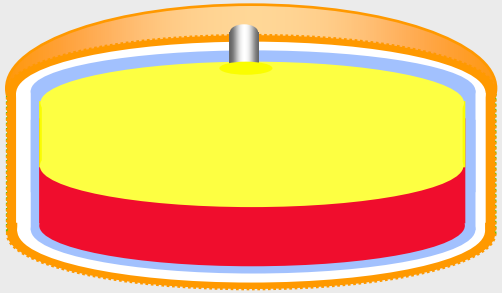


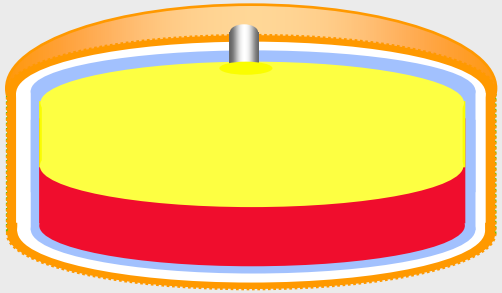
Science For A Better Life

QbD in der Praxis – systematisches Vorgehen bei der Entwicklung pharmazeutischer Herstellprozesse

Adrian Funke

Symposium der Fachgruppe Arzneimittelkontrolle / Pharmazeutische Analytik der DPhG

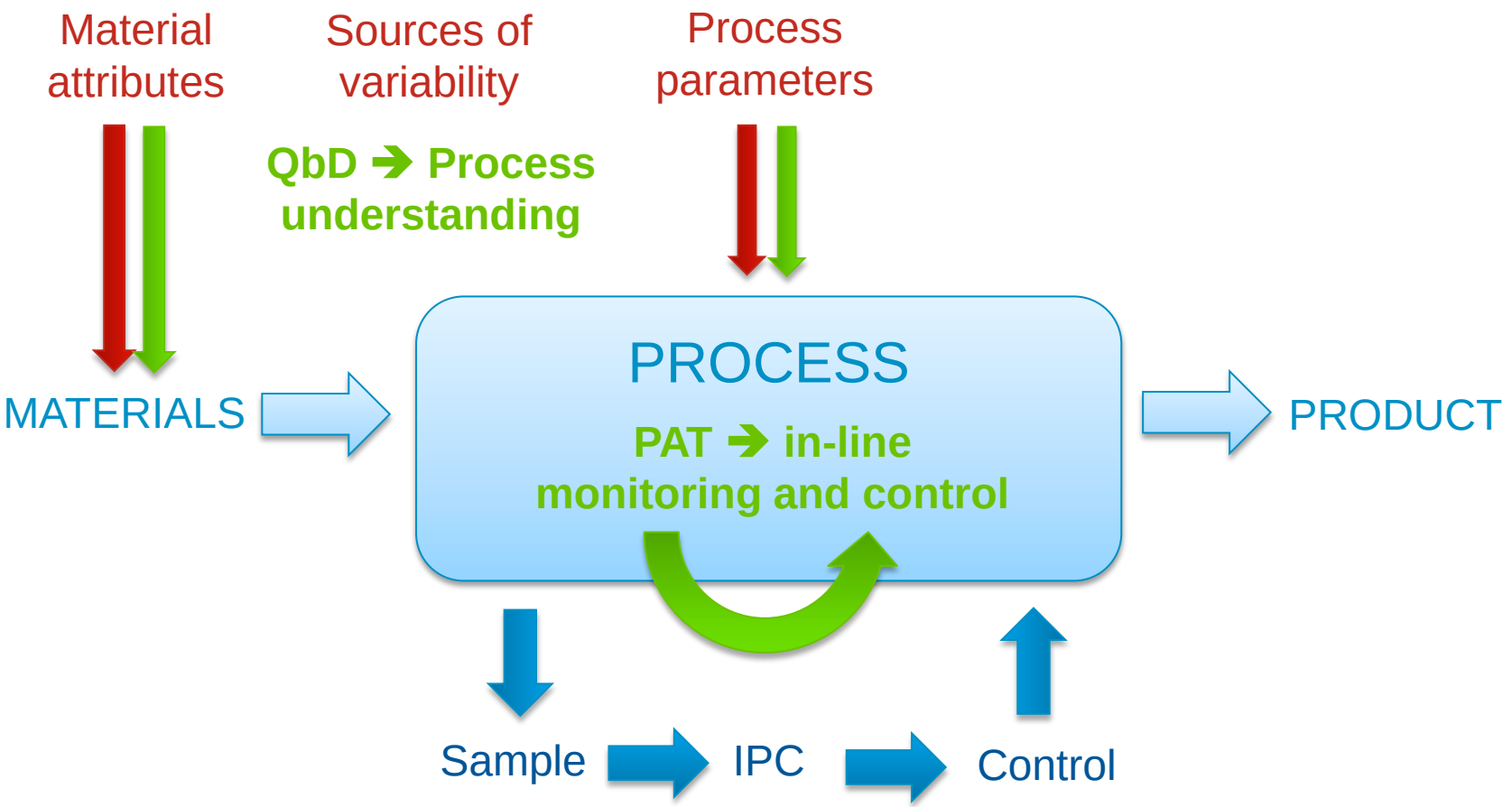
Freiburg – 8. Oktober 2013



Agenda

- Introduction & Definitions
- Process Development according to QbD
  - Quality Target Product Profile (QTPP)
  - Critical Quality Attributes (CQA)
  - Iterative Risk Management (FMEA)
  - Process Development (CPP) – Design of Experiments (DoE)
- QbD Case Study: active coating process
- Summary

Introduction



Quality by Design (QbD)

What it is:

ICH Q8: Quality by Design (QbD): 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.

