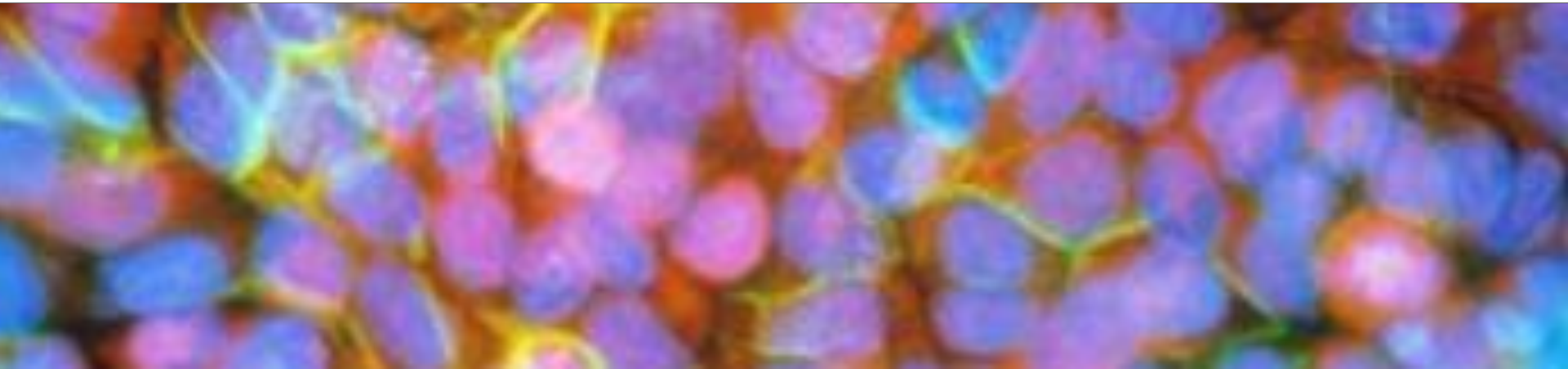
The role of statistics in ensuring quality in pharmaceutical manufacturing

Jens Lamerz

EFSPI Workshop Regulatory Statistics, 13. Sept. 2016



What is Quality by Design (QbD)?

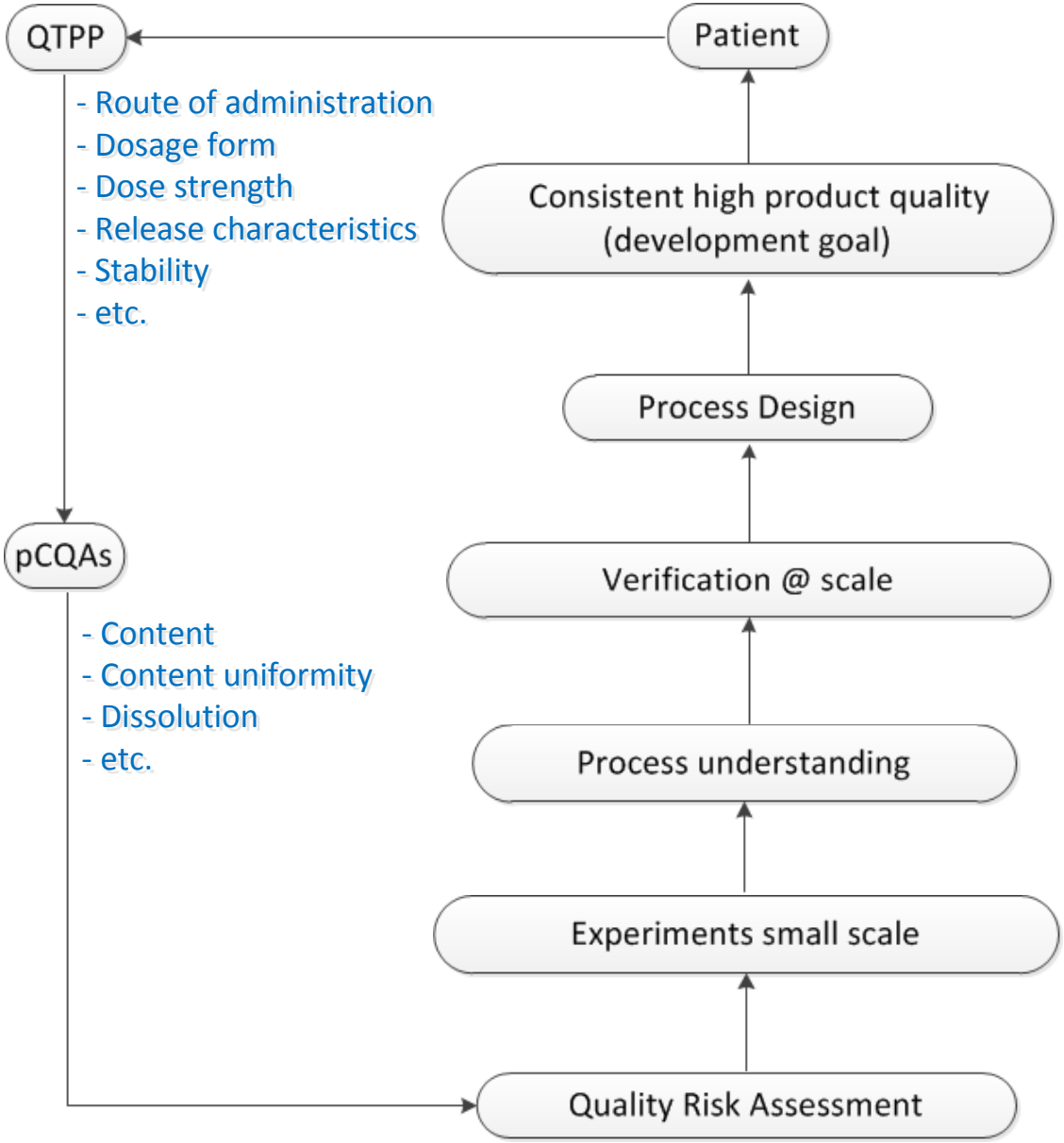
ICH Q8R2: *QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"*

in other words:

"Doing now what patients need next"

Slide by Martin Wunderlich

What is Quality by Design (QbD)?



