MANUFACTURING CONTROL STRATEGY FOR CELL, GENE AND TISSUE PRODUCTS

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INTRODUCTION

- What is a manufacturing control strategy?
- Why is it important?
- Common issues
- Dispel a few QbD *delusions* as I go.

EU MEDICINES DIRECTIVE

Directive 2001/83/EC; Annex I, part I, 3.2.1.1

EU: Definition of a biological medicinal product

- A biological medicinal product is a product, the active substance of which is a biological substance.
- ……
- and that needs for its characterisation and the determination of its quality a **combination of physico-chemical-biological testing**, **together with the production process and its control**.

Note: active pharmaceutical ingredient (API) = active substance = drug substance (DS).

ICH Q8

Quality cannot be tested into products

Quality cannot be tested into products;
i.e., quality should be built in by design

ICH Q8: Pharmaceutical Development (3.2.P.2)

Objectives of a control strategy

Control Strategy [my expanded interpretation]

A control strategy is designed to ensure that a product of required quality will be produced consistently.

The elements of the control strategy ….. should describe and justify how in-process controls and the controls of input materials ([starting and raw materials], drug substance and excipients), intermediates (…), container closure system …… contribute to the final product quality.

Controls should be based on product, formulation and process understanding and should **at a minimum** include control of the **critical process parameters** and material attributes [e.g. starting/raw materials, intermediates, DS and 1° packaging specifications].

ICH Q10: Pharmaceutical Quality System

What is a control strategy?

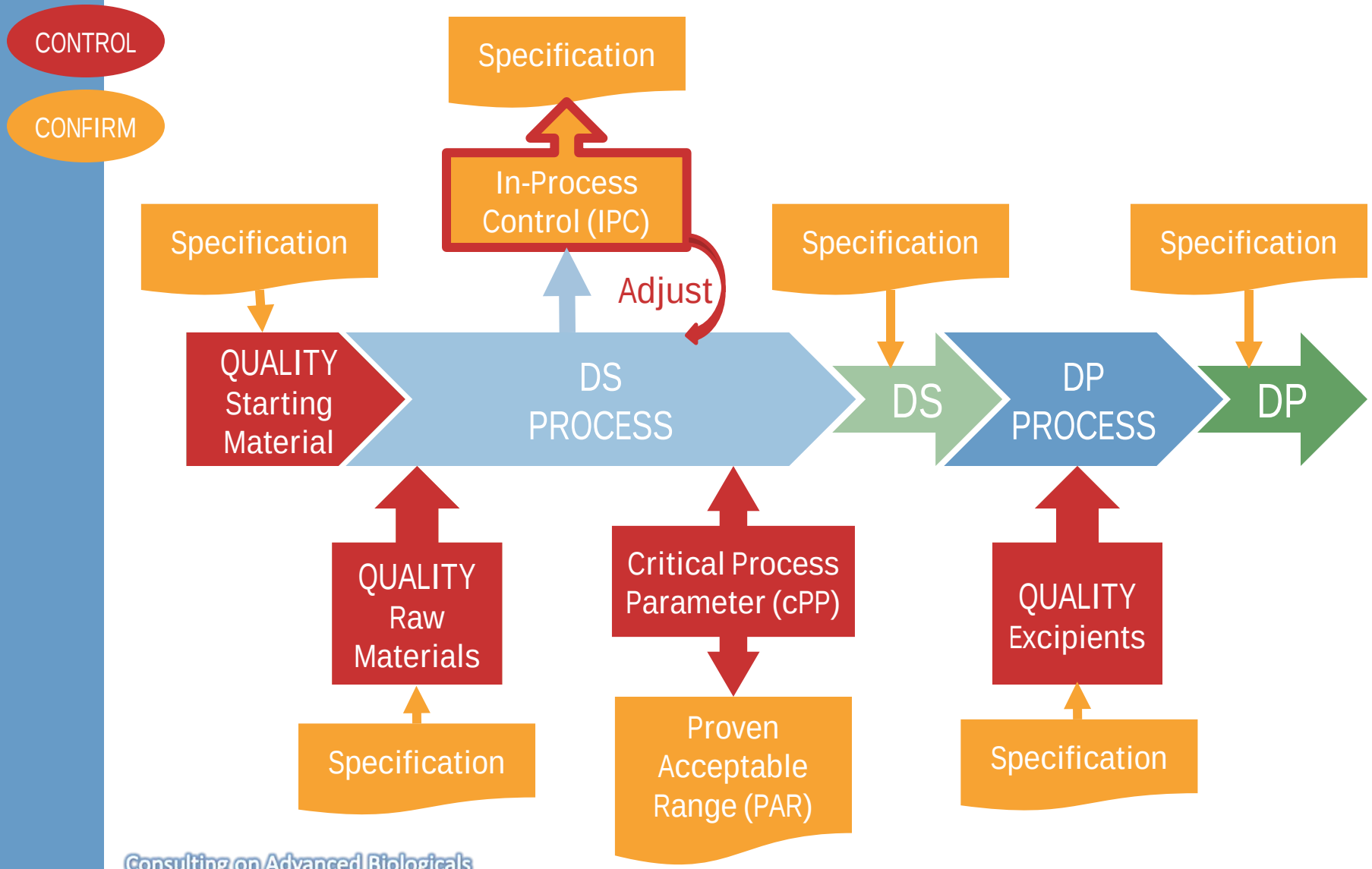
Control Strategy [my expanded interpretation]
A planned set of controls, derived from current product and process understanding, that **assures process performance and product quality**.
The controls can include parameters [(critical) process parameters] and attributes [(critical) quality attributes] related to drug substance and drug product materials and components [starting and raw materials, intermediates, excipients], facility and equipment operating conditions [(critical) process parameters], in-process controls, finished product specifications [release specifications], and the associated methods and frequency of monitoring and control.

