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CONSULTANCY | PROJECTS | INTERIM MANAGEMENT | AUDITING & TRAINING

Planning for successful and efficient ATMP development

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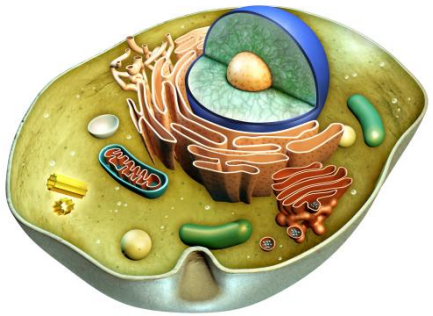
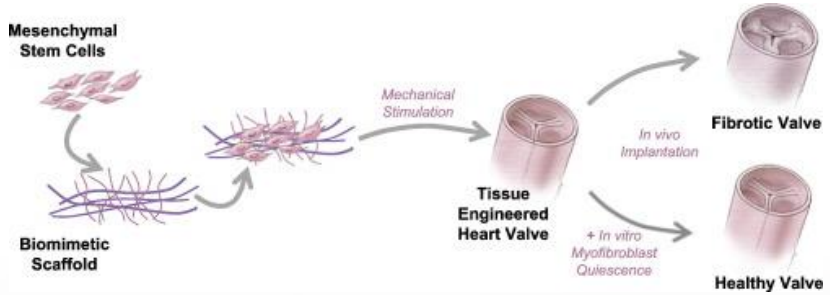
ATMP DIVERSITY