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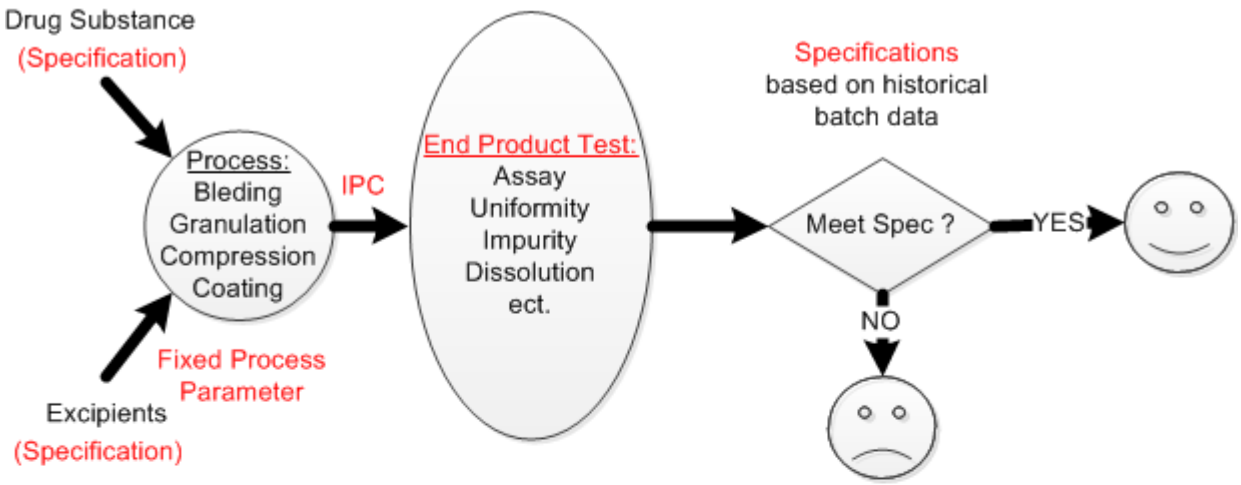
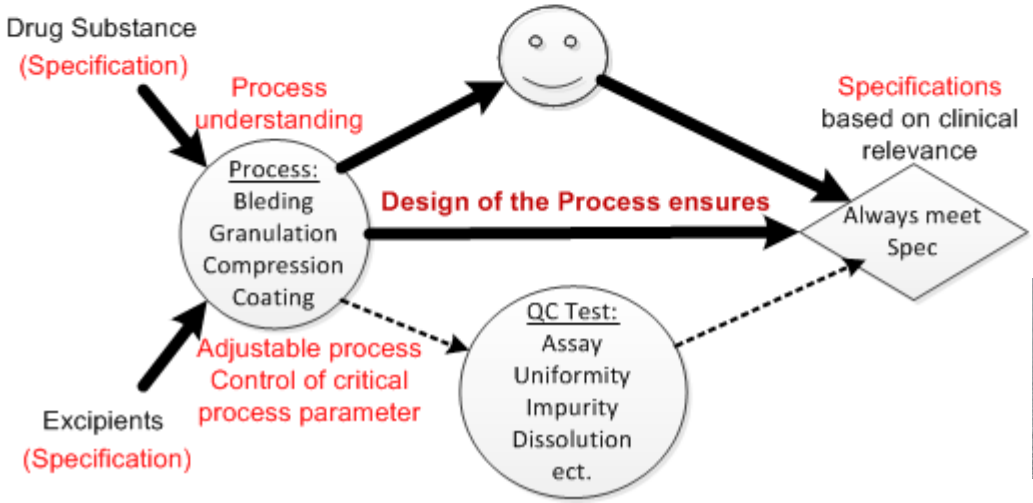
Quality by End Product Testing



Quality by Design



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Safety & Efficacy and the Critical «C's»

CMAs

Critical
Material
Attributes

Active **P**harm. **I**ngredient

Examples:

Particle Size of API

Excipients

CPPs

Critical
Process
Parameters

Examples:

Amount of water

Drying Temp.

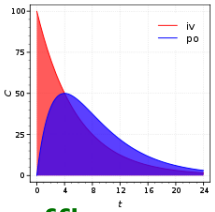
CQAs

Critical
Quality
Attributes

Examples:

Dissolution

Genotoxic Impurities



efficacy

safety

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Roche

Roche

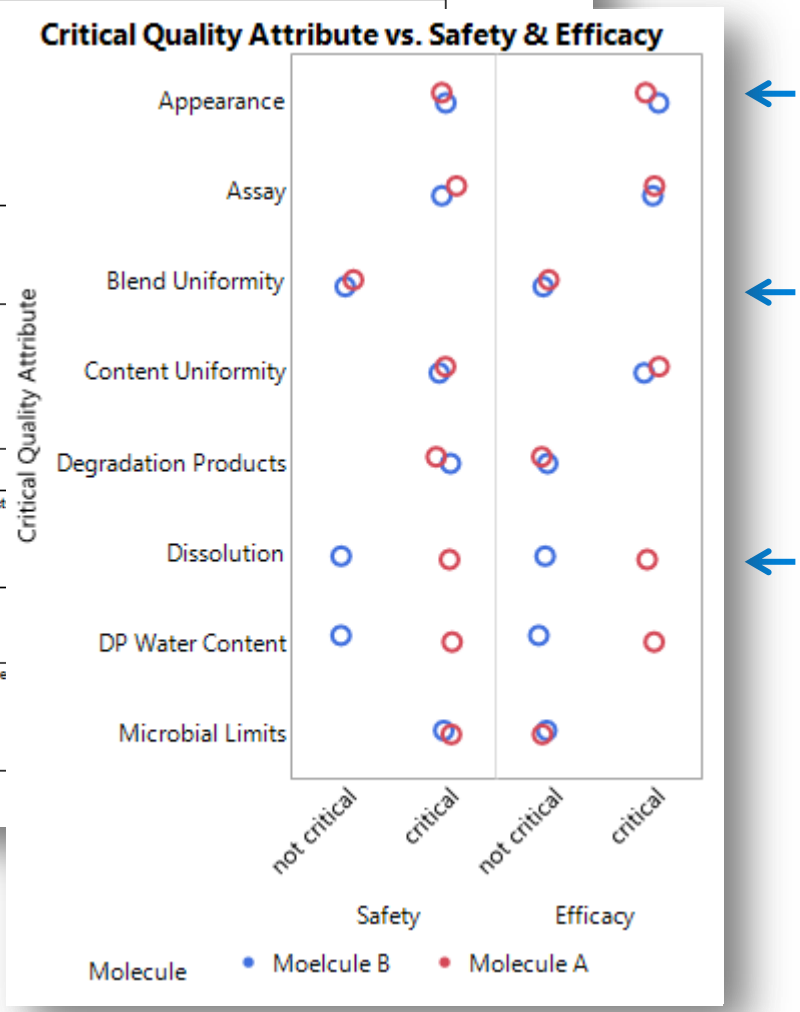
Table P.2-2 **Identification and Justification of Drug Product Critical Quality Attributes**

