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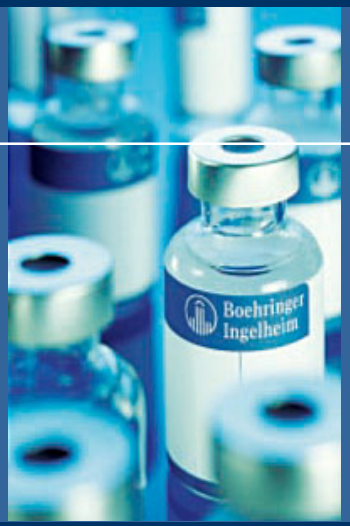

Sep 30, 2009 'QbD/PAT Conference 2009', Heidelberg

A Structured Approach to Process Design

Dr. Gerd Fischer

About this Presentation

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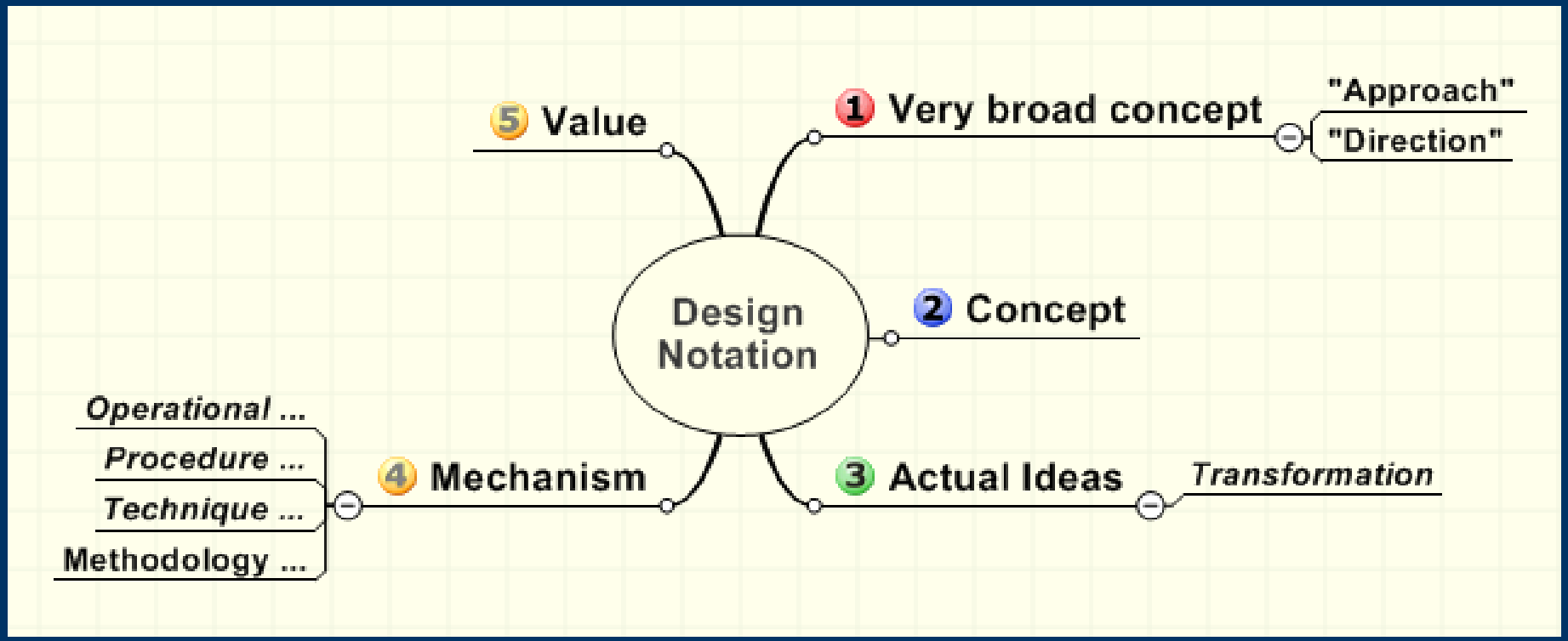
This should be a purely conceptual lecture

'Process Design' is presented as a broad level descriptive concept to illustrate how it is linked to operational concepts

