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Insights through analytics

Quality by Design (QbD) and the Design of Experiments (DoE):

Why, How, Who

Prof Ron Kenett

ron@kpa-group.com

Agenda

- Background
- Introduction to QbD – Why
- Introduction to DoE – How
- Case studies - Who

http://apps.pharmacy.wisc.edu/esp/prog/IsraelQBD
http://ce.pharmacy.wisc.edu/courseinfo/archive/2012Israel

The Hebrew University of Jerusalem
The School of Pharmacy Institute for Drug Research

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Quality by Design in Stem Cell Transplantation:
Rational translation from bench to bed

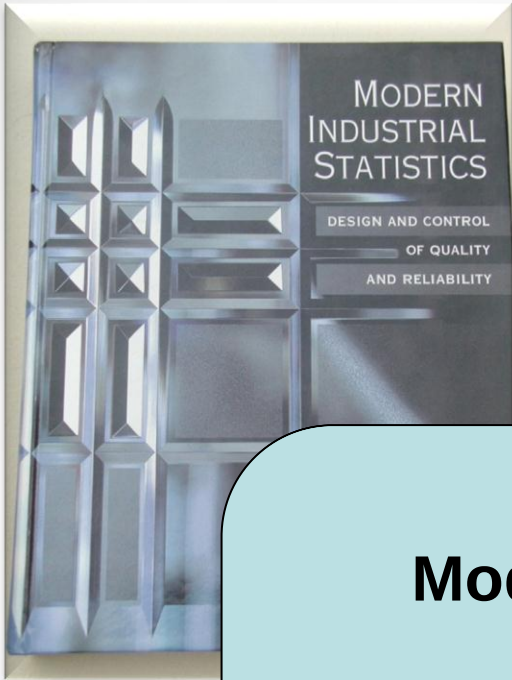
Wednesday, May 1st, 2013

Faculty of Medicine, Butnar Building, **Butnar Small Hall**, Ein Kerem, Jerusalem

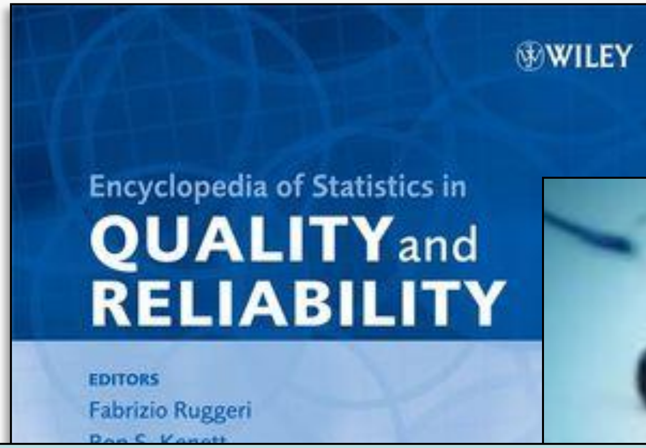
13:00 – 18:00

A Half Day Conference for Multidisciplinary Brainstorming

Participation is free with pre-registration by sending an email with subject: *QbD in Stem Cell Transplantation* to avrir@ekmd.huji.ac.il

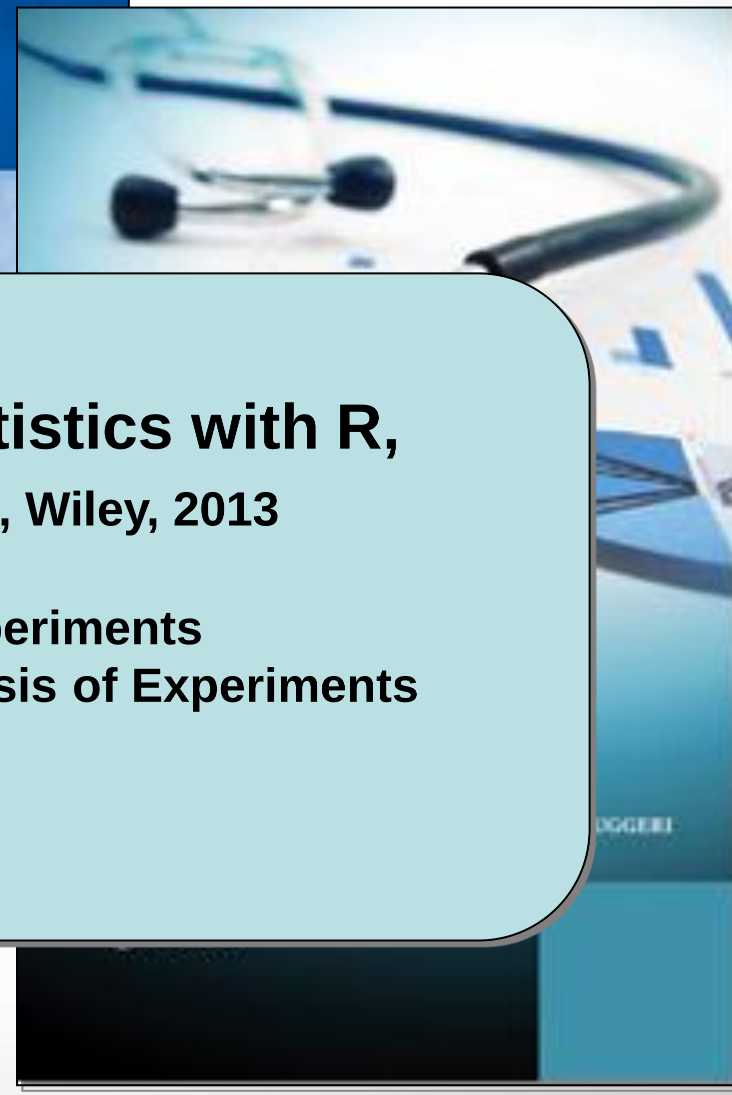


1998
2000
2004



2007

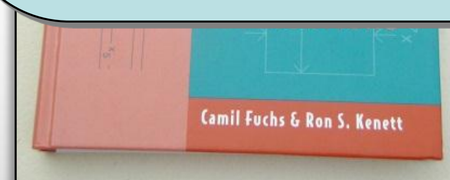
2012



Modern Industrial Statistics with R, MINITAB and JMP, Wiley, 2013

Part IV: Design and Analysis of Experiments

- 11. Classical Design and Analysis of Experiments
- 12. Quality by Design
- 13. Computer Experiments



1998

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2004

Innovation

Stagnation

Challenge and Opportunity on the Critical Path to New Medical Products

FDA

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

March 2004

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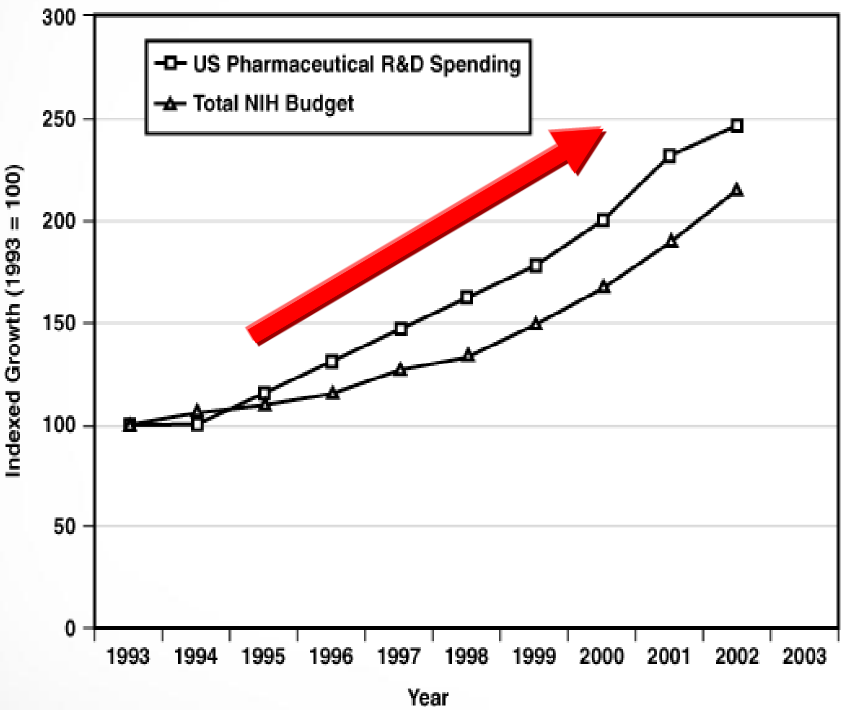
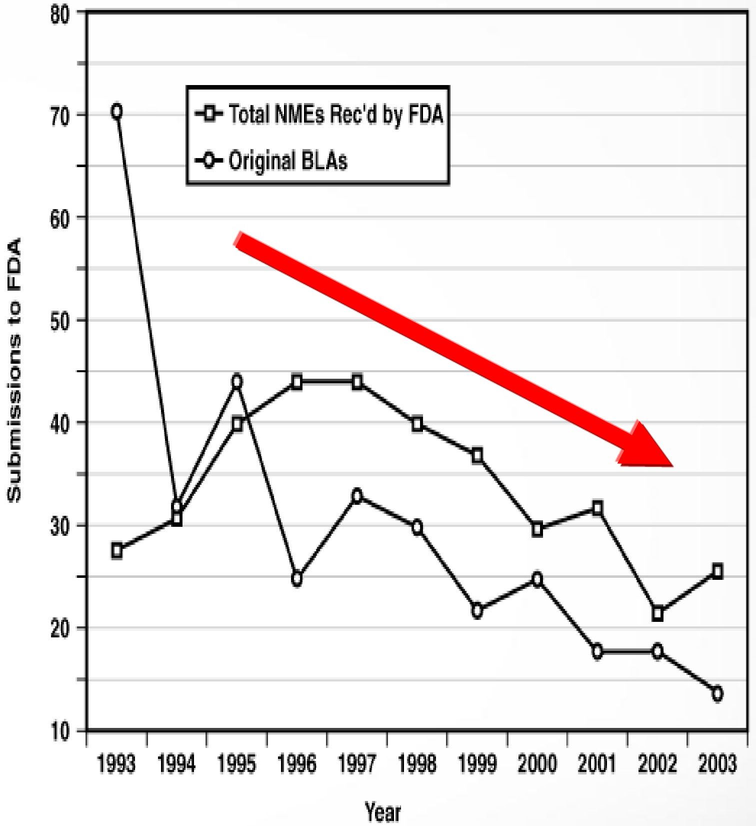
Food and Drug Administration, Challenge and opportunity on the critical path to new medical products, March 2004.

Figure 1: 10-Year Trends in Biomedical Research Spending



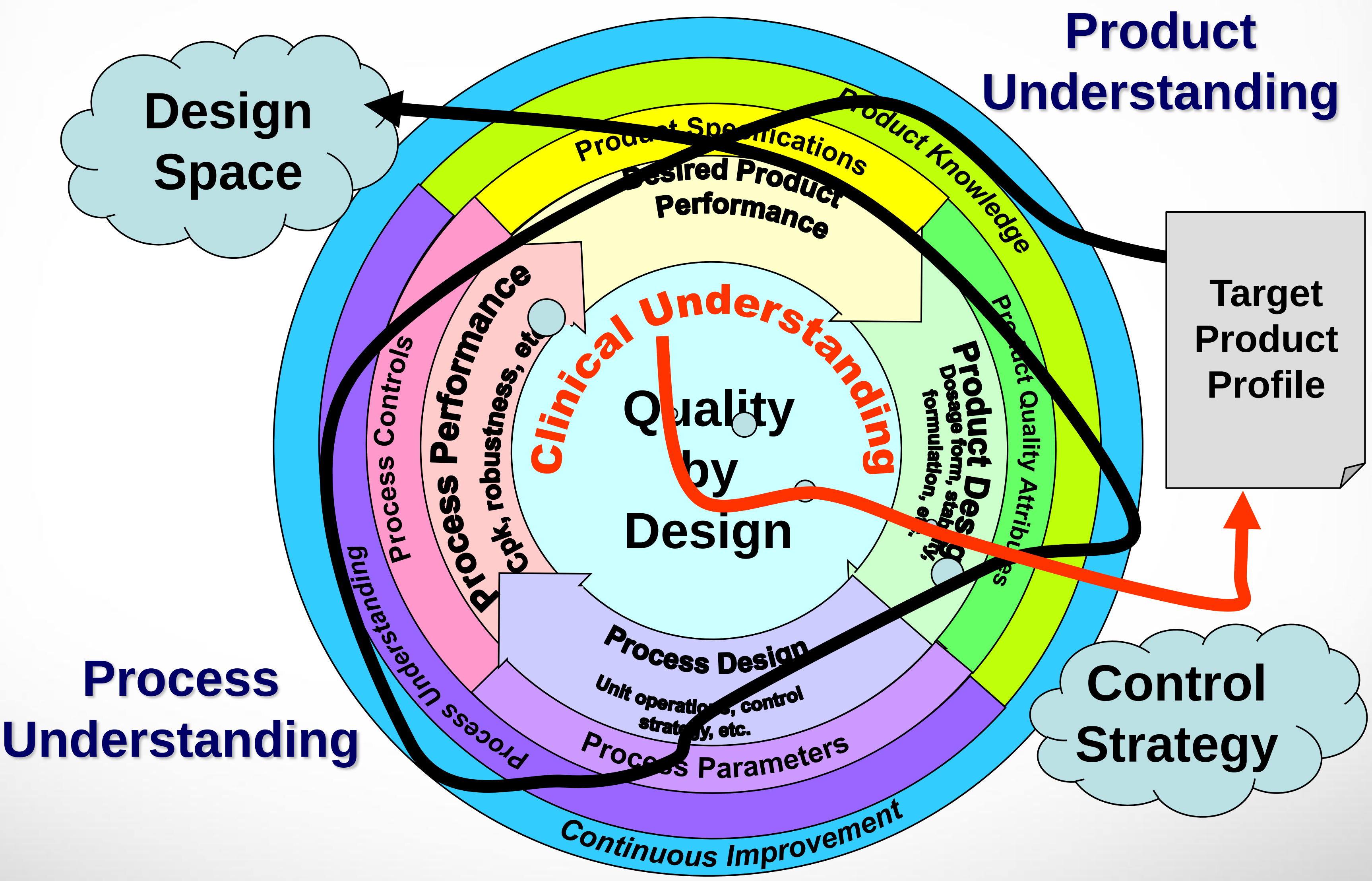
The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statiststical Sourcebook 2002/2003).