➔ **Science and risk based approach to development**

Why to make use of QbD?

- Process and product understanding

➔ *advantages: robustness, reduced risks & costs*

- Emerging regulatory requirement
- Systematic development activities

Process Analytical Technology (PAT)

What it is:

"PAT" initially used by FDA in a broad sense of "QbD"

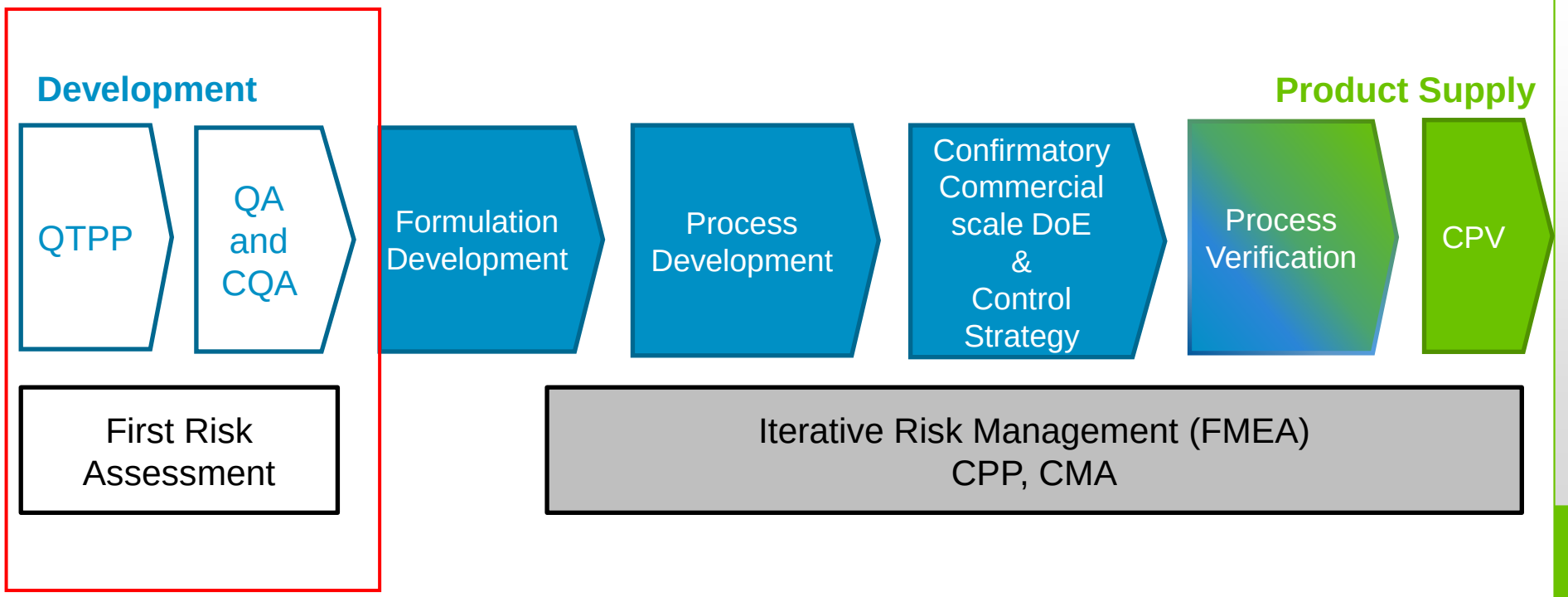
more specifically: in-line/on-line analytical instruments and tools used to monitor and control process parameters

Why to make use of PAT?

- Enhanced process understanding
- Immediate feedback and process control
  ➔ **Option for real-time release**
- Continuous process monitoring

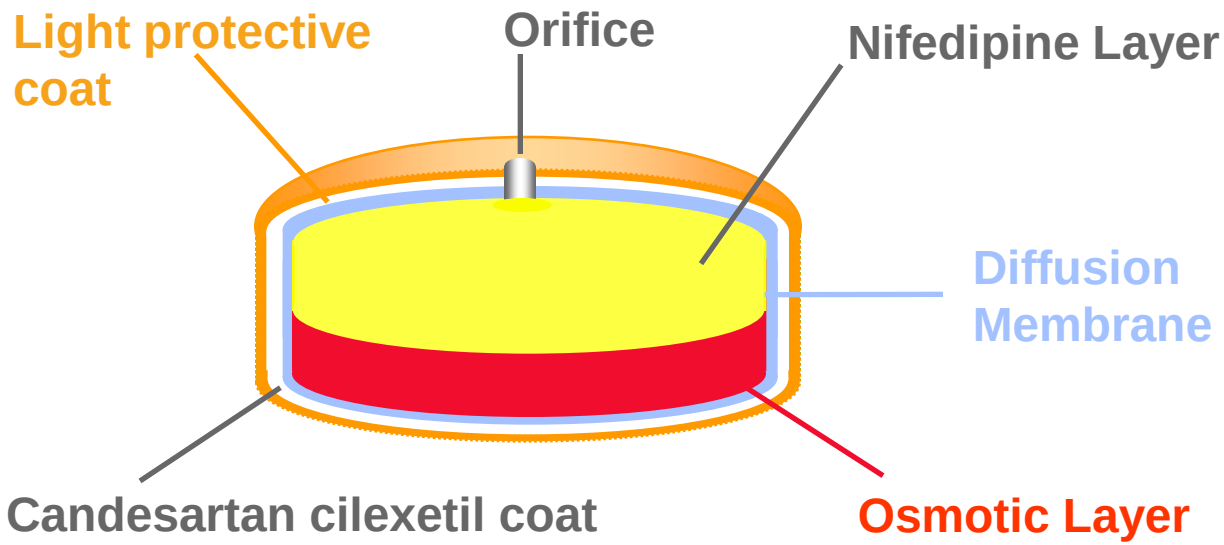
➔ **Enables quality control for continuous manufacturing**

