ICH-GCG ASEAN

Q8(R2): Pharmaceutical Development

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Disclaimer:

- The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.

Overview

- About Pharmaceutical Development
  - General considerations/Structure
  - New paradigm
  - Design space
  - Real time release testing
  - Control strategy
- Examples
- Conclusions

Objective of Pharmaceutical Development

- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- Quality cannot be tested into products; i.e., quality should be built in by design.
- Information from pharmaceutical development studies can be a basis for Quality Risk Management.
- Strategy:
  - Minimum approach
  - Enhanced knowledge approach

Q8(R2): Structure – Parent Guideline

- Parent guideline: Structured according to CTD-Q.
  - Pharmaceutical development: Introduction
  - Components of the drug product
    - Drug substance - Excipients
  - Drug product
    - Formulation development
    - Overages
    - Physicochemical and biological properties
  - Manufacturing process development
  - Container closure system
  - Microbiological attributes
  - Compatibility
- Glossary

Q8(R2): Structure - Annex

- Introduction
- Elements of Pharmaceutical Development
  - Quality Target Product Profile
  - Critical Quality Attributes
  - Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs
  - Design Space
  - Control Strategy
  - Product Lifecycle Management and Continual Improvement
- Submission CTD-Q
  - Quality Risk Management and Product and Process Development
  - Design Space
  - Control Strategy
  - Drug Substance related Information
- Glossary
- Appendix 1/2

Pharmaceutical Development

- At a minimum:

  In all cases sufficient development has to be done, so that a product can be released to the market

  - Defining Quality Target Product Profile
  - Identifying critical quality attributes of the drug product
  - Determining quality attributes of the starting materials (drug substance, excipients)
  - Selecting an appropriate manufacturing process
  - Defining a control strategy

Pharmaceutical Development

- Enhanced approach
  - A systematic evaluation understanding and refining formulation and manufacturing process
    - Identifying the material attributes and process parameters that can have an effect on product CQAs
    - Determining the functional relationships that can link material attributes and process parameters to product CQAs
  - Establishing an appropriate control strategy

General considerations – Additional Opportunities

- Depending on the level of development (scientific understanding) achieved and an adapted quality system in place, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:
  - Risk-based regulatory decisions (reviews and inspections);
  - Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
  - Reduction of post-approval submissions;
  - Real-time release testing, leading to a reduction of end-product release testing.

Quality Product Target Profile

- Intended use in clinical setting, route of administration, dosage form, delivery systems
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate for the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended market product

Example from IWG Case Study:

Quality Target Product Profile (QTPP) Safety and Efficacy Requirements

Tablet	Characteristics / Requirements	Translation into Quality Target Product Profile (QTPP)
Dose	30 mg	Identity, Assay and Uniformity
Subjective Properties	No off-taste, uniform color, and suitable for global market	Appearance, elegance, size, unit integrity and other characteristics
Patient Safety – chemical purity	Impurities and/or degradates below ICH or to be qualified	Acceptable hydrolysis degradate levels at release, appropriate manufacturing environment controls
Patient efficacy – Particle Size Distribution (PSD)	PSD that does not impact bioperformance or pharm processing	Acceptable API PSD Dissolution
Chemical and Drug Product Stability: 2 year shelf life (worldwide = 30ºC)	Degradates below ICH or to be qualified and no changes in bioperformance over expiry period	Hydrolysis degradation & dissolution changes controlled by packaging