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

Quality by Design (QbD)



Moheb Nasr, *Pharmaceutical Quality for the 21st Century*, 2nd QbD Conference; Jerusalem, 5-6 May 2010

Quality by Design - A 4 Stage Process

Design Intent	**The Active Pharmaceutical Ingredient chemical and physical characteristics and Drug Product performance targets are identified for the commercial product.**
Design Selection	**The API manufacturing process and the DP formulation and manufacturing process are selected to achieve the Design Intent for the commercial product.**
Control Definition	**The largest contributors to Critical Quality Attributes variability are established and controls defined to ensure process performance expectations are met.**
Control Verification	**The performance of the API and DP processes in manufacturing are measured to verify that the controls are effective and the product performance acceptable.**

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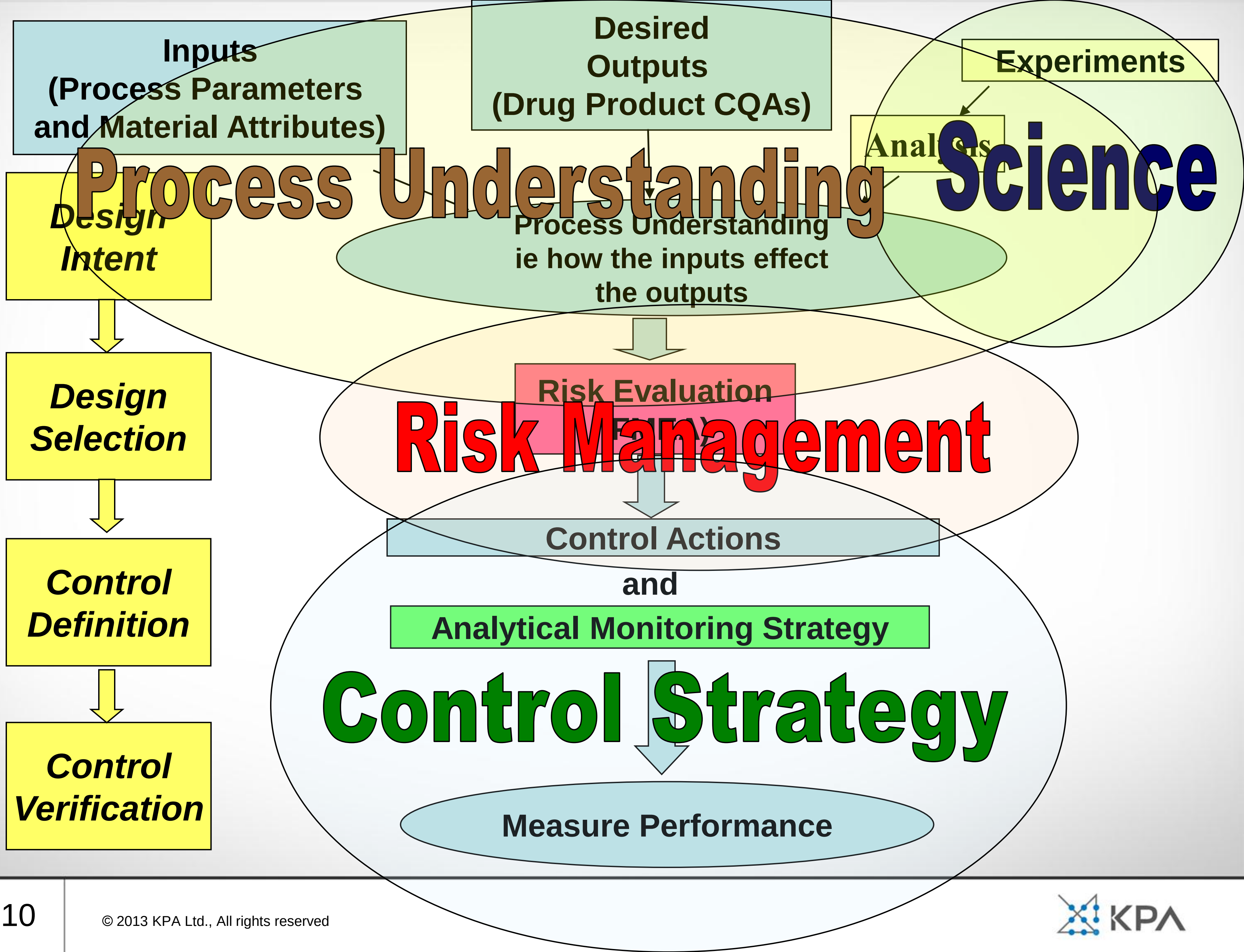
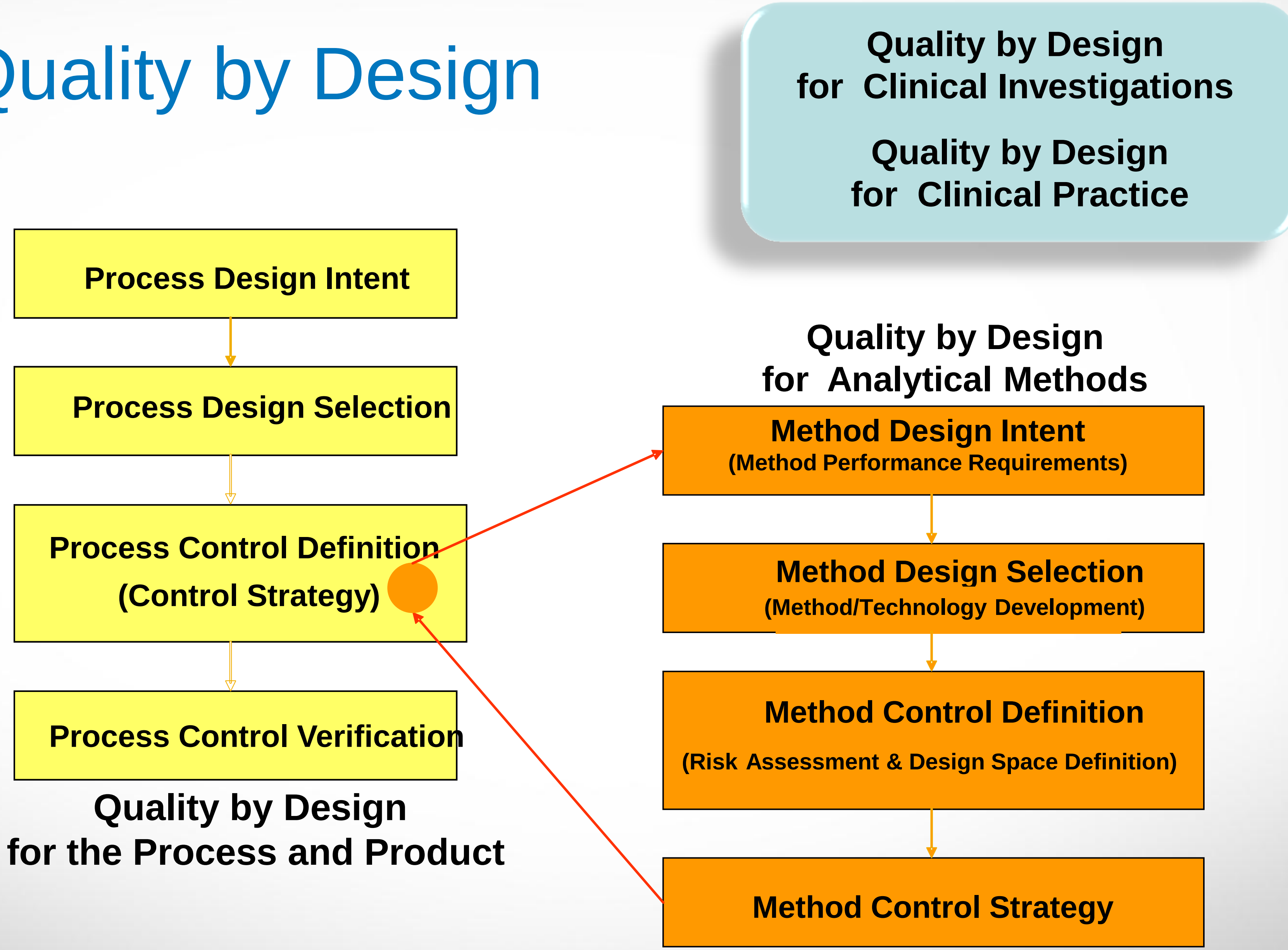


Inputs
(Process Parameters
and Material Attributes)
Desired
Outputs
(Drug Product CQAs)
Experiments
Analysis
Science
Process Understanding
Design
Intent
Process Understanding
ie how the inputs effect
the outputs
Design
Selection
Risk Evaluation
(FMEA)
Risk Management
Control
Definition
Control Actions
and
Analytical Monitoring Strategy
Control Strategy
Control
Verification
Measure Performance

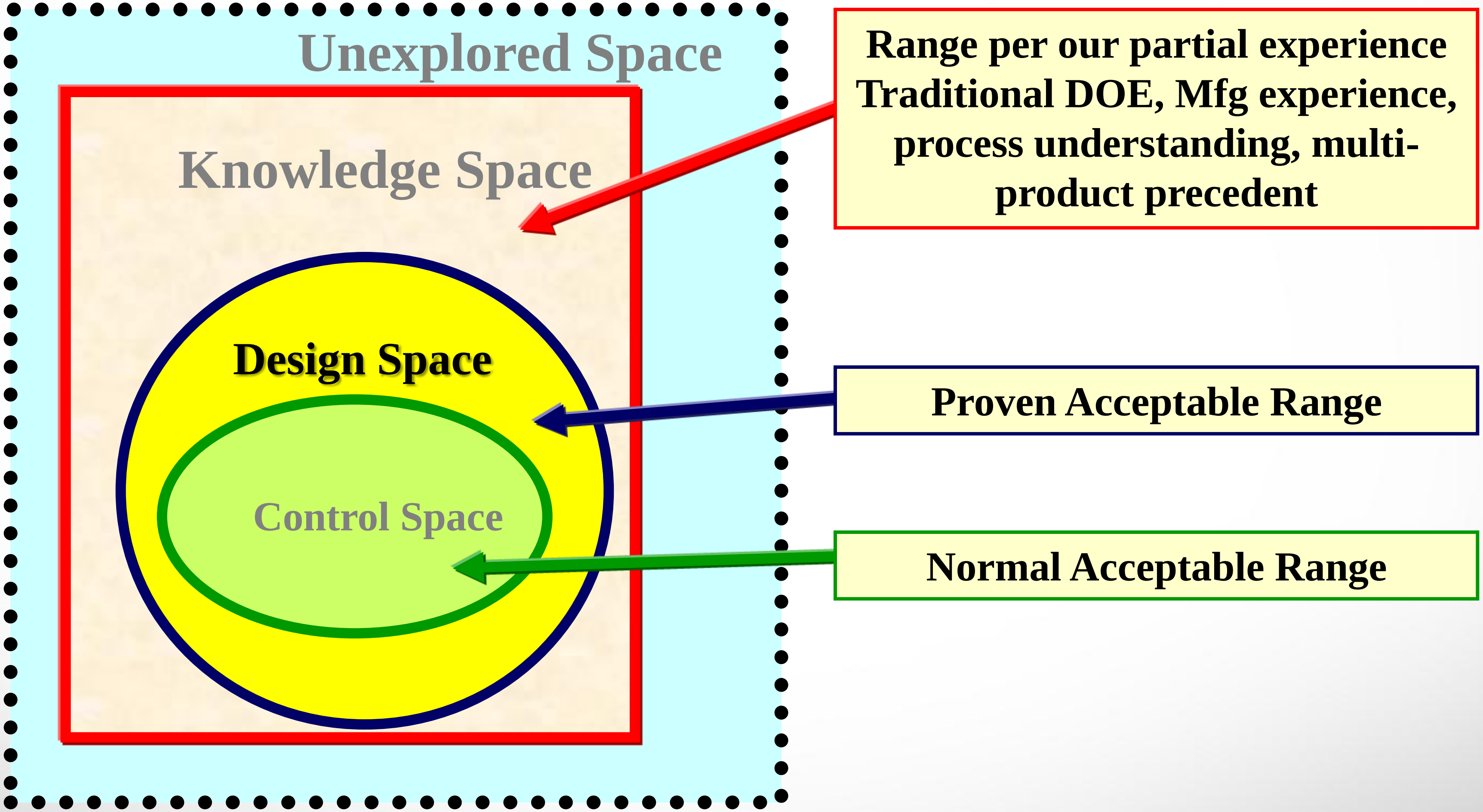
Quality by Design



Design Space

- **Multidimensional combinations** of the product characteristics
- **Interactions of inputs** variables
- **Interactions** of process parameters
- Changes within the **design space** are not considered a regulatory change
- QbD information and conclusions need to be shared with the FDA – Do and Tell

Design Space



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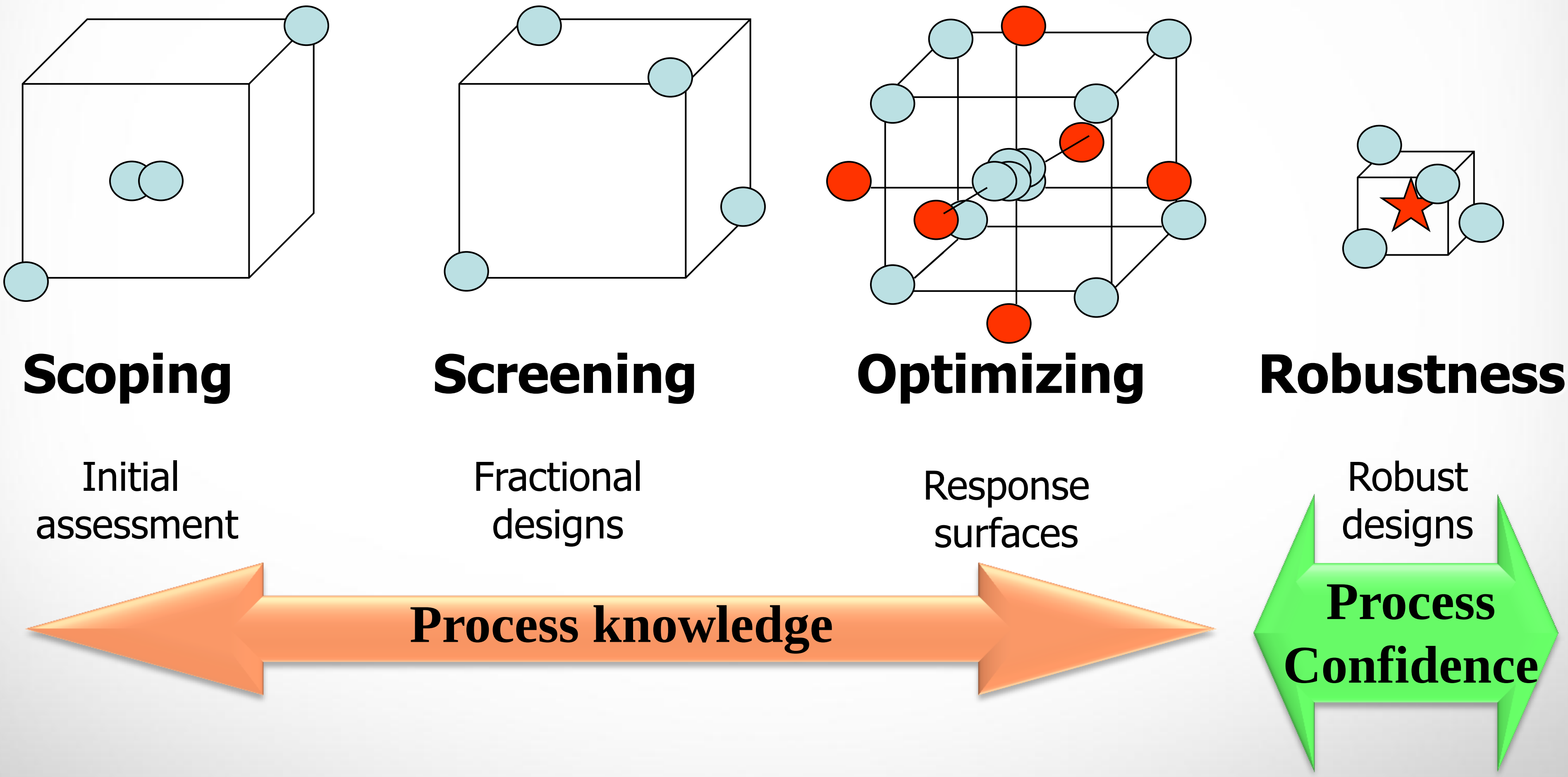
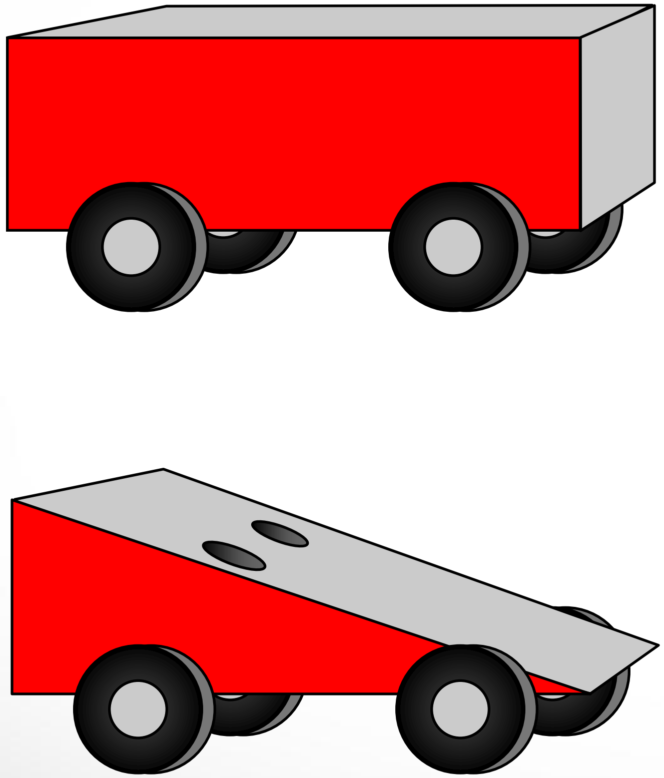
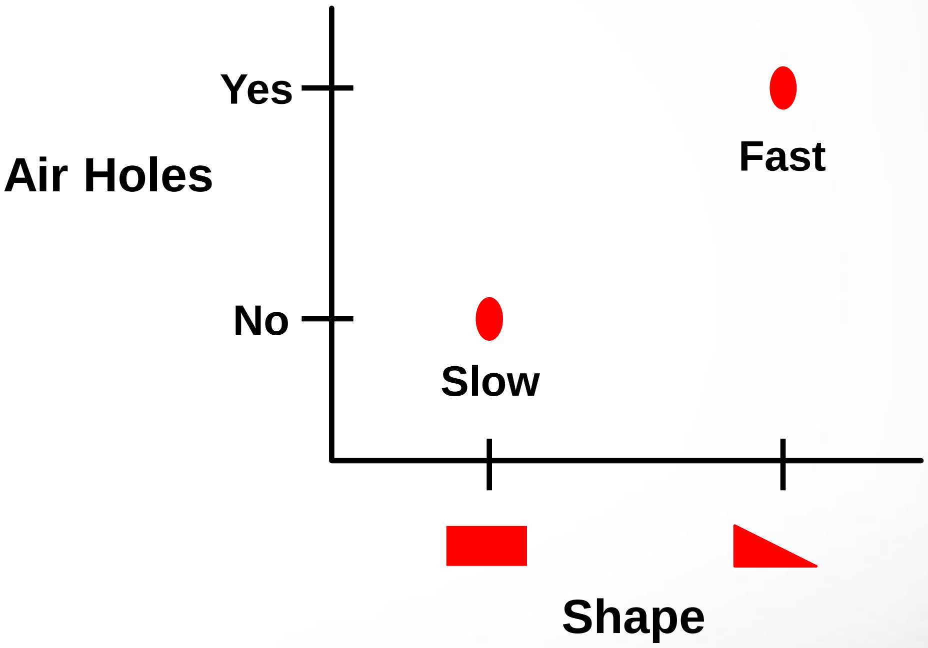
Experimental Design Strategy