Process development according to QbD



QTPP Quality Target Product Profile
(C)QA (Critical) Quality Attribute
CPP Critical Process Parameter
CMA Critical Material Attribute
FMEA Failure Mode Effect Analysis
CPV Continued Process Verification

Dosage Form Design



Formulation Principle:

Combination of two different release mechanisms: Nifedipine XR + Candesartan IR

- Gastro-intestinal therapeutic systems (GITS): osmotically driven release of nifedipine
- Immediate release film coating containing Candesartan cilexetil, up to 32 mg
- Colored light protective coating

➔ **6 functional features within 1 tablet !**

QTPP (Quality Target Product Profile)

QTPP-Element	Target
Dosage form	Fixed dose combination tablet
Route of administration	Oral
Dose strength(s)	z different dose strengths combinations: x / y mg
Tablet shape and size	easy to handle by the patient, not bigger than …
Appearance	coated tablet, dose strength differentiation via colour and imprint
Dissolution	Osmotically controlled release dissolution profile of nifedipine Immediate release dissolution profile of candesartan cilexetil
Identity	Positive for both DS
Solid state form	Stable polymorphs
Assay	Meets ICH Q6A criteria
Degradation products	Meets ICH Q3B and Q6A criteria
Uniformity of dosage units	Meets pharmacopoeial acceptance criteria
Microbiological quality	Meets pharmacopoeial acceptance criteria
Stability	36 months at room temperature
Container closure system	Suitable container closure system to achieve the target shelf-life and in-use stability

First Risk analysis
➔ Critical Quality attributes

Assay & Content uniformity of nifedipine
- controlled via blending and tableting

In vitro dissolution of nifedipine
- osmotically controlled
- special attention is given to the uniformity of organic coating process

Assay & Content uniformity of candesartan cilexetil
- depends on uniformity of active coating process and accuracy of endpoint determination

Focus of this presentation

In vitro dissolution of candesartan cilexetil
- depends on DS particle size and film thickness

Purity / Stability
- nifedipine chemical stability: controlled via light protective coating
- candesartan cilexetil chemical stability: special attention is given to composition and DS particle size
- dissolution profiles: special attention is given to selection of packaging materials

Microbiology
- no specific risks identified

Active film coating
Non-standard application of a standard unit operation

Content Uniformity Challenge

- Coating process capability (coating uniformity):
  4 – 5 % standard deviation of coating weight may be achieved (optimal conditions)

- Pharmacopoeial requirement: $$AV = k \cdot s + \left|\overline{X} - M\right| \leq 15\%$$

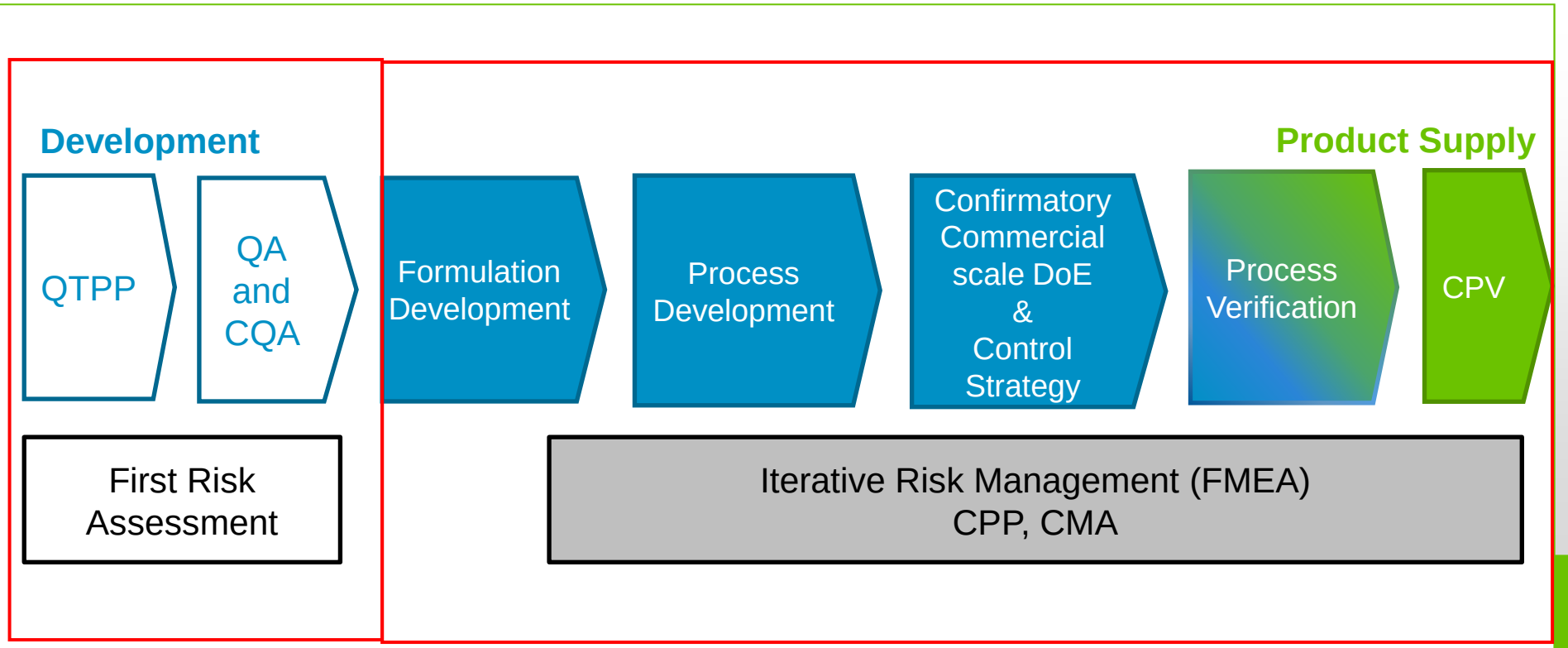
  Example:
  $$CUT = 97.4\% \pm 4.8\% \qquad n = 10$$
  $$AV = 2.4 \cdot 4.8\% + \left|97.4\% - 98.5\%\right| = 12.62\%$$