Prior Knowledge

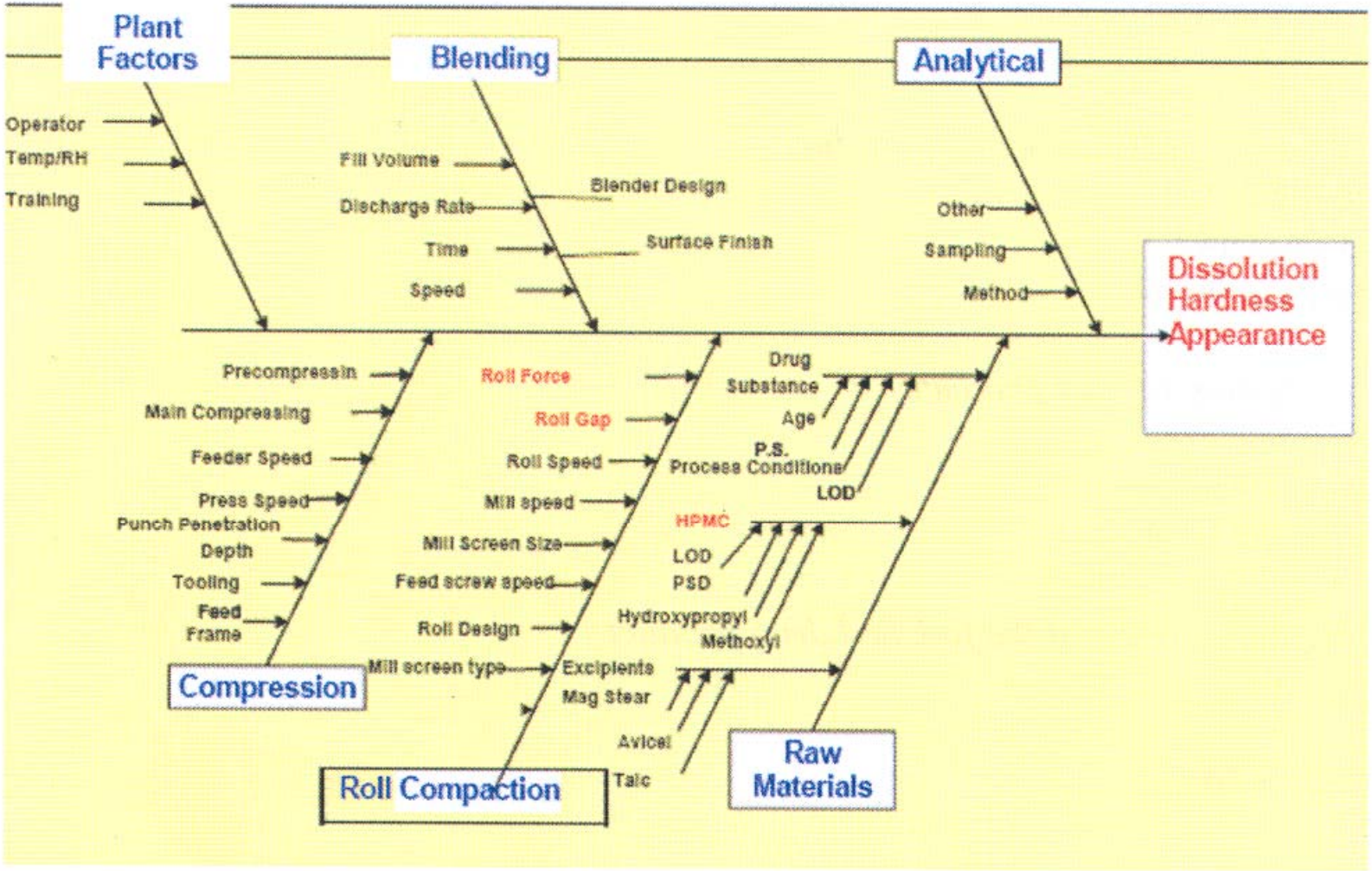
- No formal definition: based on competence, experience of the manufacturer. No need to reinvent the wheel.

- Use of prior knowledge: e.g. basic chemistry
  - Active substance (AS): R-NH_2 maleate salt + excipient lactose
  - AS + Maleate acid: Michael reaction
  - AS + Lactose: Maillard reaction
  - 4% degradation after 6 months accelerated testing

Pharmaceutical Development and Risk Assessment

- Formal use of risk management tools to identify for instance potential CQAs and/or CPPs
- Critical Quality Attribute (CQA): Property or characteristic that should be within an appropriate range to ensure the desired product quality, e.g.
  - Polymorphism
  - Particle size
  - ……
- Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Fishbone diagram



Example from IWG Case Study:
Overall Risk Assessment for Process

- no impact to CQA
- known or potential impact to CQA
- current controls mitigate risk
- known or potential impact to CQA
- additional study required

* includes bioperformace of API and safety (API purity)

Process Steps

CQA	Drug Substance						Drug Product					
	Coupling Reaction	Aqueous Extractions	Distillative Solvent Switch	Semi-Continuous Crystallization	Centrifugal Filtration	Rotary Drying	Manufacture Moisture Control	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance*												
Dissolution												
Assay												
Degradation												
Content Uniformity												
Appearance												
Friability												
Stability-chemical												
Stability-physical												

Example from IWG Case Study:
Risk Assessment (FMEA): Purity Control

What is the **Impact** that ---------- will have on purity? 1) minimal **5) moderate** 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely **5) moderately likely** 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain **5) moderate** 9) unlikely

Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Distillative Solvent Switch	Temperature / Time, etc.	1	5	1	5	Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)	9	5	1	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	9	5	1	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	9	1	5	45	Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Antisolvent percentage (charge ratio)	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Crystallization temperature	1	5	1	5	Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters	1	1	1	1	These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.

