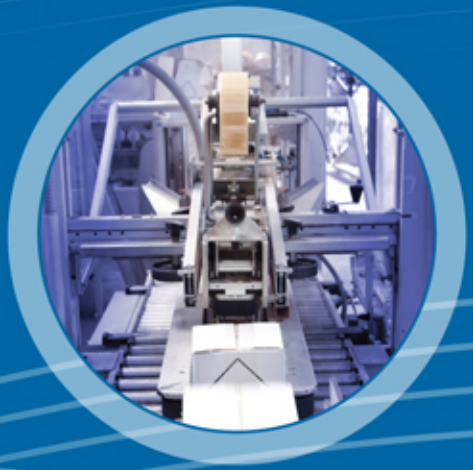
Connecting People, Science and Regulation®

Case Study 5: Control Strategy



Øyvind Holte,
Norwegian Medicines Agency
Ron Ogilvie, Pfizer

Joint Regulators/Industry QbD Workshop
28-29 January 2014, London, UK

Control Strategy Case Study Team

- Carla Caramella, University of Pavia
- Maria Di Marzo, Italian Medicines Agency (AIFA)
- Øyvind Holte, Norwegian Medicines Agency
- Graham Cook, Quality Operations, Pfizer
- Ron Ogilvie, Global CMC, Pfizer

Case Study 5: Overview

- Introduction to Case Study
- Overview of Product
- Discussion Topics
  1. Controls and manufacturing operating commitments
     Linking controls to process description and Design Space
  2. Linking Control Strategy to Risk Assessment
  3. Life Cycle Management
     Linking controls to scale dependence and change management
  4. Elaboration and assessment of the dossier
     How and where to present Control Strategy in a submission

Introduction to Case Study

- How control strategy can support process understanding, process commitments, risk- and change-management
  - Relevant to all product types
    - Optimizing control strategy to depth of understanding, and to complexity
  - Sharing increased knowledge and gaining value (industry and regulators)

Introduction to Case Study

- Applicant initially believed that showing a lot of process understanding could lead to a control strategy (including Design Space) allowing for potential operational flexibility and easier subsequent optimization. Not readily achieved
- Assessor's general reflections: information presented (e.g. terminology, risk assessment, criticality tables, development, description of DoE) not initially sufficient
- Improved presentation would support more effective utilization of control strategy
  - Enhanced development encourages a focus on the most important aspects of the manufacturing process, commitments and controls

Overview of Product

- Indication:
  - Oncology
- Drug Product:
  - Immediate-release hard capsules (**simple product and process**)
  - Two strengths
- Drug Substance:
  - Convergent synthesis, late-stage palladium(O) coupling
    - **Impurity control:** Pd catalyst residues, genotoxic impurities (oncology)
  - BCS class IV (low solubility, low permeability) – **PSD critical**
  - Single crystal form identified - non-hygroscopic
  - Stable drug substance

Product Control Strategy

- Typical Approach : Understand the patient needs, and what aspects of product / process deliver these attributes
  - The Quality Target Product Profile
  - Understand Critical Quality Attributes and links to process
- Develop optimal control strategy
  - Drug product specification and other controls
    - Analytical methods
    - Input material specifications (drug substance, excipients)
    - Process description
    - In-process controls
    - GMP
- Selecting controls and manufacturing operating commitments
- Where is it optimal to control a CQA?

Components of Control Strategy that Industry and Assessors Think About

QTPP, CQAs

Pharmaceutical development

ICH Q10

Control strategy:

A planned set of controls, derived from current product and process understanding that assures process performance and product quality.

The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

PARs for CPPs *

Control of input material attributes *

Description of manufacturing process *

* Included in Design Space, when applicable

IPC

Justification for non-routine testing, RTRt. predictive models

Regardless of traditional/ enhanced approach (ref FDA-EMA Q/A)

Discussion Topic 1:
Controls and Manufacturing Operating Commitments

- **With enhanced understanding**
  - If a CQA is adequately controlled by IPC, or monitoring, is there (always) added value in describing process detail?
  - If a CQA is adequately controlled by the process, is there (always) added value in describing monitoring/ testing?
    - Optimize control and post-approval change requirements
- **Applicant can propose a mix of 'detail of process' and 'detail of testing' as appropriate**
  - Dependent on product and process understanding

Discussion Topic 1:

