**Version: 1.0**

**How to use this Annotated Template**

**Black text** = intended to be kept or adapted to your purpose (includes suggested headings/text)

**Red text** = intended to be helpful / removed once you have developed content (includes weCANreg input for new researchers developing first-in-human cell / gene therapies)

**Blue text** = intended to be kept or adapted to your purpose (includes tables and definitions from [*Parenteral Drug Association Technical Report: Gene and Cell-Based Therapy Control Strategy*](https://store.pda.org/TableOfContents/TR81_TOC.pdf)*)*

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

<Drug name / code>

**General Introduction**

Academic scientists and clinicians who discover novel cell / gene therapies often need to identify and target commercial goals, which may include licensing or company creation. They will need to augment research plans with regulatory knowledge, adding credibility to valuations that are based on market assessments. This document can help.

A QTPP is not normally submitted to regulators but helps researchers start thinking more like a regulator. It is an **optional, dynamic planning tool** **that can be adapted to suit your needs.** The process of developing your QTPP forces you to assess and understand implications of your manufacturing decisions, lending confidence to your plans. Sections of the document can be copied directly into regulatory documents.

This QTPP is unique (and called “enhanced”) because it has been customized for cell or gene therapies, and because it introduces key concepts from of Quality by Design (QbD), which is not typically a component of the QTPP. QbD concepts are important to cell and gene therapies that are highly heterogenous and complex products that are more likely to face challenges without adequate life-cycle plans helping to navigate manufacturing changes.

This will be an evolving document, and your feedback can help improve future versions. Please contact Stem Cell Network or weCANreg Consulting Group Inc. to provide input.

Consider using this box to keep track of versions and see how your QTPP evolves

|  |  |  |
| --- | --- | --- |
| **Version** | **Version purpose / Milestone** | **Date** |
|  | Investor pitch |  |
|  | Pre-clinical planning |  |
|  | Pre-CTA meeting |  |
|  | CTA (early) |  |
|  | CTA (pivotal) |  |
|  | Pre-NDS |  |
|  | NDS |  |

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Use the suggested headings, definitions, and charts to describe your product (Section 1); identify quality attributes (Section 2); assess criticality of materials (Section 3) and processes (Section 4); and summarise your control strategy (Section 5).

# Product Characteristics

Follow steps from (a) to (b) below to develop a concise, meaningful description of your product for consistent use with regulators:

1. Start simply – How would you describe your product in just a few lines?

* Refer to its source (typically human tissue, for cell-based therapies), its platform technology (how it is expanded or modified), and its key feature(s) related to function (mechanism of action), and put this in Section 1.1

1. Elaborate on key features – What distinguishes your product?

* Expand upon the Section 1.1 description to include other features of your active ingredient (referred to as your “Drug Substance” in regulatory submissions) and put them into bullet form in Section 1.2
* Ensure to identify key components of the Drug Product (which is the Drug Substance after final product formulation)

## Basic Description

e.g. Product X is a cellular immunotherapy containing allogeneic T cells isolated from peripheral blood and genetically modified *ex vivo* using a lentiviral vector carrying a chimeric antigen receptor targeting specific surface antigens.

This description summarizes highly relevant information that can quickly orient regulators. It helps to determine which reviewers will need to be engaged, and what sorts of risks may be involved. It can be copied into emails, cover letters, briefing books, and submission documents.

## Key Feature(s)

* ….

# Critical Quality Attributes (Clinically Relevant Characteristics)

For complex cell and gene therapies you will need to know which characteristics of your product are more important than others – this should be risk-based to help you focus your efforts and simplify discussions with regulators.

Follow steps from (a) to (c) below to identify, then refine your list to include clinically relevant characteristics of your product: under the headings provided:

1. Start simply – How would you describe your product?

* Use the headings provided in the table below
* Assess how others have described similar products (more information is publicly available than you might expect)

1. Refine – Which attribute measures are most relevant for each type of attribute?

* Consider whether alternative assessment methods could be more relevant, quantifiable, consistent, and accurate
* Consider whether you need more information to choose the best measure
* Assess attribute impact and uncertainty, using the definitions provided below

1. Assess – Can you assert the relative importance of your quality attributes?

* Consider whether the attribute is a Critical Quality Attribute (CQA), potential CQA (pCQA) or non-CQA using the 3x3 table provided below

Document your results in the following table. This begins to shape what may become your Drug Product specifications.

| **Attribute Type** | **Attribute** | **Impact** | **Uncertainty** | **Result** |
| --- | --- | --- | --- | --- |
| Appearance | E.g. Colour, visual debris, opacity, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Identity | E.g. cell surface marker(s) (single/multiple), genetic marker, phenotypic characteristic, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Purity | E.g. % viable cells, % desired cells, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Impurities  - Process-related  - Produce-related | E.g. non-viable cells, viable (non-target) cells, cells with unwanted growth potential, cell substrate-derived impurities (host-cell proteins & DNA), adventitious agents, particulate material, agents added during processing (e.g. DMSO), etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Dose/ concentration | E.g. # viable cells/mL, # genetic copies/mL, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Potency\* | E.g. functional assay, biological assay, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |
| Safety  - Sterility  - Endotoxin  - Mycoplasma | E.g. No detectable adventitious agents, etc. | High  Medium  Low | High  Medium  Low | CQA  pCQA  non-CQA |

\* Potency will be most challenging to predict early in development. Potency assays might be described in a pharmacopeia, but many cell and gene therapy manufacturers will need to develop assays in-house: In this case, think of what you might qualify (show data to support clinical relevance) in time for First in Human studies, and what you might validate (confirm relevance) before later stage studies.