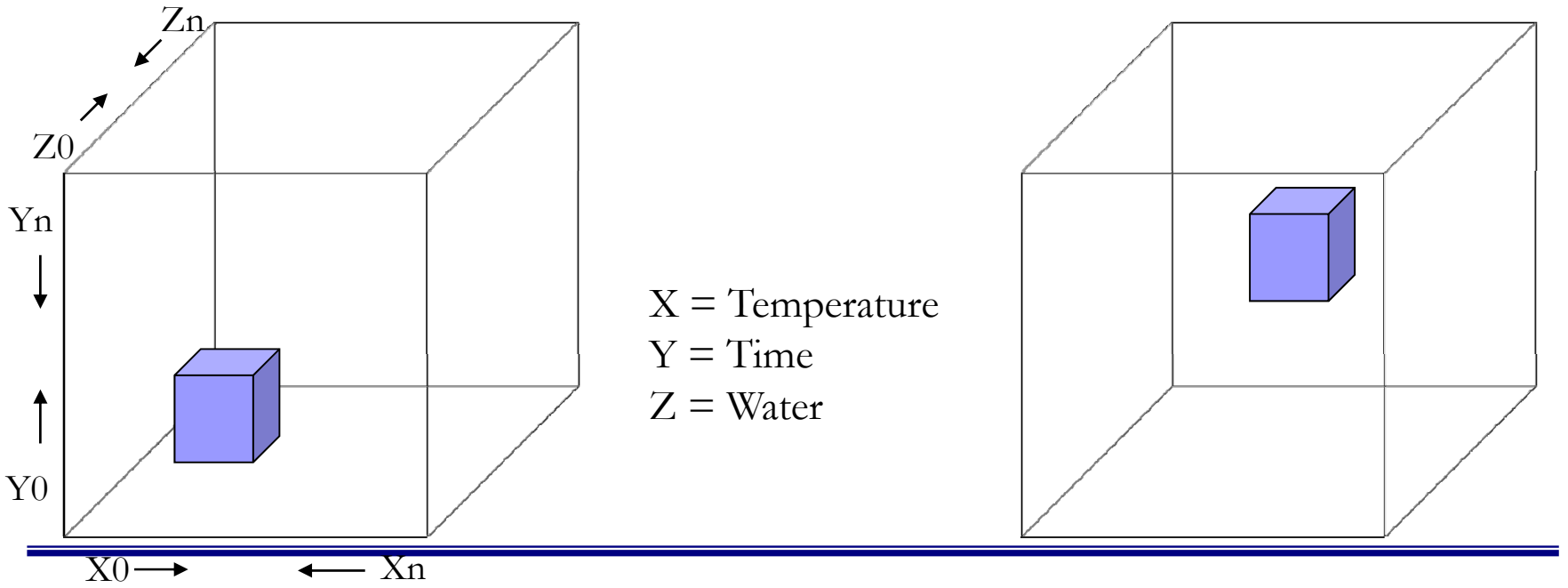
Design space - Definition

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement outside of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Design Space: possible way of illustration

Multidimensional combination and interaction of input variables/process parameters demonstrated to provide assurance of quality (multivariate analysis)

: operating ranges



Establishment of a Design Space

- Relationship and interaction between (C)PPs and (C)QAs.
- Identification of those process parameters which can influence the quality of the product
- Multivariate analysis in order to demonstrate within which ranges process parameters can be varied without affecting the quality of the product (quality attributes).

Elements of a Design Space

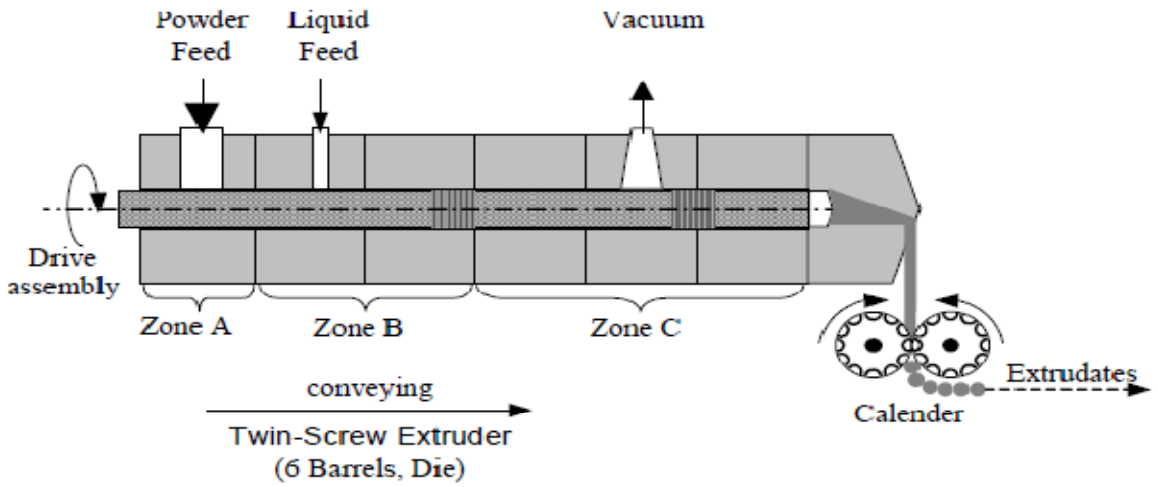
- Selection of variables:
  - Linkage and effect of process parameters and material attributes on product CQAs;
  - Identifying variables and their ranges within which consistent quality can be achieved.
- Describing a design space in a submission
  - See Appendix 2
- Unit operation design space(s)
- Relationship of design space to scale and equipment