Potential Quality Attributes of the Drug Product
Appearance
Identification
Content
Uniformity of Dosage Units
Degradation Products
Dissolution
Water Content

Genentech
A Member of the Roche Group

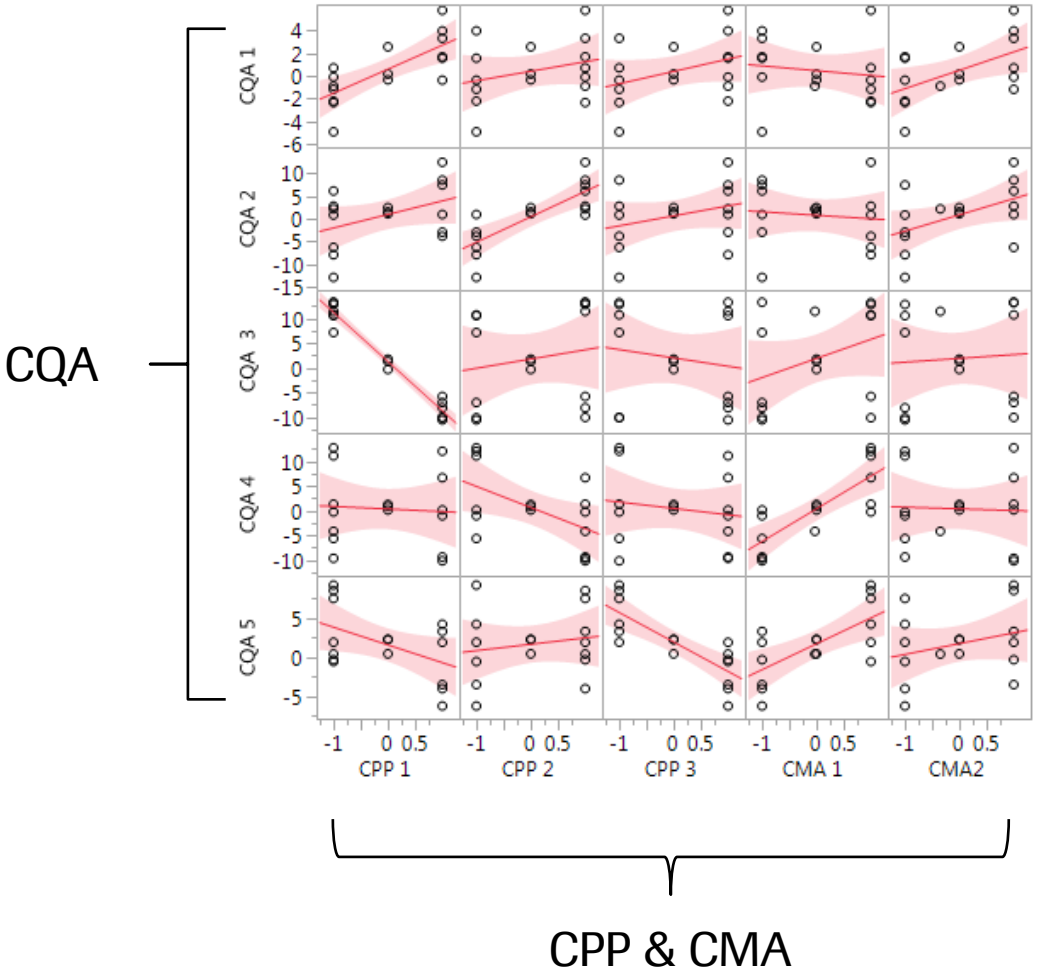
Table 2.3.P-3 **Critical Quality Attributes**

Drug Product CQA	Target	Justification
Description		
Capsule Size		
Color of Body		
Color of Cap		
Imprint Body		
Imprint Cap		
Imprint Color		
Capsule Content		
Appearance		
Color		
Identification of Alectinib HCl		
Assay/Content of Alectinib HCl		
Degradation Product		
Ethyl Chloride		
Unspecified, Each		
Total of All		
Dissolution		
Uniformity of Dosage Units		



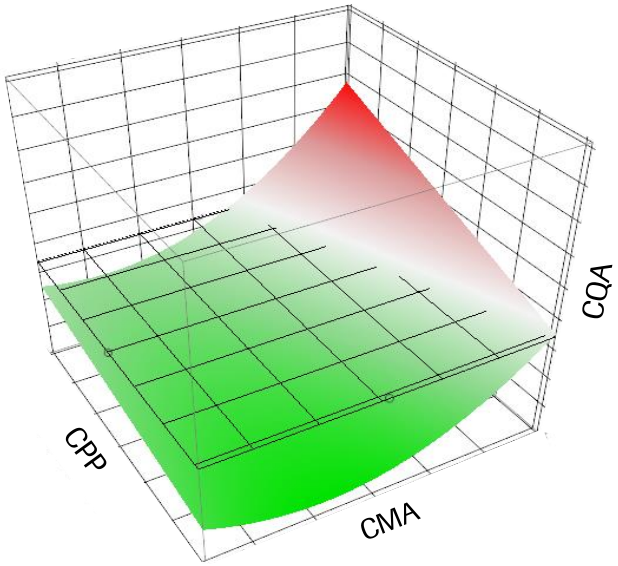
Approach

- Where appropriate, standard least squares models are established for each of the responses (CQA).



Design Space

- Design Space
  - important element of QbD
  - CQA within an appropriate limit or range ensuring the desired product quality.
  - CQA as a response from a function of CPP and CMA.