Consequences:

- Optimized coating process mandatory to achieve optimal uniformity
  ➔ Identification of optimal process parameters via **DoE** in pilot scale (**QbD**)

- Accuracy of endpoint determination is crucial
  ➔ in-line (or at least fast at-line) endpoint determination method required ➔ **PAT** !

Process development according to QbD



QTPP Quality Target Product Profile
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Definition of „criticality“

Source: ICH Q 8/9/10 Q&A from training sessions (FDA)

A. Considerations for Establishing CQAs and CPPs (2.1)

The introduction of ICH Q9 states that *"...the protection of the patient by managing the risk to quality should be considered of prime importance."* The QTPP provides an understanding of what will ensure the quality, safety, and efficacy of a specific product for the patient and is a starting point for identifying the CQAs.

As part of risk assessment, *risk analysis*, as defined by ICH Q9 is "*the qualitative or quantitative process of linking the likelihood of occurrence and **severity of harm**. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.*"

Relationship between risk and criticality:

- **Risk** includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management.
- **Quality attribute criticality** is primarily based upon severity of harm and does not change as a result of risk management.
- **Process parameter criticality** is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management.

Iterative risk management during process development

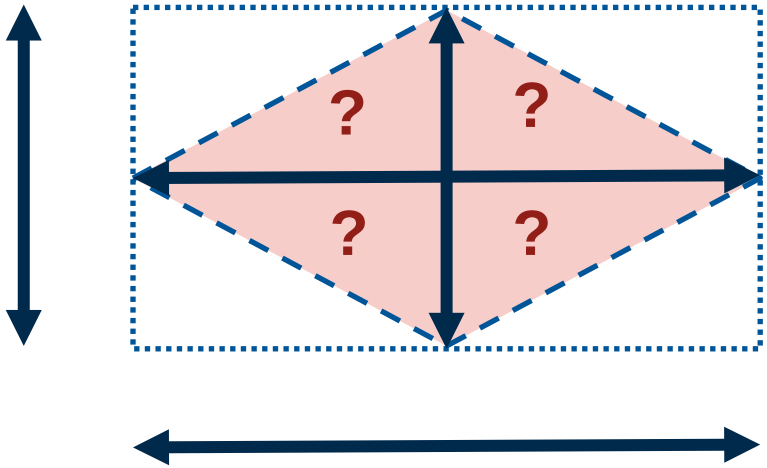
- initial FMEA
  - identify process parameters and material attributes that need to be investigated
  - define suitable depth of investigation: OVAT, DoE (cf. next slide)
- intermediate FMEA
  - document knowledge gained through process development
  - identify elements of the Control Strategy
    required in order to further reduce remaining risks to an acceptable level
- submission FMEA
  - proof that „process under control“
- lifecycle FMEA
  - summarize knowledge gained during continued process verification

➔ one risk management tool used consistently throughout process development !

OVAT = one variable at a time DoE = Design of Experiments

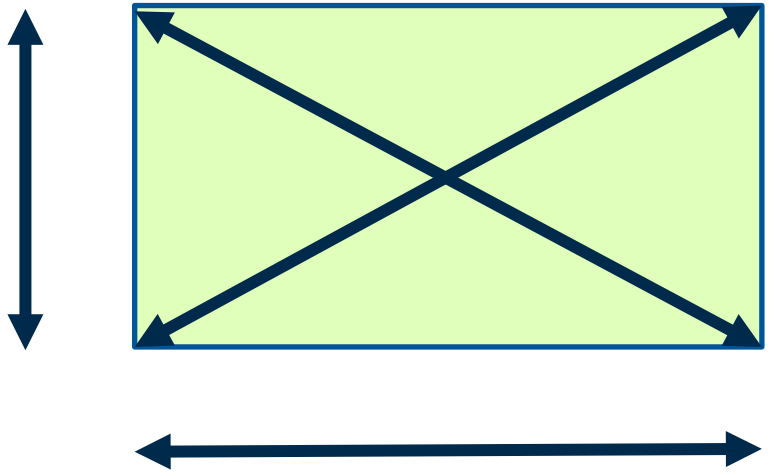
Knowledge Space generation via OVAT and DoE experiments