Elements of a Design Space

- Design space versus proven acceptable ranges
  - A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.
- Design space and edge of failure
- Control strategy

Example of a DS for an intermediate: Drug Product Melt Extrusion Process

Figure 4. Schematic of Extrusion Process



Example of a DS for an intermediate (2): Drug Product Melt Extrusion Process

CPPs:

- Ratio of Screw Speed to total Feed Rate
- Zone X Temperature

CQAs (response factors):

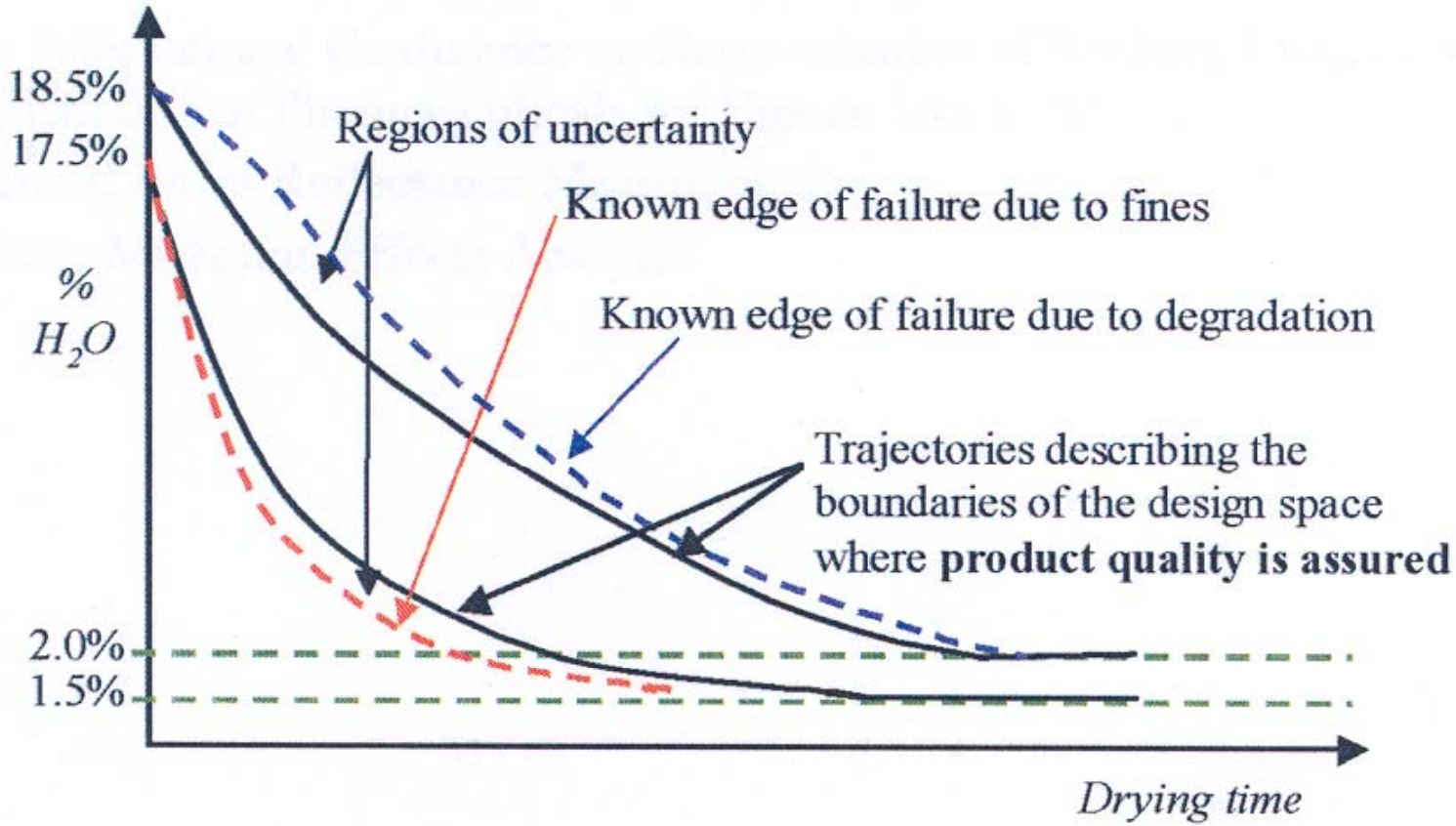
- Degradation
- Residual crystals
- Visual appearance