"Concepts are the parents of practical ideas"


Design Notation
5 Value
1 Very broad concept
"Approach"
"Direction"
2 Concept
Operational ...
Procedure ...
Technique ...
Methodology ...
4 Mechanism
3 Actual Ideas
Transformation

More Reading

ASTM 'Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology' (E2474)

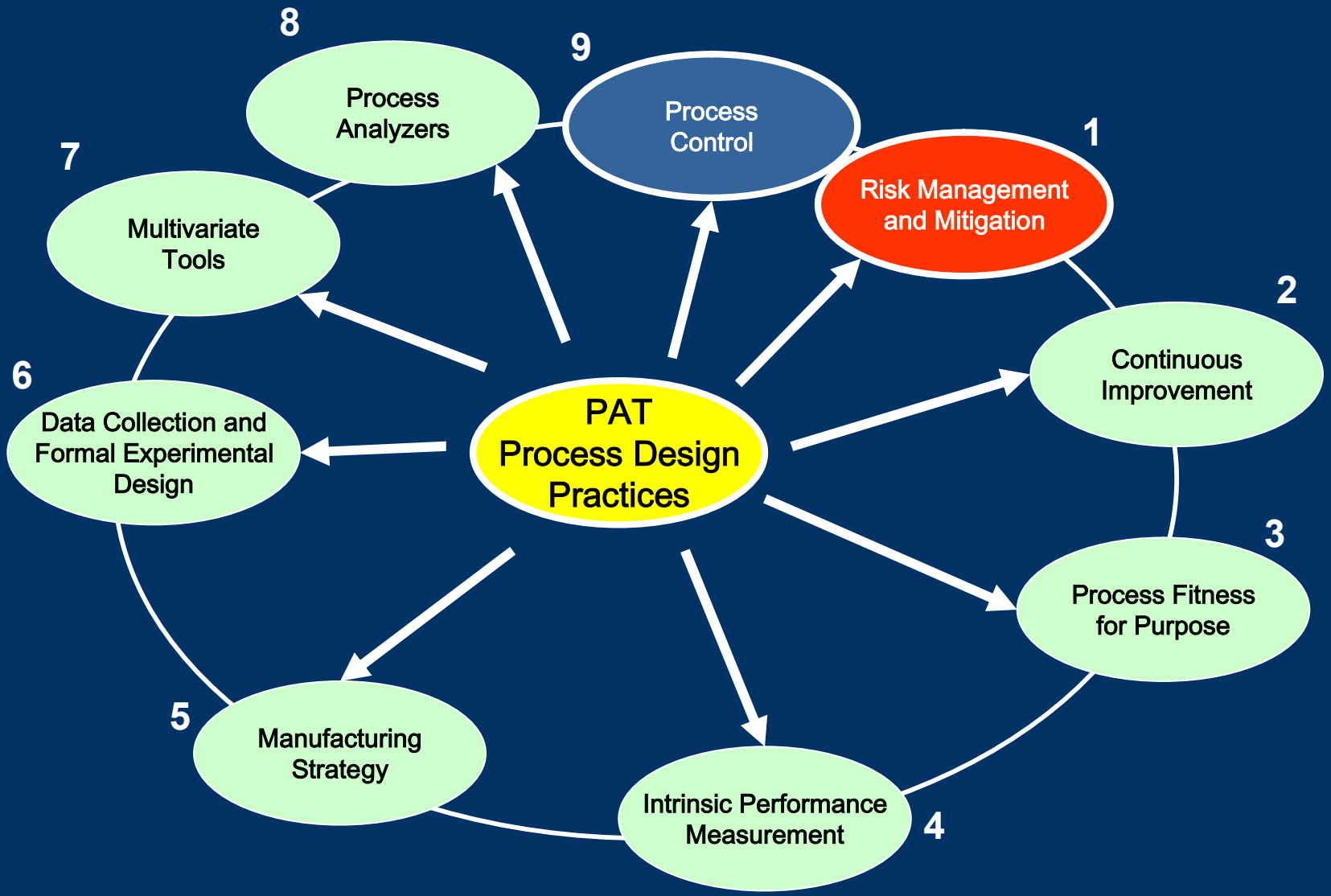
FDA Draft Validation Guidance

FDA PAT Guidance

ICH Quality Guidelines (Q8R, Q9, Q10)

Slightly different wording and definitions, but identical concepts

ASTM Standard E2474



2001 to 2009

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2001: "We need to do something different"

- "50% of production costs (i.e. process inefficiencies) are locked in before Phase III begins" (PriceWaterhouseCoopers, 2001)

2009: Quality by Design ?