OVAT = one variable at a time



Knowledge only about variation of single parameters as long as all other parameters are kept constant

DoE = Design of Experiments

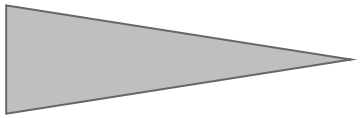


Knowledge covering full space (any combination of parameters)

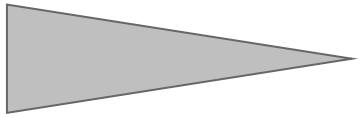
FMEA definitions

- "Failure"
  relates to unsuitable values of process parameters and material attributes, resp.

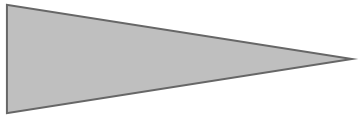
- **S**everity of effect caused by the resp. failure:

  3 = critical  1 = no/minimal impact

- Probability of **O**ccurrence of failure:

  3 = frequent
  (or: lacking knowledge)  1 = seldom or never

- **D**etectability of failure (probability of detection, independent of time of detection):

  3 = not reliably detected
  neither during process
  nor during IPC/quality control  1 = likely detected
  (based on the resp. control
  strategy in place)

Risk Acceptance Matrix

O*D \ S	1	2	3
3*3 = 9	acceptable	not acceptable	not acceptable
3*2 = 2*3 = 6	acceptable	not acceptable	not acceptable
2*2 = 4	acceptable	not acceptable	not acceptable
3*1 = 1*3 = 3	acceptable	not acceptable	not acceptable
2*1 = 1*2 = 2	acceptable	acceptable	not acceptable
1*1 = 1	acceptable	acceptable	acceptable

S = Severity O = Occurrence / Lack of Knowledge D = Detectability

Risk Acceptance Matrix

Standard FMEA calculation: ***RPN = S * O * D***

O*D \ S	1	2	3
3*3 = 9	**9**	18	27
3*2 = 2*3 = 6	6	12	18
2*2 = 4	4	8	12
3*1 = 1*3 = 3	3	6	9
2*1 = 1*2 = 2	2	4	6
1*1 = 1	1	2	**3**

S = Severity O = Occurrence / Lack of Knowledge D = Detectability RPN = Risk prioritization number

Risk Acceptance Matrix

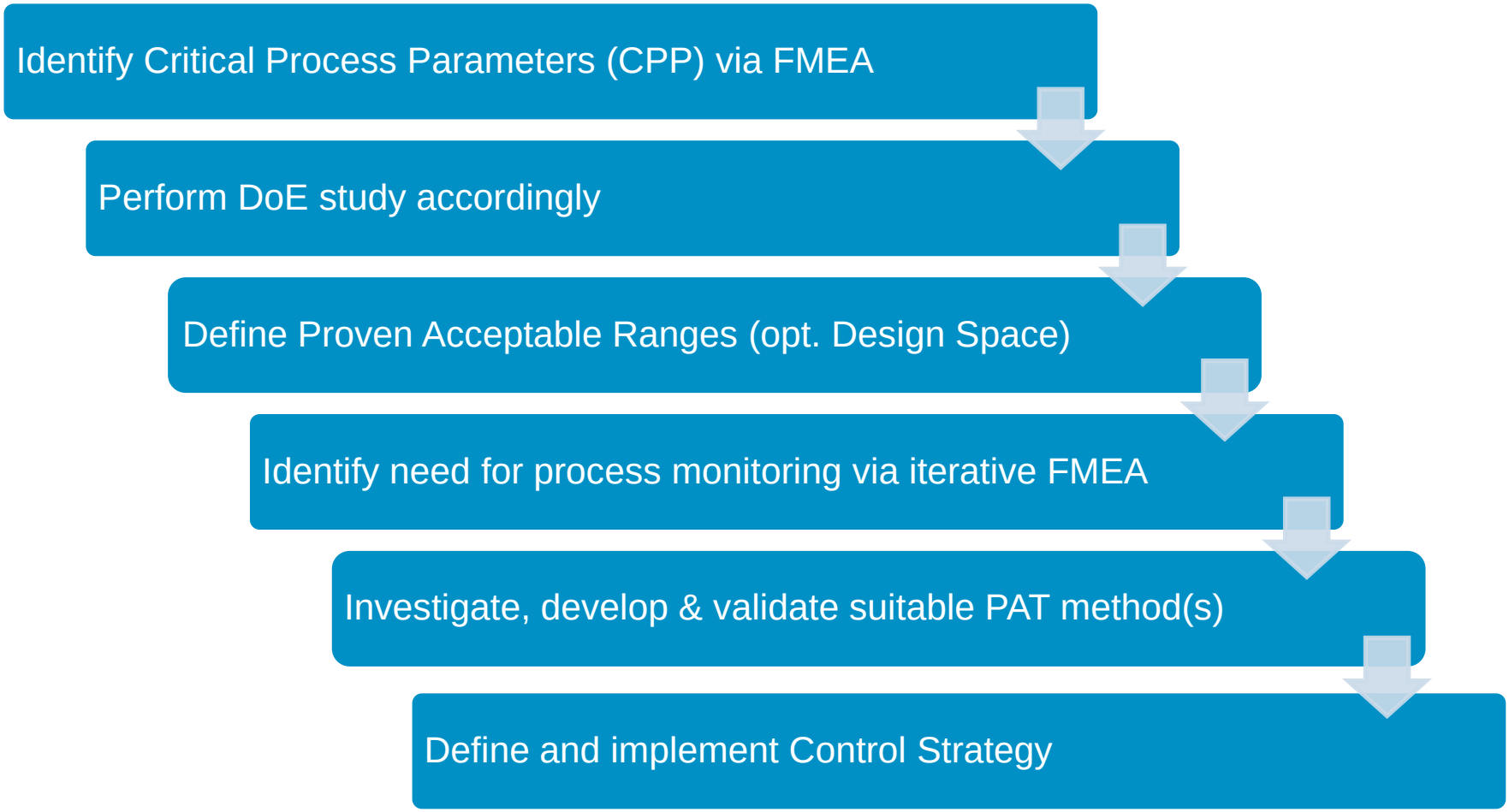
Improved FMEA calculation: ***RPN = S^2 * O * D***
RPN d 9 ➔ Acceptable Risk