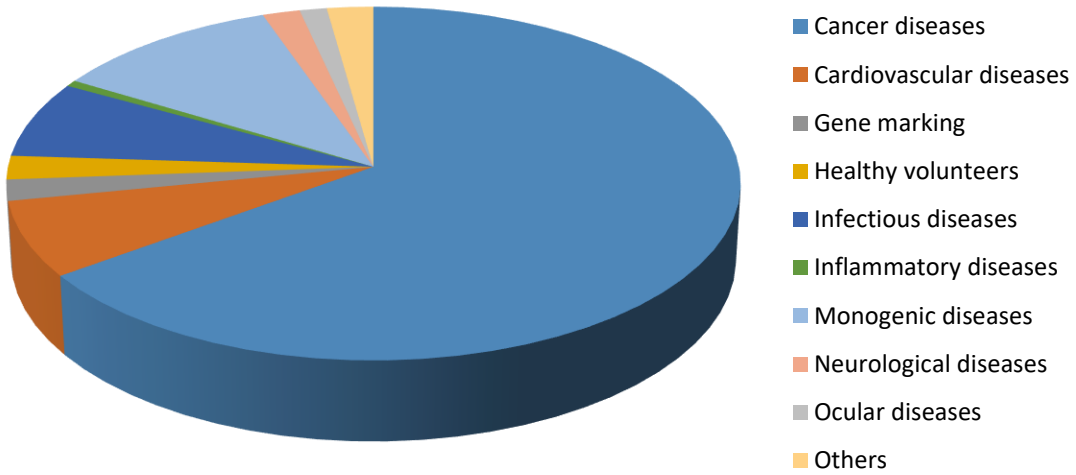




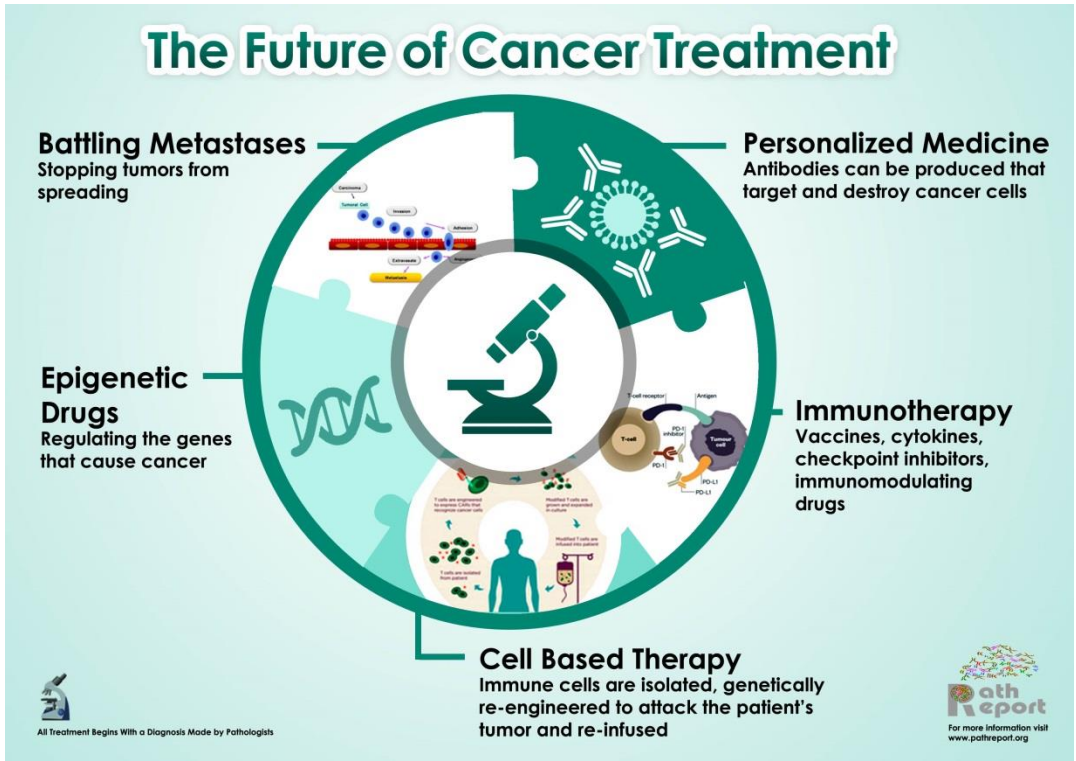
WHAT IS SPECIAL ABOUT ATMPS?

- **Game changing potential** for treatment of new indications
  - Personalized medicine: balance between standardization and case-by-case approach
- **Rapid innovative field**
  - Fast, in-depth, up-to-date knowledge of regulations is a must
- EU **regulatory framework** since 2008
  - Risk Based Approach: data requirements related to the nature of the product
- Strong involvement of **Academia** and **Start Up** companies
- **Disconnect** between academia, (start-up) companies and health agencies
- Strongly **increasing** number of **clinical trials**
- **Limited** number of marketed products
- **Challenging** Re-imbursement and Market Access

Wave of cancer therapies