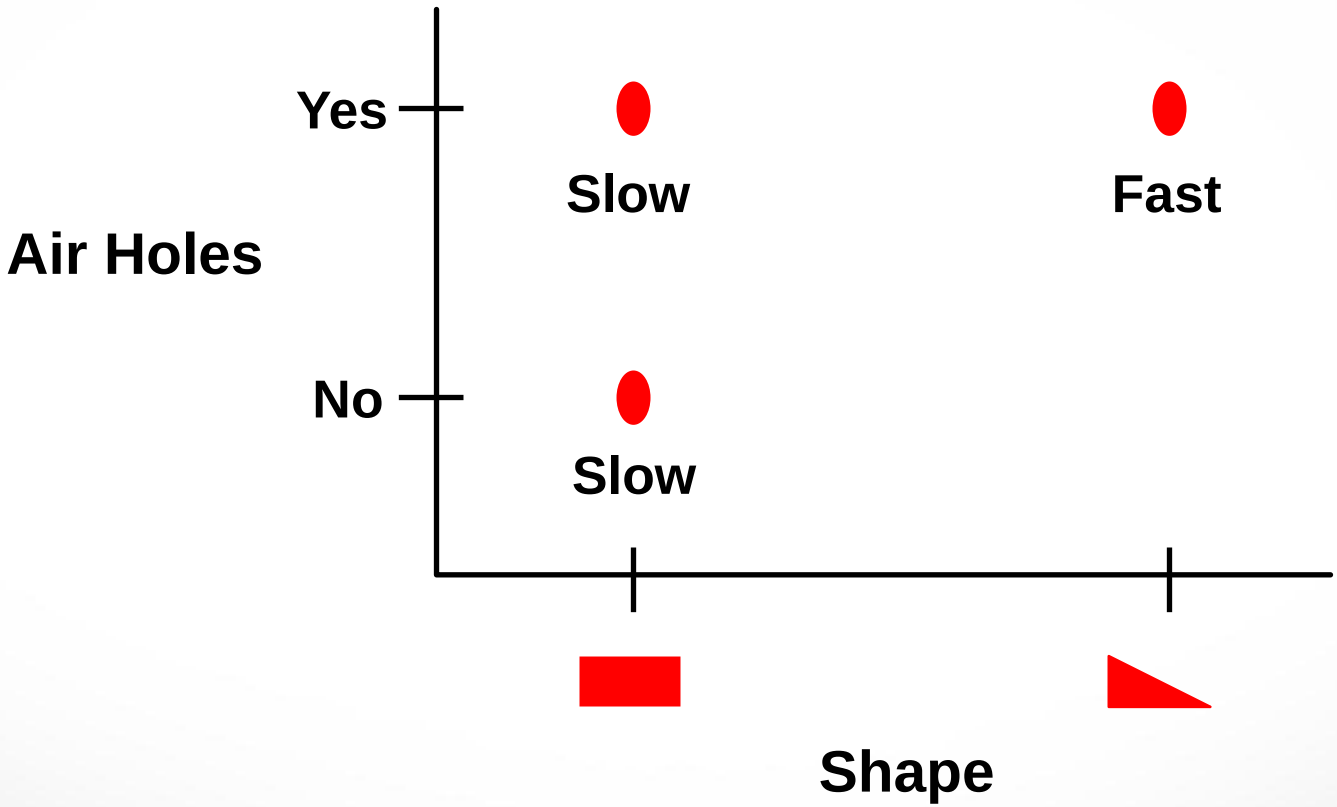
A Serious Problem...

What Factors Affect the Speed?

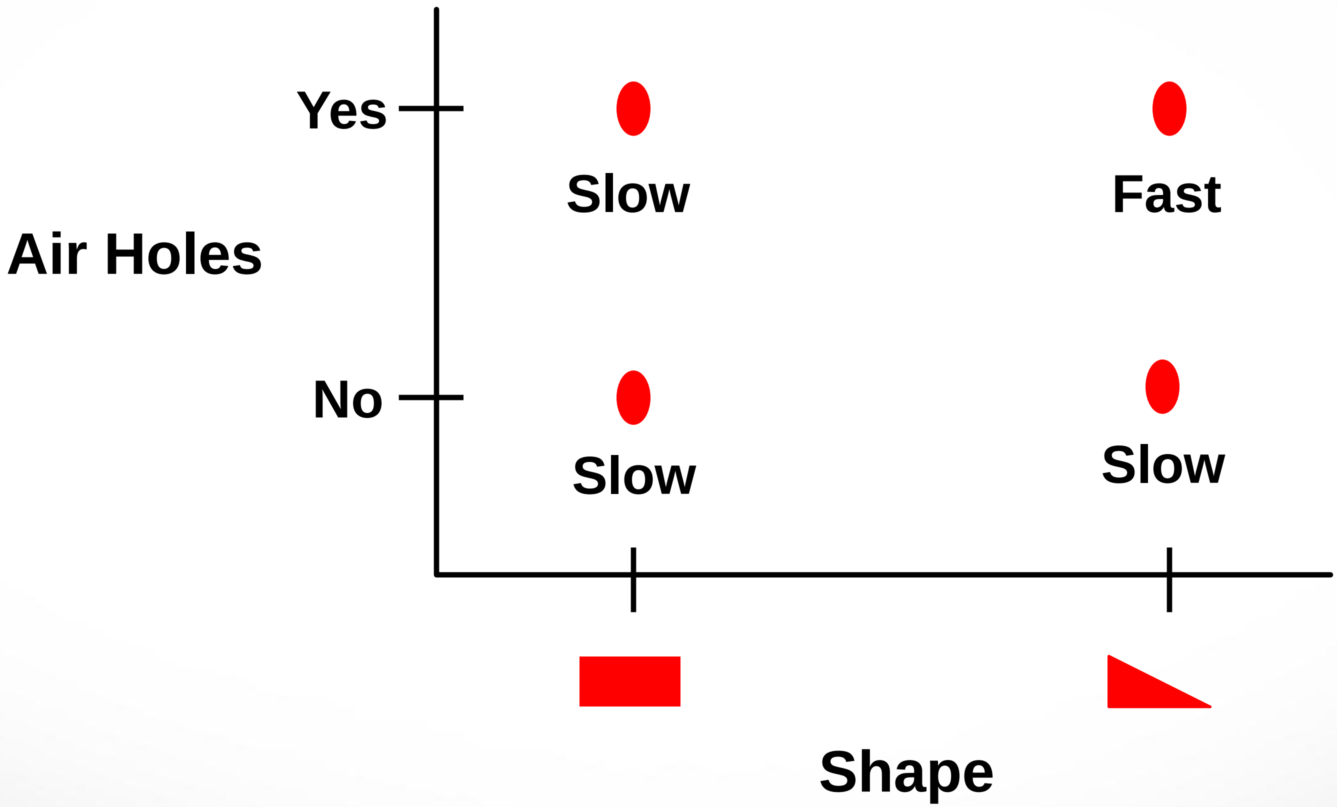




Effect of Air Holes



Effect of Air Shape



Designed Experiments

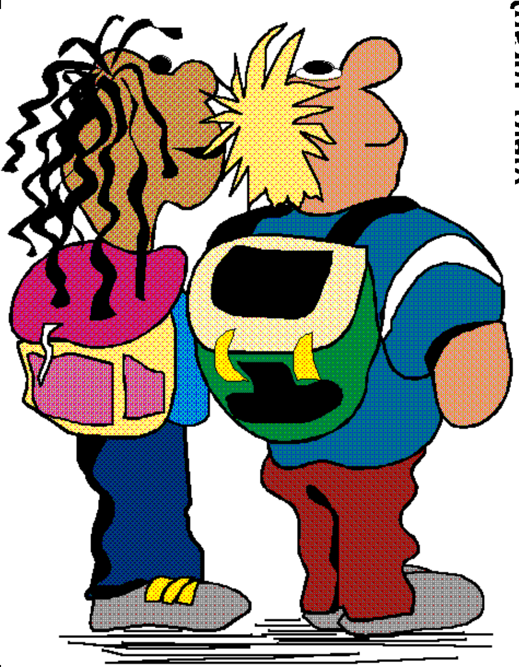
Male

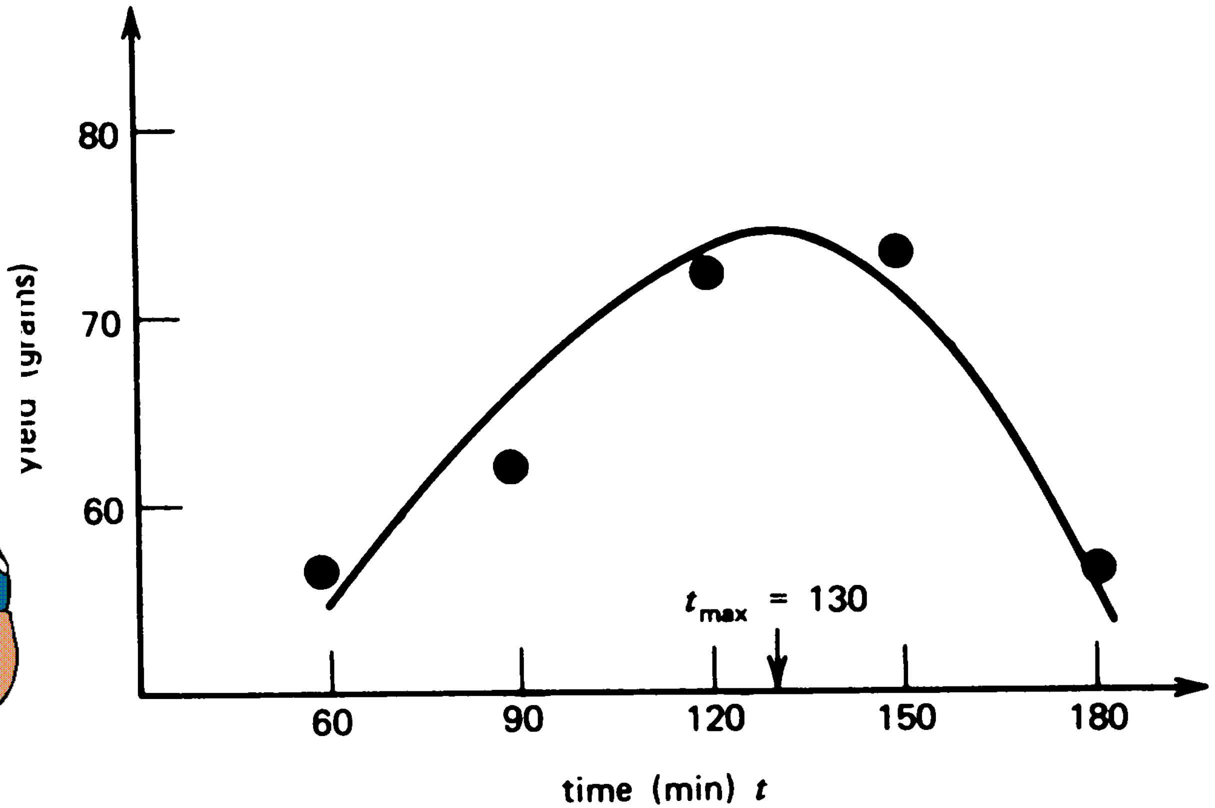
Female

Designed Experiments

One Factor at a Time

OFAT

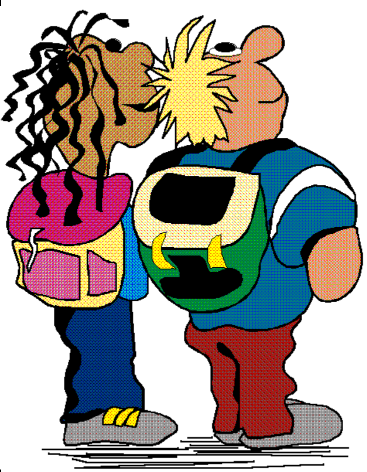


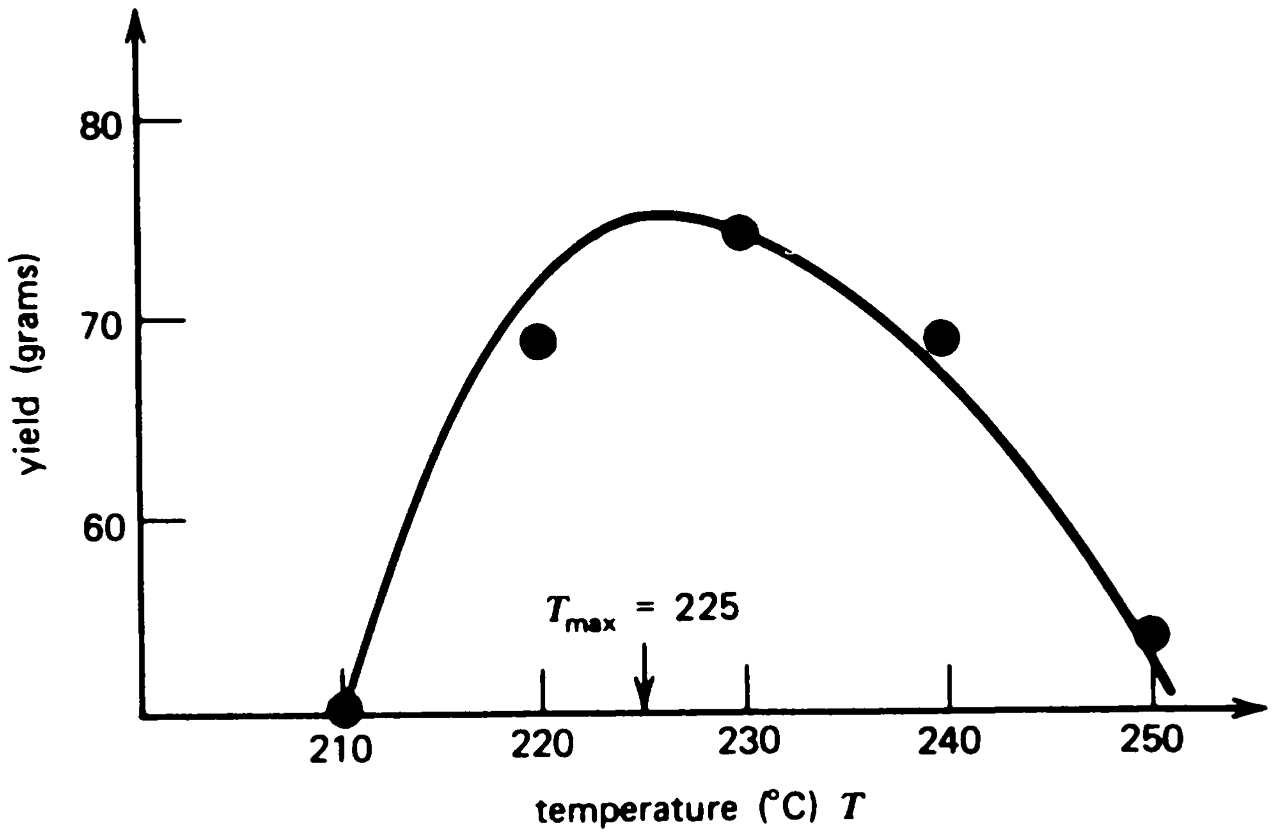


Experiment #1: Study Effects of Reaction Time on Yield
(Reaction Temperature held fixed at 225° C)

