Establish Equivalence?)

Linkage of Commercial/Exhibit Batch Process Spaces



Scale-up based upon underlying assumptions (similitude between different scales, empirical or semi-empirical models, etc)

Summary

- The clearly predefined objectives (QTPP/CQA) is a powerful tool to guide formulation and process design and to keep the product development effort focused and efficient.
- Enhanced product and process understanding builds solid foundation for developing the Control Strategy
  - including identification of critical process parameters and critical attributes of excipients, drug substance, and/or container closure systems
- Implementation of the systematic science and risk-based approach will bring significant benefits to patient, industry and regulatory agency with the high quality drug products and manufacturing efficiencies.
- Risk assessment, DOE, Prior Knowledge etc. are useful tools for QbD implementation.

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Chang, R., Raw, A.S., Lionberger, R., Yu, Lawrence, Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products, The AAPS Journal, Volume 15 (1) 2013, p. 41-52.

Chang, R., Raw, A.S., Lionberger, R., Yu, Lawrence, Generic Development of Topical Dermatologic Products: Part II: Quality by Design for Topical Semisolid Products, The AAPS Journal, in-press.