- 65% of all gene therapies in clinical trials focus on treatment of cancer diseases (in 2017: 1688 trials out of a total of 2597) source wiley database



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Regulatory perspective for ATMP development

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Development lifecycle

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DEVELOPMENT FOCUS

Begin with the End in Mind

"To begin with the end in mind means to start with a clear understanding of your destination. It means to know where you are going so that you better understand where you are now and so that the steps you take are always in the right direction"

Stephen Covey

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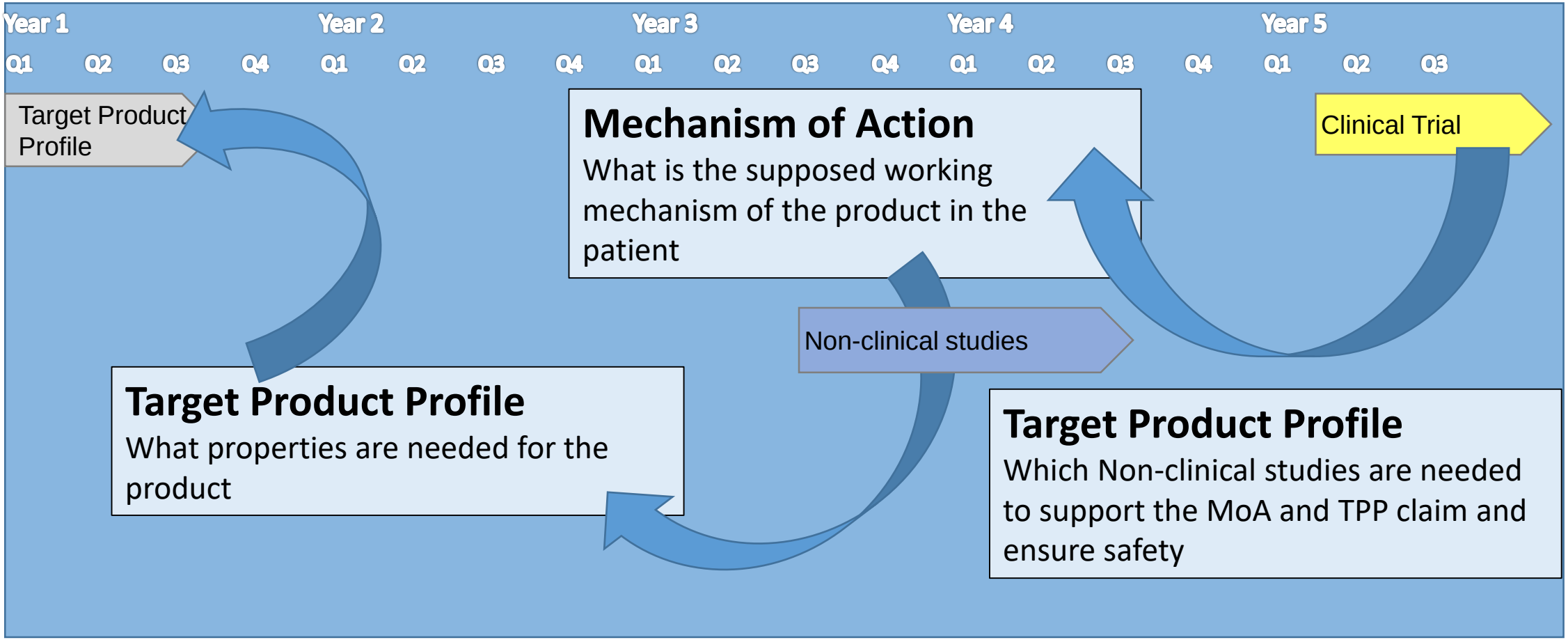
High Level development chart