ICH Q8 - Control Strategy
Identify sources of variability – and control them

- A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability.
- Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled
- Product and process understanding will support the control of the process such that **the variability** (e.g., of raw materials) **can be compensated for** in an adaptable manner to deliver consistent product quality.
  - [Particular challenge with autologous starting material]
  - [Often many more complex biological raw materials]

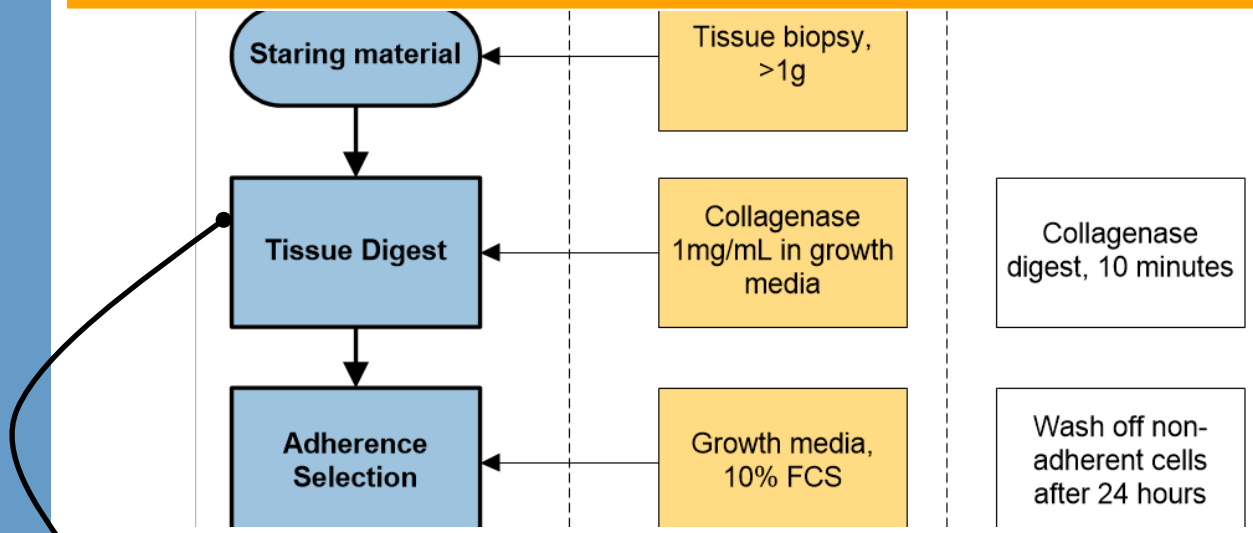
COMPONENTS OF A CONTROL STRATEGY

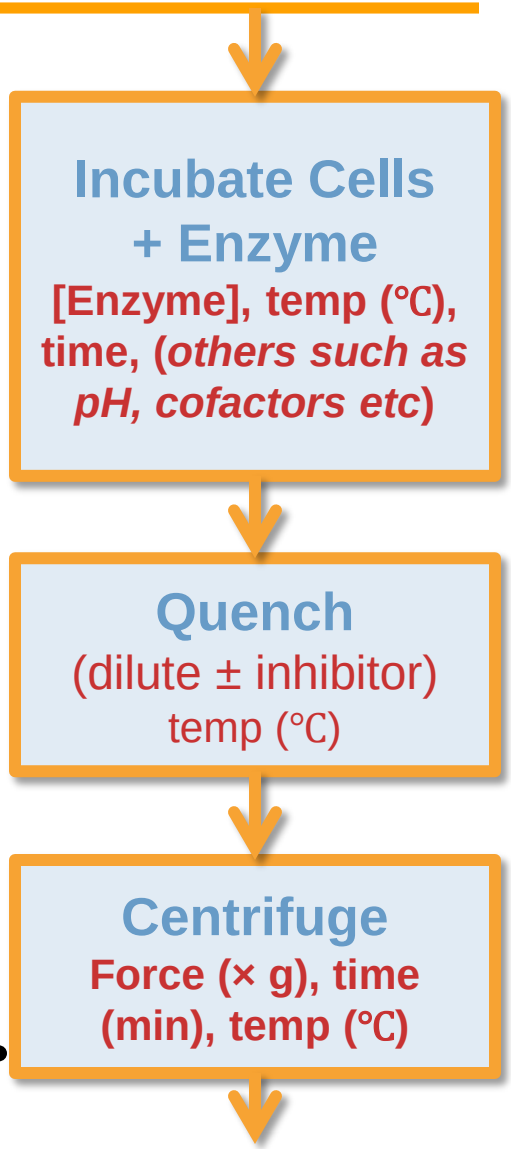
Confirmation and Control



DEVELOPING A CONTROL STRATEGY

Unit Operations



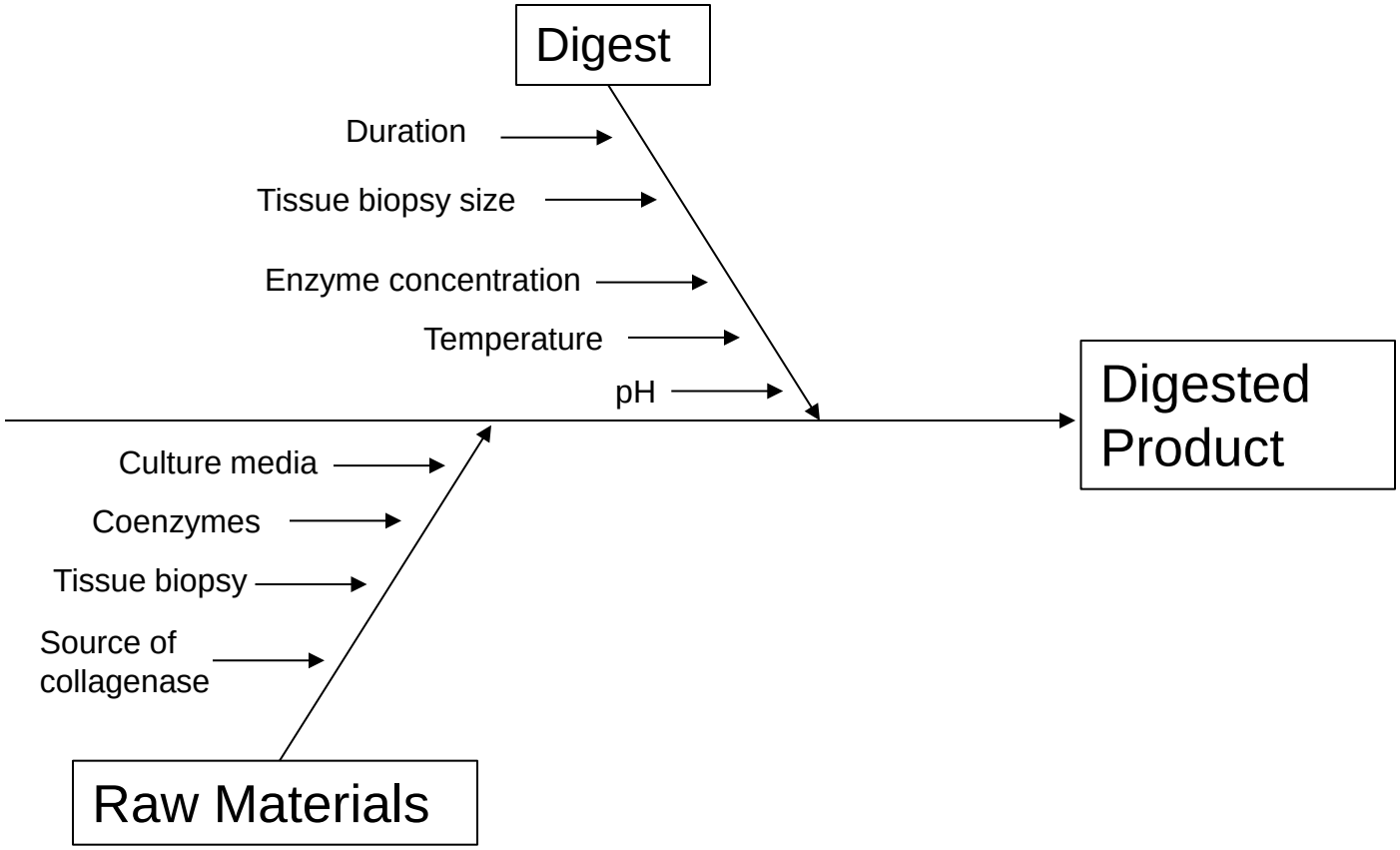


Step - overall purpose to isolate cells from tissue

Unit operations – breakdown of step based on when control (e.g. process parameters) needs to change.
[my suggestion]