DOE:

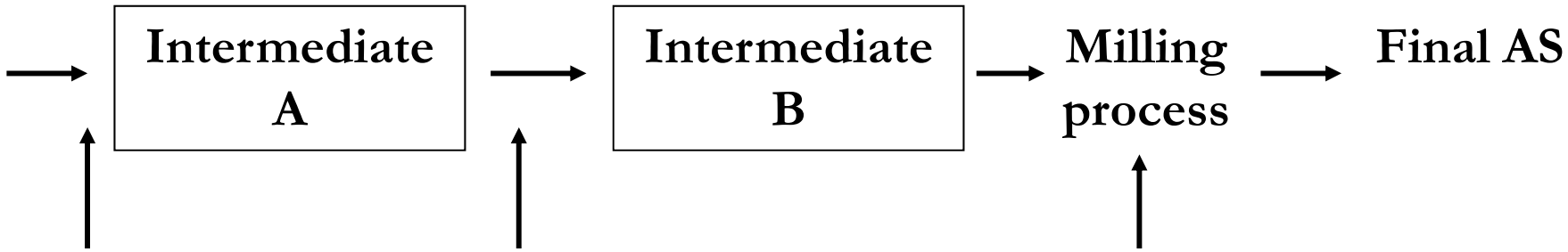
- Temperature zone X
- Temperature zone Y
- Screw speed
- Total feed rate

- Development of a model to predict degradation

EFPIA: P2 Mock Submission
Drying process and Impurities Profile and Fines



e.g. Design Space for a drug substance



temperature	solvent quantity	mat. feed rate
pH	wash quantity	mill speed
reaction time	drying temperature	.
amount solvent	.	.
.	.	.
.	.	
.		

Q8(R2): Granulation affecting Dissolution Rate (presentation)

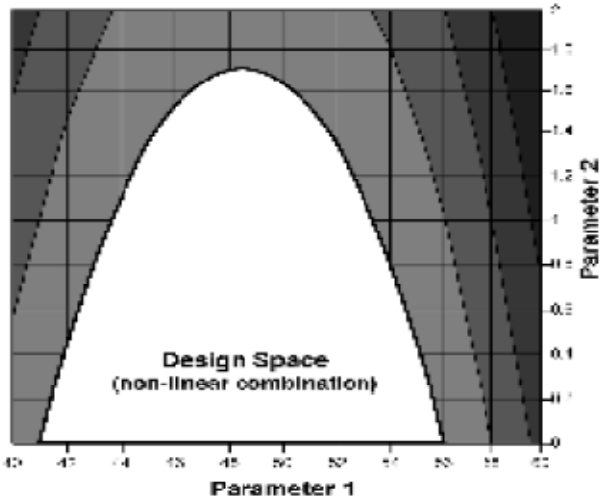


Figure 1c: Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

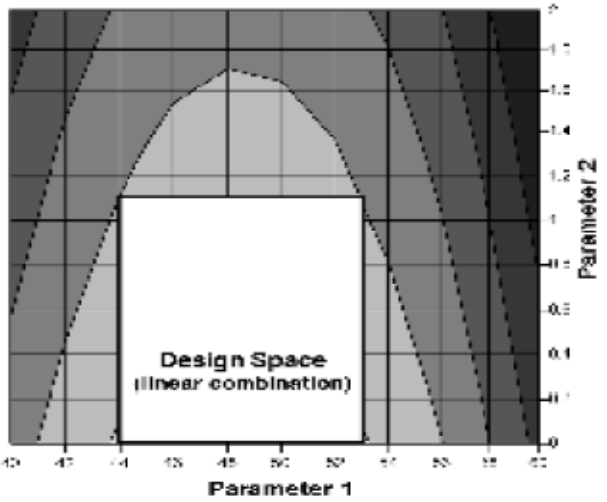


Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

Control Strategy: definition

- 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 (ICH Q10).

