**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 and removed once you have developed content (includes weCANreg input for new researchers developing first-in-human cell / gene therapies). This was based primarily on the *US FDA’s Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool*

**Target Product Profile (TPP)**

<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 TPP is not normally submitted to regulators but helps researchers start thinking more like a regulator. It should be considered an **optional, dynamic planning tool** **that can be adapted to suit your needs.** The process of developing a TPP will help you gain confidence in your clinical plans, and the document itself can contribute to regulatory activities.

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 TPP 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 identify how your product might be used to benefit patients (Sections 1 & 2); identify potential risks with use (Sections 3, 4, and 5); assert how it might work (Section 6 & 7); and be used safely and effectively (Sections 8 & 9). Ultimately, these sections will evolve throughout development until they eventually form into your Product Monograph.

# Indications and Usage

This section helps you identify your target population. You may be surprised by the number of things you can do to refine your target population using regulatory resources. Your indication and usage statement will certainly change over time to reflect the data that you gather in your pivotal clinical studies; however, setting a goal and refining it early in development helps you communicate realistic plans to regulators (and investors).

Follow steps from (a) to (f) below to develop your indication statement.

1. Start broadly – What disease(s) or condition(s) will you target?

* Consider the current clinical situation
* Consider disease epidemiology (prevalence / incidence / sub populations)
* Consider the relevance of different disease etiologies / pathologies
* Consider what companion diagnostics may be required to target patients or subpopulations of patients
* Consider patient treatment options with current Standard of Care

1. Refine – What do physicians think about legacy or current treatments, including unmet needs?

* Consider perceived efficacy, side-effects, ease of use, and quality of life measures

1. Refine further – What do patients think about current treatments?

* Consider perceived efficacy, side-effects, ease of use, and quality of life measures

1. Challenge – What do Product Monograph and Summary Basis of Decision documents tell you about current treatments? (These are available on the Health Canada website)

* Consider effectiveness (efficacy), side-effects (safety), and quality of life measures

1. Challenge further – What does the published literature say about current treatments?

* Search for product- or technology- specific regulatory guidance documents
* Consider reports on effectiveness, side-effects, and quality of life measures

1. Reality check – Is the relative high-risk of cell/gene therapies likely to provide sufficient benefit compared to alternatives in the Canadian context?

* Consider key opinion leader perspectives (note – this will take some networking, but it is likely worthwhile because you can develop relationships that can support regulatory interactions, including pre-submission meetings attendance)
* Consider patient advocacy perspectives (note – this will take some networking, but it is likely worthwhile as regulators begin to consider patient input into the review process)

Place your indication statement into the table below under the Target heading and insert key learnings / considerations / notes you want to follow-up on throughout developing as Annotations. Cite things so you can refer to them in the future.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| Use 1 line for each & consider sequencing them strategically. |  |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Dosage & Administration

This section assumes that your cell / gene therapy is likely to be administered via injection and may require reconstitution or dilution before use, because that is most likely for cell & gene therapies. Your responses will naturally evolve as more data become available.

Follow steps from (a) to (d) to describe your anticipated (ideal) dosage & administration – this has relevance to clinical safety and efficacy.

1. Start broadly – How / where do you think the product will be administered?

* Consider ideal conditions of use (i.e. environment, circumstances, healthcare practitioner training, etc.) and what amount is likely needed for your anticipated route of administration
* Consider potential categories of risks and benefits associated with such administration
* Consider findings from your pre-clinical research, with a focus on safety finding

1. Refine – Is your anticipated dosage form and route of administration effected by transportation logistics?

* Consider (co-)packaging, shipping, and product administration needs
* Consider potential risks and risk mitigation options

1. Refine further – how much active ingredient might you give?

* Consider how you are likely to measure active ingredient amount / potency (this may come from your QTPP development process)
* Consider the practicality of producing the necessary amount
* Consider what is known about formulating at the required concentrations
* Consider and cite theoretical and pre-clinical information
  + Anticipate the min. and max. dose range that might produce a therapeutic effect
  + Refer to this again after you complete Section 7 – Clinical Pharmacology

1. Challenge – What dose range was used for analogous products?

* Review regulatory guidance for the class of product (if available)
* Review trial database, Product Monographs, and Summary Basis of Decision
* Assess for relevance

Describe your dosage and administration into the table below under the Target heading and insert key learnings / considerations / notes (such as parameters / constraints) you want to follow-up on throughout developing as Annotations. Cite things so you can refer to them in the future.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| E.g. X# cells suspended in Y mL cryopreservation solution and frozen, to be thawed <Z hours prior to administration via single bolus injection/infusion into \_\_\_\_\_\_\_\_. |  |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Contraindications & Drug Interactions

This section will identify patient populations you will not be able to target. It will be quite difficult to develop early in development. Regulators (and your potential investors) will appreciate the added credibility of revised target population (and revised market assessment).