Controls and Manufacturing Operating Commitments

- **CQA: Particle size distribution (PSD) of drug substance**
  - Critical, as BCS 4 and solid oral dosage form
- In submission, applicant proposed PSD control BUT only mentioned that ”Drug substance ... may be milled” and did not detail conditions for particle size reduction
  - Had known that different conditions / inputs could be used to meet PSD requirement (but didn’t present this)
- Assessor asked for detail of processing conditions as PSD is critical and is a result of milling parameters/ conditions
  - Regulatory expectation that all critical manufacturing steps are described in appropriate detail
- PSD is adequately controlled by testing – discussed what level of description is needed
  - The milling PROCESS should be described
  - For this product / understanding, description at the level of milling principle is sufficient)
  - Manufacturing process description balanced to controls applied, supported by increased sharing of knowledge of milling presdented in the dossier
- To ensure that the change to a different milling type would be subject to variation application

Discussion Topic 1:

Controls and Manufacturing Operating Commitments

- The previous example looked at balance / selection between input / output controls and commitments
- A second example – the link between acceptance criterion and operating conditions
- Controls (compliance with acceptance criteria) are linked to manufacturing operating conditions
  - They establish the boundary conditions for manufacturing
- A change to an acceptance criterion of an attribute can change acceptable range of manufacturing conditions
- The applicant had proposed an acceptance criterion for an impurity (Pd) that was ‘safe’ but was not close to batch data / manufacturing experience
- The applicant was requested to tighten the limit

Discussion Topic 1:

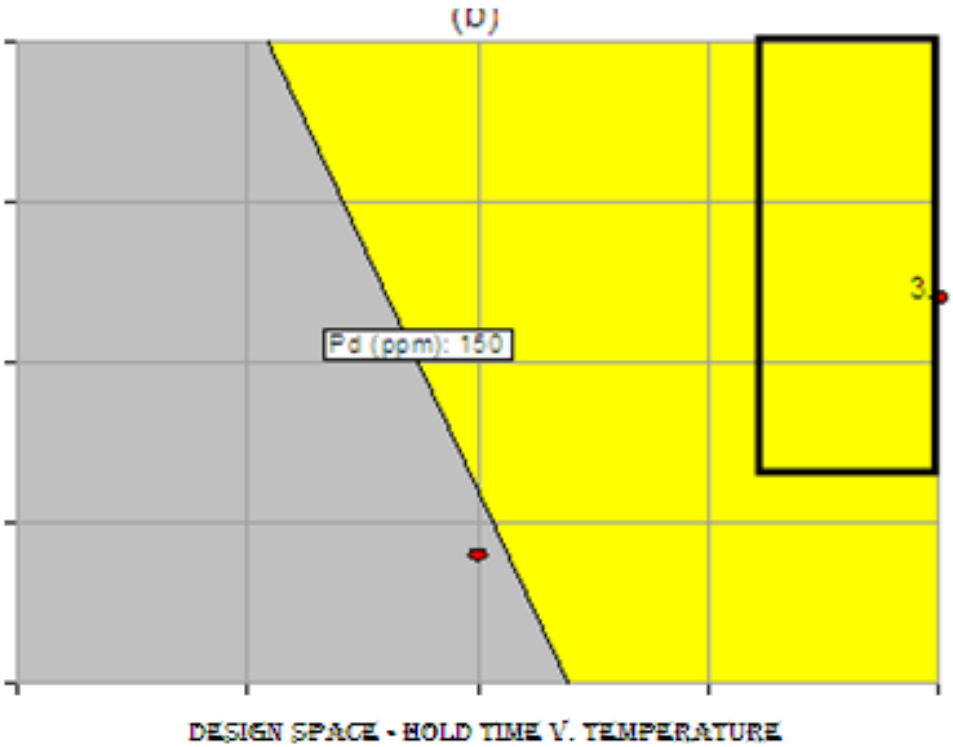
Controls and Manufacturing Operating Commitments

Residual Pd in the drug substance

It was demonstrated that residual Pd can be controlled upstream by a Design Space