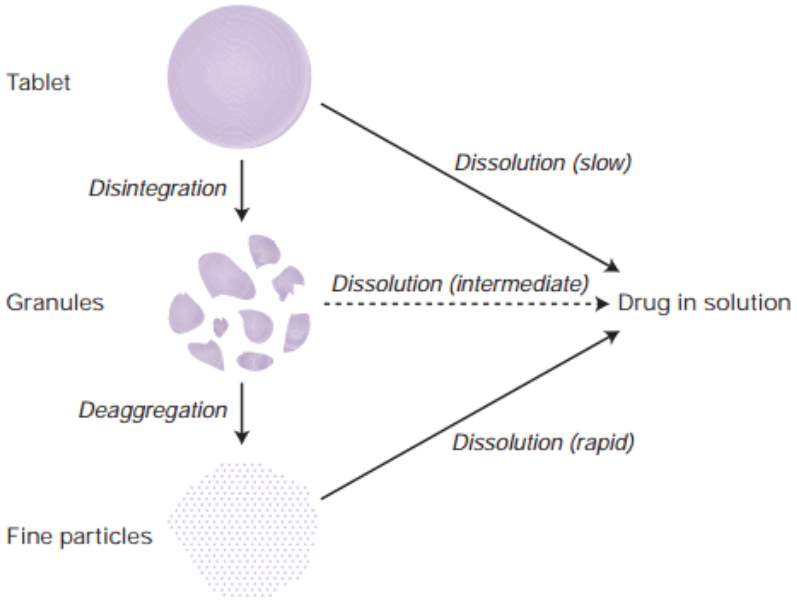


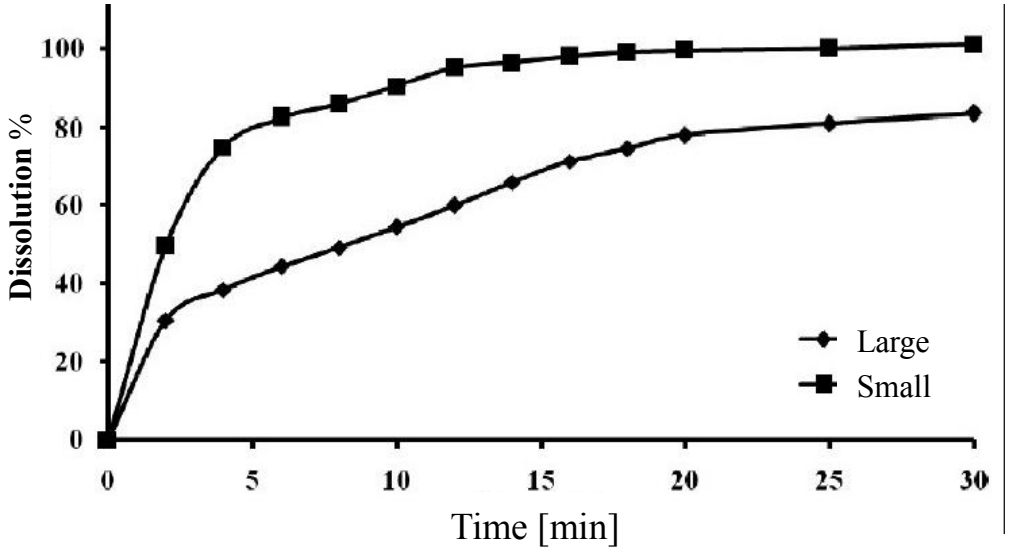
$$y_{CQA} = \alpha_1 \times CPP_1 + \beta_2 \times CMA_1 + \gamma_3 \times CPP_1 \times CMA_1 + \ldots + \varepsilon$$

Example I

Assuring stable Dissolution by controlling Amorphous Content

Dissolution of Tablets

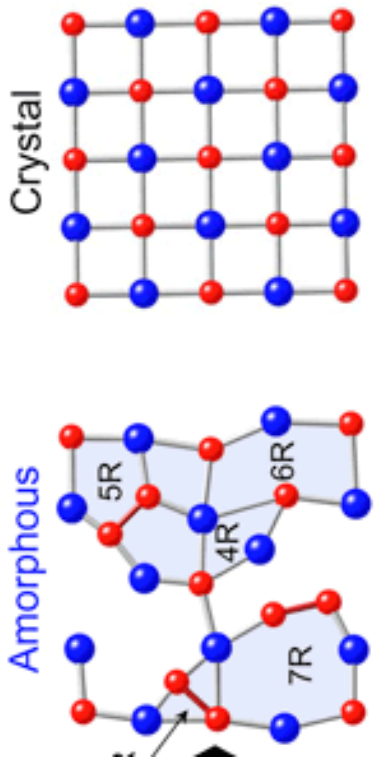


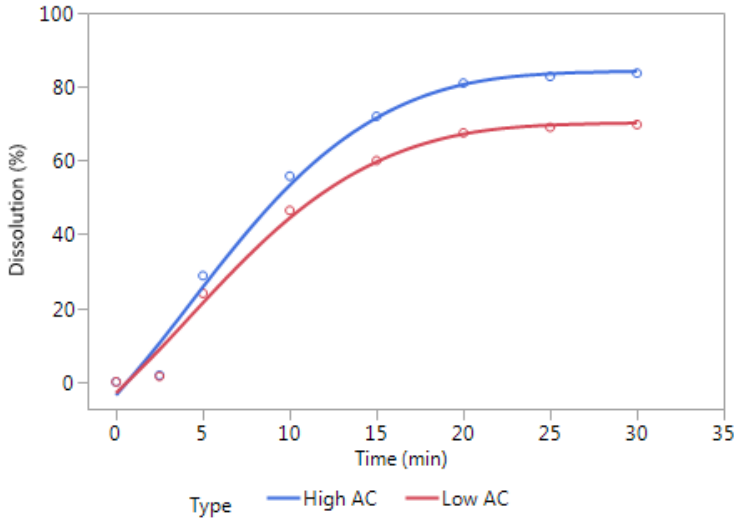


- The higher the surface the faster the dissolution.
- Smaller particles have a higher surface than large particles.
- API is milled to reduce particle size and thus control dissolution rate.