One Factor at a Time

OFAT





Experiment #2: Study Effects of Reaction Temperature on Yield
(Reaction Time held fixed at 130 minutes)

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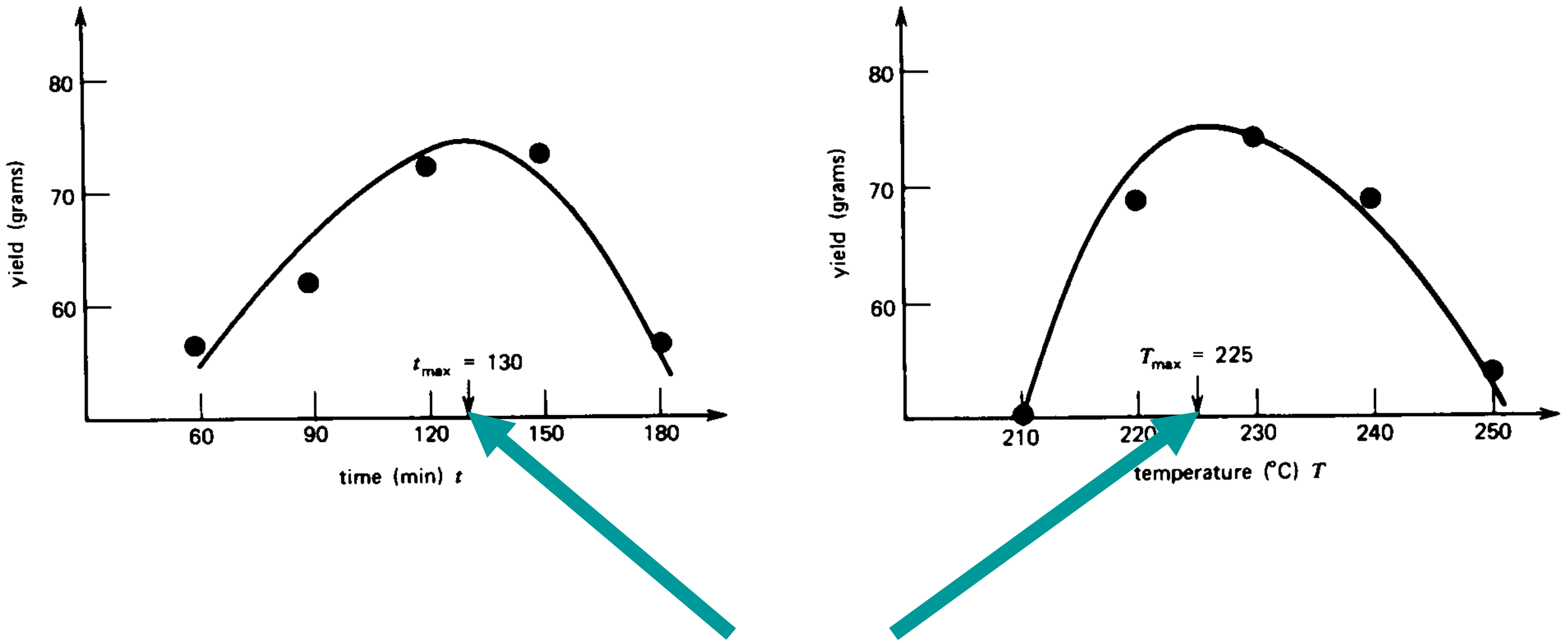
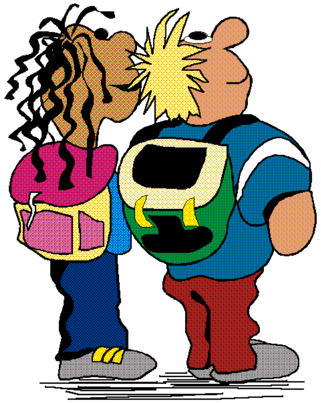
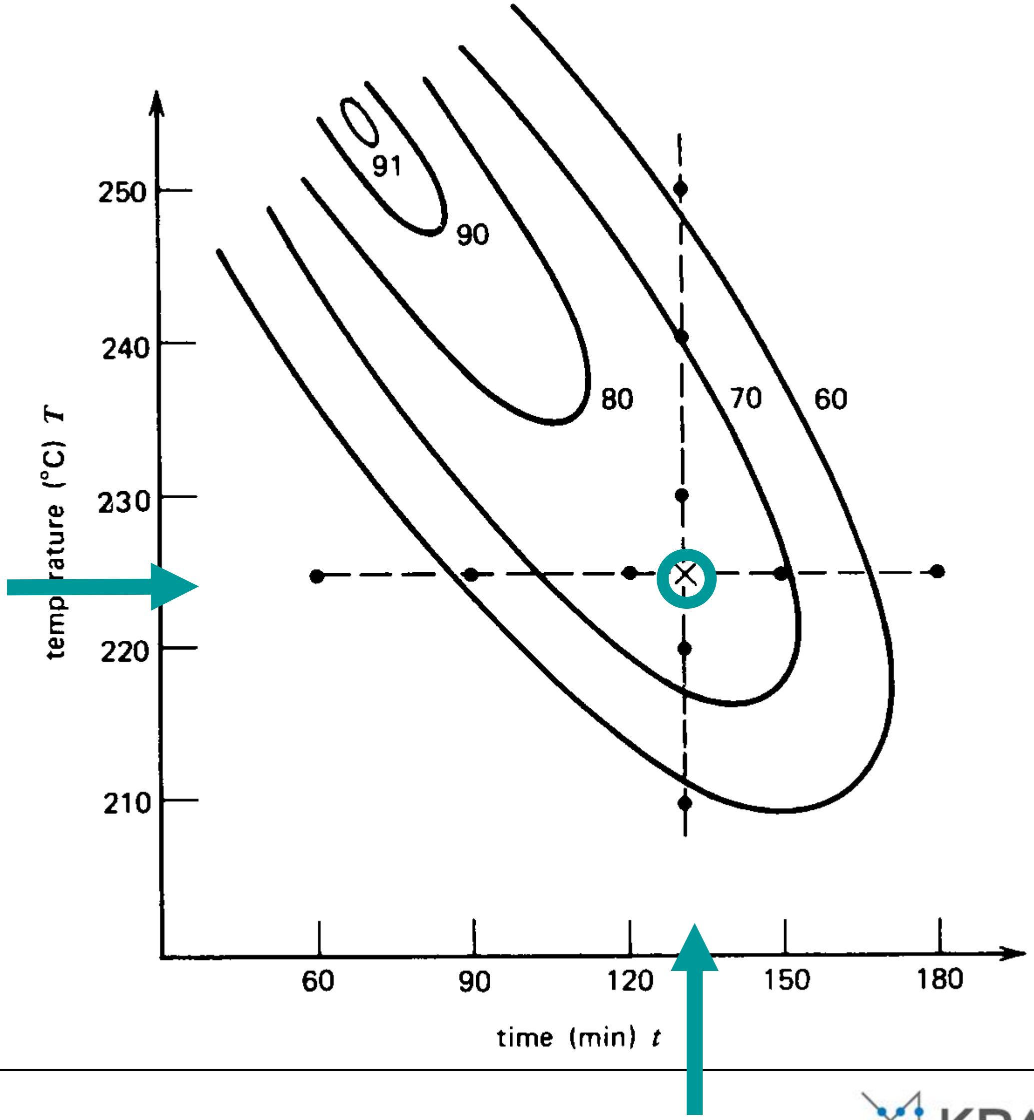
One Factor at a Time



T=130 m, T = 225 C

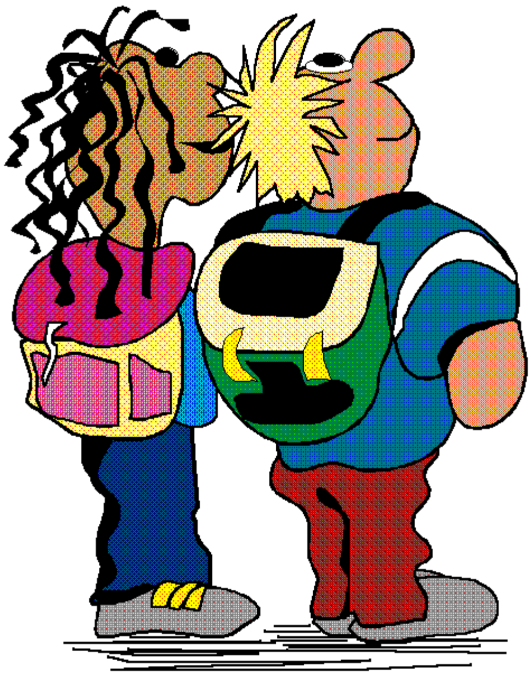
One Factor at a Time

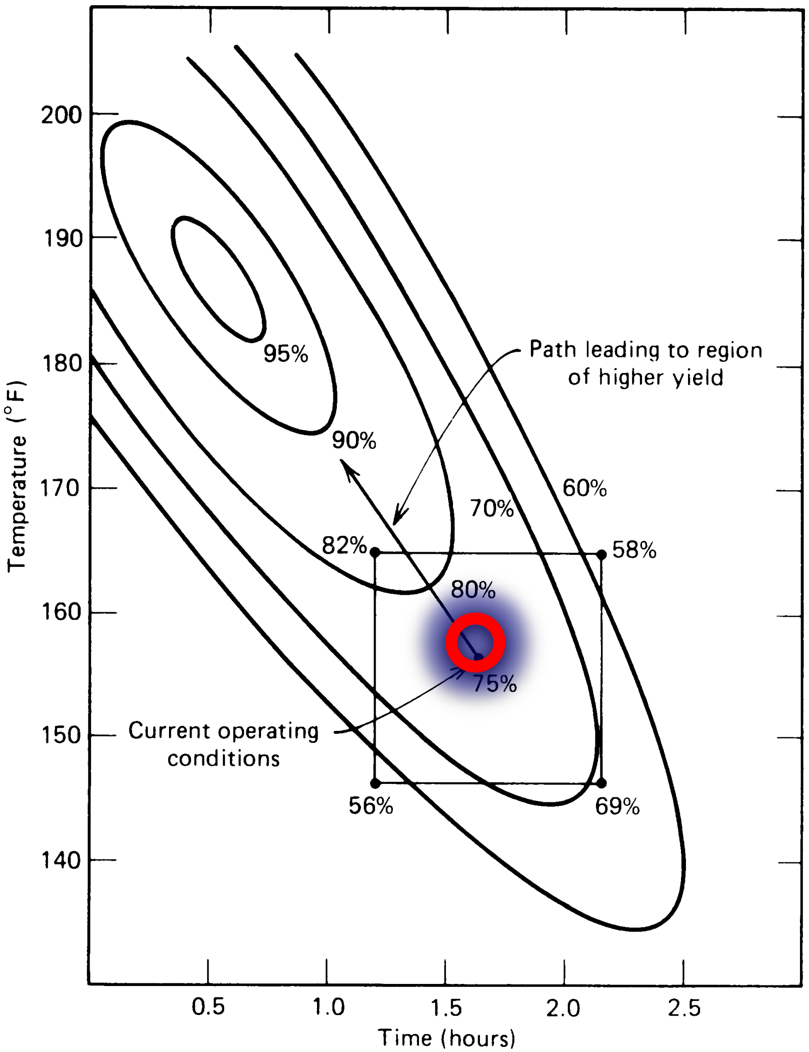




Reaching the top

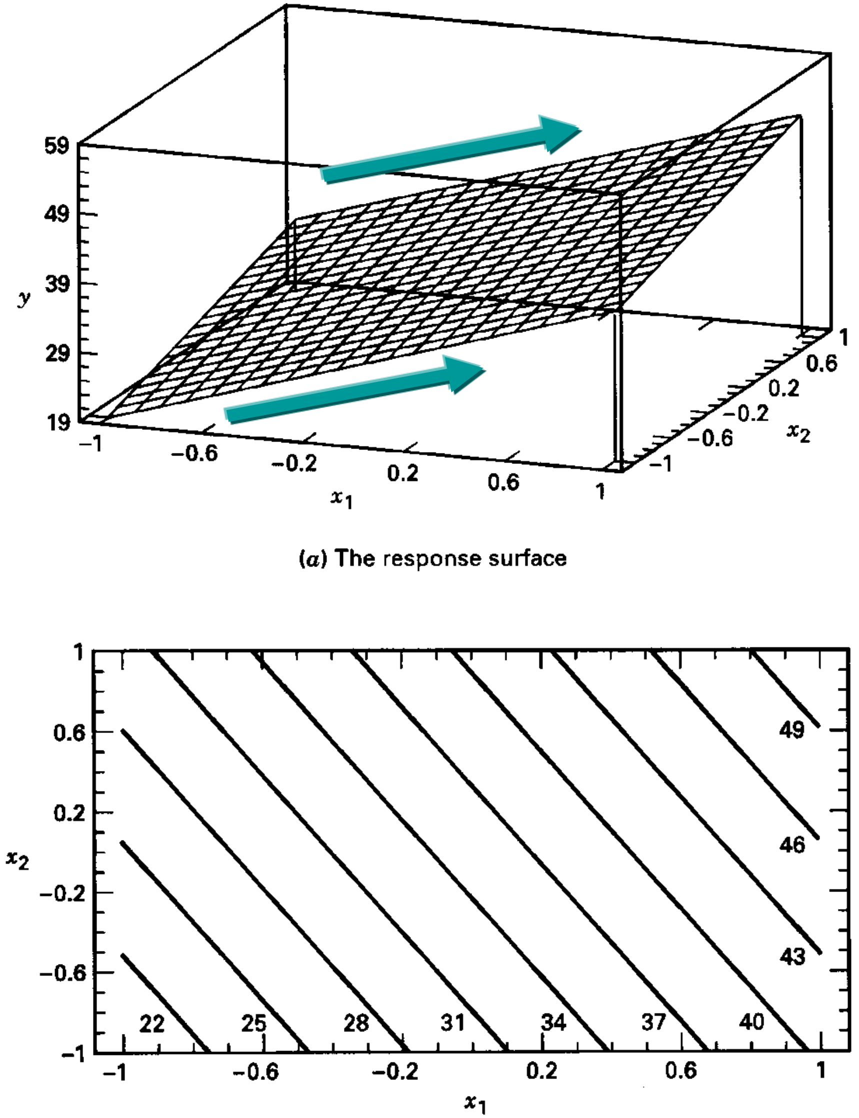
DoE





Regression Model and the associated Response Surface

$$\hat{y} = 35.5 + 10.5x_1 + 5.5x_2$$



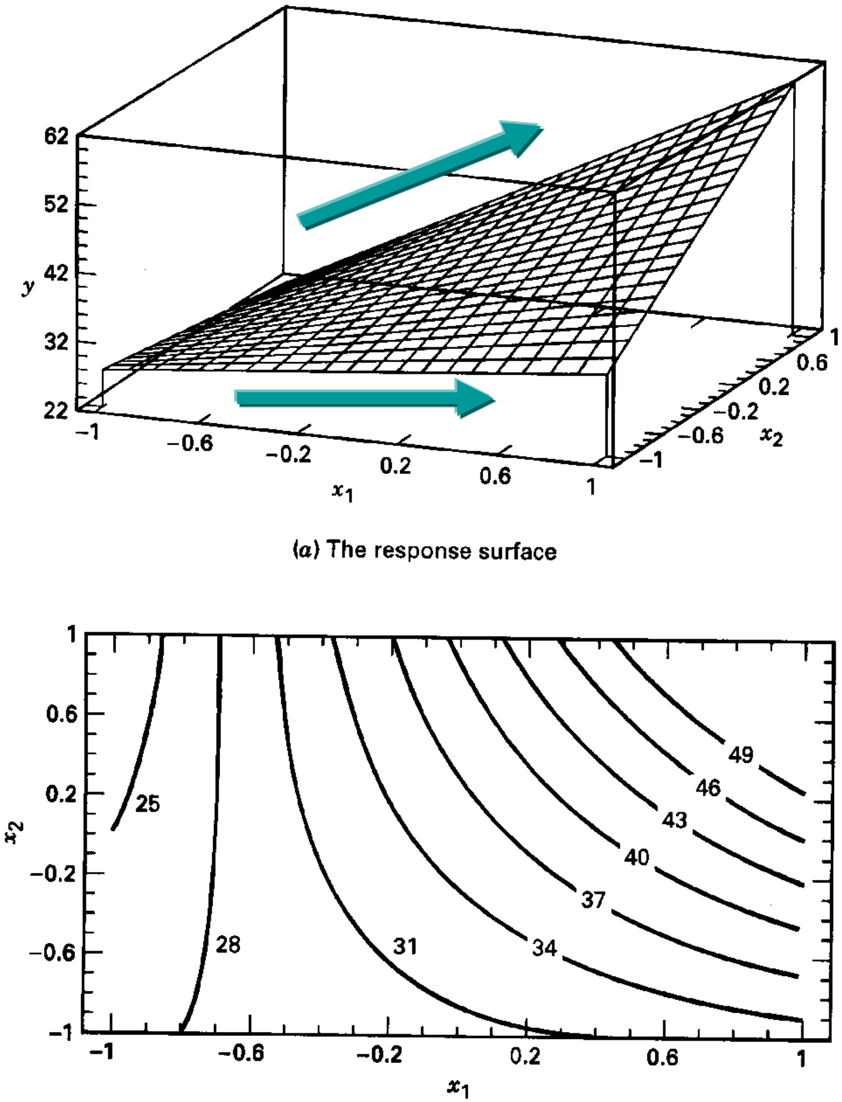
(a) The response surface

(b) The contour plot

Figure 5-5 Response surface and contour plot for the model $\hat{y} = 35.5 + 10.5x_1 + 5.5x_2$.