Control Strategy

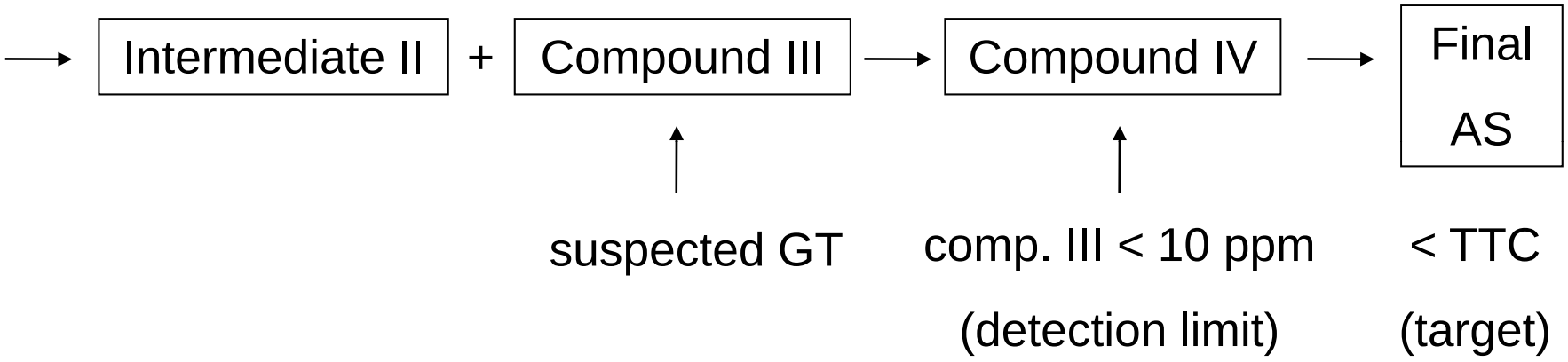
- Minimal or enhanced approach:

  a Control Strategy is always needed
- Not to be confused: control strategy and batch release
- Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records.
- Has to be established based on Formulation/ Manufacturing Development
- Introduced in Manufacturing (in-process controls) and Control of Drug Product

New paradigm: Setting Specifications – e.g. Control of Impurities

- Drug substance:
  - Identification of process parameter(s) (CQP) in the synthesis influencing the generation of a specific impurity in the final product: introduction of a specific in-process control: tightening of pH range.
  - Introduction of a specific purification step e.g. to limit a potential genotoxic impurity below TTC (degradation of this impurity).

Setting specification:
GTI example from an application



- To control impurities at an intermediate rather than at the end product

Real Time Release Testing

- To base the release of a product on product and process understanding rather than on end product testing alone and/or on the results of batch analysis.
- This implies
  - Understanding the science around the product and process
    - Identifying the parameters (critical) of active, excipients, process influencing the quality
  - Establishment of a control strategy –risk based- which
    - monitors the important parameters influencing the CQAs;
    - gives the basis for RTR or reduced end product testing.

Real Time Release Testing (RTRT)

- Example: Sterilisation
  - Injectables: compliance with the specification “sterile”:
    - via parametric release rather than with the conventional Ph.Eu. “Sterility test”;
    - monitoring of critical parameters (time, pressure, temperature, ….)
- Example: dissolution
  - Release parameters e.g.
    - Particle size active substance and/or excipients
    - Hardness of the tablet
    - ……..

Appendix 1. Differing approaches to P2

- Illustration of potential contrasts between minimal and enhanced (QbD approach).
- It is not a black or white situation: current practices in industry vary and typically lie between the two approaches