No end testing of Pd was necessary

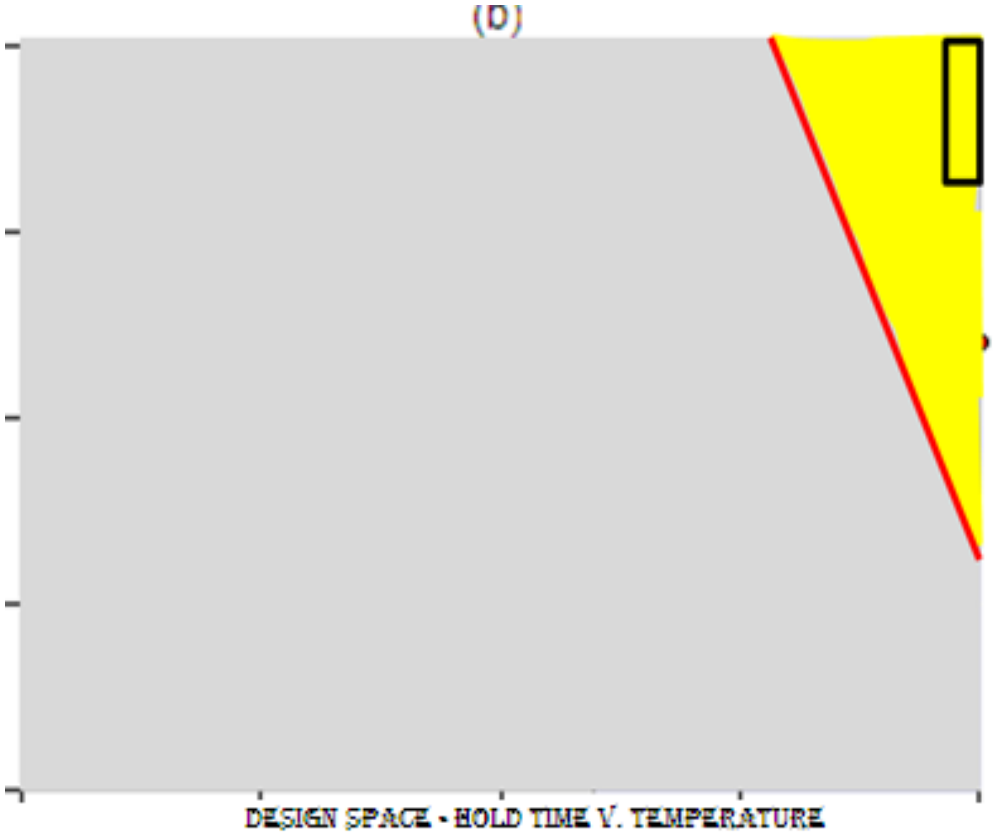
This is the Design Space at the proposed limit



Discussion Topic 1:

Controls and Manufacturing Operating Commitments

- **Residual Pd in the drug substance**
- Applicant was requested to narrow Pd limits in line with batch results
- Revised Design Space to meet tighter Pd limit in drug substance would be much smaller