Images by pharmamirror.com

Control Dissolution rate by controlling % amorphous API of content

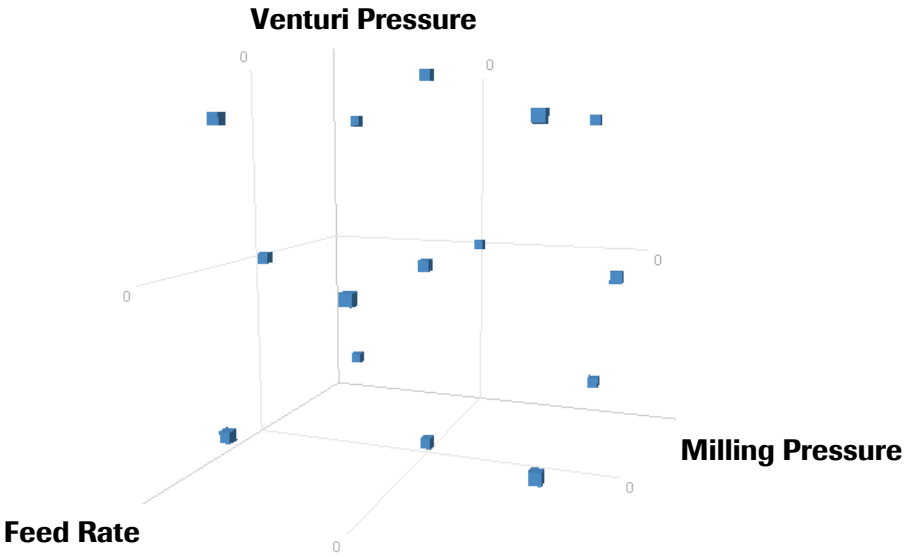


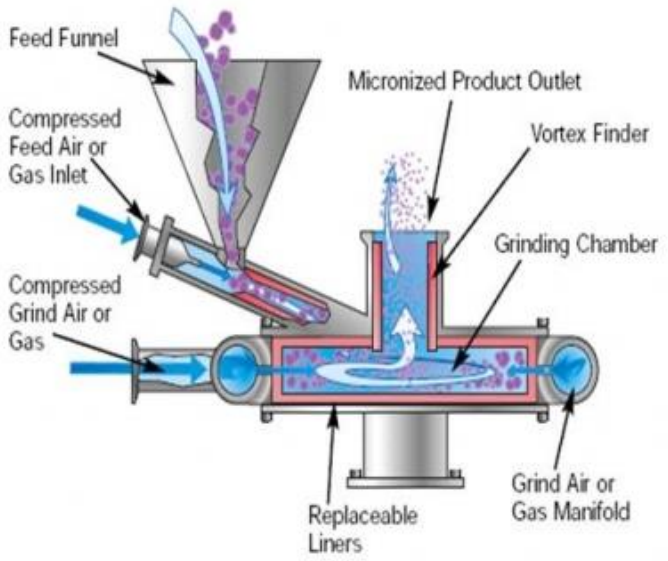


- Milling can introduce variable amounts of amorphous content in API.
- Concern of HA: variability in the % of amorphous content may alter dissolution rate and/or bioavailability.

Simulated Data.

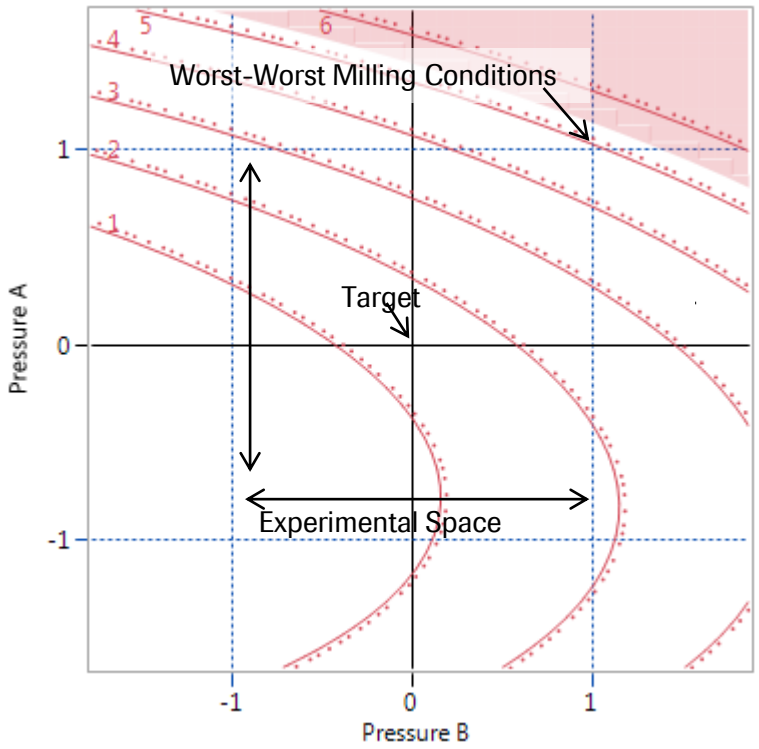
DoE of Milling API studies Amorphous Content

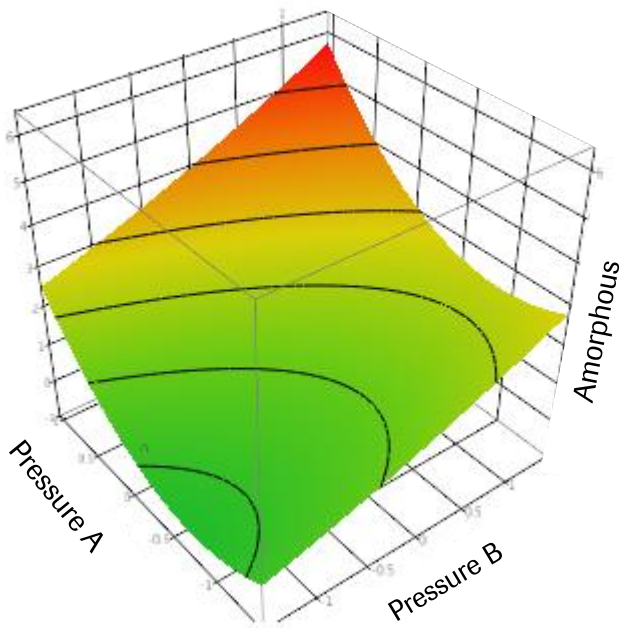




- Full Factorial (+) Design studied effect of **F**eed **R**ate, **M**illing **P**ressure and **V**enturi **P**ressure on amorphous content.

Result & Conclusion of Example I





- Jet milling of API within the proven acceptable ranges for the process parameters will produce Drug Substance with an amorphous content that is considered acceptable (typically ≤5%).

Simulated Data.