## Criticality Assessments

You can loosely estimate the “criticality” (general importance) of attributes as high/medium/low, based on impact (severity) x likelihood (uncertainty), defined as follows:

|  |  |
| --- | --- |
| **Impact (Severity) Assessment** | |
| **Rating** | **Impact** |
| Negligible to Low | Marginal patient impact; no potential for decreased safety; attribute is not expected to impact safety or efficacy |
| Medium | Small potential for patient impact that does not change the overall risk/benefit profile for the product; attribute may have a manageable adverse effect, but significant patient impact is improbable |
| High | Significant to catastrophic patient impact, changing the risk/benefit profile of the product |

|  |  |
| --- | --- |
| **Criteria for Uncertainty Scoring of Product Attributes** | |
| **Uncertainty** | **Prior Knowledge** |
| Low | Extensive literature available on this attribute; in-house data (in vitro, nonclinical, or clinical) available |
| Medium | Attribute well understood based on scientific rationale; in-house data (in vitro, nonclinical, or clinical) available |
| High | Limited scientific understanding of this attribute; no clinical experience; limited in-house data |

.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Uncertainty** | | |
|  |  | **Low** | **Medium** | **High** |
| **Impact** | **Low** | non-CQA | non-CQA | pCQA |
| **Medium** | pCQA | pCQA | pCQA |
| **High** | CQA | CQA | CQA |

# Critical Process Parameters (Impactful manufacturing Steps)

Health Canada’s Biologics and Radiopharmaceuticals Drugs Directorate says, “the process is the product”. This is particularly important for cell and gene therapies, which are highly variable, complex, and difficult to characterize. Follow steps from (a) to (c) to assess and describe how you expect to control your manufacturing process, which is made up of Unit Operations (definable steps).

1. Start generally – What are your manufacturing Unit Operations?

* Summarize operations in a basic flow diagram under Section 3.1
* Describe Unit Operations in text under Section 3.2

1. Add detail – What are your process parameters?

* Add details to Section 3.2 regarding inputs/outputs, and potential controls

1. Assess – Can you identify potential Critical Process Parameters?

* Conduct a “Criticality Assessment” using definitions and tables at the end of this section, and summarize them in Section 3.3

## Manufacturing Flow Diagram

Insert a process flow diagram.

## Unit Operation Descriptions

Elaborate on your manufacturing flow diagram by describing each step in its own box:

**Basic description:** (unit operation 1, 2, 3, etc.)

**Severity score:** (see below to determine High/Medium/Low)

**Occurrence Score:** (see below to determine 1/4/7/10)

**Detection Score***:* (see below to determine 1/4/7/10)

## Critical Process Parameters

| **Operation** | **Severity** | **Occurrence** | **Detection** | **Score** |
| --- | --- | --- | --- | --- |
| Unit operation 1 | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |
| Unit operation 2 | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |
| Unit operation <…continue> | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |

## Criticality Assessment

You can loosely estimate the “criticality” (general importance) of process parameters, based on impact (severity) x likelihood (occurrence) x ability to detect, with each defined as follows:

|  |  |  |
| --- | --- | --- |
| **Rank** | **Rating** | **Severity Criteria** |
| 10 | High | Small to moderate change of this parameter has a significant impact on a CQA |
| 5 | Medium | Large change of this parameter or a small change in parameter, in combination with other factors, has a significant impact on a CQA |
| 1 | Low/Negligible | The parameter has no impact on CQAs |

|  |  |  |
| --- | --- | --- |
| **Rank** | **Rating** | **Occurrence Criteria** |
| 10 | Frequently | Parameter exceeding the acceptable range is likely to happen frequently. Automated control systems operate very close to, or outside of, the known limits of the acceptable ranges, or manual activities have high error rates. |
| 7 | Fairly frequently | Parameter exceeding the acceptable range is likely to happen fairly frequently. Automated controls operate close to known limits of acceptable range, or manual activities have moderate error rate. |
| 4 | Fairly infrequently | Parameter likely to exceed the acceptable range fairly infrequently. Automated controls operate within known limits of the acceptable range, or manual activities have low error rates. |
| 1 | Infrequently | Parameter is not likely to exceed the acceptable range. Automated controls operate well within known limits of acceptable range, or manual activities have negligible error rates. |

|  |  |  |
| --- | --- | --- |
| **Rank** | **Rating** | **Detection Criteria** |
| 10 | Impossible | Process parameter being out of range is not detected at all or not until the product reaches the patient. |
| 7 | Moderate | Process parameter being out of range can be detected by qualified batch release procedures. |
| 4 | Highly Likely | Process parameter being out of range typically detected prior to the final unit operation. |
| 1 | Almost Certain | Process parameter being out of range is routinely detected in the actual unit operation in a manner that allows for immediate remediation. |

# Critical Material Attributes (Impactful Ingredients)

All manufacturing materials will be produced internally or sourced externally. Their quality will be integral to your product quality, safety, and efficacy. Human- and animal-derived materials are particularly important to cell and gene therapies. Cell and gene therapies often require unique materials that are not yet widely used or available.