RISK ASSESSMENT TOOLS

FACTORS IMPACTING COLLAGENASE DIGEST STEP



Ishikwaha (Fishbone) Diagram For Collagenase Digest Step

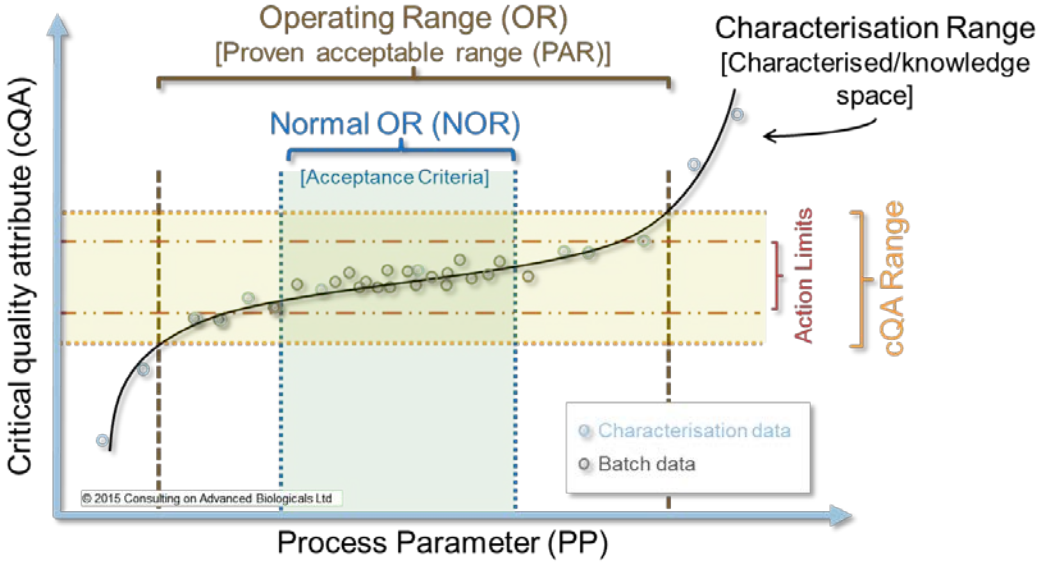
CRITICAL PROCESS PARAMETERS

ICH Q8: Minimal Approach

- ICH Q8 says a minimal approach to process development is largely empirical
- Tends to explore one variable at a time
- Focus on optimisation and reproducibility

My Experience

Currently tendency to select just a few parameters to explore
Not always a clear rationale for choice
Rarely explored in much detail
Hard to argue well-controlled.



CRITICAL PROCESS PARAMETERS

ICH Q8: Enhanced, Quality-by-design Approach

- 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
- Focus on control strategy and robustness
  - Use of statistical process control methods

- THIS TAKES **MUCH MORE** WORK (DATA)!

PROCESS CONTROLS

ICH Q8: Minimal Approach

- Process controls
  - In-process tests primarily for go/no go decisions
  - Off-line analysis
- Specifications (intermediates, DS, DP)
  - Primary means of control
  - Based on batch data available at time of registration

My Experience

Relevance of in process tests often unclear

- Tendency to over-use viability (always set as >70%)

PROCESS CONTROLS

ICH Q8: Enhanced, Quality-by-design Approach

- Process controls
  - PAT tools utilised with appropriate feed forward and feedback controls
  - Process operations tracked and trended to support continual improvement efforts post approval
- Specifications
  - Part of the overall quality control strategy
  - Based on desired product performance with relevant supportive data

- THIS TAKES **MUCH MORE** WORK (DATA)!

CONCLUSIONS

- The general principles in ICH Q8 are relevant
- QbD is unrealistic, but the tools may be useful.
- Developing a quality target product profile (QTPP) is likely to be helpful

END

THANK YOU

CONTROL STRATEGY COMPONENTS

Key Definitions

- **Critical Quality Attribute (CQA):**

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (generally associated with the drug substance, excipients, intermediates and drug product) *ICH Q8(R2)*

- **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 *ICH Q8(R2)*

CONTROL STRATEGY COMPONENTS

Key Definitions

- **In-Process Control:**

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications *ICH Q7*

- **In-Process Tests:**

Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release *ICH Q6A*

CONTROL STRATEGY COMPONENTS

Key Definitions

- **Quality**

The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A).

- **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.

CONTROL STRATEGY COMPONENTS

Key Definitions

- **Quality Target Product Profile (QTPP)**

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

CASE STUDY

ATMP EXAMPLE

Hyalograft C autograft

(characterised viable autologous chondrocytes expanded in vitro, seeded and cultured on a hyaluronan-based scaffold)

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- Validation of the washing steps have been conducted through **validation of the removal of process-related impurities**.
- The description of the manufacturing process for both the drug substance and drug product is considered limited and the available control measures suggest an uncontrolled process. There is insufficient detail of the operating conditions for each step (volumes used etc, with working ranges) which **suggests poor process control**.
- Raw materials are not qualified for human use and the applicant should either provide information on the manufacturing and quality of those materials or change them into materials that are approvable for human use. In the latter case, **additional comparability studies would be needed**.