Target Product Profile (TPP)

- Begin planning of product development with the ultimate goal in mind – product labeling
- TPP: Format for a summary of a drug development program described in terms of labeling concepts. (FDA definition adapted from Guidance: Target Product Profile – a strategic development process tool)
- Benefits:
  - Strategic planning tool,
  - Facilitates interaction with regulatory agencies,
  - Facilitates interaction with investors and stakeholders
  - Facilitates planning for a successful non-clinical and clinical development as well as design of manufacturing plans

General
Indication and Usage
Mechanism of Action
Dosing and Administration
Effect of Therapy
Clinical considerations
Safety
Intellectual Property
Manufacturing
Cost of Goods

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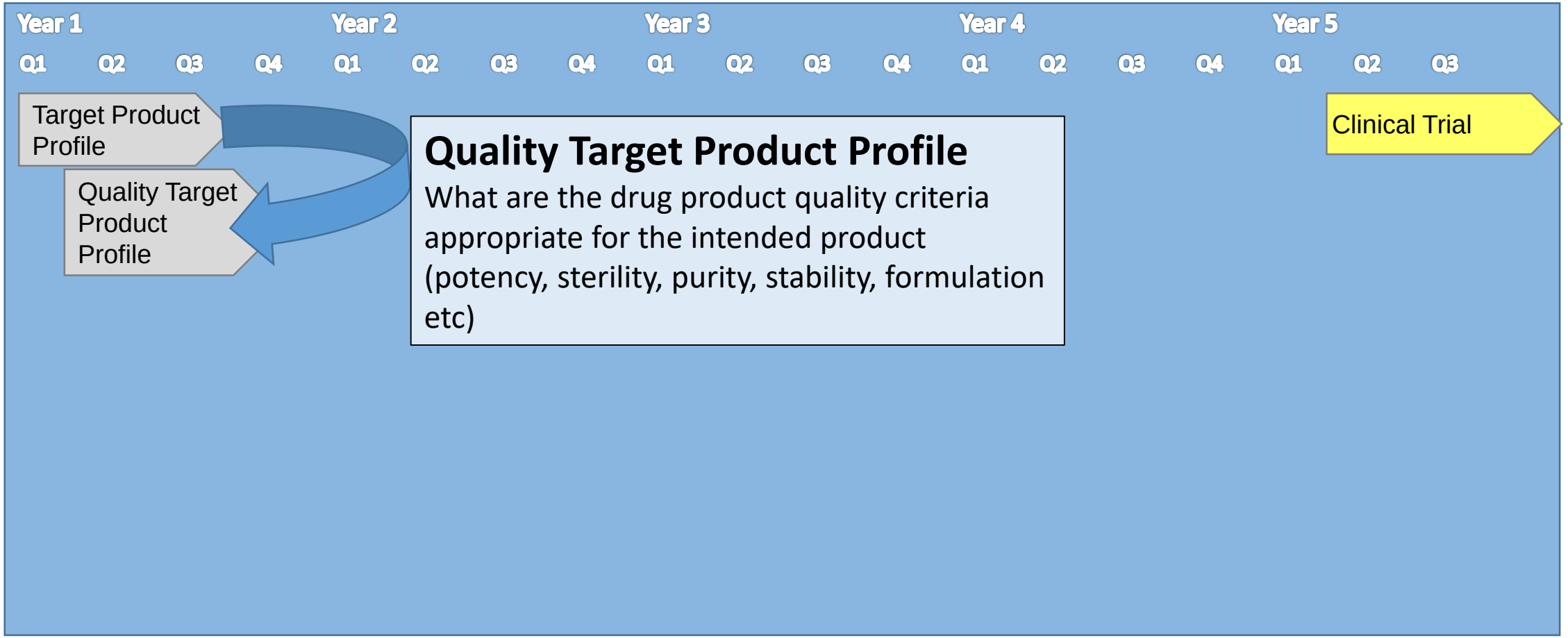
Kymriah TPP Example