The Effect of Interaction on the Response Surface

$$\hat{y} = 35.5 + 10.5x_1 + 5.5x_2 + 8x_1x_2$$



(a) The response surface

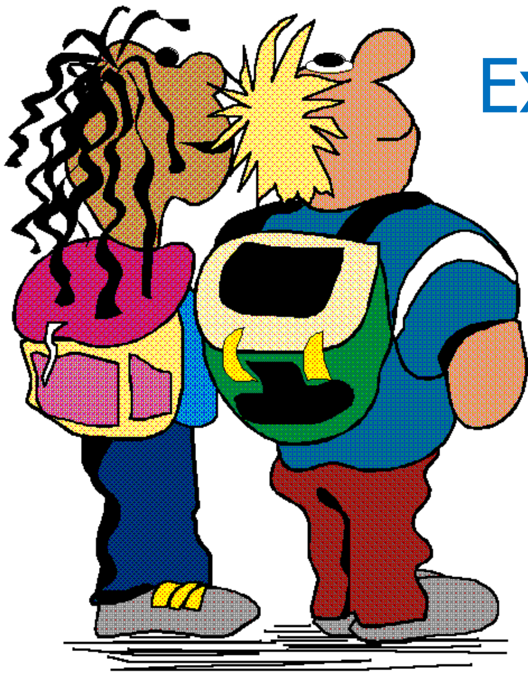
(b) The contour plot

Figure 5-6 Response surface and contour plot for the model $\hat{y} = 35.5 + 10.5x_1 + 5.5x_2 + 8x_1x_2$.

The Path of Steepest Ascent

DoE

Design of Experiments



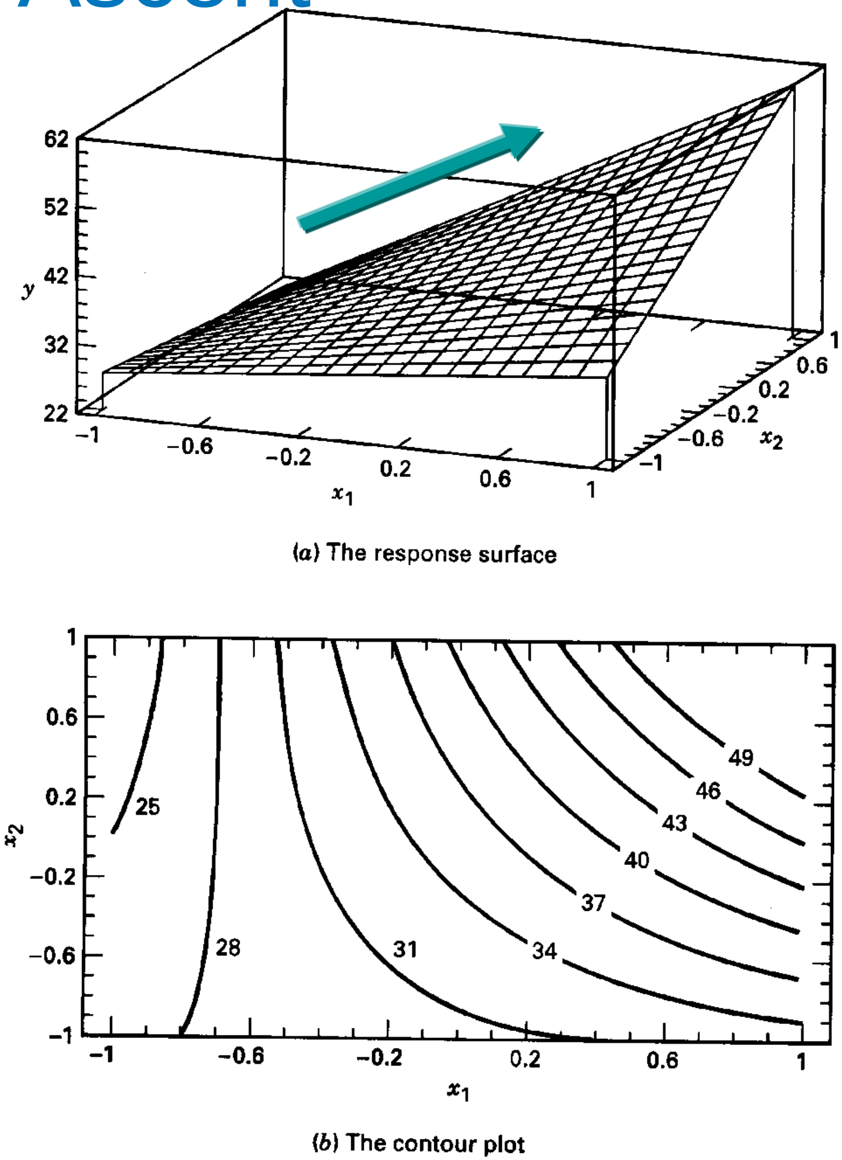


Figure 5-6 Response surface and contour plot for the model $\hat{y} = 35.5 + 10.5x_1 + 5.5x_2 + 8x_1x_2$.

A DoE Checklist

ב מ ג ר צ מ ס ש

מה הבעיה הנחקרת ?

מה המשתנה הכמותי המאפיין את הבעיה הנחקרת ? Response

מהם הגורמים הניתנים לשינוי במסגרת הניסוי ? Factors

מהן רמות הגורמים המשתתפים בניסוי ? Levels

מהם הצרופים הקובעים את מערך הניסוי ? Experimental Array

מה מספר החזרות שיתבצעו בכל נקודת ניסוי ? Replicates

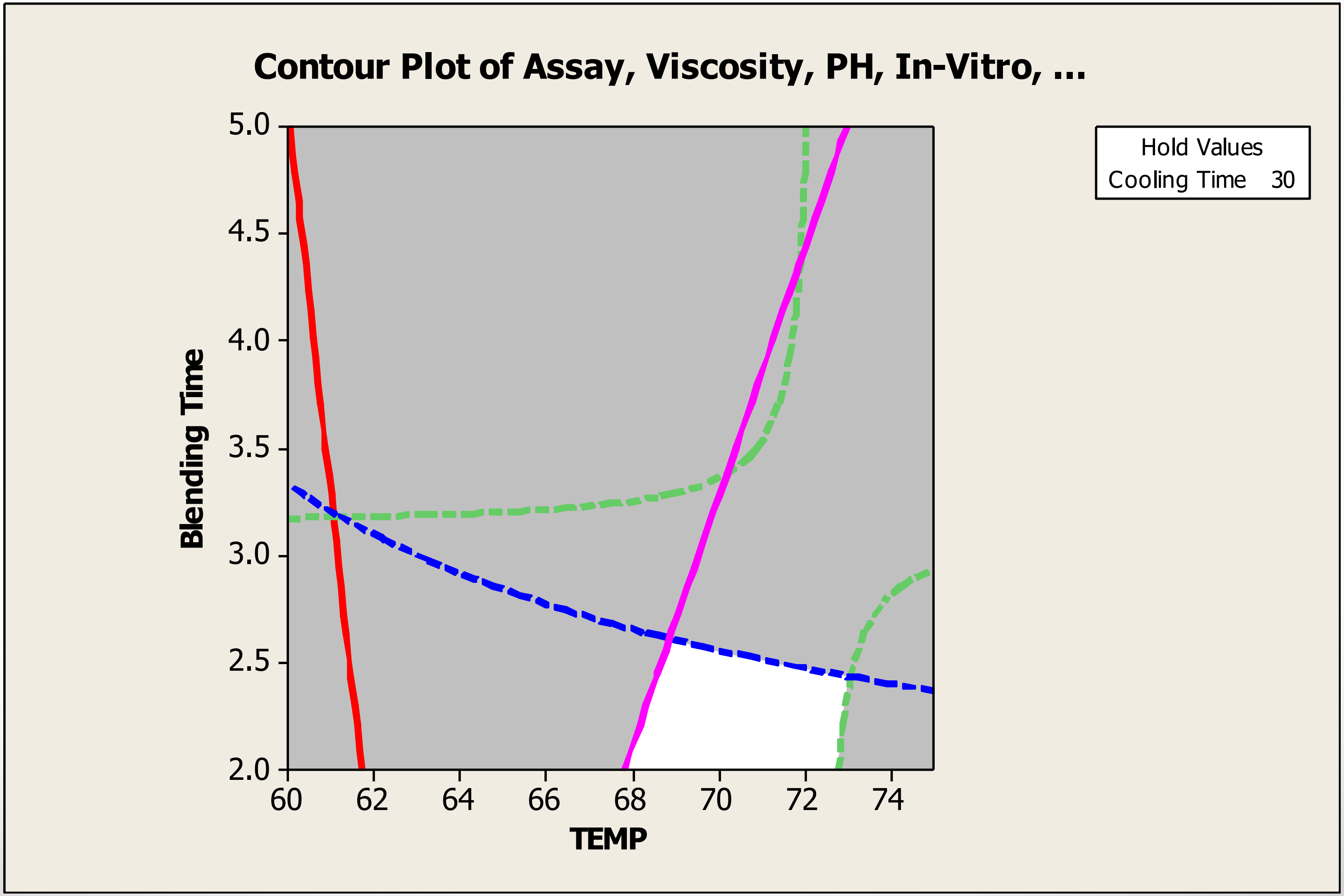
מהו סדר או פרוטוקול הניסוי ? Order

מהי שיטות איסוף וניתוח הנתונים מהניסוי ?

Factors and Levels

Formulation	Temperature (°C)	Emulsion creation time (min)	Cooling time (min)
D078	60	2	30
D081	**67.5**	**3.5**	**105**
D082	75	2	180
D077	75	5	30
D080	60	5	180
D079	60	2	180
D075	75	2	30
D084	**67.5**	**3.5**	**105**
D083	75	5	180
D076	60	5	30

Design Space



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Agenda

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ACE

Foam

HPLC

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http://www.pharmaqbd.com/files/articles/QBD_ACE_Case_History.pdf
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf

Conformia CMC-IM Working Group

Pharmaceutical Development
Case Study: "ACE Tablets"

Prepared by CMC-IM Working Group
March 13, 2008

Version 2.0

ACE

Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms

Introduction to the Example

This is an example pharmaceutical development report illustrating how ANDA sponsors can move toward implementation of quality by design (QbD). The example builds on acetriptan tablets (ACE) case study by treating that product as the reference product for the development of a generic product.

Quality by Design for ANDAs: An Example for Modified Release Dosage Forms

Introduction to the Example

This is an example pharmaceutical development report illustrating how ANDA applicants can move toward implementation of quality by design (QbD).

The purpose of the example is to illustrate the types of pharmaceutical development studies ANDA applicants may use as they implement QbD in their development process and promote discussion on how OGD would use this information in review.

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Target Product Profile of ACE

ACE

Quality Attribute	Target	Criticality
Dosage form	Tablet, maximum weight 200mg	Not applicable
Potency	20 mg	Not applicable
Pharmacokinetics	Immediate release enabling Tmax in 2 hours or less	Related to dissolution
Appearance	Tablet conforming to description shape and size	Critical
Identity	Positive for acetriptan	Critical
Assay	95 – 105%	Critical
Impurities	ACE12345 NMT 0.5%, other impurities NMT 0.2%, total NMT 1%	Critical
Water	NMT 1%	Not critical – API not sensitive to hydrolysis
Content Uniformity	Meets USP	Critical
Resistance to Crushing (Hardness)	5-12kP	Not critical since related to dissolution
Friability	NMT 1.0%	Not critical
Dissolution	Consistent with immediate release, e.g., NLT 75% at 30mins	Critical
Disintegration	NMT 15mins	Not critical, a precursor to dissolution
Microbiology	If testing required, meets USP criteria	Critical only if drug product supports microbial growth

DOE Study – API and Magnesium stearate (Lubricant) Interaction Study

ACE

Responses:

- Tablet hardness
- Dissolution average at 30 min.
- Tablet weight uniformity

Factors:

- Acetriptan particle size D90: 10, 25 & 40 µm
- Lubricant (Magnesium Stearate) level: 1, 1.5 & 2%

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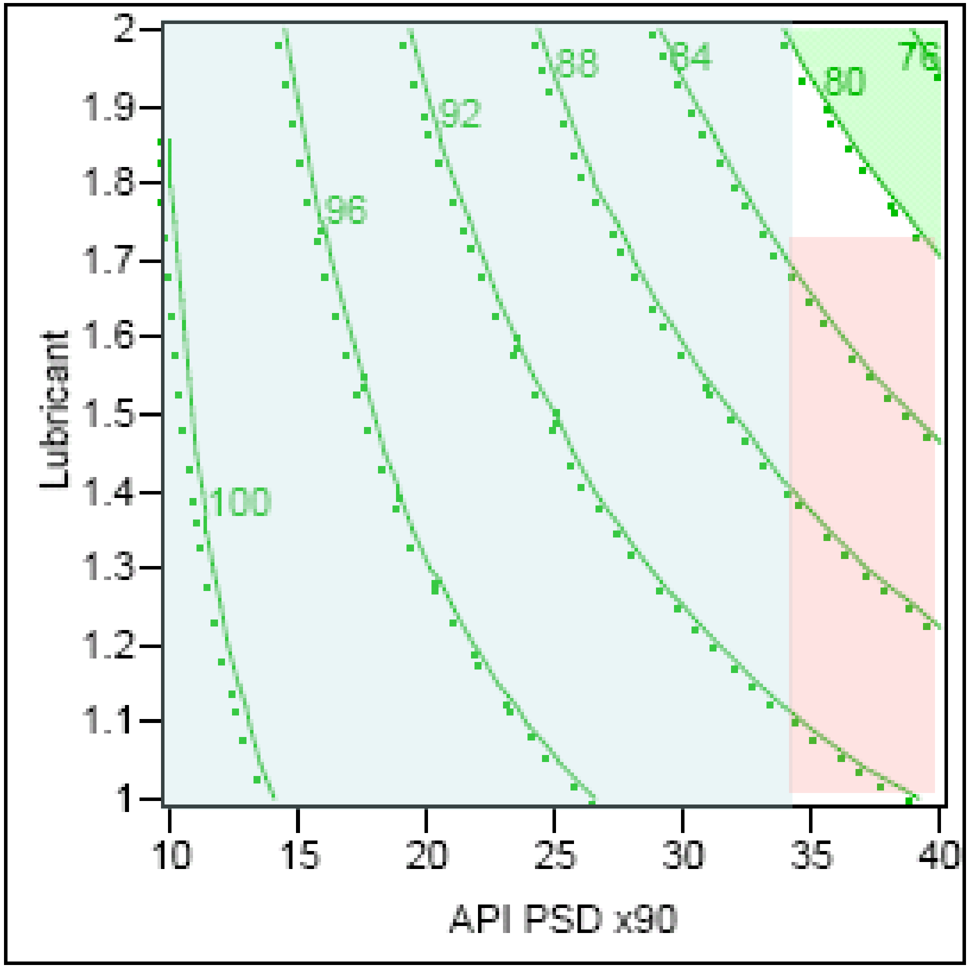
Contour Plot of Dissolution at a Set Target Tablet Hardness of 12kP