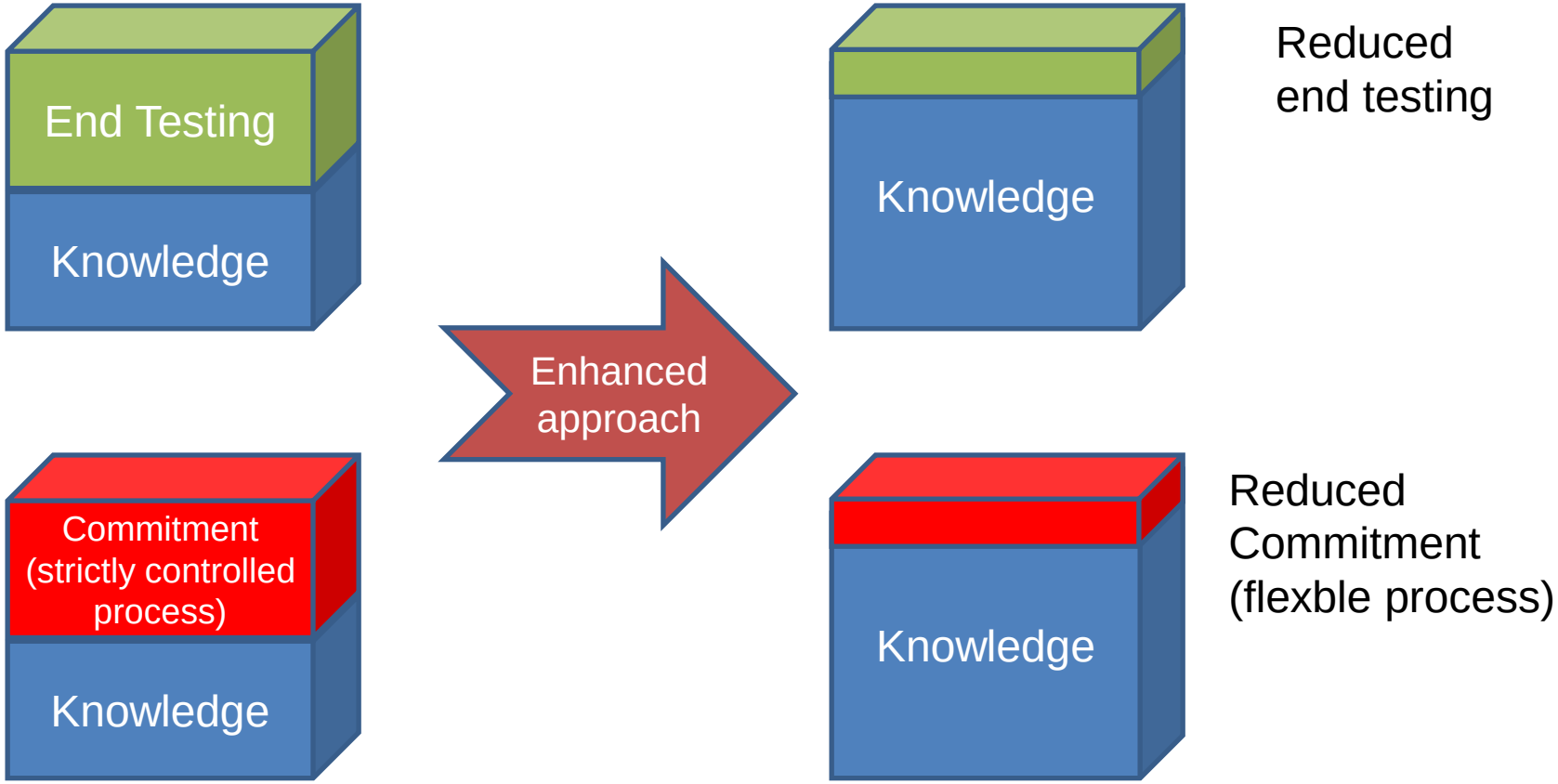


Discussion Topic 1:
Controls and Manufacturing Operating Commitments

- Observations/Learnings
  - Both approaches to control strategy can be acceptable (testing, or by process operating conditions)
  - What should acceptance criteria be based upon? Efficacy/ safety or process capability?
  - The initially proposed Pd limit in the drug substance specification assured patient safety (Option 2 limit)
    - Acceptance criteria set the target for quality, and thus the establishment of a manufacturing process
    - Boundaries of Design Space should not be overly constrained, as this could have a negative impact on process capability

Discussion Topic 1:
Controls and Manufacturing Operating Commitments

- **Enhanced knowledge** – assurance of quality same or enhanced

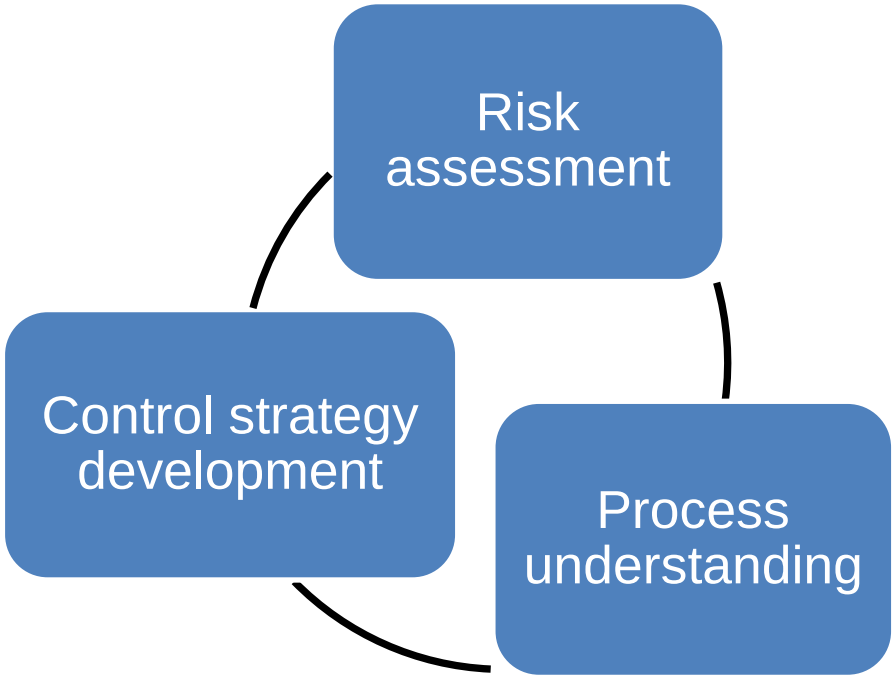


Discussion Topic 2:
Linking Control Strategy to Risk Assessment

- Development of Control Strategy should be accompanied by conclusions from Risk Assessment <u>as necessary</u>
  - In particular, when the final control strategy may seem less robust than typically seen for traditional products
    - reduced end testing
    - flexible manufacturing process
    - a particular parameter does not need monitoring or control
    - quality assurance more reliant on process understanding