O*D \ S	1	2	3
3*3 = 9	9	36	81
3*2 = 2*3 = 6	6	24	54
2*2 = 4	4	16	36
3*1 = 1*3 = 3	3	12	27
2*1 = 1*2 = 2	2	8	18
1*1 = 1	1	4	9

S = Severity O = Occurrence / Lack of Knowledge D = Detectability RPN = Risk prioritization number

Risk acceptance (RPN) does not change criticality (S)
➔ risk acceptance and criticality are different concepts!

Case Study: active coating process



Process Development: DoE in pilot scale

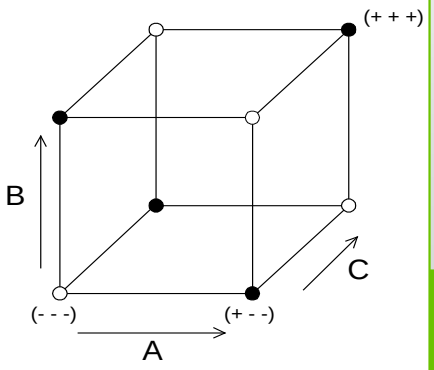
$2^{(n-1)}$ + 3 design, 5 factors

Constant

- Composition of tablet cores: 30 mg nifedipine GITS
- Composition of coating suspension
- Coater configuration: BFC 50, 5 spray guns (1.0 mm), spray gun position
- Control exhaust air temperature (42°C), inlet air max. 60°C, air flow: 1000 m³/h

Variable factors (low – central – high)

- Drum load: 133.000 – 143.000 – 153.000 tablets
- Drum speed: 12 – 13 – 14 UpM
- Spray pressure: 1.7 – 1.8 – 1.9 bar
- Spray rate: 60 – 90 – 120 g/min
- Spray time: 150 – 225 – 300 min