ACE

(Dissolution Acceptance Criteria > 80%)



ACE

Summary – Formulation Components Studies

The formulation composition is concluded to be:

Acetriptan particle size	d_{90} 10-35 microns	d_{90} 35-40 microns
Acetriptan concentration	10%	10%
Croscarmellose level	3-4%	3-4%
Mg Stearate level	1-2% (intragranular) 0.25% (extragranular)	1-1.75% (intragranular) 0.25% (extragranular)
Microcrystalline cellulose	40% (intragranular)	40% (intragranular)
Lactose monohydrate	38.75 - 40.75%*	39.00 – 40.75%*
Talc	5%	5%

* Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate

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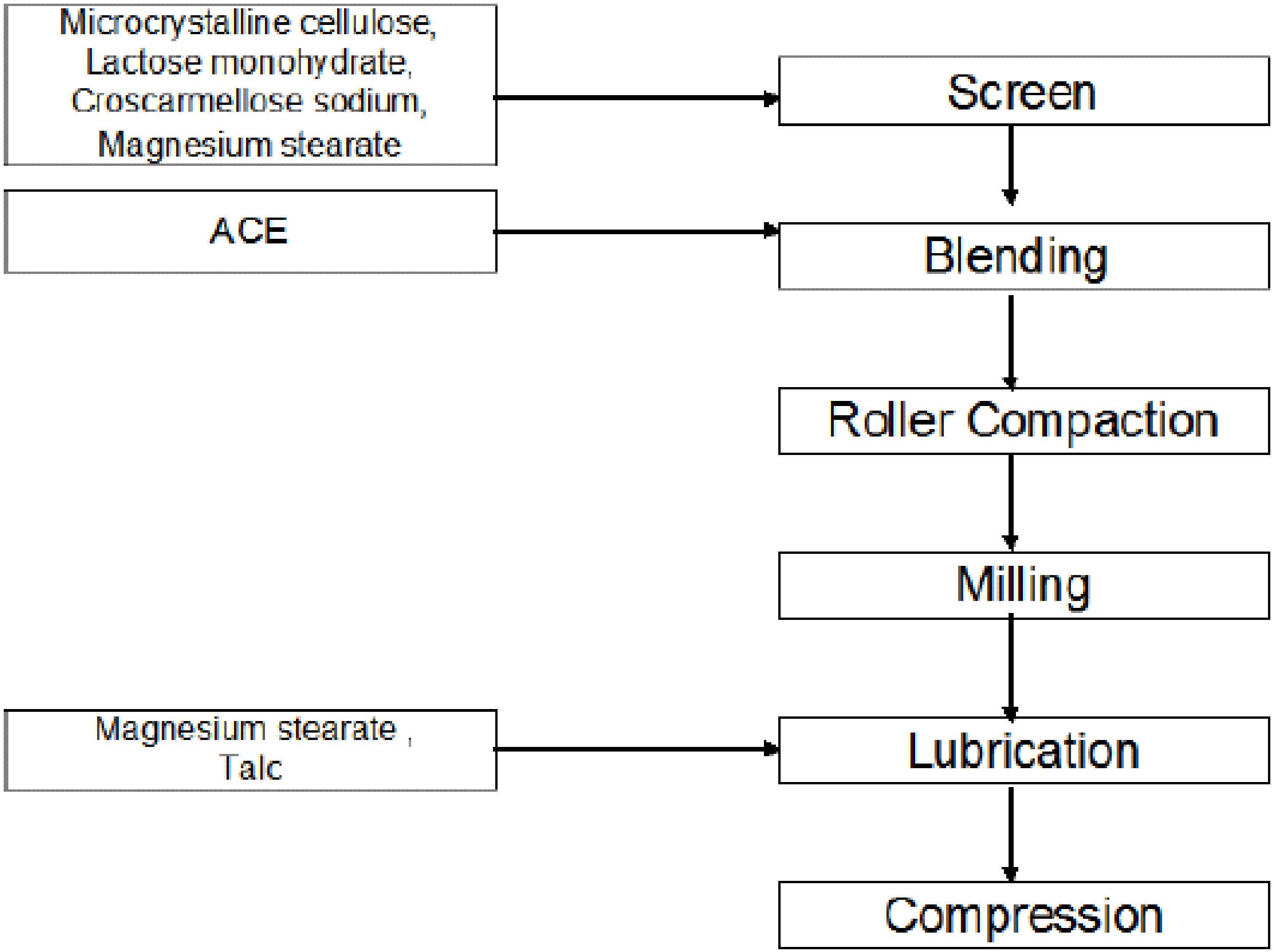
Manufacturing Process Development



ACE

Risk Assessment – Unit Operations

	Variables and unit Operations					
CQA's	Formulation Composition	Blending I	Roller Compression	Milling	Lubrication	Compression
Appearance	Low	Low	Low	Low	High	High
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	High
Impurities	High	Low	Low	Low	Low	Low
Content Uniformity	High	High	High	High	Low	High
Dissolution	High	Low	High	High	High	High

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ACE

Process Optimization – Blending Unit Operation

Response:

NIR: Near-infrared spectroscopy – to test the uniformity of the blending.

Factors:

- Range of Humidity: 20-70%RH
- Acetriptan Particle Size: D90 10-40μm
- MCC Particle Size: D50 30-90μm

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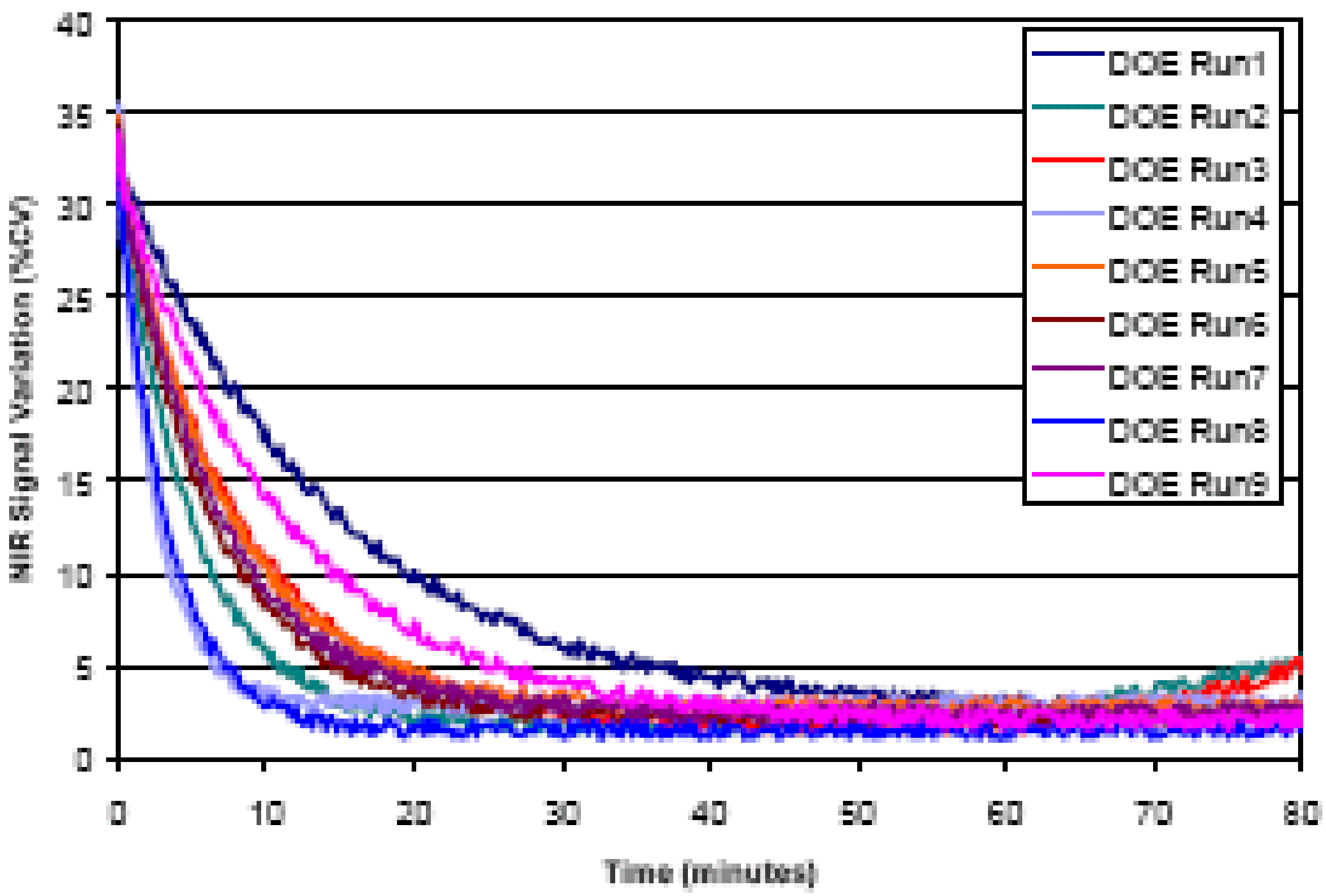
NIR For the DOE Study



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Process Optimization – Roller Compaction and Milling

ACE

	Variables and unit Operations	
CQA's	Roller Compression	Milling
Appearance	Low	Low
Identity	Low	Low
Assay	Low	Low
Impurities	Low	Low
Content Uniformity	High	High
Dissolution	High	High

Process Optimization – Roller Compaction and Milling

ACE

Responses

Final Product Attributes:

- Tablet Weight
- Tablet Hardness
- Tablet Friability
- Tablet Disintegration Time

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Process Optimization – Roller Compaction and Milling

ACE

Factors Investigated

Ingredients:

1. Acetriptan Particle Size (10 and 40µm)
2. Magnesium Stearate Level (1.25 and 2.25% w/w)
3. Croscarmellose Sodium Level (3 and 4% w/w)

Process:

1. Roller Pressure (50 and 150 bar)
2. Mill Screen Size (0.039 and 0.062 inches)
3. Mill Speed (600 and 1200 rpm)

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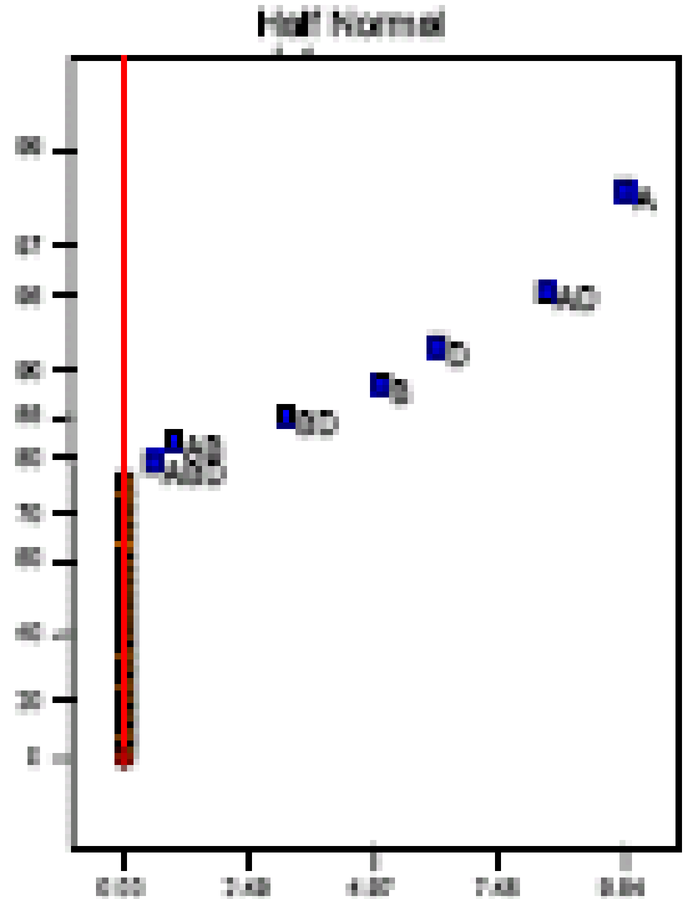
Significant Factors for Final Product Attributes

ACE

Response: Dissolution

- A: API level
- B: MgSt level
- C: CCS level
- D: Roller pressure
- E: Mill screen size
- F: Mill speed



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DOE 2 - Roller Compaction

ACE

Factors:

- Acetriptan PS: d_{90} 10-40µm
- Magnesium stearate level: 1-2% intragranular
- Roller Pressure: 50-150 bar

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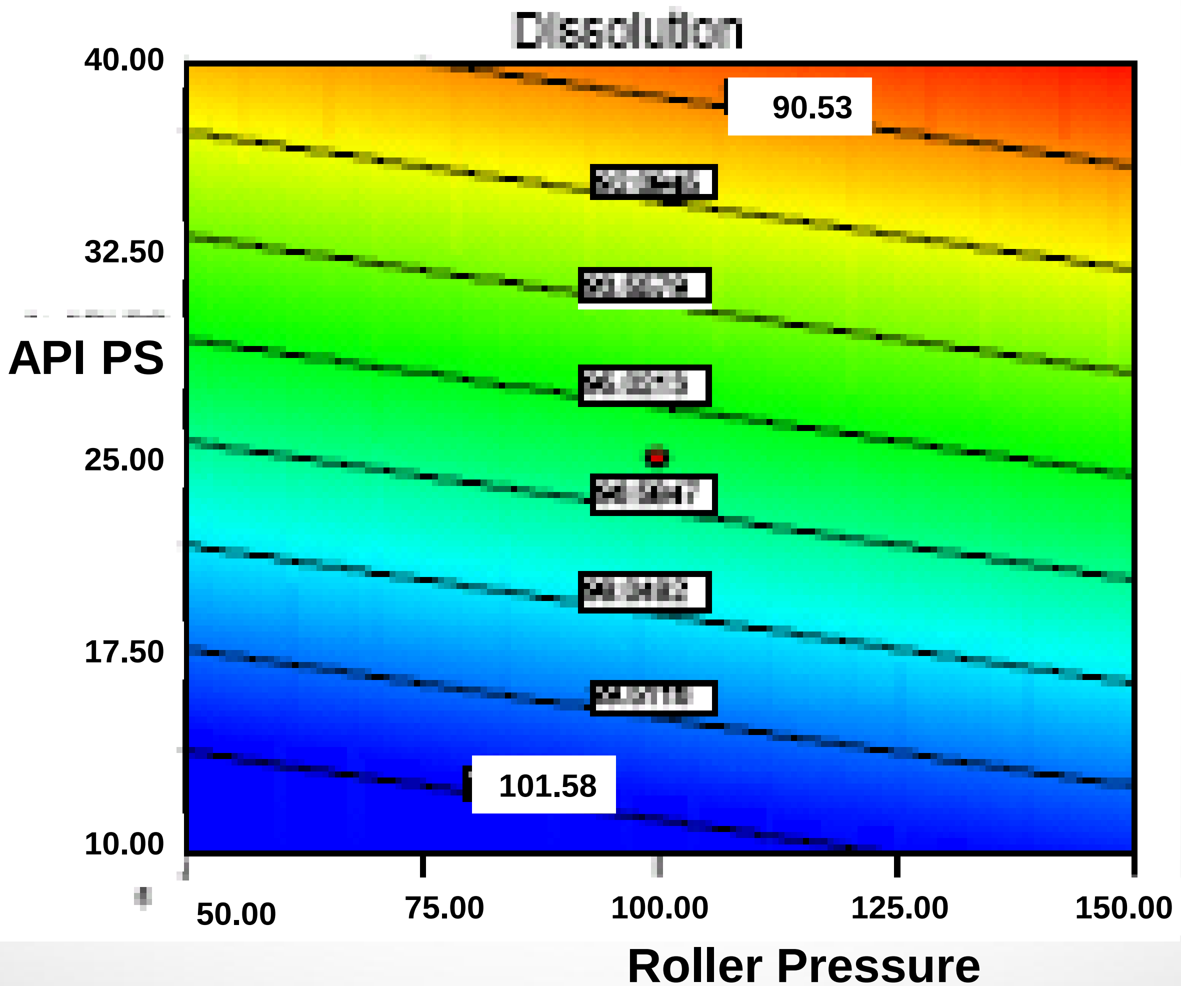
Contour Plot For API particle size and Roller Pressure vs. Tablet Dissolution (at 1% Mg. St. Level)

ACE



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Design Space for ACE tablets

ACE

Formulation, blending, compaction and milling parameters		
Acetriptan particle size	d_{90} 10-35 microns	d_{90} 35-40 microns
Acetriptan concentration	10%	10%
Microcrystalline cellulose (MCC)	40% (intragranular)	40% (intragranular)
MCC particle size (d_{50})	30 - 90 micron	30-90 micron
Croscarmellose level	3-4%	3-4%
Lactose monohydrate	38.75 - 40.75%*	39.00 – 40.75%*
Lactose particle size (d_{50})	70 – 100 micron	70 – 100 micron
Talc	5%	5%
Mg Stearate level	1-2% (intragranular) 0.25% (extragranular)	1-1.75% (intragranular) 0.25% (extragranular)
Blender	Any diffusive blender	Any diffusive blender
Humidity	20-70% RH	20-70% RH
Relative ribbon density	0.68-0.81	0.68-0.81
Granule GSA (cm^2/100g)	12,000-41,000	12,000-41,000
Hardness (kN)	5 -12	5-12
Mean core weight 20 cores	194-206mg	194-206mg
Individual core weights	190-210mg	190-210mg
Scale	Any	Any
Site	Any certified site using equipment of same principles	Any certified site using equipment of same principles

*Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate used in order to ensure 200mg overall tablet weight.