- Regulatory opportunities for implementing QbD
- Manufacturing performance improvements ?

Still Today's Practice ?

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Finding a NCE or NBE

Develop the product

Develop the process

Get regulatory approval

Begin Manufacture

Market and reap the benefits as fast as possible

Avoiding mishaps (e.g., FD483, warning letter, rejects, recall)

Almost no innovation in manufacturing

Quotes from 'The Gold Sheet'

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Cost of QbD-related process design experiments mounts and regulatory incentives languish

McKinsey consultant argues that the QbD business case is strong but little understood

Are we satisfied with 'Right First Time' 93.3% ('3 sigma') ?

The Design Objective

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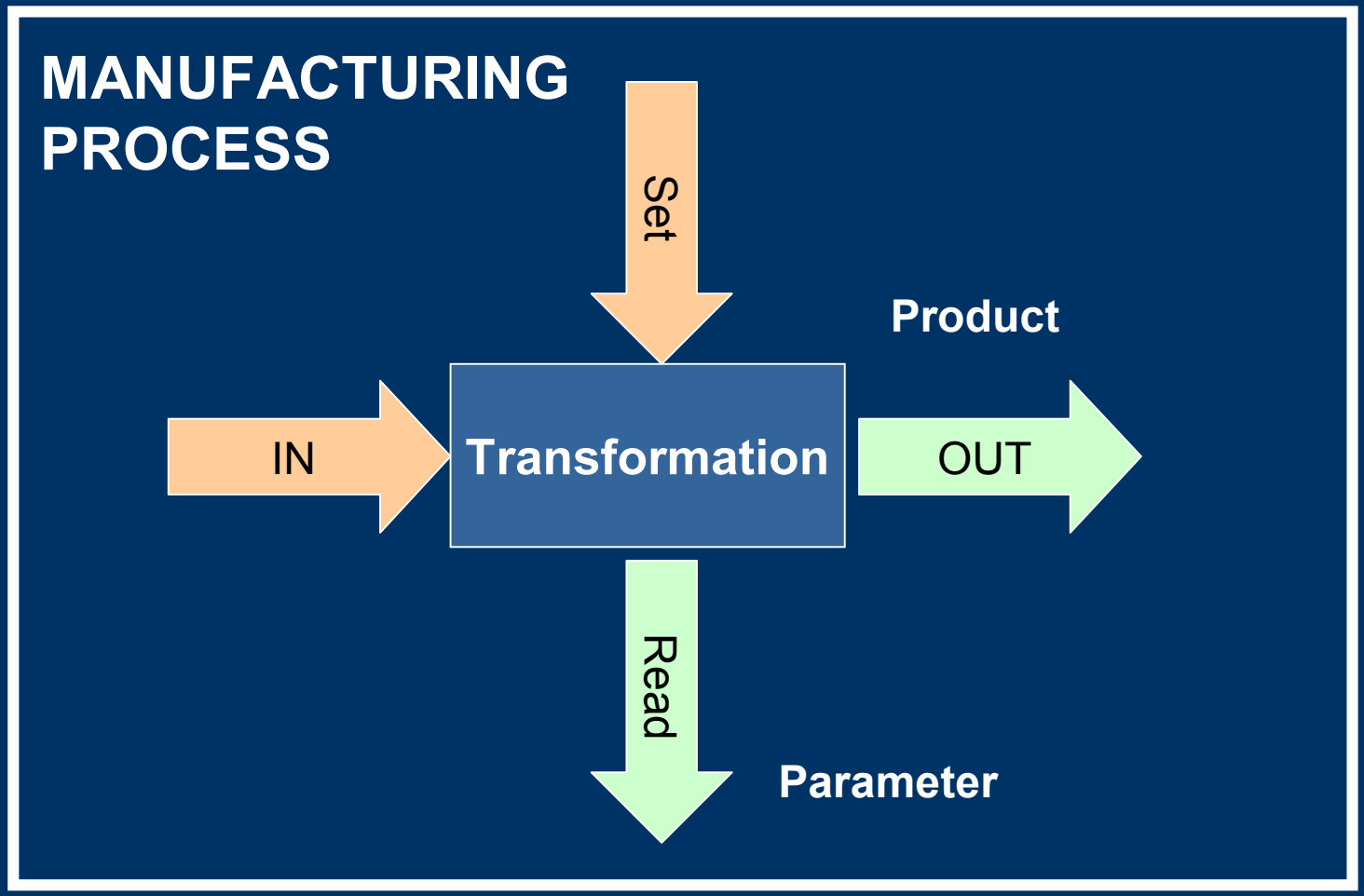
Manufacturing processes should be designed to manage variation and consistently supplying products of the desired quality

