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

AUDIENCE SURVEY

- Of the 17 ATMP submitted to the EMA (centralised procedure) since 2001, how many had concerns raised about their control strategy?
- Note: 8 were not approved; 9 were approved.

a) About half of the 8 that were not approved
b) Mostly those that were not approved (n=8)
c) Most of them

Concerns about the overall Process Control Strategy is a common issue at approval

- Only 2 of the 17 submissions didn't have significant concerns raised
  - Likely still had minor questions

They were:

- Imlygic – oncolytic virus (approved)
- Cerepro – adenovirus vector
  - *but only the second time it was submitted*

Concerns about the overall Process Control Strategy is a common issue at approval

- Meaning 8/9 approved products had significant issues with the control strategy at submission
- Resolved during the procedure
  - Usually requiring more studies/data
  - Delaying approval
  - Sometimes requiring further work post-approval

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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).

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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?

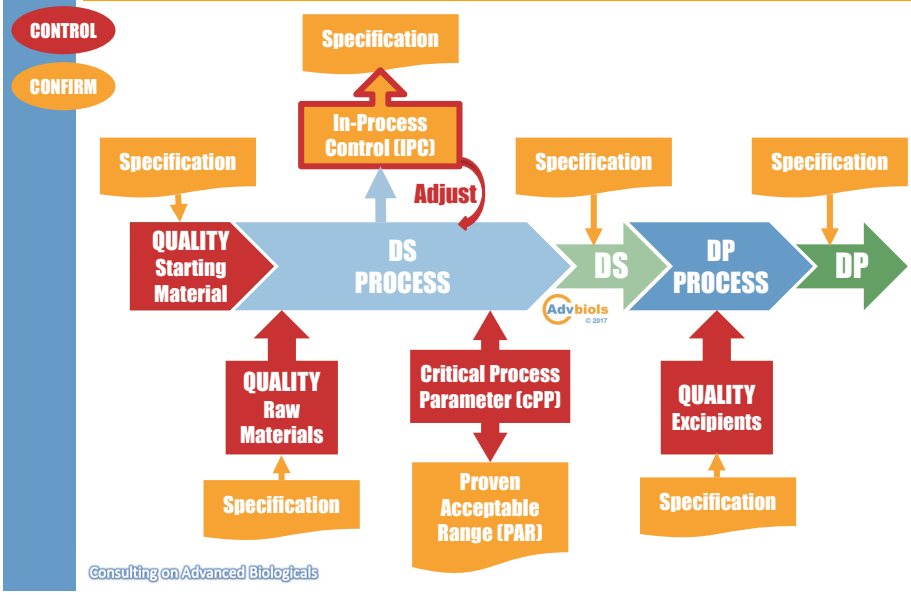
Control Strategy [my expanded interpretation]
A planned set of controls, derived from current product and process understanding, that **assures process performance and product quality**.
The controls can include parameters [(critical) process parameters] and attributes [(critical) quality attributes] 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



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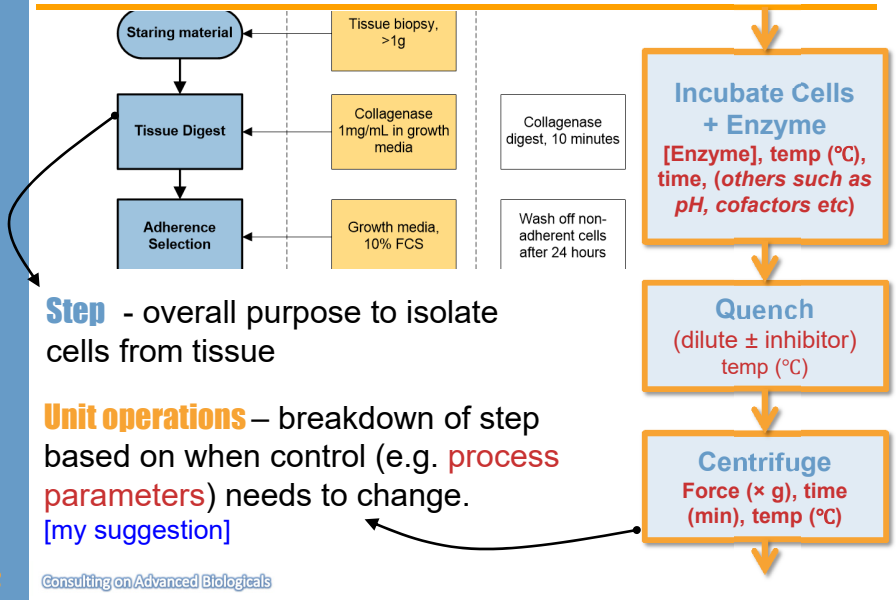
DEVELOPING A CONTROL STRATEGY

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]

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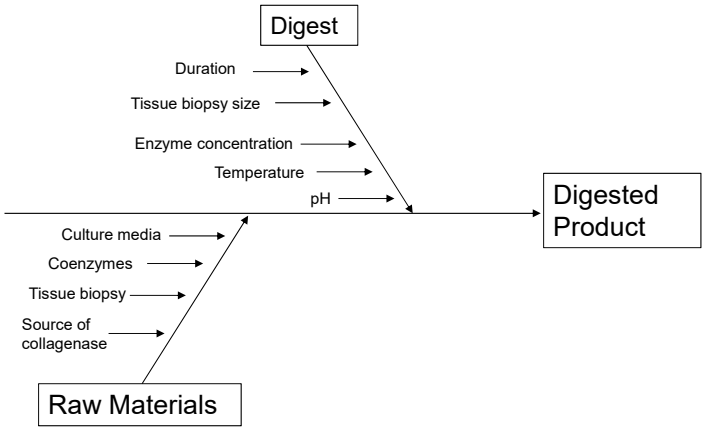
RISK ASSESSMENT TOOLS

FACTORS IMPACTING COLLAGENASE DIGEST STEP



Ishikwaha (Fishbone) Diagram For Collagenase Digest Step

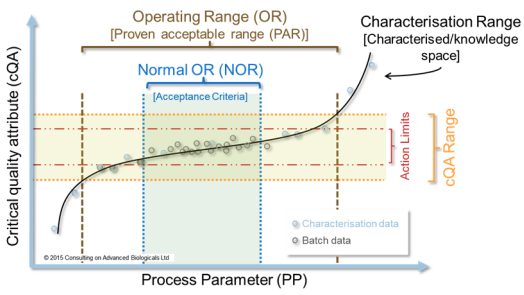
CRITICAL PROCESS PARAMETERS

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.



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%)

BREAKDOWN OF ISSUES RAISED

ATMP SUBMISSIONS TO THE EMA SINCE 2001

	Gene Therapy Medicinal Product						Cell-based Medicinal Products										M
Advbiols © 2017	Cerepro	Advexin	Gendux	Cerepro#2	Glybera	Imlygic	Strimvelis	Zalmoxis	Heparesc	Holoclar	Spherox	MACI	Provenge	Hyalograft C	OraNera	ChondroCelect	Apligraf
Process Control	M	M	M		M		O	X	M	M	M	M	M	M	X	X	M
Starting material							O		M_F						X		M
Raw materials quality/spec									O	M		X?	X	M			M
Intermediates										X				M		X	O
In-process testing							?		M	M		X?			X	X?	O
Process parameters											M			X	X	X?	O
Release testing	X	M			M		O	M	M	O	M	X	M	M	X	X	M
Justification of specifictions		X	X		M			X	M_F	X	X_F	X	M	M	X		O

DRAFT RESULTS

CONCLUSIONS

- The general principles in ICH Q8 and ICH Q10 are relevant
- 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.