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- A **major objection** is raised concerning the **control strategy** for the key intermediate (cell suspension) the drug substance and the drug product. Of particular concern is the lack of control on the cell expansion phase……..
- This lack of control of the DS manufacturing process is also mirrored by the lack of control at the level of drug substance and drug product. Specifications for release testing should include identity, purity, potency, impurities, sterility, cell viability and cell number, unless suitably justified.

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- The **deficiencies in process control** are a significant factor in the major objection raised for DS/DP process validation. It is considered the lack of suitable pre-set specifications and controls precludes a proper process validation exercise. More significantly in terms of process validation, the applicant has not performed an appropriate validation exercise, i.e. the manufacture of 3 consecutive full-scale 'commercial' batches (maximum foreseen batch size). Instead the applicant has processed 5 biopsies, divided each in half and processed each half at the maximum or minimum operating condition. This is a development study, not a validation study.

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- There are **significant deficiencies in the characterisation** of the drug substance and therefore a **major objection is raised**. In terms of characterisation of cells on the scaffold, the analysis is restricted to analysis of chemical degradation products of the scaffold and homogeneity of cell distribution on the scaffold so the combination product is **poorly characterised in terms of key quality attributes**. The applicant appears to have conducted limited characterisation studies (few reported in the non-clinical part) to identify the critical quality attributes on the actual key intermediate (cell suspension) DS or DP.

CASE STUDY

TISSUE-ENGINEERING EXAMPLE

OraNera

Cultured Autologous Mucosa Epithelial Cell Sheet (CAOMECS)

EMA/CAT WITHDRAWAL ASSESSMENT REPORT

ORANERA

- The production process was **insufficiently validated** – it was not demonstrated that the manufacturing process was **capable of reproducible commercial manufacture**
- **Characterisation parameters not yet established** for batches produced in a modified process, or in a process that can yield clinically efficacious cell sheets
- In batch data submitted for 26 patients, several batches did not meet proposed specifications, so the **control strategy is considered insufficient**

EMA/CAT WITHDRAWAL ASSESSMENT REPORT

ORANERA

- Number of studies planned to be performed after final implementation of new control methods remain to be conducted:
  - Additional stability study
  - Comparability study between previous and current process
  - Final process validation using three consecutive batches with all of the established specifications

CASE STUDY

ATMP EXAMPLE

Glybera

(Alipogene tiparvovec)

EMA/CAT PUBLIC ASSESSMENT REPORT

GLYBERA (Alipogene tiparvovec)

- The applicant did not consider the evaluation of comparability of the two products in terms of **potency** necessary as AMT011 has been qualified independently of AMT-010 on the basis of non-clinical studies. This is considered acceptable as **toxicology and pharmacology studies were repeated with AMT-011**.

- Note: AMT010 (plasmid/HEK293 process)
- AMT011 (bacculovirus/insect cell process)!!!!

BUT

Changes Can Have Consequences

EMA/CAT PUBLIC ASSESSMENT REPORT

GLYBERA: Consequence of the change.

- Muscle toxicity at the proposed dose has been observed in animal models as well as in clinical studies, and it was unclear whether this may, in part, be **due to the high levels of these impurities**. It was concluded that either the analytical assays used to test impurities are not sensitive enough (based on the declared LOD's), or the current purification strategy is not robust enough to remove these impurities to an acceptable level. Therefore, the applicant was **asked to improve the process** for example by introducing additional chromatography / diafiltration steps in order to generate product with significantly less process related impurities i.e. cellular and baculovirus DNA and protein; and/or develop more sensitive impurity assays.

PART 4

Designing/Developing A Control Strategy

DEVELOPING A CONTROL STRATEGY

Enhanced vs traditional approach

- Can use combination of approaches for CQAs/steps/unit operations
- Traditional approach:
  - Set points and operating ranges set narrowly based on observed data to ensure consistency of manufacture
  - More emphasis on assessment of CQAs at stage of the DS
  - Provides limited flexibility in operating ranges to address variability (e.g., in raw materials)
- Enhanced approach:
  - Generates better process/product understanding so sources of variability can be identified in more systematic way
  - Development of more meaningful and efficient controls
  - Strategy developed through iterations process understanding increases
  - Flexibility in operating ranges for process parameters

DEVELOPING A CONTROL STRATEGY

Key points to consider

- Define the control strategy
  - What are the quality criteria (QTPP)?
  - Break down process into unit operations
  - Initial design of specific product & process
  - Assess prior knowledge to understand materials, process and product with their impact
  - Risk assessment for process steps and variables
    - Assure all CPPs are identified during QRA
  - Determine type of controls appropriate for each variable
  - Set Specifications
- Scale-up considerationsQuality system requirements of control strategy

DEVELOPING A CONTROL STRATEGY

Key points to consider

- Strategy should ensure each DS CQA is within the appropriate range, limit, or distribution to assure quality
- DS specification is one part of a total control strategy
- Not all CQAs must included in DS specification. CQAs can be:
  - (1) included on the specification and confirmed through testing the final drug substance
  - (2) included on the specification and confirmed through upstream controls
  - (3) not included on the specification but ensured through upstream controls e.g.
    - In process testing
    - Measurements of process parameters/material attributes that are predictive of a drug substance CQA
    - Process Analytical Technology (PAT) can enhance control of the process and maintain output quality.