In-house materials will need to be qualified (and eventually validated), and all external suppliers will need to be pre-qualified, quarantined at arrival until released by SOP (including a review of Certificates of Analysis), and periodically audited.

Follow steps from (a) to (c) to identify and assess the relative importance of your materials from a risk perspective.

1. Start broadly – What materials do you use in your manufacturing process?

* Describe all your materials using headings under Section 4.1

1. Organize your list – How would regulators categorize them?

* Consider what is a Starting Material / Raw Material of Biological Origin / Ancillary Reagent / Excipient / Consumable

1. Assess – Can you identify potential Critical Material Attributes?

* Conduct a “Criticality Assessment” by using the definitions and tables at the end of this section, and summarize this in Section 4.2

## Materials used

Consider using subheadings for Starting Materials, Raw Material of Biological Origin, Ancillary Reagents, Excipients, Consumables, etc.

**Material description (1, 2, 3, etc.):**

**Source:**

**Control description:** e.g. pharmacopeial grade, GMP, clinical grade, etc.

**Impact Classification:** (High/Medium/Low)

**Occurrence Score:** (1/4/7/10)

**Detection Score***:* (1/4/7/10)

## Critical Material Attributes

| **Raw Material** | **Control(s) in place** | **Severity** | **Occurrence** | **Detection** | **Score** |
| --- | --- | --- | --- | --- | --- |
| Material 1 |  | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |
| Material 2 |  | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |
| … |  | High (10)  Medium (5)  Low (1) | 10  7  4  1 | 10  7  4  1 | 1 - 100 |

## Criticality Assessment

|  |  |  |
| --- | --- | --- |
| **Rank** | **Impact** | **Impact Criteria** |
| 10 | High | Small to moderate change of this parameter has a significant impact on a CQA |
| 5 | Medium | Large change of this parameter or a small change in parameter, in combination with other factors, has a significant impact on a CQA |
| 1 | Low | The parameter has no impact on CQAs |

|  |  |  |
| --- | --- | --- |
| **Rank** | **Rating** | **Occurrence Criteria** |
| 10 | Frequently | Raw material attribute variability is frequently expected (i.e., more frequently than 1 in 10 batches of the raw material). Raw material is complex and likely to degrade or introduce a degradant to the process. Failure of the raw material attribute is likely to happen frequently. |
| 7 | Fairly frequently | Raw material attribute variability is expected fairly frequently (i.e., probability of 1 in 10 to 1 in100 batches of the raw material). Raw material is somewhat complex and somewhat likely to degrade or introduce a degradant to the process. Failure of the raw material attribute is likely to happen fairly frequently. |
| 4 | Fairly infrequently | Raw material attribute variability is expected fairly infrequently (i.e., probability of 1 in 100 batches of the raw material). Raw material is fairly simple in nature and unlikely to degrade or introduce a degradant to the process. Failure of the raw material attribute is likely to happen fairly infrequently. |
| 1 | Infrequently | Raw material is consistent and simple. Failure due to the raw material attribute is likely to happen infrequently (i.e., almost never). |

|  |  |  |
| --- | --- | --- |
| **Rank** | **Rating** | **Detection Criteria** |
| 10 | Impossible | Failure of the raw material attribute is not detected at all or not until the product reaches the patient. |
| 7 | Moderate | Failure of the raw material attribute can be detected by batch release procedures. |
| 4 | Highly Likely | Failure of the raw material attribute is likely to be detected prior to the final unit operation. |
| 1 | Almost Certain | Failure of the raw material attribute is likely to be detected prior to its use in the process. Appropriate controls are in place to maintain stability of the material attribute after testing and prior to its use in the process. |

# Control Strategy

Ultimately, you will need to be able to communicate your risk-based approach to product quality by stating how your Critical Material Attributes combine with your Critical Process Parameters to result in a Drug Product that meets the needs of your Critical Quality Attributes.

Follow steps from (a) to (c) to state how these come together. This may be used in regulatory documents such as the Quality Overall Summary.

1. Start Broadly – What do you know about what needs control?

* Consider what you know about your CPP (Section 3) & CMA (Section 4)
* Consider what you may not know about your CPPs and CMAs

1. Augment – What Quality Management Systems will be in place?

* Consider how your facility can support you to control product quality

1. Refine – What potential risks /mitigation is available?

* Consider how these might change over time as the process, analytical methods, variability, and risks become better understood.
* Consider how in-process tests can support the control of your product

Document your findings in a couple paragraphs.