- all sources of variation are identified, defined and controlled
- critical product attributes are controlled to target for all individual units of a product

Variation


MANUFACTURING PROCESS
Set
Product
IN
Transformation
OUT
Read
Parameter

Criticality – not a Static Status

Criticality of a process or material parameter or attribute depends on level of Risk, which is a function of Design, Understanding, and Control
(FDA)

Process Design

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The systematic conversion of information about needs for a product into knowledge about how to manufacture this product
(ASTM)

"Variation is part of all processes" (Deming)

Design Process

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Inputs: information about product structure, composition, desired quality attributes, etc.

Initial design concepts based on institutional knowledge, intuition, experience, first principles, etc.

Identification of feasible design options from development studies

Detailed process development

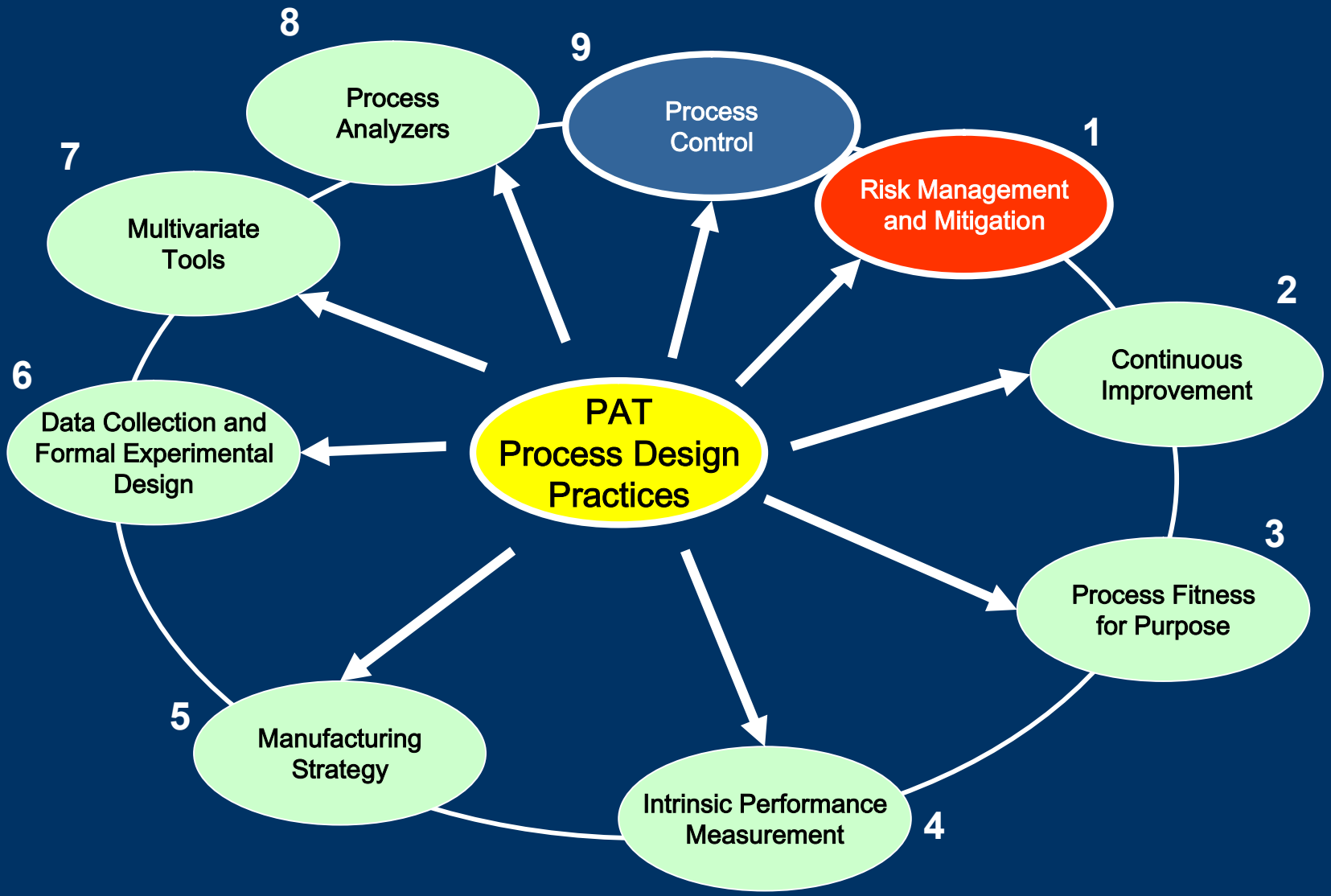
Design review, learning, and feedback

Design Space

The multi-dimensional region where flexible conformity to established standards is achieved

Within this region, the values of variables are considered acceptable

ASTM Standard E2474



Risk

A potential future event or condition

Would result in a deviation from the expected or planned

Probability is > 0% but < 100%

Consequences of the future event or condition will be adverse, unfavorable, or negative

Risk Management

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Risk Management is the act or practice of controlling risk

Quality Risk Management and methodology is applied on each step

- Information and learning is fed-back and fed-forward between all steps

Continuous Improvement

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An iterative process of design improvement

Measured vs. 'process fitness' indicators, e.g.

- Product characteristics
- Process characteristics
- Process systems
- System components
- Economical aspects

What are meaningful Measurements

Products define processes, processes deliver products

Process performance:

- Multivariate, statistically, controlled, 'real-time'

Product quality:

- Inferential, univariate, measurement

Intrinsic Performance Assessment