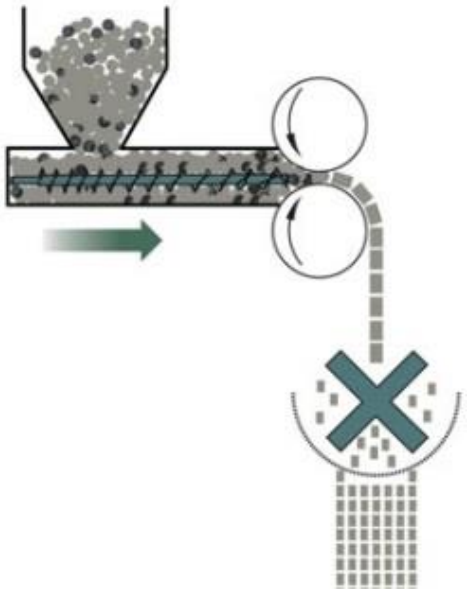
Example II –

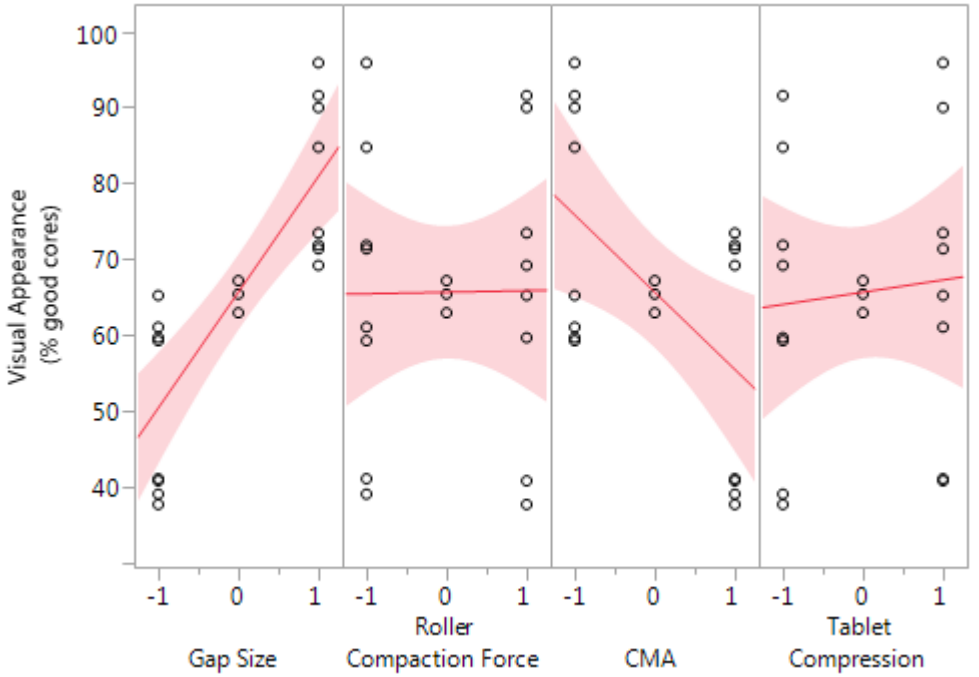
Controlling Visual Appearance of Tablets

Visual appearance of tablet cores was a problem.

Photos left by Stefanie Peter, photo right by Alfred Hitchcock Psycho, 1960

Controlling visual appearance with Gap Size

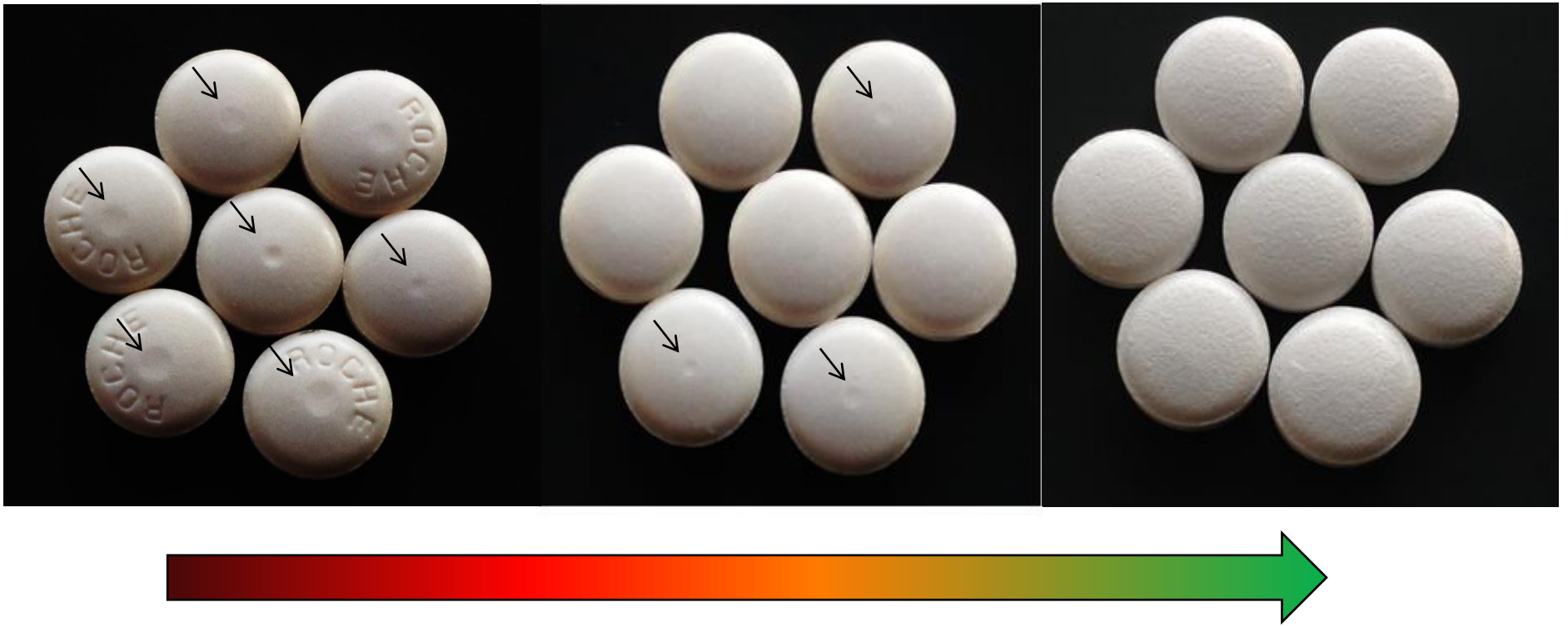




- Roller compaction compresses blends of API and excipients to improve flow ability, avoid de-mixing and improve tablet compression properties.
- By adjusting RC gap size and controlling CMA, visual appearance was highly improved.