General	CAR T example (Kymriah)
Primary product indication	CD-19 directed genetically modified autologous immuno-cellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)
Patient population	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
Mechanism of Action	chimeric antigen receptor T cell (CAR-T) therapy, which re-programmes the patient's T cells with a transgene encoding a chimeric antigen receptor (CAR), while identifying and removing CD19-expressing malicious cells.
Dosing and Administration	0.1 to 2.5 x 10^8 CAR-positive viable T cells, 10ml to 50ml suspension per bag / Intravenous (IV) infusion
Primary Endpoint	overall remission, as determined by the Independent Review Committee (IRC) assessment during the 3 months after administration.
Safety, IP, Manufacturing, Cost of Goods, Pricing and re-imbursement	

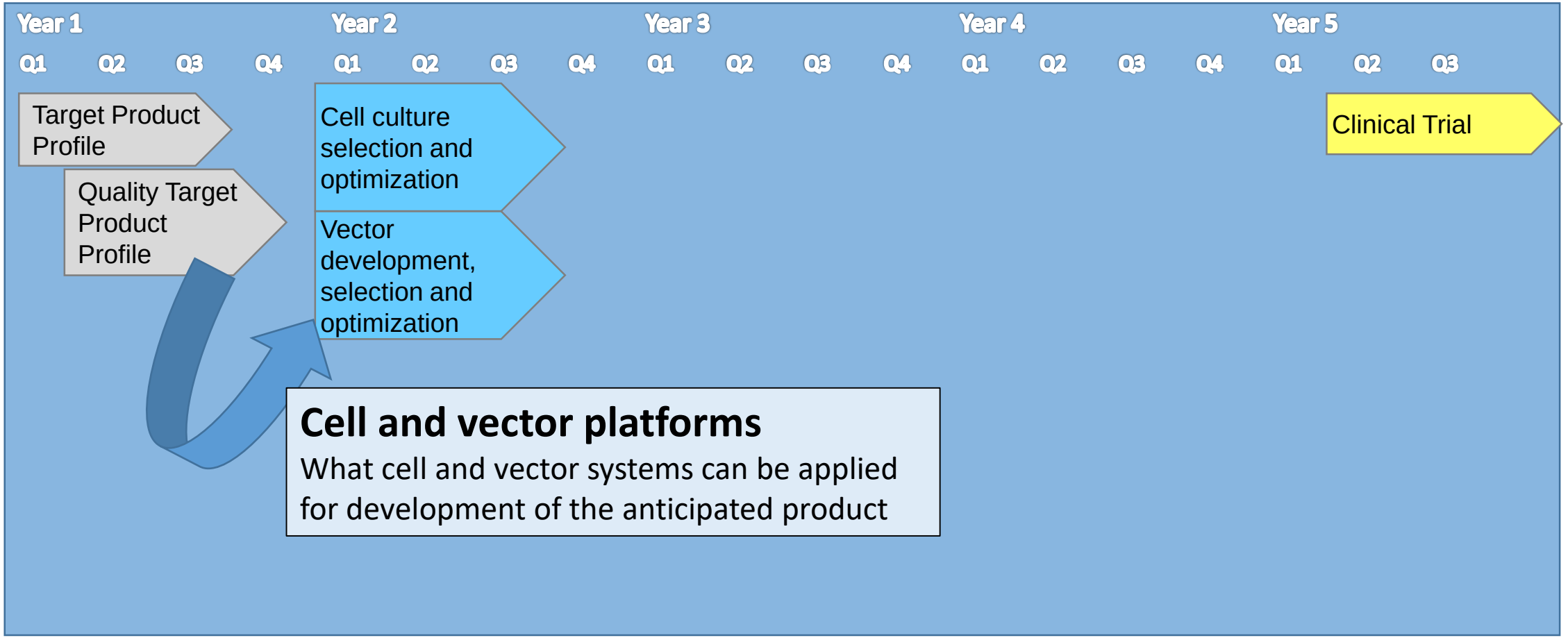
High Level development chart



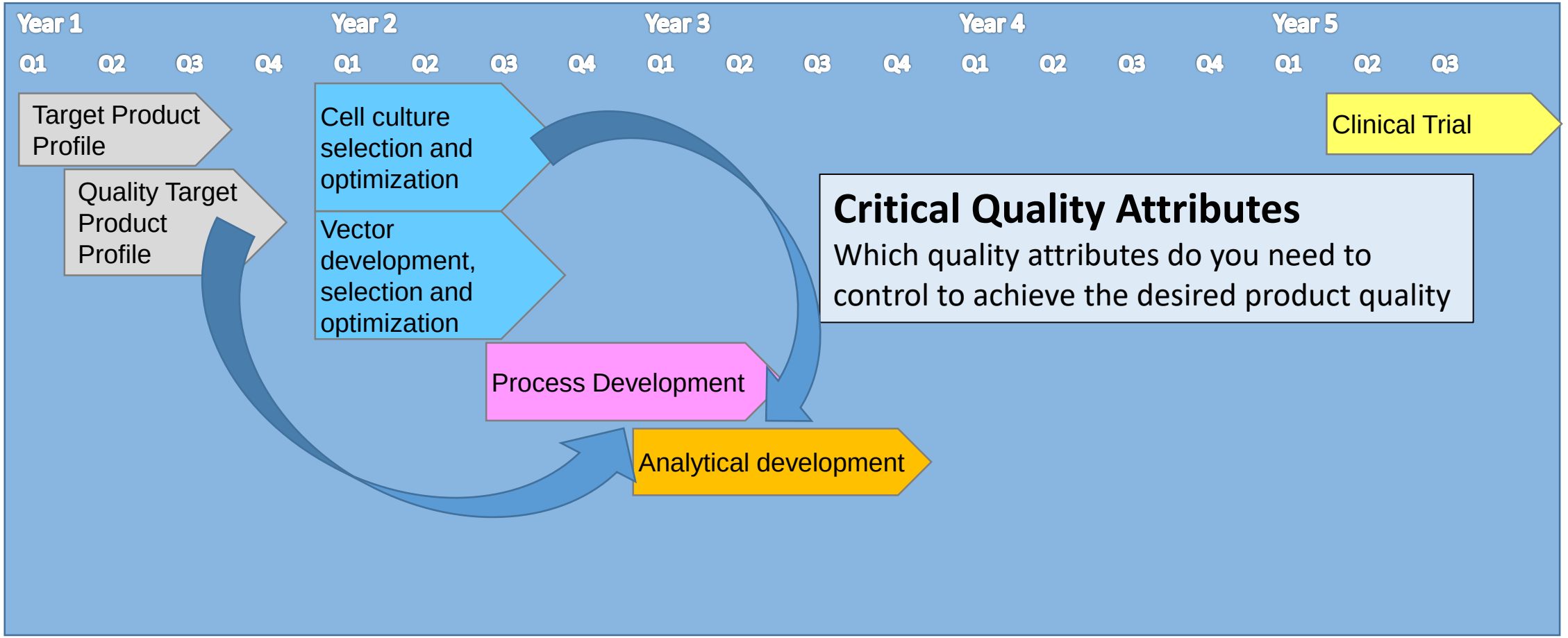
Quality Target Product Profile

- Definition (ICH Q8): *prospective* summary of the quality characteristics of a drug product that *ideally* will be achieved […], taking into account safety and efficacy […]
  - *Essential* element of pharmaceutical development (even under traditional/empirical approach)*
  - Starting point for identifying CQAs
  - Summary of *quality* characteristics that ideally will be achieved
  - Quality characteristics ensuring *patient safety and efficacy*
  - No defined format
  - *Tool*: not expected to be submitted as part of MAA dossier
- Benefits
  - Strategic planning tool
  - Facilitates communication with manufacturer, interaction with regulatory agencies, interaction with investors and stakeholders
  - Facilitates planning for a successful non-clinical and clinical development batches and design of manufacturing plans