DEVELOPING A CONTROL STRATEGY

Unit Operations

- Break down process into unit operations
  - Process flow step numbers are useful, e.g.
    - 1, 2, 3 (unit operations)
    - 1.1, 1.2 1.3 (sub-steps within unit operation)
    - Or similar.
- Each step should have a defined purpose; e.g.
  - Wash step (case study 1)
  - Enzyme digest step (case study 2)

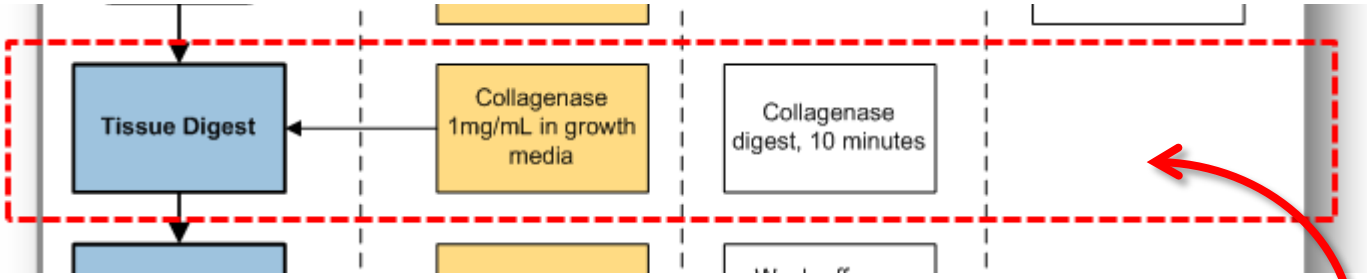
DEVELOPING A CONTROL STRATEGY

In-process Controls

- In-process controls can help to ensure a process step has achieved its intended effect.
- IPC may be necessary for next unit operation, e.g. cell count, purity/impurity level etc (possibly critical IPC).
- Allows early batch failure (e.g. catastrophic failure)
- May allow process adjustments (e.g. adjustment of concentration) prior to next step.
- General information for process problem solving (useful but not critical)

DEVELOPING A CONTROL STRATEGY

Set In-process Controls



Collagenase step IPC:
Cell yield: $>10^6$ (viable) nucleated cells
Viability: *>70%*

Viability might be included because it:

- indicates a problem with the digest (based on optimisation experiments)
- influences the next step (adherence to flask),

DEVELOPING A CONTROL STRATEGY

Setting specifications

- No single approach, depends on the attribute;
  - Broadly impurities are typically limit tests for release/stability, e.g. < X
  - In almost all cases microbial and adventitious agents are no growth, not detected etc.
    - Suitability based on limit of detection and specificity
- Most other attributes have ranges, e.g. purity
  - How to set these?

    1) based on process capability (i.e. batch data)

    2) based on clinical qualification (i.e. patient exposure)

    Or a combination of both?

DEVELOPING A CONTROL STRATEGY
Common approach to setting specifications

- A common approach by industry is to use specification limits based on mean ± 2 or 3 x s.d.
  - Regardless of the number of data points (batches) and the distribution of the data (normal/ non-normal)?
  - Regardless of clinical qualification?
- Consider the statistical relevance based on available data e.g. fewer data points means the variability is less well understood and mean ± 2 or 3 s.d. may not make sense
- Early in development specifications usually set more empirically.
  - Detailed justifications not expected
- Late in development/approval more data should allow a statistical approach to support the proposed specification
  - But **make sure it makes sense scientifically** (don't be led by stats).
  - Are the proposed specifications within those used clinically (esp P3)?

DEVELOPING A CONTROL STRATEGY
Specification general requirements and considerations

- Normally, the following tests are considered applicable to all drug substances and drug products
  - Identity
  - Purity/Impurity
  - General tests, including e.g. appearance and safety (endotoxin, bioburden/sterility)
  - **Potency**
  - Content
- Since the specifications are chosen to confirm the quality, the manufacturer should provide the rational and justification for including and/or excluding testing for specific quality attributes
  - Make use of data generated during process development, process and product characterisation
  - Prior knowledge (e.g. platform knowledge) and pharmacopoeia requirements to be considered

DEVELOPING A CONTROL STRATEGY

Submission

- Describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality.
- These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the critical process parameters and material attributes.