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Foam

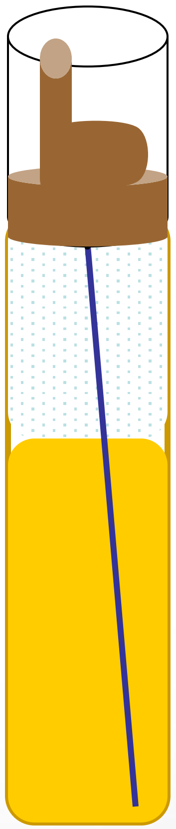
An Oily Foam Drug Product Example

The goal is to design a process suitable for routine commercial manufacturing that consistently delivers a product that meets its quality attributes.

The Product

Foam

- 2% of Active Material
- Oily Foam
- Dip Tube (?)
- Propellant
- Valve
- Actuator
- Can



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Target Product Profile

Foam

Quality Attribute	Target at time 0	Target at end of shelf life	Criticality
Dosage form	Foam	Foam	NA
Potency	2%	2%	NA
Appearance	White foam	White foam	Critical
Assay	95-105%	90-110%	Critical
Impurities	Not More Than…	As per USP 33 monograph	Critical
Water	NMT	-	Critical
Safety	NLT other products in the market	NLT other products in the market	Critical
Microbiology	Meets USP criteria	Meets USP criteria	Critical
Delivery amount	Meets USP criteria	Meets USP criteria	Critical
Shelf Life	NLT 24 months	NLT 24 months	Critical

Foam

Prior Knowledge

- API is sensitive to extensive heat. (24 hr. at 80^0C are equivalent to 1 month at 40^0C.)
- API is sensitive to water.
- Manufacturing and Packaging Processes includes heating.

- Manufacturing Process: API is exposed to 60^0C.
- Packaging Process: Above 55^0C.
- Bulk should be visually clear.

Foam

Questions that are looking for answers:

Manufacturing:

1. Specify manufacturing equipment
2. Filtering the bulk; is it essential?
3. Is there a need to cool down the bulk in the storage container?

Packaging:

1) Immediate filling vs. bulk reheating for packaging, any differences?
2) Epoxy containers vs. PAM containers, any differences?
3) Propellant type and concentration – Determine levels
4) Dip tube – Can we use them?
5) Determine the limits of filling specification for the bulk and propellant.
6) Leakage tests – Do we pass them?
7) Vacuum effect: Design on target formulation

Foam

Manufacturing and Packaging Process

Inactive ingredients → Heating to 80°C

↓

Cooling to 60°C

↓

Active ingredient → Dissolution of active ingredient, for 30 minutes at 60°C

↓

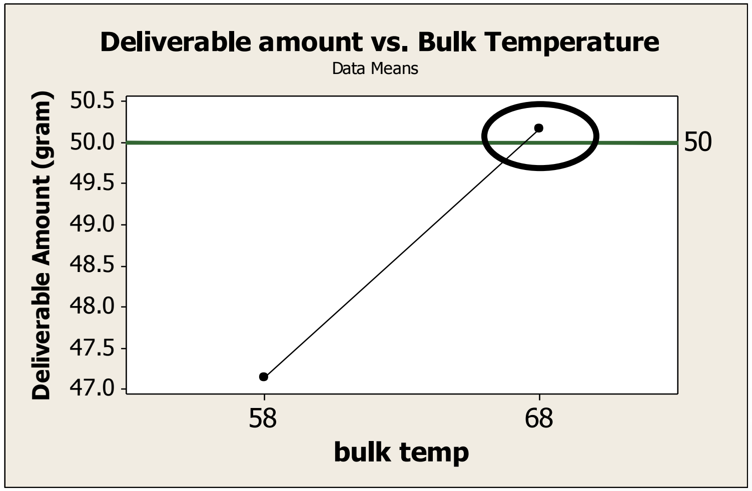
Packaging at minimum temperature of 55°C

Foam

1. What is the preferable packaging temperature?

Aerosol Performance

Deliverable Amount:



KPA

Foam

Packaging Experiment: Factors and Levels

Packaging Process Parameters:

1.	Packaging Temp.:	58 or 68^{0}C
2.	Vacuum:	-0.2 or -0.5bar
3.	Bulk Filling Range:	50.5 - 56.0g
4.	Gas Filling Range:	3.5 - 6.5g

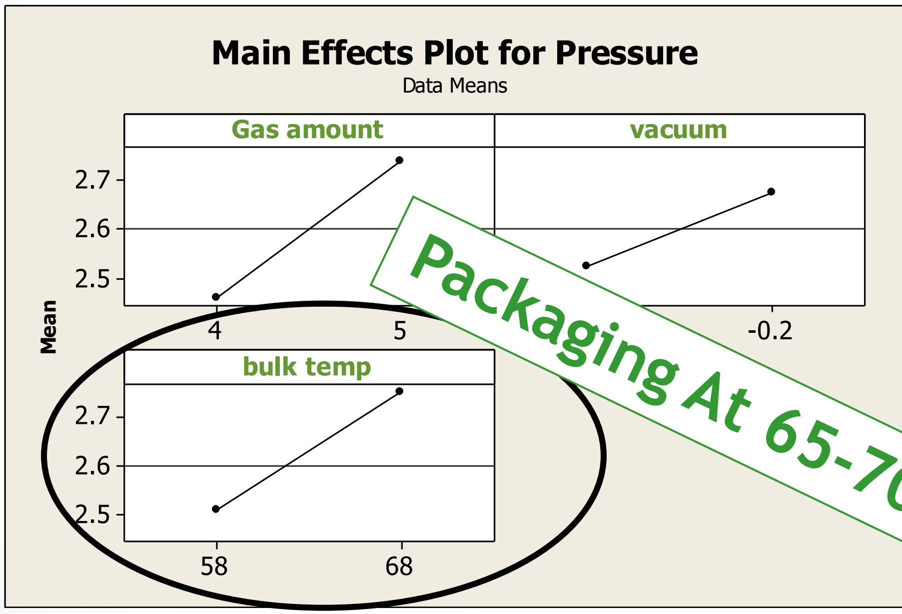
Packaging System Parameters:

1.	Can:	Epoxyphenolic or PAM
2.	Dip tube:	With or without

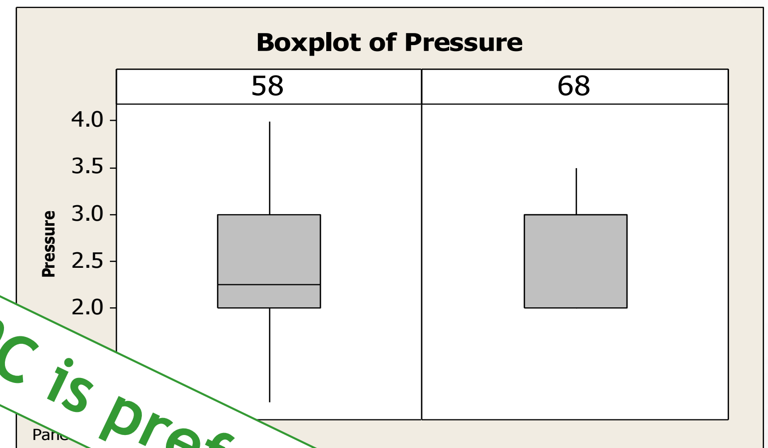
KPA

Foam

2. What is the effect of the factors on pressure?



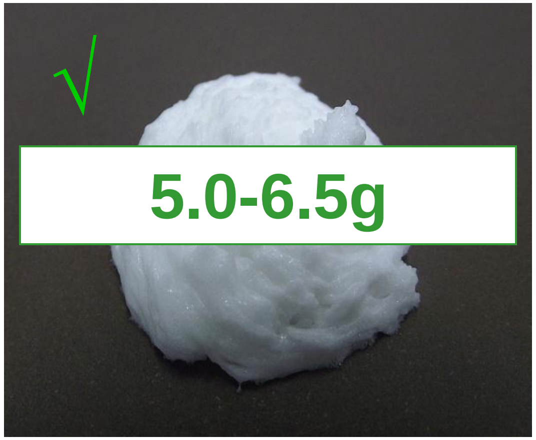
Packaging At 65-70^{0}C is preferred



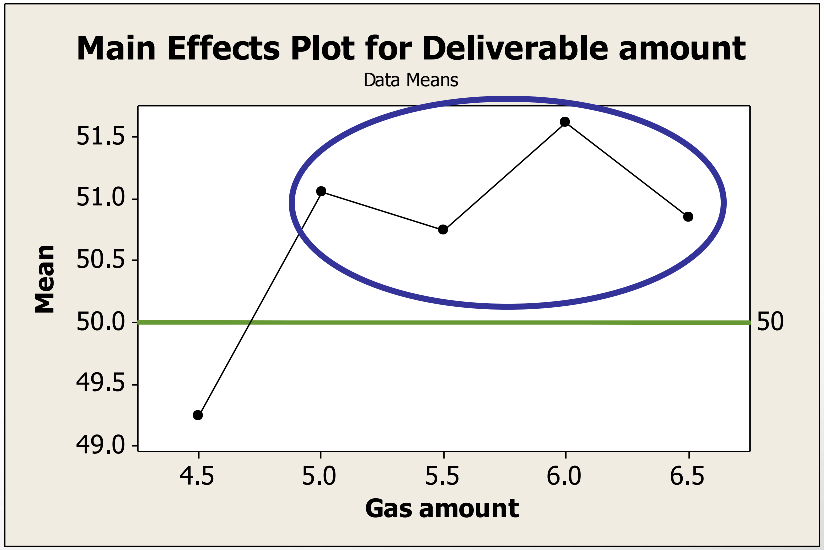
When p… ng at 58^{0}C the pressure va… ability between different cans is higher

3. What is the preferable gas filling range?

Appearance:



Deliverable Amount:



Foam

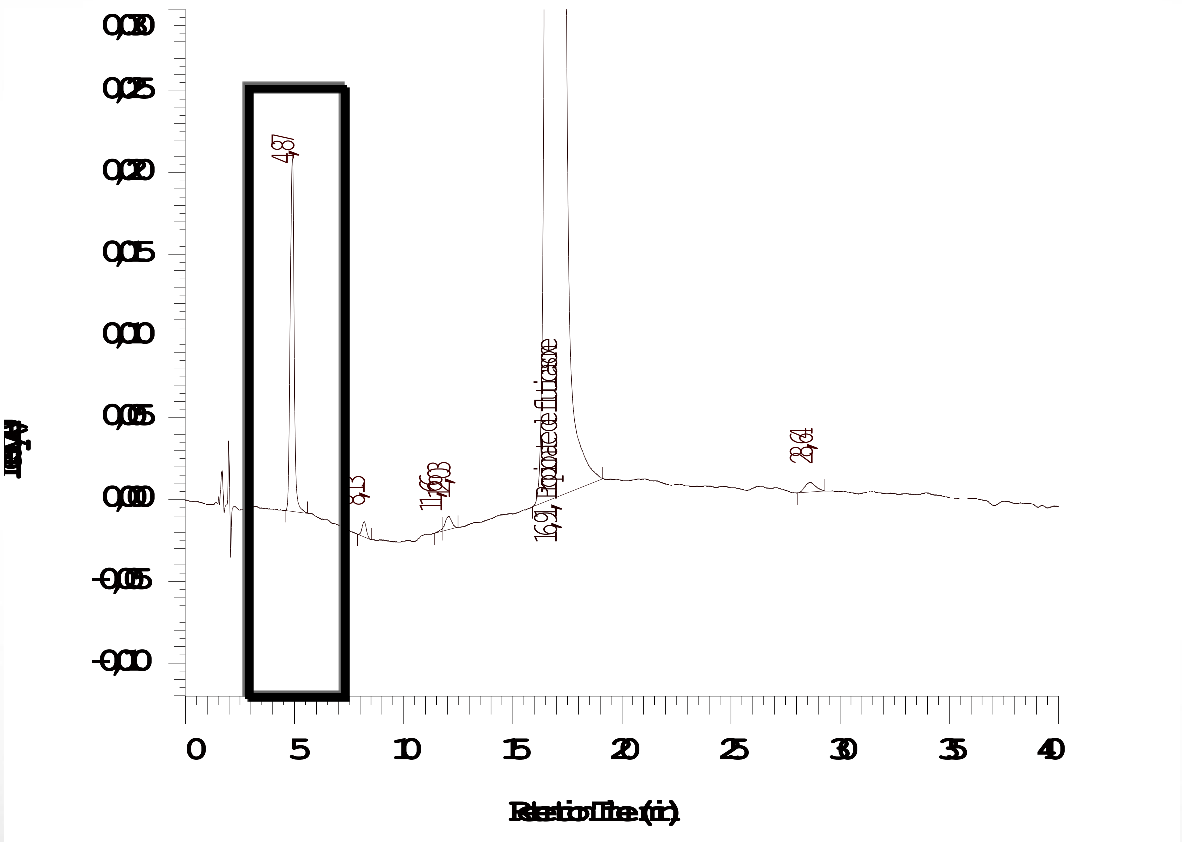
Packaging Ranges and Design Space

Parameter	Approved Range/ Design Space
Packaging Temperature	65-70^{0}C
Immediate/ Reheating for packaging	Immediate/ Reheating
Gas Filling Range	5.0g-6.5g
Bulk Filling Range	51.0-54.0g
Dip Tube	Better without dip-tube

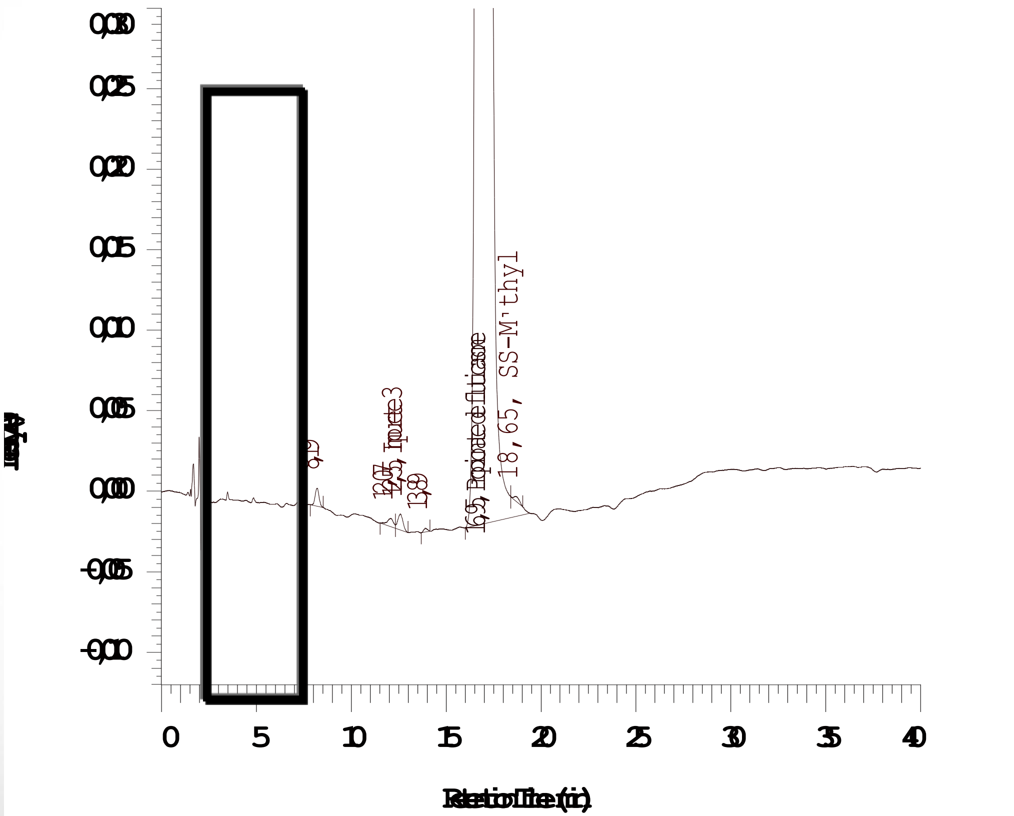
Analytic Methods Development

DryLab simplifies and speeds the process of developing good chromatographic separations or methods by allowing to model changes in separation conditions using a personal computer.