High Level development chart



High Level development chart



Critical Quality Attributes

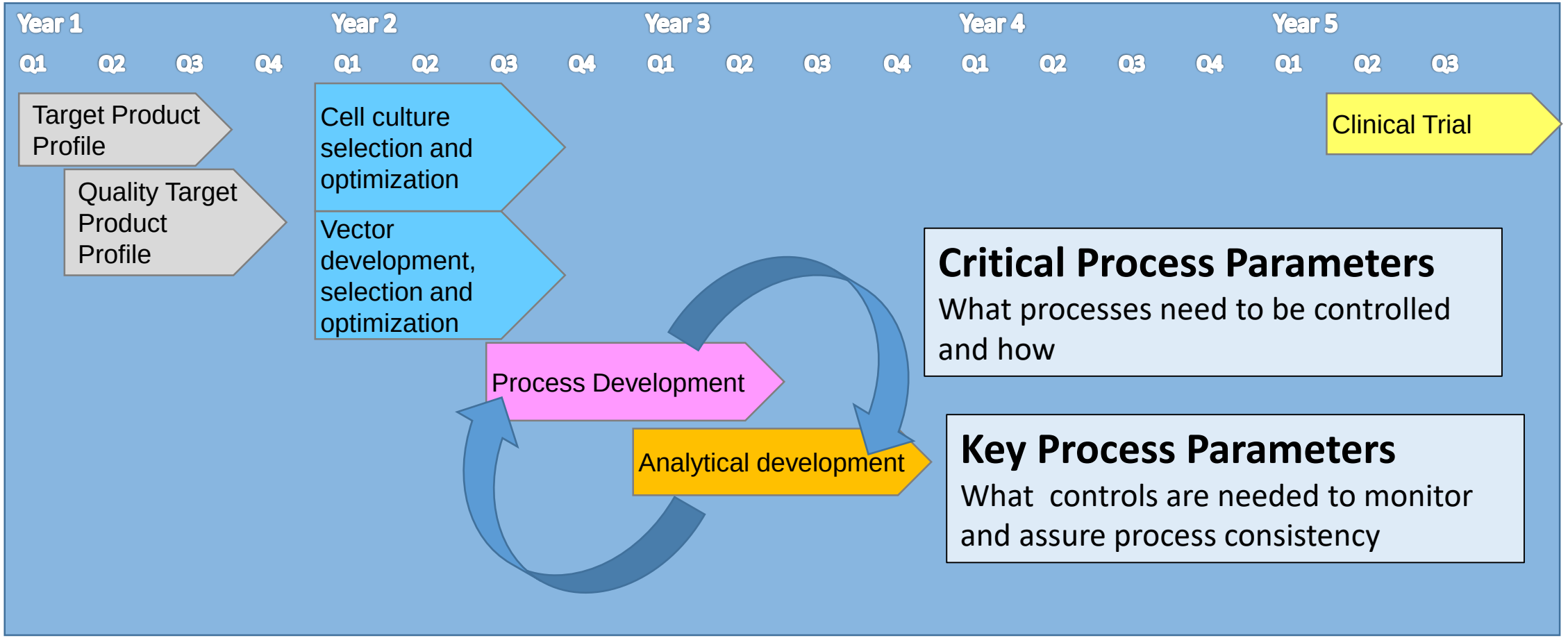
- Critical quality attribute (CQA):

  Physical/chemical/(micro-)biological property that should be in an appropriate limit/range to ensure […] product quality*

- pCQAs derived from*:
  - QTPP
  - Compendia and Guidelines
    - Ph. Eur., USP
    - ICH, EMA, FDA
  - Prior knowledge (similar product)

Kymriah Example CQAs
Identity (CAR qPCR)
Cell Viability
Percentage of viable CD19+ B Cells
Total Cell count
Number of viable cells
Dose (CAR positive viable T-cells)
Sterility
Release of IFNɣ in response to CD19 expressing target cells
Etc