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Process assessments and control systems are integral components of the manufacturing operations

cf. "Process Analyzers"

Conventional design approaches still rely on separation of process' from 'process output assessment' (by sampling, averaging, and off-line testing)

Manufacturing Process

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Major design options are related to

- Material transitions:
  Unit-to-unit consistent quality will be achieved only if all material transitions are the same for all units
- Scaleability:
  Processes should be designed for scaleability or scale-independent

In continuous processing, scale is a function of time

rather than a function of volume

Data and Experimental Design

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Experimental design tools are used to collect data throughout the design space

Multivariate tools are used to generate values for

- the critical quality attributes
- factors linked to process condition

Process Models

- descriptive, predictive, controlling

Process Model Categories

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Statistical –
empirical, correlative …

Phenomenological –
causal / mechanistic, based on first principles …

Theoretical –
mechanistic, first principles

Process Analyzers

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In-, on-, at-line process analytical tools are used for rapid measurements which can be used to evaluate material attributes and process performance and enable process control

cf. "Intrinsic Performance Measurements"

A manufacturing process can not be made faster than the measurement that evaluates its quality

(in other words, sampling and off-line testing restricts possibilities for cycle time reduction)

Process Control (Definitions)

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Pharmacist: "Process control is …"

- "… achieved when we can produce many sequential batches that readily meet specification"
- "… established post-facto (open loop)"

Pharmaceutical Engineer: "Process control is …"

- "… an automated system where an artificial intelligence, developed using a process model, continuously monitors and corrects the process to keep every variable as close to its set point as possible"

What does this mean ?