Chromatogram with true signal at 4.9 min.

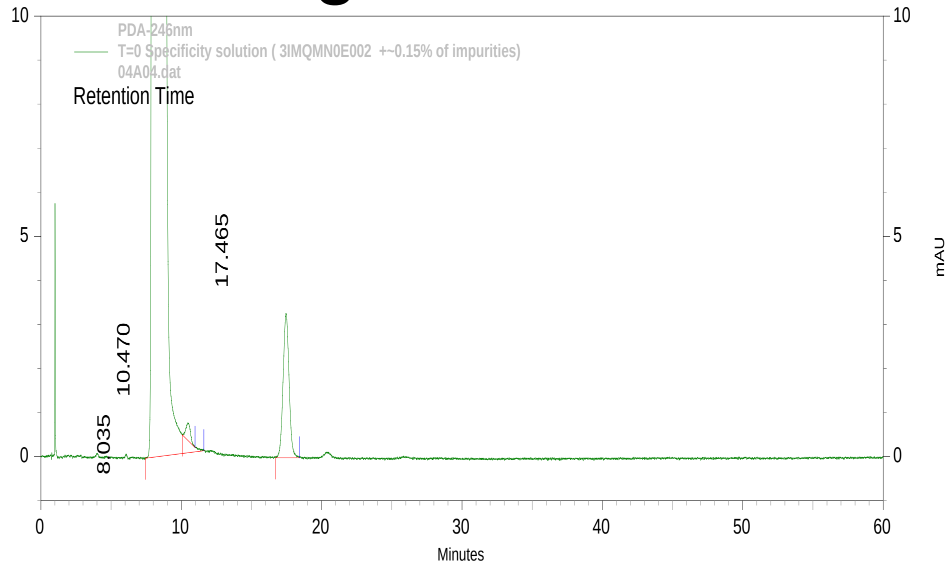


Chromatogram with false negative signal at 4.9 min.

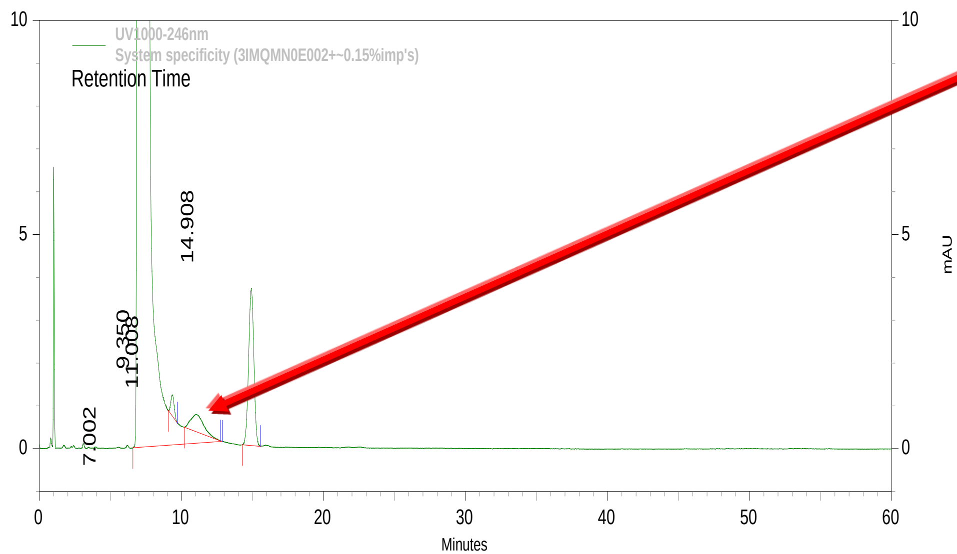


Chromatogram with false positive signal at 11 min.

HPLC



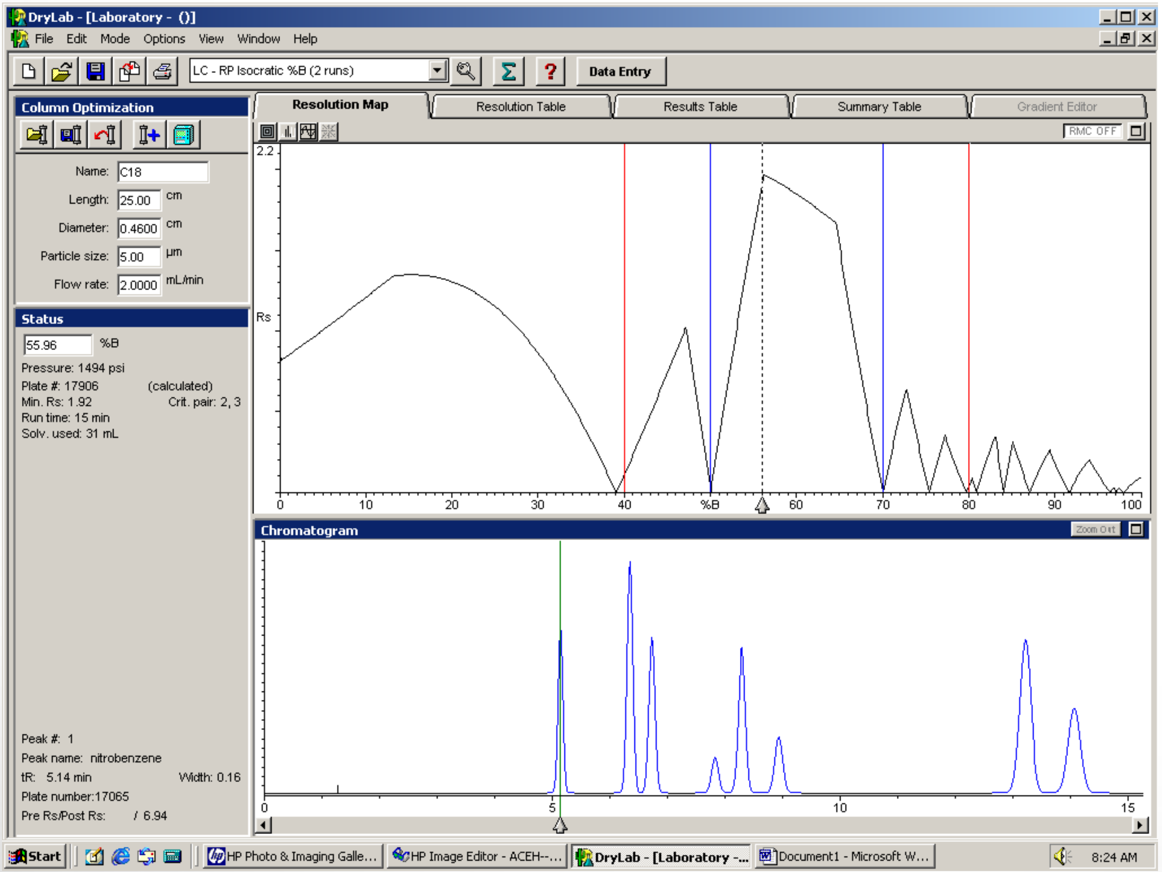
Typical chromatogram of related substances.



Chromatogram of related substances with False-positive Signal (peak at 11 min).

Simulated Chromatograms

HPLC



DryLab® 2000 Plus

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Development of Analytical Methods

HPLC

Run Order	n-Hexane/EtOH [v/v]	DEA[ml]	T[°C]
1	4	2ml	15°C
2	5.7	0.5ml	15°C
3	5.7	2ml	40°C
4	4	0.5ml	40°C

Bates, R., Kenett R., Steinberg D. and Wynn, H. (2004), *Robust Design using Computer Experiments,* The 13-th Conference on Mathematics for Industry 21-25 June 2004 Eindhoven, The Netherlands.

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Development of Analytical Methods

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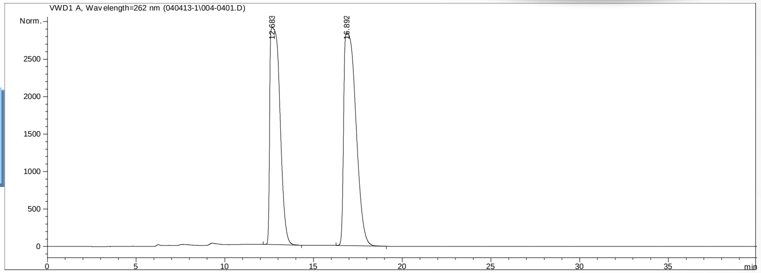
1



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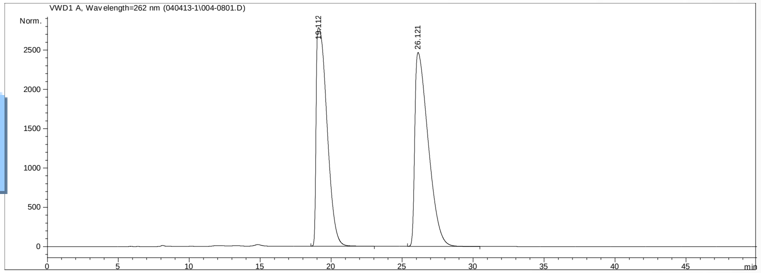

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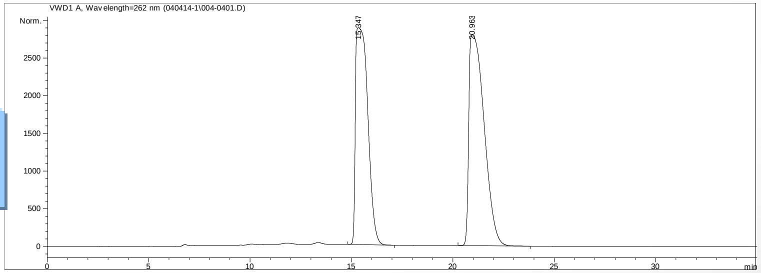

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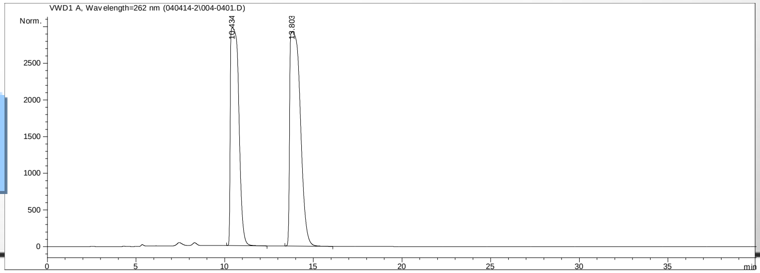

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HPLC

Simulation Experiments Analysis

#	Mobile Phase	T[°C]	RT[min] Isomer #1	RT[min] Isomer #2	Resolution
1	800ml n-Hexane 200ml EtOH 2ml Diethylamine(DEA)	15° C	RT =12.683 Tailing=3.0 Plates=2239	RT =16.892 Tailing=2.8 Plates=2758	3.56
2	850ml n-Hexane 150ml EtOH 0.5ml Diethylamine(DEA)	15° C	RT =19.113 Tailing=3.6 Plates=2938	RT =26.122 Tailing=3.3 Plates=3709	4.48
3	850ml n-Hexane 150ml EtOH 2ml Diethylamine(DEA)	40°C	RT =15.347 Tailing=3.0 Plates=2867	RT =20.963 Tailing=3.4 Plates=3576	4.40
4	800ml n-Hexane 200ml EtOH 0.5ml Diethylamine(DEA)	40°C	RT =10.434 Tailing=3.3 Plates=2236	RT =13.803 Tailing=3.7 Plates=2459	1.32

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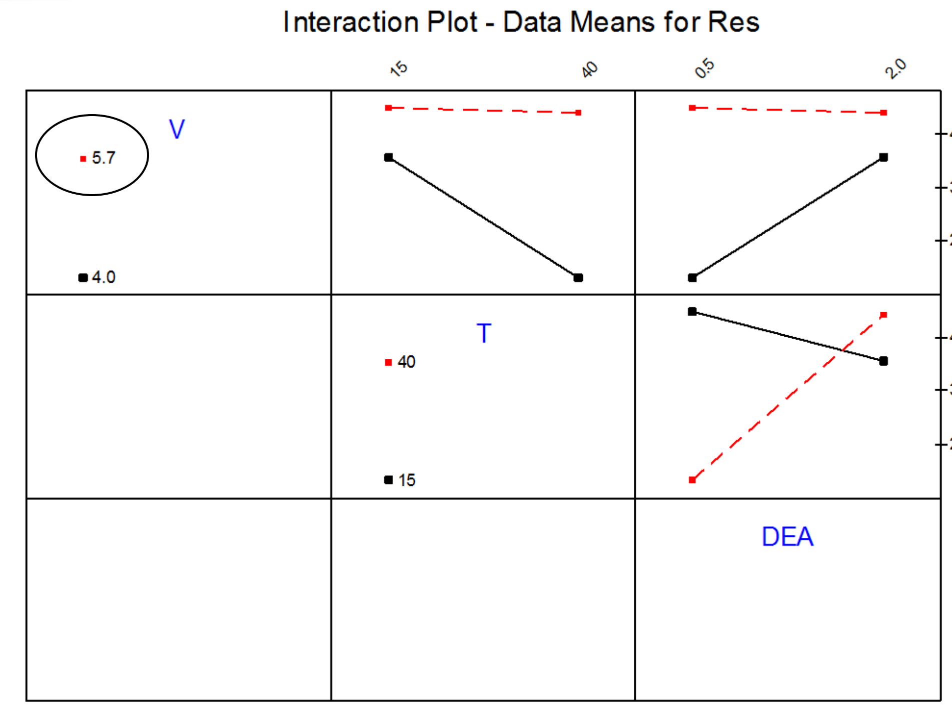
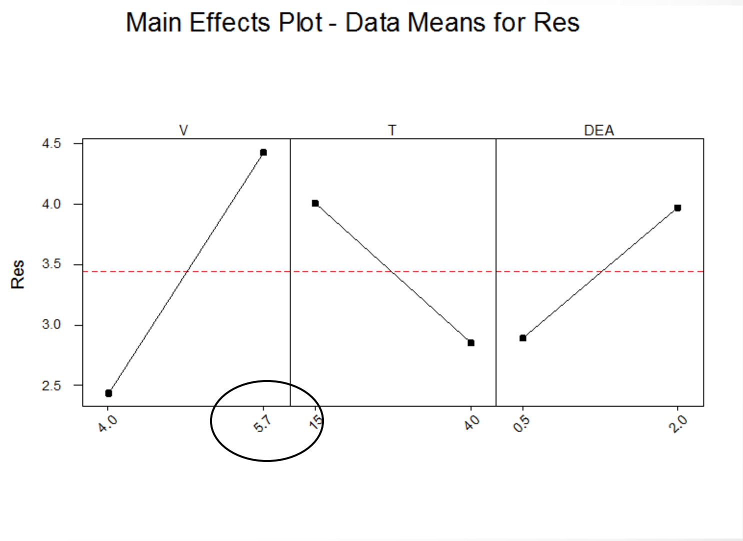
HPLC

Simulation Experiments Analysis





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