Appendix 1. Overall Pharmaceutical Development

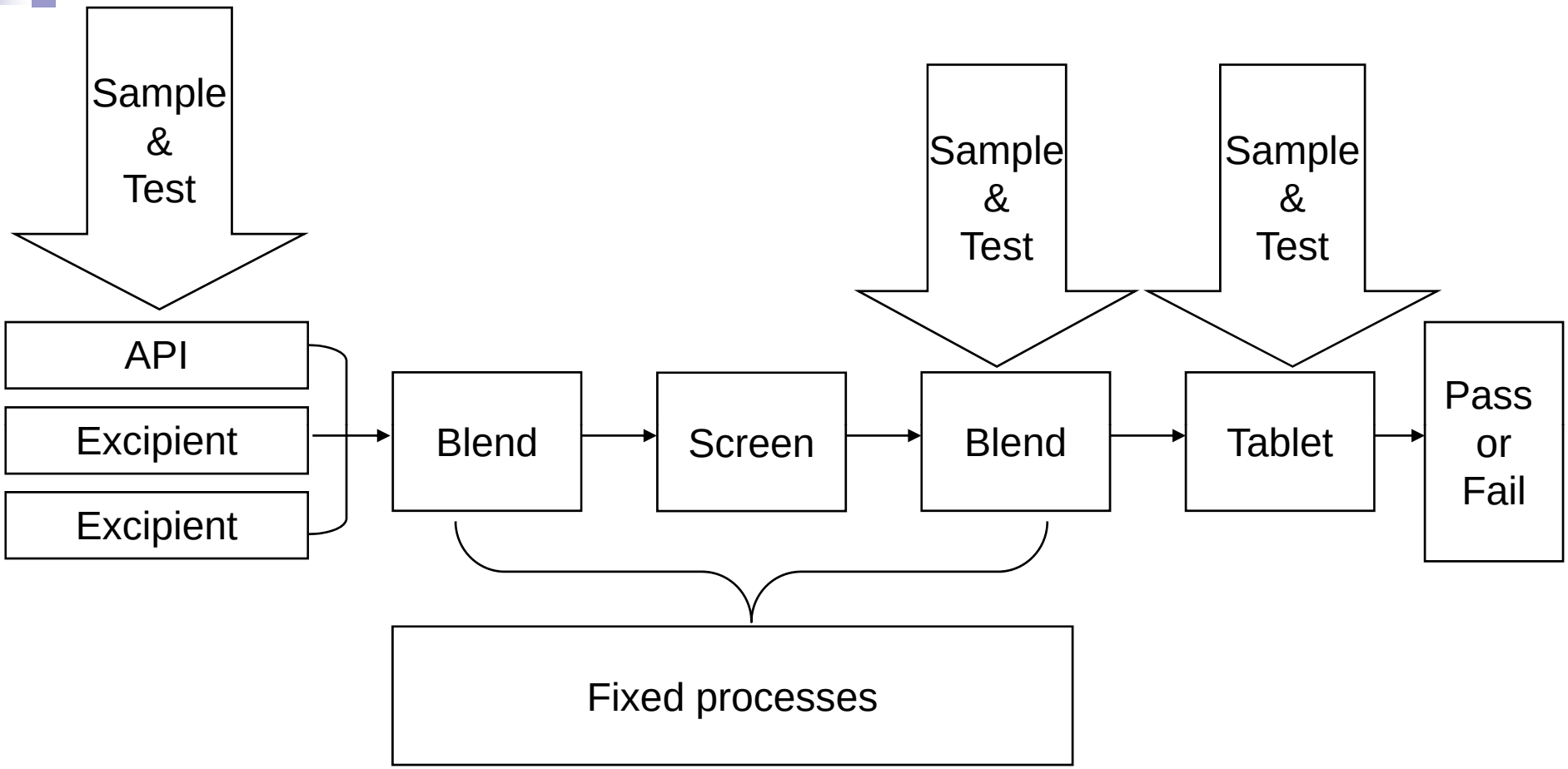
- Minimal Approaches
  - Mainly empirical
  - Developmental research often conducted one variable at a time
- Enhanced, Quality by Design Approaches
  - Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs
  - Multivariate experiments to understand product and process
  - Establishment of design space
  - PAT tools utilised

Appendix 1. Manufacturing Process

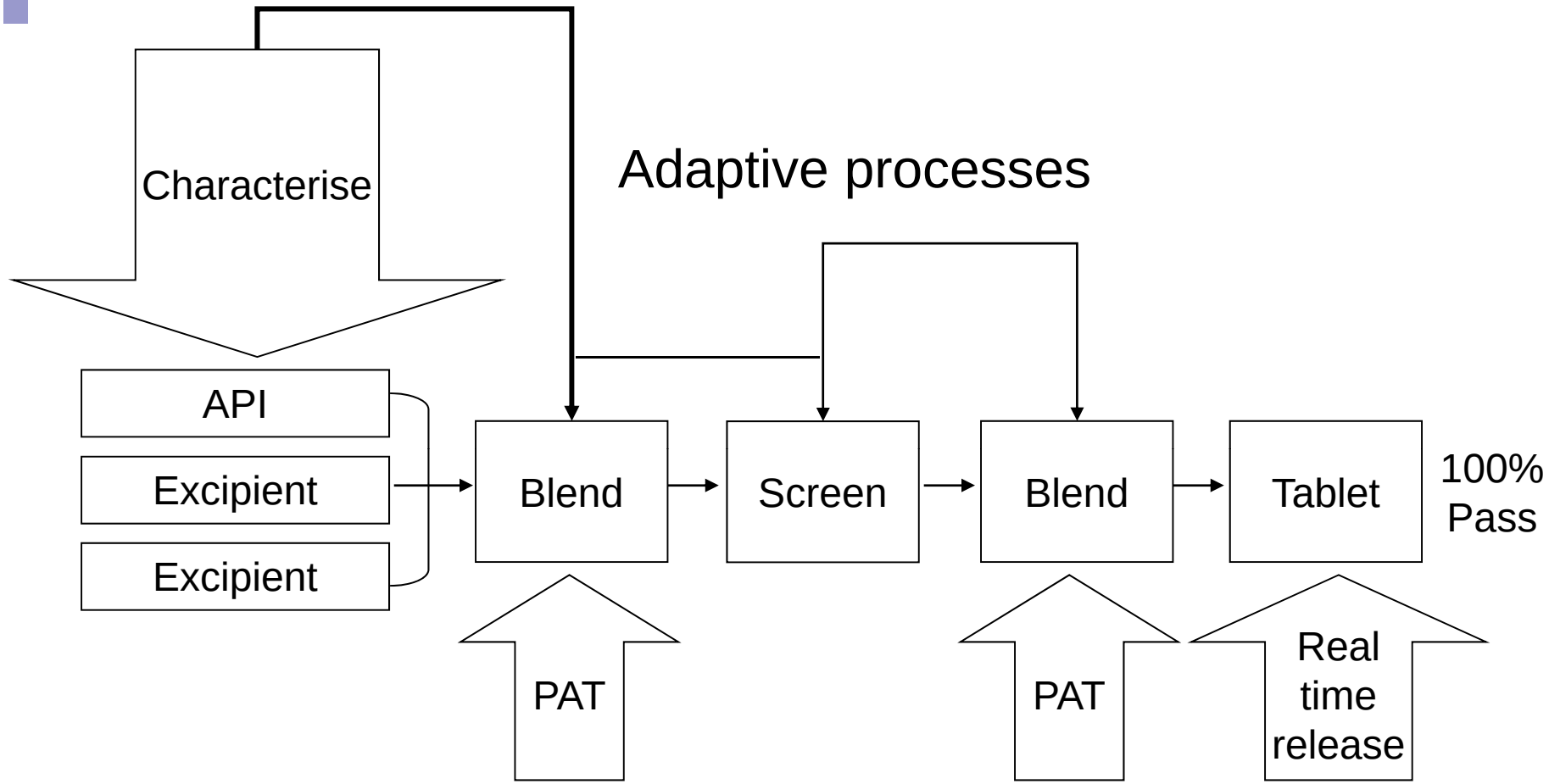
- Minimal Approaches
  - Fixed
  - Validation primarily based on initial full-scale batches
  - Focus on optimisation and reproducibility
- Enhanced, Quality by Design Approaches
  - Adjustable within design space
  - Lifecycle approach to validation and, ideally, continuous process verification
  - focus on control strategy and robustness
  - Use of statistical process control methods