Pharmacist and Process Engineer may talk about different things

- Defining the process is not the same as executing the process

Assets should be capable to enable controlling the process

- The process determines the manufacturing equipment needed

Today's practice is typically the opposite i.e. to fit a process into equipment available at hand

Process Control

Process Control is based on feedback / feedforward loops

- Ensure both the desired process trajectory and final product quality
- Process endpoints are based on achieving desired critical quality attributes

Linking 'Process Design', 'Process Validation', and PAT

Process Validation Stages (FDA)

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Stage 1 – Process Design

The commercial process is defined during this stage based on knowledge gained through development and scale-up activities

Stage 2 – Process Qualification

… the process design is confirmed as being capable of reproducible commercial manufacturing

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control

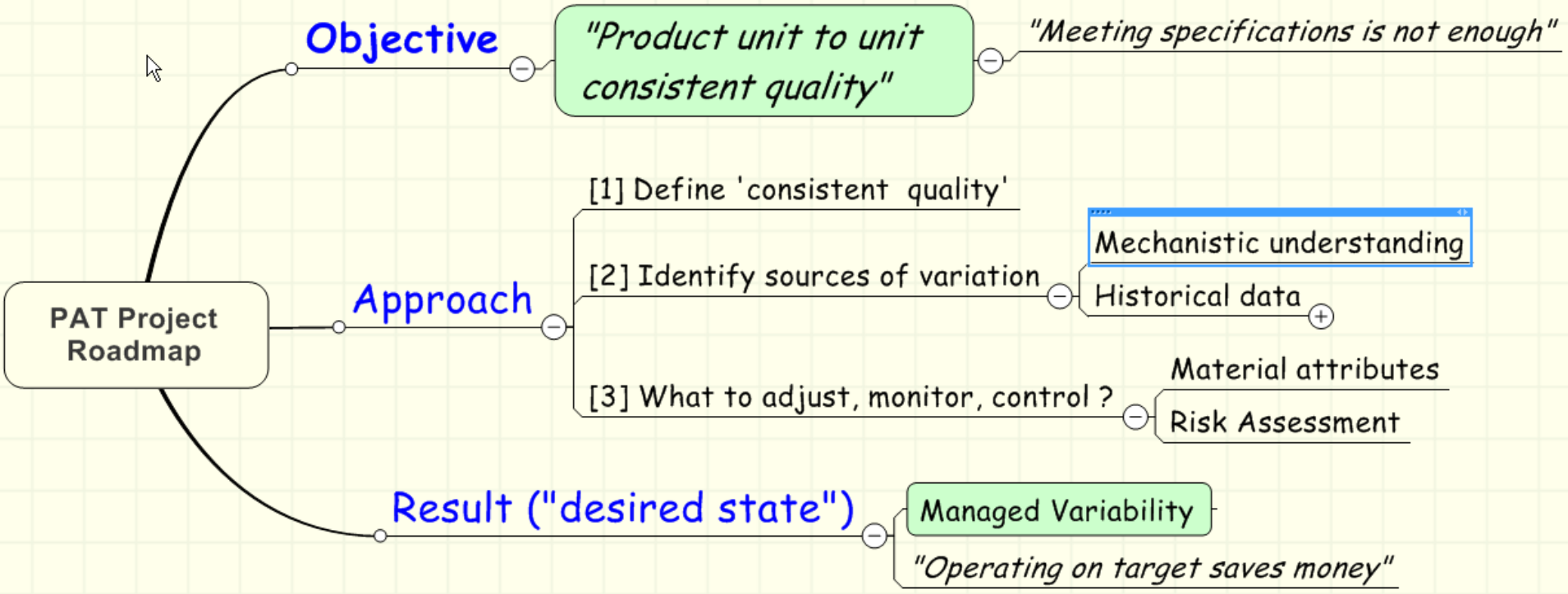
PAT and Process Design

PAT is a conceptual approach to quality assurance

PAT enables specific approaches to process qualification

- process design and process qualification focussed on the measurement system and control loop