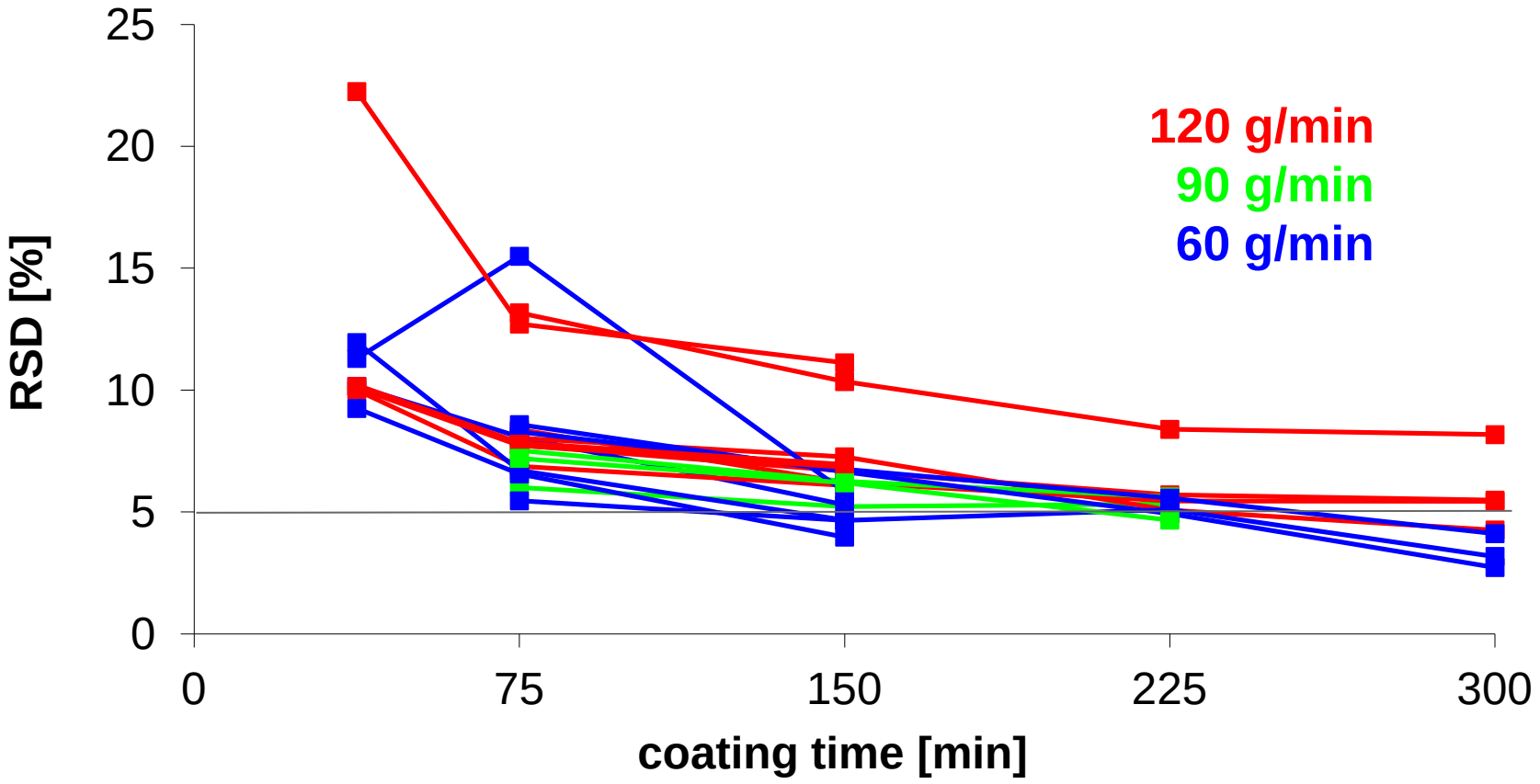


Output

- **Content uniformity** (n=30)
- 3 or 4 samples taken during the process per batch depending on overall process time

➔ 1950 single tablet samples for assay that were also used for feasibility assessment of an at-line NIR model (PAT)

DoE results: Content Uniformity as a function of spraying rate and time



DoE results: ANOVA

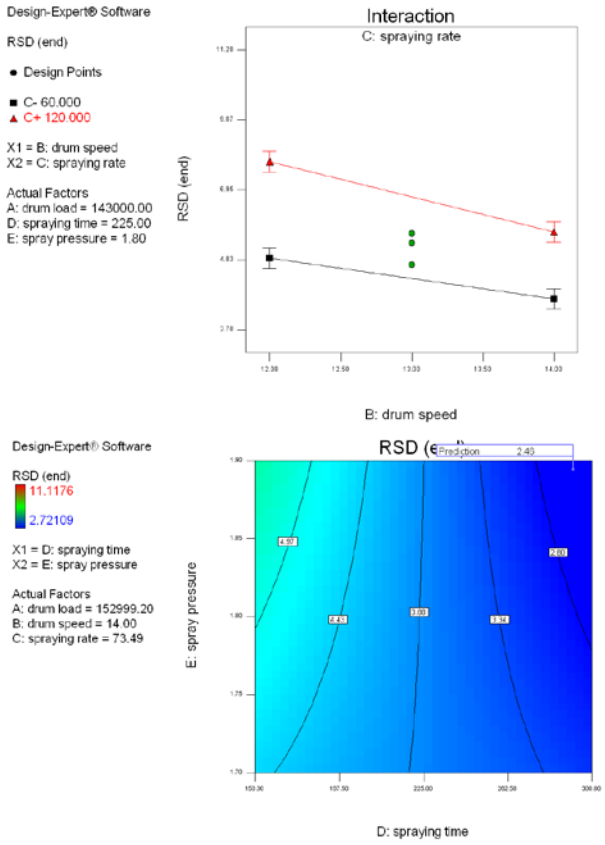
Significant effects of process parameters and parameter interaction detected.

Suitable statistical model could be established and used for **optimization**

➔ Top-line results:

- In order to achieve best content uniformity (lowest RSD):
  - maximize drum rotation speed (14 rpm in BFC50) and
    – *depending on the intended dose strength* –
  - minimize spray rate (60-80 g/min in 40 kg scale)
  - maximize coating time (3-5 hours in 40 kg scale)