Simulated Data.

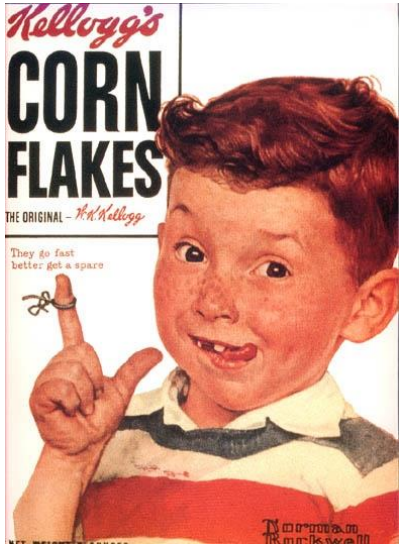
By adjusting Roller Compaction gap size, visual appearance was highly improved.



Photos are modified.

DP Process Validation –

A story about thieves, blends and the Corn Flakes effect



DP Process Validation (PV)

- Proves that the DP manufacturing process delivers safe and efficacious capsules.
- Manufactured at commercial scale: after this successful PV, the product can be shipped to patients.
- Performed according to PV protocol, with predefined specifications
  - Dissolution of API over time
  - Homogeneous and correct level of API in process steps (e.g. after blending and encapsulation)
  - Appearance
  - …

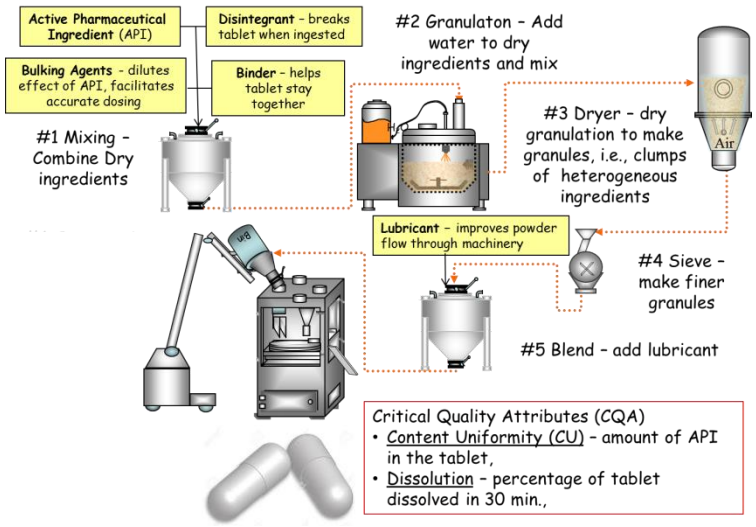
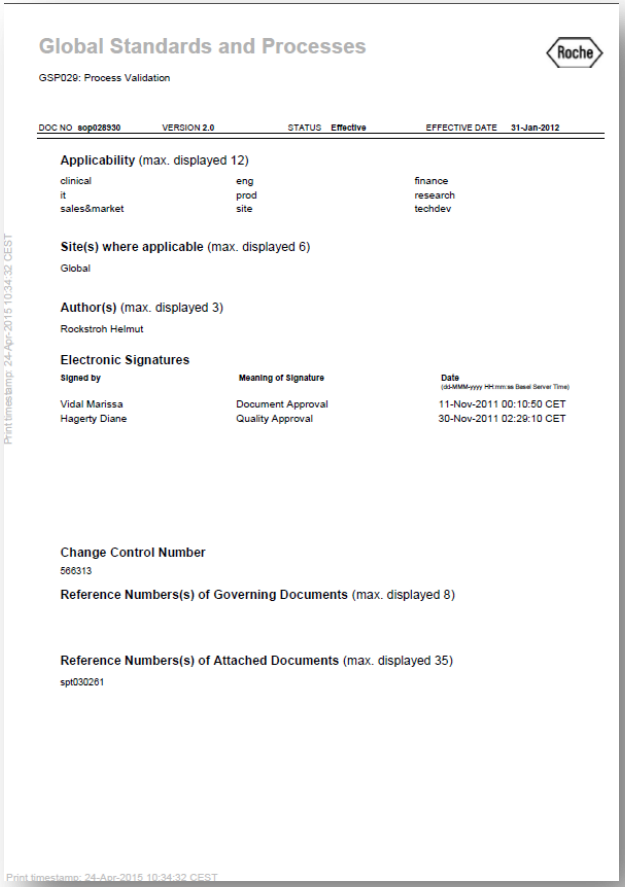


Figure by Dan Coleman, modified

DP Process Validation (PV)

- Lesson learned from a previous filing: FDA strongly recommended to include statistical analysis of “variability” and their sources in forthcoming Roche process validations.
- Roche SOP on Process Validation has been updated.
- Example of variance component analysis performed in Process Validation in a small Molecule NDA filing.



Global Standards and Processes

GSP029: Process Validation

DOC NO sop028930 VERSION 2.0 STATUS Effective EFFECTIVE DATE 31-Jan-2012

Applicability (max. displayed 12)

clinical	eng	finance
it	prod	research
sales&market	site	techdev

Site(s) where applicable (max. displayed 6)

Global

Author(s) (max. displayed 3)

Rockstroh Helmut

Electronic Signatures

Signed by	Meaning of Signature	Date (dd-MMM-yyyy HH:mm:ss Basel Server Time)
Vidal Marissa	Document Approval	11-Nov-2011 00:10:50 CET
Hagerty Diane	Quality Approval	30-Nov-2011 02:29:10 CET

Change Control Number

566313

Reference Numbers(s) of Governing Documents (max. displayed 8)

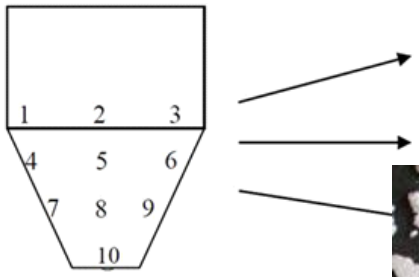
Reference Numbers(s) of Attached Documents (max. displayed 35)

spt030261

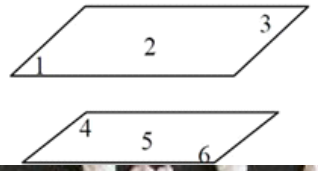
Print timestamp: 24-Apr-2015 10:34:32 CEST

Example Blend Uniformity – is the content uniformly distributed?