Example of a Possible Control Strategy Summary – Biotechnological Products

Drug Substance CQA	Control Strategy for Drug Substance CQA	Section(s) in CTD where Detailed Information is Located
Contaminants in biologically sourced materials (Viral Safety)	Summaries of viral safety information for biologically-sourced materials	3.2.S.2.3
	Detailed information including for materials of biological origin, testing at appropriate stages of production and viral clearance studies	3.2.A.2
Residual Host Cell Proteins	Design space for an individual unit operation (e.g., see Example 3)	3.2.S.2.2
	Target range for consistent removal assured by validation	3.2.S.2.5
	Analytical procedures and their validation	3.2.S.4.2 and 3.2.S.4.3
Specific Glycoforms	Controls implicit in the design of the manufacturing process including a summary of process control steps (e.g., cell culture conditions, downstream purification, holding conditions etc.)	3.2.S.2.2
	Characterisation to justify classification as CQA (cross reference to nonclinical/clinical sections if relevant)	3.2.S.3.1
	Control of Critical Steps, Testing program and specifications	3.2.S.2.4 and/or 3.2.S.4.1
	Justification of specification	3.2.S.4.5
	Stability	3.2.S.7

DEVELOPING A CONTROL STRATEGY

Regulator Expectations

- Regulators evaluate the control strategy and establish whether the risk has been adequately controlled
- Inspector reviews the implementation of the control strategy at site, including adaptation at scale up, and the adequacy of the site quality system to support it

QUESTION

1. Who is following a QbD approach to development?
2. Who thinks they have, or will by approval, know all their CQA?
3. Who thinks they have, or will by approval, have identified all their critical process parameters, i.e. those that impact their CQA?
4. Who thinks their product and process are, or will by approval, well understood?
5. Of those who said YES to Q4, who are following a QbD?
6. Of those who said NO to Q4, who are following a QbD?

QUALITY BY DESIGN

Help, Hype or Hindrance?

- Some people think (Quality by Design) is applicable to ATMPs….

BUT

- QbD requires **more** characterisation and many developers are even not achieving the minimal process standards!
- ATMP processes are fixed with limited flexibility - QbD involves establishing a design space and working anywhere within this (not considered a change as results in product with similar quality)

CRITICAL PROCESS PARAMETERS

ICH Q8: Enhanced, Quality-by-design Approach

- Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs
- Multivariate experiments to understand product and process
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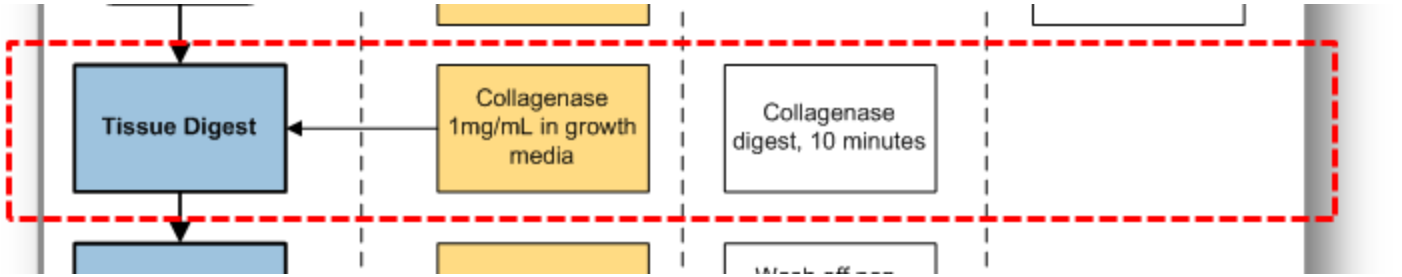
USE RISK ASSESSMENT TOOLS
IDENTIFYING LIKELY PP/QA

Assuming you want to retain the *in situ* characteristics of the cells but release them from the tissue.

Characteristics	Parameters
phenotype/genotype - *cellular active* - *cellular impurity* viability proliferative capacity cell yield biological activity indicators of early cell damage	Time/duration enzyme type enzyme supplier pH temperature size of tissue pieces reaction media composition co-enzymes Stability of enzyme in solution