High Level development chart



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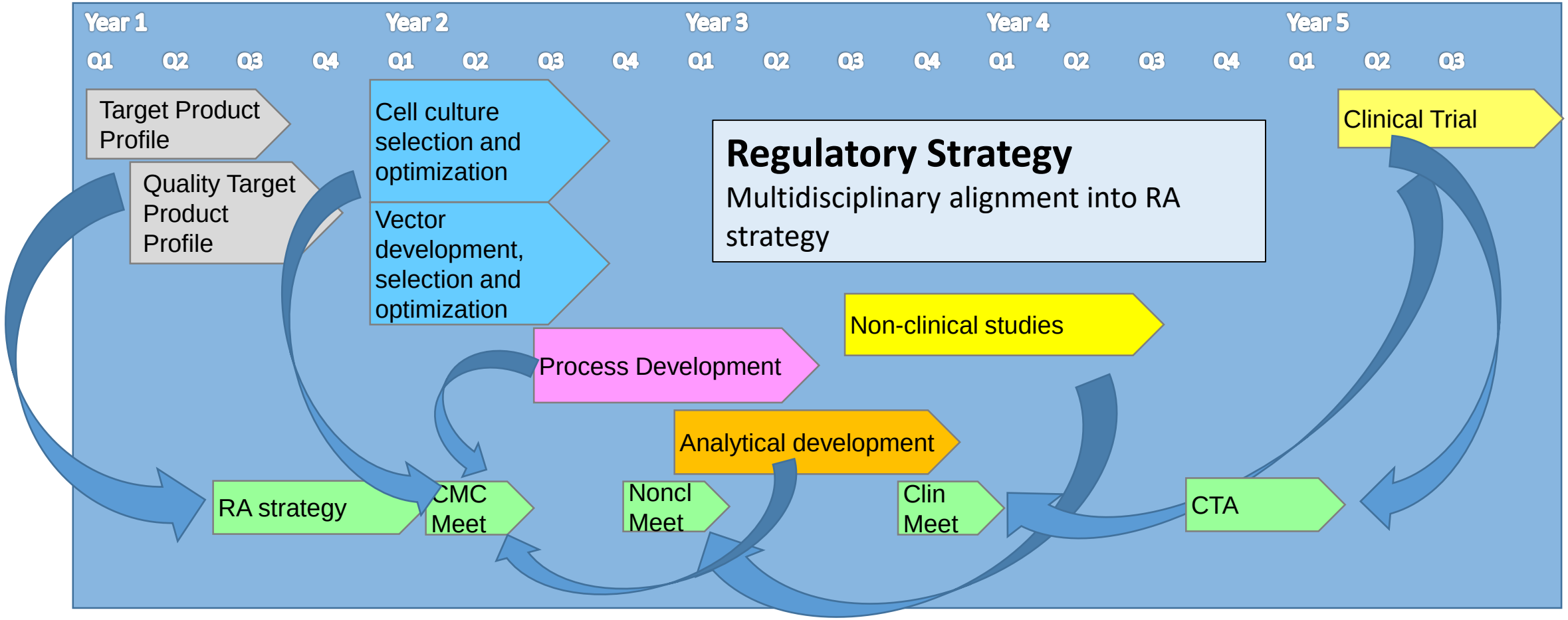
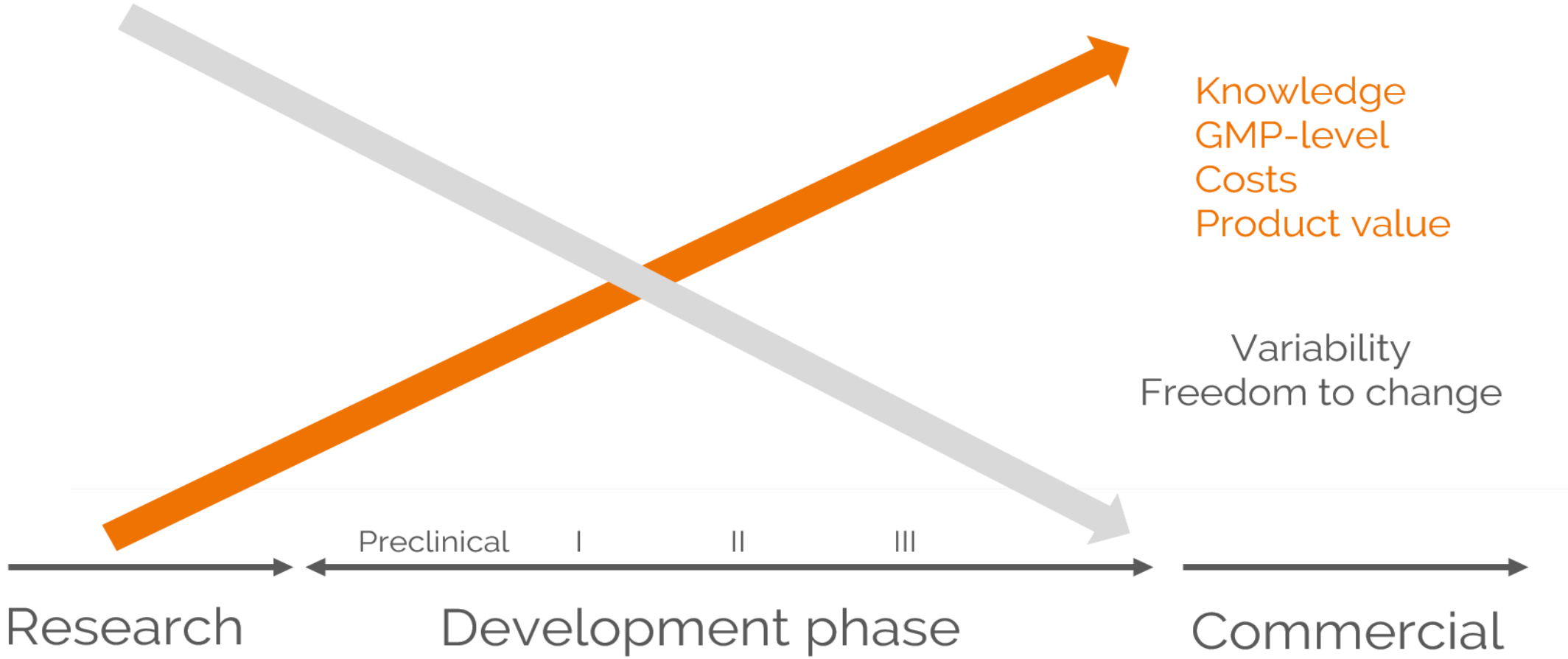