Appendix 1. Process Controls

- Minimal Approaches
  - In-process tests primarily for go/no go decisions
  - Off-line analysis
- Enhanced, Quality by Design Approaches
  - PAT tools utilised with appropriate feed forward and feedback controls
  - Process operations tracked and trended to support continual improvement efforts post-approval



Quality Criteria met if:
- Meets specification(s) (off-line QC tests)
- GMP Procedures followed



Standards and acceptance criteria for a PAT/QbD approach are not the same as a “Test to Document Quality” approach

Appendix 1. Product Specifications

- Minimal Approaches
  - Primary means of control
  - Based on batch data available at time of registration
- Enhanced, Quality by Design Approaches
  - Part of the overall quality control strategy
  - Based on desired product performance with relevant supportive data

Appendix 1. Control Strategy

- Minimal Approaches
  - Drug product quality controlled primarily by intermediates (in-process materials) and end product testing
- Enhanced, Quality by Design Approaches
  - Drug product quality ensured by risk-based control strategy for well understood product and process
  - Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing

Appendix 1. Lifecycle Management

- Minimal Approaches
  - Reactive (i.e., problem solving and corrective action)
- Enhanced, Quality by Design Approaches
  - Preventative action
  - Continual improvement facilitated

Conclusion

- *The new Paradigm to Quality is based on a sound combination of science (enhanced scientific knowledge), use of risk management tools and the establishment of an efficient Quality System.*
- Consequences on the Evaluation of Dossiers for Submission for MA
  - Science based application files
  - Change in review process
    - Enhanced collaboration between assessors and inspectors already at time of submission and during life cycle of the product
    - Clarification of respective responsibilities

Conclusion

- Pharmaceutical development: strategic choice of a company
- Establishment of a design space
  - More development needed
  - More process and product understanding.
  - More robustness of the process
  - More manufacturing flexibility
  - Less batch failure
- Needs further discussion:
  - Data versus knowledge: what does that mean?
  - Amount of data to be submitted or located at site?

Pharmaceutical Development and/ QbD

- Quality by Design as in Q8(R2)
  - *Systematic approach* to development that begins with predefined objectives and emphasises product and process understanding and control, based on sound science and quality risk.
  - A more systematic approach to development may include, for example, incorporation of *prior knowledge*, results of experimental studies using *design of experiments*, *use of quality risk management*, and *use of knowledge management* (see ICH Q10) throughout the *lifecycle* of the product.

Pharmaceutical Development (QbD): *Demystification*

- A systematic approach will facilitate the process to achieve quality and should automatically generate more knowledge.
- Not necessarily new requirements:
  - Pharmaceutical development has anyhow to be done
  - QbD does **not** require the establishment of e.g., design space or real time release testing: a company might decide based on full scientific understanding not to establish a design space or RTR testing.
  - The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant *(strategic decision of a company)*

Thank You for Your Attention