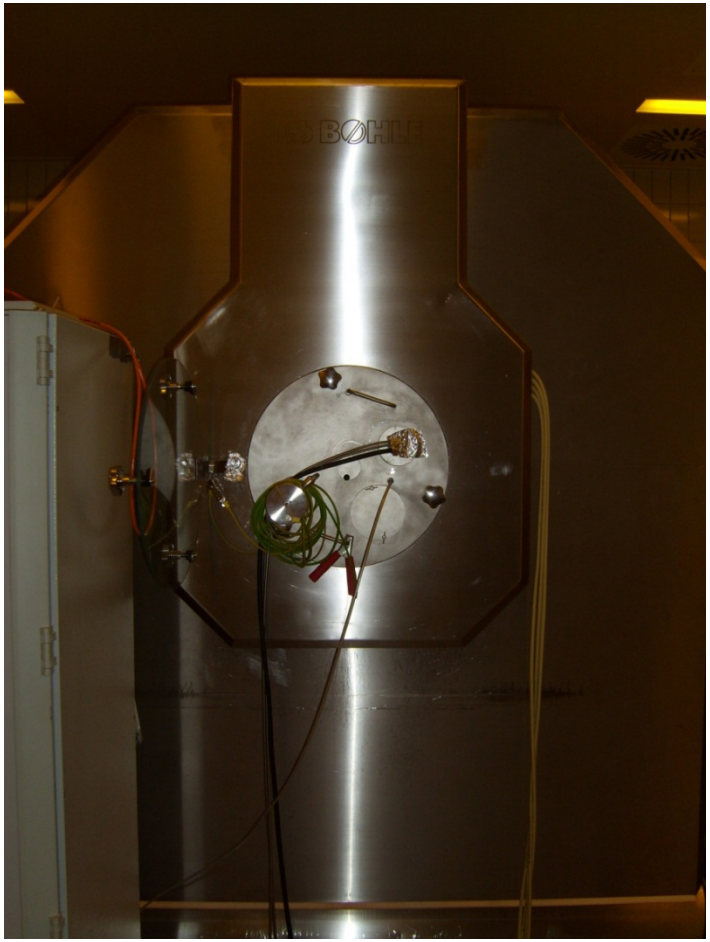
- Desired RSD levels
  (point estimate and confidence intervals)
  are achievable
  using optimized process conditions



Determination of Coating Endpoint

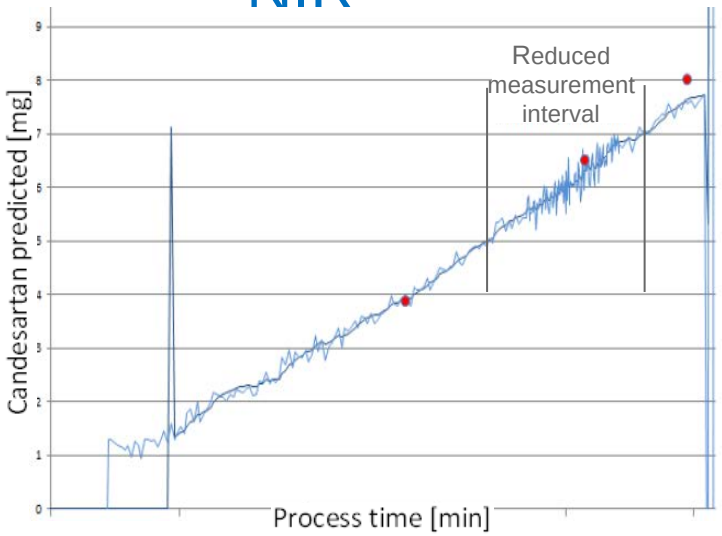
Change (increase) of parameter	Detection method	Measurement	Issues
Sprayed coating suspension mass	Weighing	In-line	Biased by spraying loss
Film Mass	Weighing	At-line (fast)	Covers film and tablet core, Biased by water content
Film thickness	Terahertz	In-line ?	Accuracy and Robustness not sufficient
Active ingredient content	HPLC	At-line (slow)	Long process interruptions
Active ingredient content	NIR	In-line	Feasibility to be checked
Active ingredient content	Raman	In-line	Feasibility to be checked

in-line monitoring: comparison NIR vs. Raman

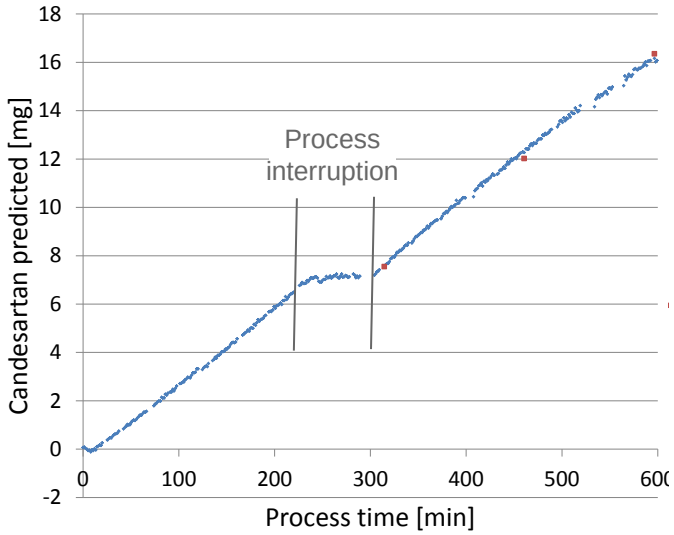


in-line monitoring: comparison NIR vs. Raman

NIR



Raman



In-line NIR and Raman spectra obtained during active coating runs in commercial scale

- higher accuracy
- lower scattering
- shorter measuring times

Summary

Case Study:

- active coating process is challenging with regard to both intra-tablet coating uniformity and accuracy of average coating amount per tablet.
- the variability has been reduced by systematic process development using design of Experiments (**DoE**).
- process control strategy has been elaborated using in-line Raman spectroscopy as an IPC for the endpoint determination of the coating process (**PAT**).
- As a result, robust active coating process has been achieved (**QbD**).

General conclusion:

- invest efforts into QbD and PAT during process development in a focused way based on a sound risk assessment
- return during commercial production:
  ➔ processes that are robust and fully understood

Thank you!

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Martina Smikalla
Tobias Laich
Horst-Dieter Friedel

Dejan Djuric
Andreas Altmeyer
Jochen Thies

Waltraud Kessler

Axel Zeitler

… and thank you for your attention !