USE RISK ASSESSMENT TOOLS
OPTIMISATION

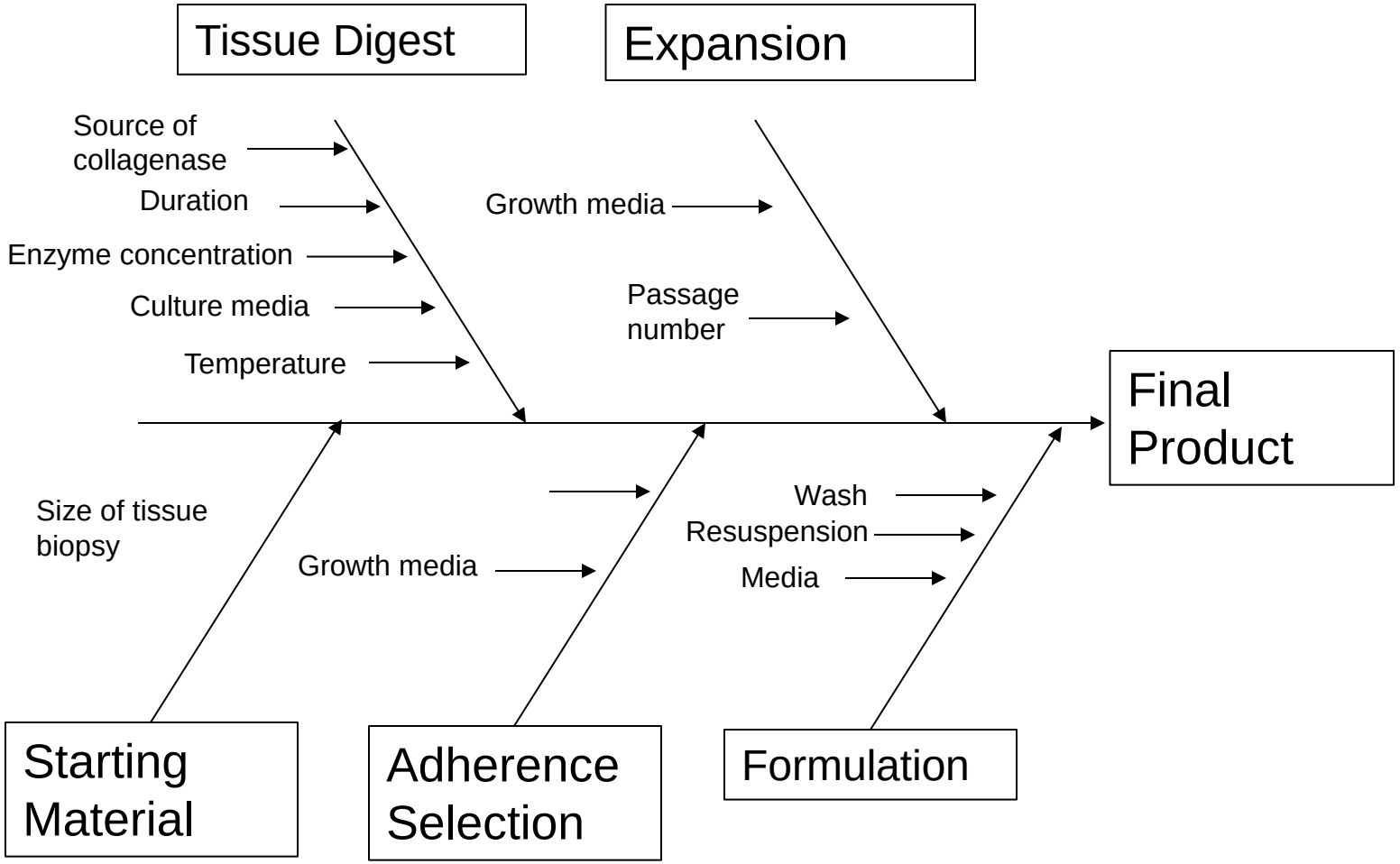


Assumptions: Since collagenase works between pH: 6 – 8, this is outside the range that the cells are happy in and controlled by the buffer system of the culture medium, so not a 'critical' parameter here, and little value in measuring it in-process.
CO_2 is a critical parameter because the culture media chosen is dependent on CO_2 to maintain pH. This is easily controlled continuously by the incubator.

Step characterisation conclusions
No cells are released during the first 5 minutes
Yield of curicytes doesn't increase after 10 minutes
After 15 minutes the proportion of fibroblasts in the curicyte starts to increase significantly.
After 20 minutes viability starts to decrease significantly
Optimum time therefore determined to be 10 minutes, with an operating range of ± 2 minutes where quality is not significantly altered.

USE RISK ASSESSMENT TOOLS

ISHIKWAHA (FISHBONE) DIAGRAM - CURZALL



What are you trying to achieve?

- Design and development of a manufacturing process that can consistently and reliably (ideally robust) manufacture batches of product.
- Identify all sources of variability and control these sources through appropriate control strategies

Taking into consideration your

- Target product profile (TPP)

Recommend developing a

- Quality target product profile (QTPP)

CONTROL STRATEGY COMPONENTS MAY INCLUDE…

- Specifications
- Risk Assessment
- CQAs, CPPs and non-CPPs
- Process Monitoring
- Procedural Controls (batch records, SOPs, material inventory)
- In-Process Tests and In-Process Controls (IPC)
  - Controls on material attributes (raw/starting materials, intermediates)
  - Controls on drug substance (e.g., release testing).
  - Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality
  - Controls for unit operations that have an impact on product quality

CRITICAL QUALITY ATTRIBUTES

Do you know which they are?

- Some or all of the tests for identity, purity (incl. impurities), potency, content etc could or should be cQA, but;
  - Its up to you to demonstrate for the specific test, e.g. potency, used is a cQA
  - It might not be
  - Just because you call it a potency test it doesn't mean it is a good measure of potency or a cQA – you need to prove that.

For example

- Viability >70%
- When its almost always >90%
- Is this providing sufficient control?

CRITICAL QUALITY ATTRIBUTES

If you are not certain of your cQA……

- How can you determine which process parameters are critical?
  - It might be some of your process parameters are irrelevant
- This can include concentration of a raw material
  - Are you using more then you need to (CoGs)?
- Also relates to quality of raw material
  - You might be paying for a higher quality than is necessary (CoGs)