The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk (ICH Q9)

Discussion Topic 2:
Linking Control Strategy to Risk Assessment



- Observations/Learnings
  - Risk assessment/ conclusions should be clearly associated to individual process/ control proposals
    - Individual process attributes are the ones subject to control strategy
  - The output from the risk assessment and subsequent experimental work is used to develop and finalize the control strategy
    - Can be iterative – the more one understands, the more one can continue to refine commitments and controls

Discussion Topic 3:
Links from Control strategy to Life-Cycle Management

- Post-Approval Events/ Changes
  - How can a well-developed control strategy support verification at production scale, scale change, and other lifecycle changes?
    - Well-developed control strategy can operate independently of scale
    - Can be independent of where in Design Space one operates
      - For example, an impurity set by a Design Space can be assured by the same specification test irrespective of scale, or where in Design Space one operates
    - Following a change, a Design Space complemented by (additional) controls is 'less at risk' than a Design Space operating by parametric control alone
  - How can the complementary value of established controls be considered in overall change management ?

    (along with scale-dependent process knowledge) ?

Discussion Topic 3:
Links from Control Strategy to Life-Cycle Management

- More effective utilization of control strategy
  - Enhanced knowledge focuses necessary manufacturing commitments and controls, and supports movements from traditional commitments and controls
  - The understanding that supports Manufacturing process description / Design space can be balanced by complementary control strategy
  - A robust and well explained Control Strategy can facilitate empowered change management, the approval of a post-approval change management protocol or a Design Space verification protocol

Discussion Topic 4:
Elaboration and Assessment of the Dossier

- Control Strategy in submission : manufacturing operating commitments + control tests
- How and where can Control Strategy be presented in a submission ?
  - A clear presentation of the control strategy, and its development, in a submission is essential to realize the added value of enhanced knowledge in the marketing authorization
  - Control commitments are spread across the dossier: CTD does not dedicate a section to Control Strategy
  - Overall understanding not easily provided to assessor

Discussion Topic 4:
Elaboration and Assessment of the Dossier

- Observations/Learnings
  - Control Strategy summary (tabular format?)
  - Development of control strategy:
    - For Drug Substances, S.2.6 is probably suitable for a Summary of the various Control Strategy elements
      - Development of synthesis including quality of starting materials, intermediates and reagents
    - For Drug Products, a Summary could be presented within P.2 (between P.2 and P.2.1?)
      - Development of single Control Strategy elements where appropriate: P.2.2, P.2.3

Discussion Topic 4:
What did Applicant Provide in the MAA ?

Drug Substance CQA	Acceptance Criterion	Control Strategy	Critical Process Parameters	Reference
Attribute 1	Specification	What aspects of product / process understanding provide control	What process parameters are committed to linked to this CQA	Where in the CTD can more detail be found
Attribute 2				
Attribute 2				
Attribute 3				

Discussion Topic 4:

Discussion of the Value of such Summary Tables

- Summary tables of Control Strategy for Substance and product considered valuable
- Show linkage from “what patient needs” (QTTP) to “process understanding and controls / manufacturing commitments”
- Applicant’s example was one of several control summary tables used in MAA
  - top down (from QTPP to CQAs to controls) and bottom up (from process to CQAs)
- Perhaps the information could be provided in one table for DS and one table for DP
- Ideally all risks to quality would be addressed (not only specified attributes)
- Ideally links to further discussion / understanding / risk assessment would be included
  - There may be many ways to format such summary level information
    - The team discussed other examples ...