Simplified PAT Project Roadmap



Continued Process Verification

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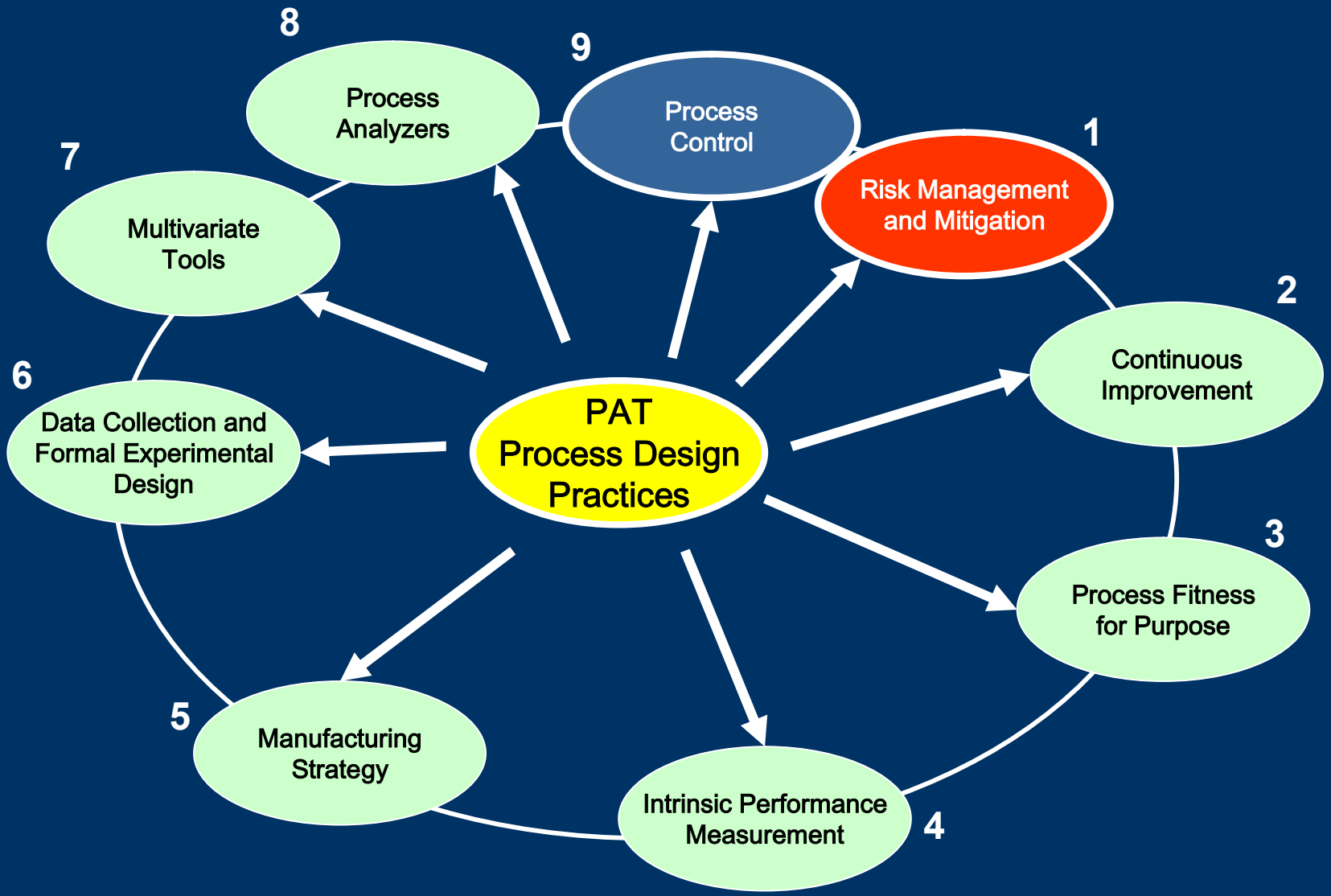
Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits

read more: FDA (Draft) Validation and PAT Guidances

Summary


8
Process Analyzers
9
Process Control
1
Risk Management and Mitigation
7
Multivariate Tools
2
Continuous Improvement
6
Data Collection and Formal Experimental Design
PAT Process Design Practices
3
Process Fitness for Purpose
5
Manufacturing Strategy
Intrinsic Performance Measurement
4

Conclusion

Process Understanding is the foundation to establish

- manufacturing process incl. process control
- risk mitigation strategy
- product quality assessment and release concepts
- quality assurance concepts and quality processes to safeguard process outcome

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"Whether we like it or not, the future lies ahead"

(Ken Leiper)