A



Sites viewed from the side



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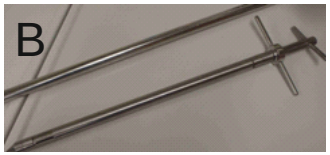
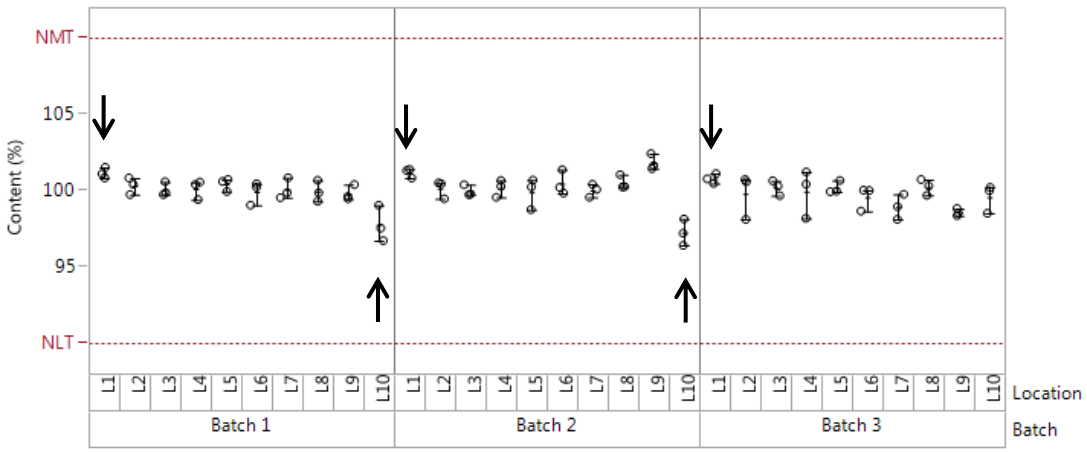
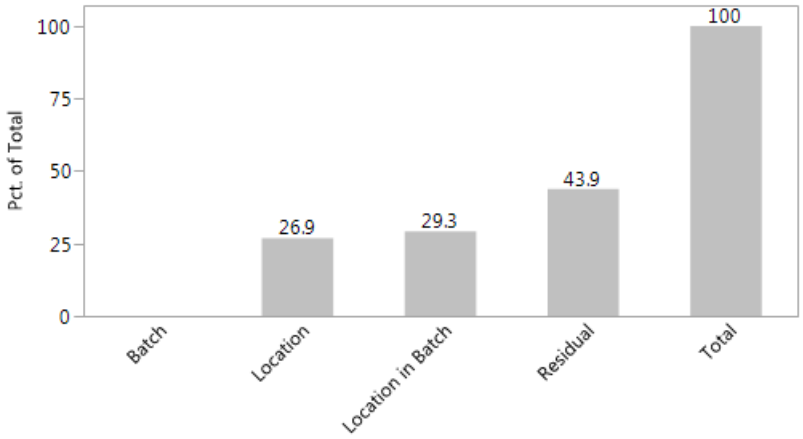


Example Blend Uniformity
Meets formal specifications, but …





- All individual BU content values are within 90% - 110%,
- content in loc 1 is elevated, and loc 10 of the 1st and 2nd batch is decreased.
- Variance components help to quantify magnitude.
- Encapsulation as final step would confirm homogeneity of content over all capsules (CU).

Simulated Data

When and Why is this useful?

- Blend Uniformity – no specification on the variance components, but …
  - if BU meets formal specification: helps to quantify magnitude of strange findings (e.g. batch1 & 2, location 10) and discuss their relevance.
  - if BU does not meet formal specification: useful for root cause analysis Isn't it strange that API is significantly higher on the bottom than on the top?

Disclaimer & Conclusion I

- Disclaimer: It's not always that colorful – but always fun!
- Quality by Design –
  - Improves understanding of and control over the process,
  - Facilitates changes of process parameters,
  - Aims to build safety and efficacy into a tablet,
  - statisticians can help!

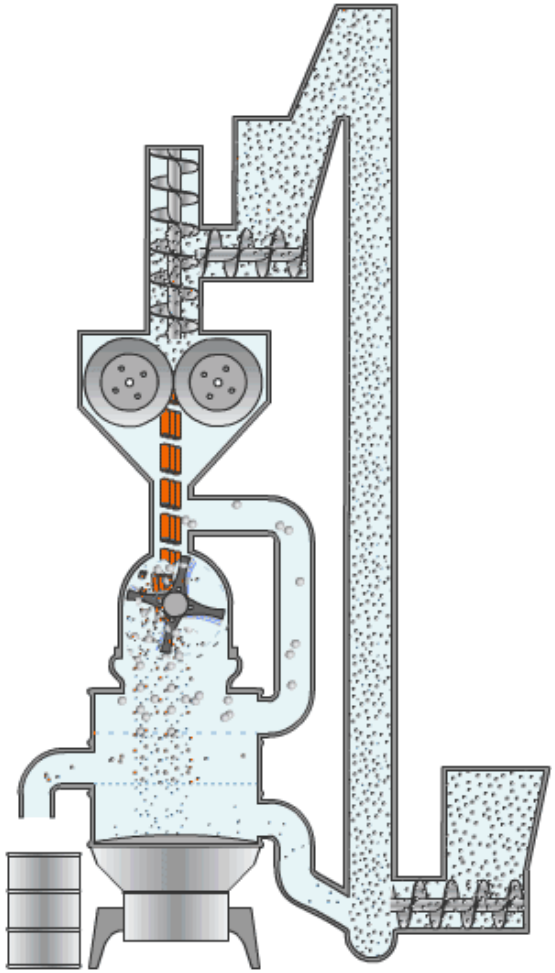
Conclusions
Benefits of Statisticians in Technical Development

- Design and analysis of experiments plus appropriate interpretation can offer a rationale and facilitate discussion.
- Statistical models were successfully presented to health authorities.
- Statisticians in technical development can facilitate a smooth and fast filing procedure.

Picture from zazzle.com

Acknowledgement

- Dan Coleman
- Martin Wunderlich
- Christiane Fröhlich
- Dirk Spielvogel
- Marc Lindenberg
- Laura Jerke



- Carsten Timpe
- Sigrid Pieters
- Peter Luetolf
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- Oskar Kalb

Doing now what patients need next