Follow steps (a) then (b) to begin to predict potential population subgroups to monitor.

1. Start broadly – What patient conditions may be relevant to safety?

* List common conditions/ comorbidities & identify sub-populations affected
* Identify common drugs used to treat those conditions / comorbidities

1. Refine – Which contraindications/drug interactions are most likely?

* Compare and consider the putative mechanism of action for relevance
* Review literature, including Real World Evidence (where possible)
* Leverage Product Monographs from analogous / same class of products

List anticipated contraindications and drug interactions in the table below under the Target heading and insert key learnings / considerations / notes (such as parameters / constraints) you want to follow-up on throughout development as Annotations. Cite things so you can refer to them in the future.

|  |  |
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| **Target** | **Annotations** |
| Draft a statement about Contraindications, and develop a bullet list of potentially concerning concurrent medications | Draft a broader list of potential contraindications and drug interactions, identifying sources of information |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Adverse Reactions, Warnings and Precautions

This section will identify known and theoretical risks. It will be quite difficult to develop early in development; however, you may be able to predict potential risk mitigation options such as warnings that may eventually be required in your product labelling, which you may wish to discuss with regulators and are relevant to your early market plans.

Follow steps from (a) to (c) to begin to predict potential safety risks to monitor.

1. Start broadly – What categories of risk may be relevant?

* Review regulatory guidance for the technology (if available)
* Review regulatory guidance for the disease indication (if available)
* Review regulatory guidance for the route of admin (if available)
* Assess relevance of your findings
* Conduct a preliminary risk assessment, considering anticipated severity & likelihood

1. Rank risks – What anticipated risk do you consider high, medium, or low?

* Calculate anticipated severity / likelihood and sort accordingly into groups

1. Refine – What level of risk (high/medium/low) could be considered acceptable?

* Review Summary Basis of Decision documents for products with the same indication
* Consider risks from various perspectives (patient, clinician, economic, etc.)

List anticipated safety risks in the table below under the Target heading, using the Adverse Reactions or Warnings & Precautions subheadings, and insert key learnings / considerations / notes you want to follow-up on throughout development as Annotations. Cite things so you can refer to them in the future.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| Adverse Reactions Draft a list of potential Adverse Reactions, categorize them according to body system, and prioritize them from most to least severe. Warnings & Precautions Draft a list of potential Warnings & precautions that may require specific communication prior to administration | Provide reference to key sources of information |

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# Use in Specific Populations

This section helps you compartmentalize target populations, which will inform clinical development and market plans. Although special populations may arise from data you collect in trials, you can target or avoid populations based on early pre-clinical data or known / theoretical risks associated with the putative mechanism of action.

Follow steps from (a) to (b) identify special populations.

1. Start broadly – Do important demographic / baseline subgroups exist?

* Consider age / gender / race as potential determinants
* Consider disease factors as potential determinants (baseline, previous illness, concomitant illness, previous treatments)
* Consider other factors e.g. weight, antibody levels, metabolic status, health habits (smoking, alcohol use, drug use), menstrual/pregnancy/lactation status

1. Refine – Can subgroups help predict safety / efficacy outcomes?

* Consider the evidence to support prognostic power (validated / qualified?), based on available literature or available regulatory documents

List special considerations for use in specific populations under the Target heading below and predict whether avoidance / modified administration may be required. Consider using the subheadings provided. Insert key learnings / considerations / notes you want to follow-up on throughout development as Annotations. Cite things so you can refer to them in the future.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| Pregnancy:Labor and Delivery:Nursing Mothers:Pediatric Use:Geriatric Use:Additional Subsections: | Indicate why you might anticipate inclusion/exclusion/special instructions, citing sources of information |

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# Product Description

This section encourages you to link your clinical plans to manufacturing plans. You should define your product in a separate manufacturing plan (QTPP) and highlight here how your product characteristics are related to your putative mechanism of action.

Consider postponing this section until you have developed a Quality Target Product Profile. Alternatively, consider the following steps from (a) to (c) below.