Discussion Topic 4:
Elaboration and Assessment of the Dossier

- Control Strategy Summary table (example)

Attribute	QTPP Target	Control strategy	Specification		Process control	Material attributes	CTD
			Method	Criteria			
Route of administration	Oral	Product design/ development	NA	NA	NA	NA	P.2.2
Potency	Complies with EC directive	Capsule fill weight End testing	End testing (HPLC)	95-105 %	Capsule fill weight (IPC) DS Assay	NA	P.5.1
Water content	Assure quality	Controls on ingoing materials and packaging	Not proposed	Not proposed	NA	DS Moisture Excipient controls Packaging type selected	S.4.1 S.6 P.4.1
Product release	Immediate release	DP end test Process controls DS PSD requirement	Dissolution	Q 80% 30 min	Hardness (IPC) and compression force (parameter)	Drug substance: PSD	S.4.1 P.3.3 P.3.4 P.5.1 P.5.2

Cont.

Discussion Topic 4:
Elaboration and Assessment of the Dossier

- Control strategy elements should be provided (and justified) in CTD where appropriate:
  - Specification (S.4.1 /S.4.5, P.5.1 / P.5.6)
  - Associated test methods (S.4.2, S.4.3, P.5.2, P.5.3)
  - Description of manufacturing process (S.2.2, P.3.3)
  - Control of materials (S.2.3, P.3.4, P.4.1)
  - Control of critical steps/ intermediates (S.2.4, P.3.4)

General Learning regarding submission and review of ‘enhanced’ Control Strategy

- Improved communication during a procedure can often avoid “misunderstanding” and “disagreement”
  - Lack of clarity, or inappropriate level of detail in the dossier
    - Applicants need to think hard about how to make submission content clear and ‘compelling’ – assessor has to be able to reach same conclusions as applicant
  - Lack of clarity in requests for supplementary information (or in responses)
    - Be clear why information is being requested / is being provided – context helps !

Control Strategy Case Study:

LEARNING - Same Considerations for Industry and Assessors

All parties can ask themselves:

- Are CQAs sufficiently assured by the control strategy proposed ?
  - If not, what additional controls / commitments (or justification) should be considered?
- Does risk assessment conducted need to be shared in more detail to justify ‘enhanced’ (reduced) elements of commitments and controls (if these do not seem to sufficiently assure quality)?
- Does the experimentation conducted allow the applicant to conclude to substitute end-product testing and / or establish flexible processing / Design Space ?
- Does the Control Strategy assure quality across the lifecycle?
  - If not, what additional controls or change management commitments should be considered ? (DS verification; non-routine tests etc.)

Back-Up Material

- Example from Tallinn IWG Training
  - Alternative approaches to CQA control

Discussion Topic 1:
Acceptable Alternative Approaches to CQA Control

From IWG Q8, Q9, Q10 Workshop (Tallinn, 2010)

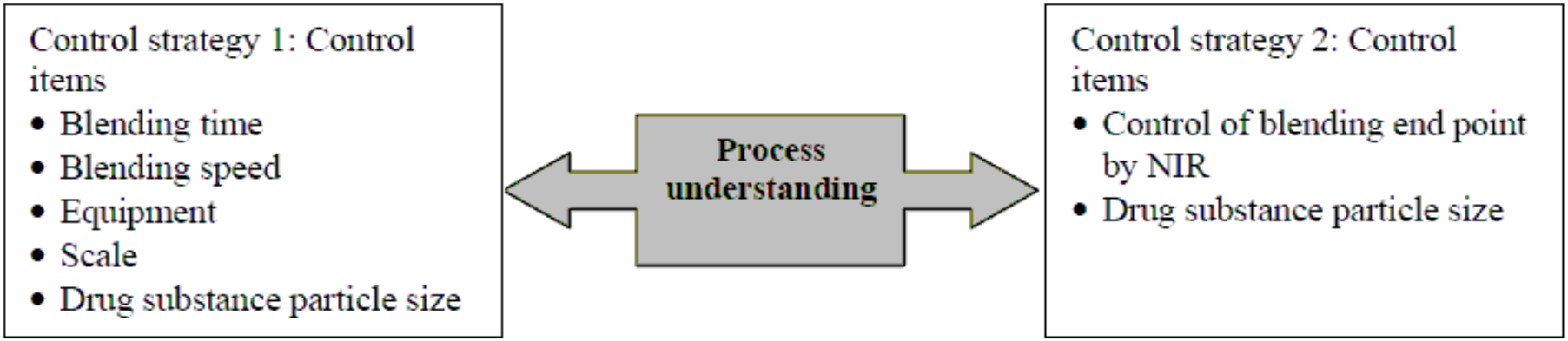


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

Note) In the case of employment of control strategy 1, it is possible that drug substance partcle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.