1. Start broadly – What components do you have in your product?

* Consider both Active Ingredients and Excipients
* Identify potential impurities

1. Refine – What are your anticipated quality attributes?

* Consider what attributes might be critical to efficacy
* Consider what attributes might be critical to safety
* Assess the relative importance (high/medium/low)

1. Challenge – What does publicly available information tell you?

* Consider study publications

Identify the key components, and anticipated safety / efficacy attributes under the Target heading and ensure this is consistent with any Quality Target Product Profile (QTPP), if available. Consider using the subheadings provided. Insert key learnings / considerations / notes you want to follow-up on throughout development as Annotations. Cite things so you can refer to them in the future.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| Key componentsAnticipated safety attributesAnticipated efficacy attributes | Capture additional information |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Clinical Pharmacology

This section continues to bridge what is known about the product and what is known about the patients and disease, using pre-clinical data. It can be used to lend credibility to your clinical plans and goals.

Follow steps from (a) to (c) to better assert how the potential benefits to your patient population are likely to outweigh the risks.

1. Start broadly – What is the putative Mechanism of Action?

* Identify what is known about the biodistribution / engraftment compared to wild-type cells
* Assess whether the biodistribution / engraftment could contribute to efficacy or safety, based on the putative mechanism of action
* Determine if there is a link between product, where it goes, and how it functions

1. Refine – What assays might help predict clinical effects?

* Consider available functional assays, in-house functional assays, correlative assays
* Assess assay status (e.g. qualified vs validated)

1. Refine further – Are these linked to anticipated quality attributes?

* Review Summary Basis of Decision for analogous products
* Review published literature for analogous products

Draft a statement describing the putative mechanism of action under the Target heading, then identify the ideal or likely biodistribution / engraftment profile. Use subheadings, as required, and revisit your responses to Section 2 – Dosage and Administration to ensure consistency.

|  |  |
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| **Target** | **Annotations** |
| Mechanism of ActionBiodistribution / Engraftment | Capture additional information here, including a rationale and critical parameters, citing sources (human, in vitro, and in vivo animal studies) and acknowledging limitations to pre-clinical studies |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Safety

The benefits and risks of administering a drug must outweigh the benefits and risks of not administering the drug (or administering an alternative treatment). This section helps lay out only a component of the equation, which you can refer to in multiple regulatory documents throughout development. This section will certainly evolve with study data.

Follow steps (a) to (c) to describe the anticipated safety of your product.

1. Start broadly – What theoretical safety concerns exist?
2. Refine – What safety concerns has this process highlighted?

* Consider therapeutic alternatives for the proposed indication & usage
* Consider potential risks relating to dosage and administration
* Consider contraindications & drug interactions
* Consider anticipated adverse reactions, warnings, and precautions
* Consider special populations
* Consider what is known about quality attributes
* Consider what is known about the MoA and biodistribution / engraftment

1. Refine – What are relatively important risk concerns?

* Consider anticipating severity and likelihood, and prioritize accordingly

Draft a statement under the Target heading, identifying key potential risks and asserting the risk acceptability profile. Consider using the subheadings provided, which are taken from Health Canada’s guidance for cell therapy clinical trial applications:

|  |  |
| --- | --- |
| **Target** | **Annotations** |
| ToxicityImmunogenicityTumorigenicityEctopic Tissue FormationOther | Capture additional information and cite sources |

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| **Comments:**  Keep track of additional thoughts, considerations, and feedback you have received here. |

# Efficacy

The benefits and risks of administering a drug must outweigh the benefits and risks of not administering the drug (or administering an alternative treatment). This section helps lay out only a component of the equation, which you can refer to in multiple regulatory documents throughout development. This section will certainly evolve with study data.

Follow steps from (a) to (e) below to describe the anticipated efficacy of your product.

1. Start broadly – What efficacy endpoints do you think are important?

* Consider all disease, clinical and behavioural assessments

1. Refine – What efficacy endpoints did competitors use at this stage?

* See trial database, Summary Basis of Decision, and Product Monographs

1. Refine further – What efficacy endpoints were considered important?

* By regulators (Summary Basis of Decision)
* By HTA bodies (e.g. CADTH CDEC Final Recommendation)
* By economists (e.g. CADTH Pharmacoeconomic Report)
* By patients (e.g. CADTH Patient Group Input Submissions)
* By clinicians (e.g. CADTH Clinical Report)
* Other

1. Challenge – How important / relevant / measurable are the outcome measures?

* Consider the validity /specificity
* Assess relevance to putative mechanism of action

1. Challenge further – What results do patients get for your top priority (primary) endpoint?

* Mean / variability

Draft a few bullets describing your target efficacy for the indication and usage.

|  |  |
| --- | --- |
| **Target** | **Annotations** |
|  | Capture additional information and cite sources |

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