BASIC PRODUCT DEVELOPMENT



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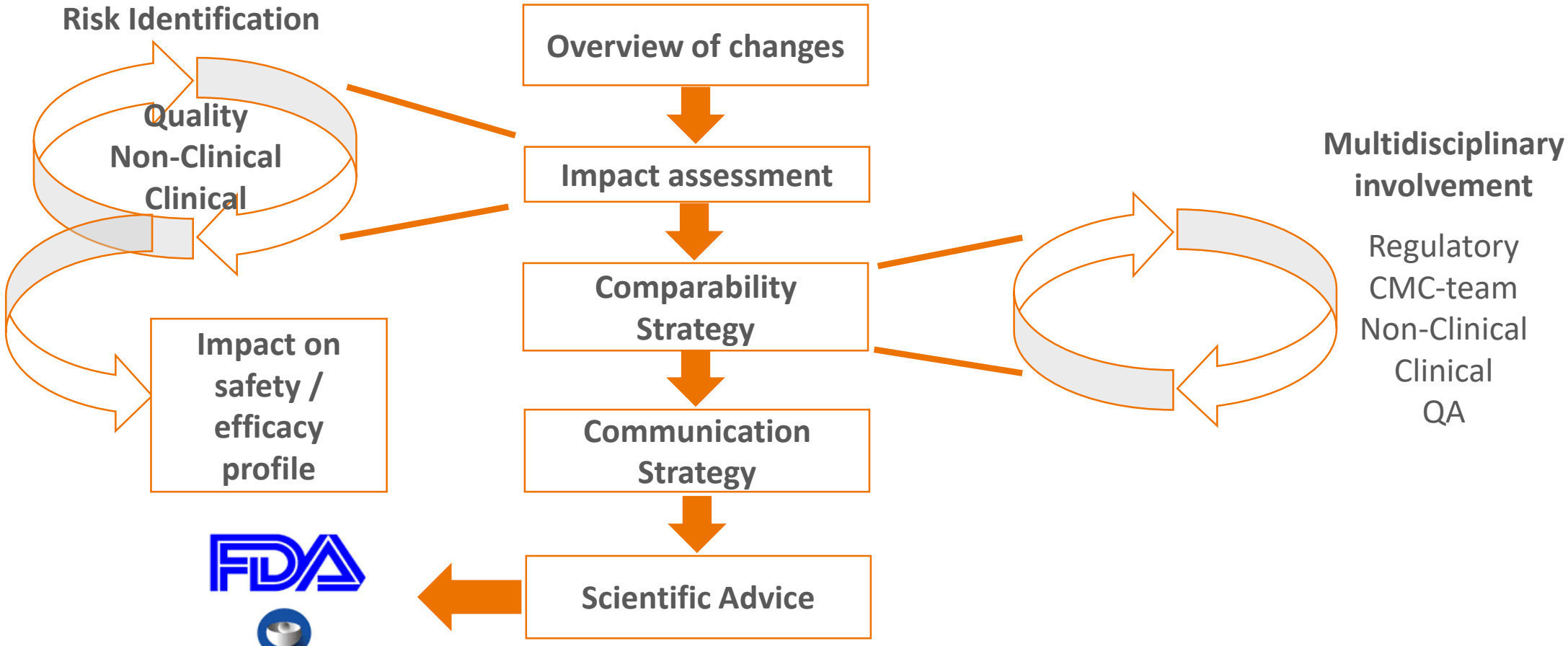
DESIGN MODIFICATIONS AND COMPARABILITY



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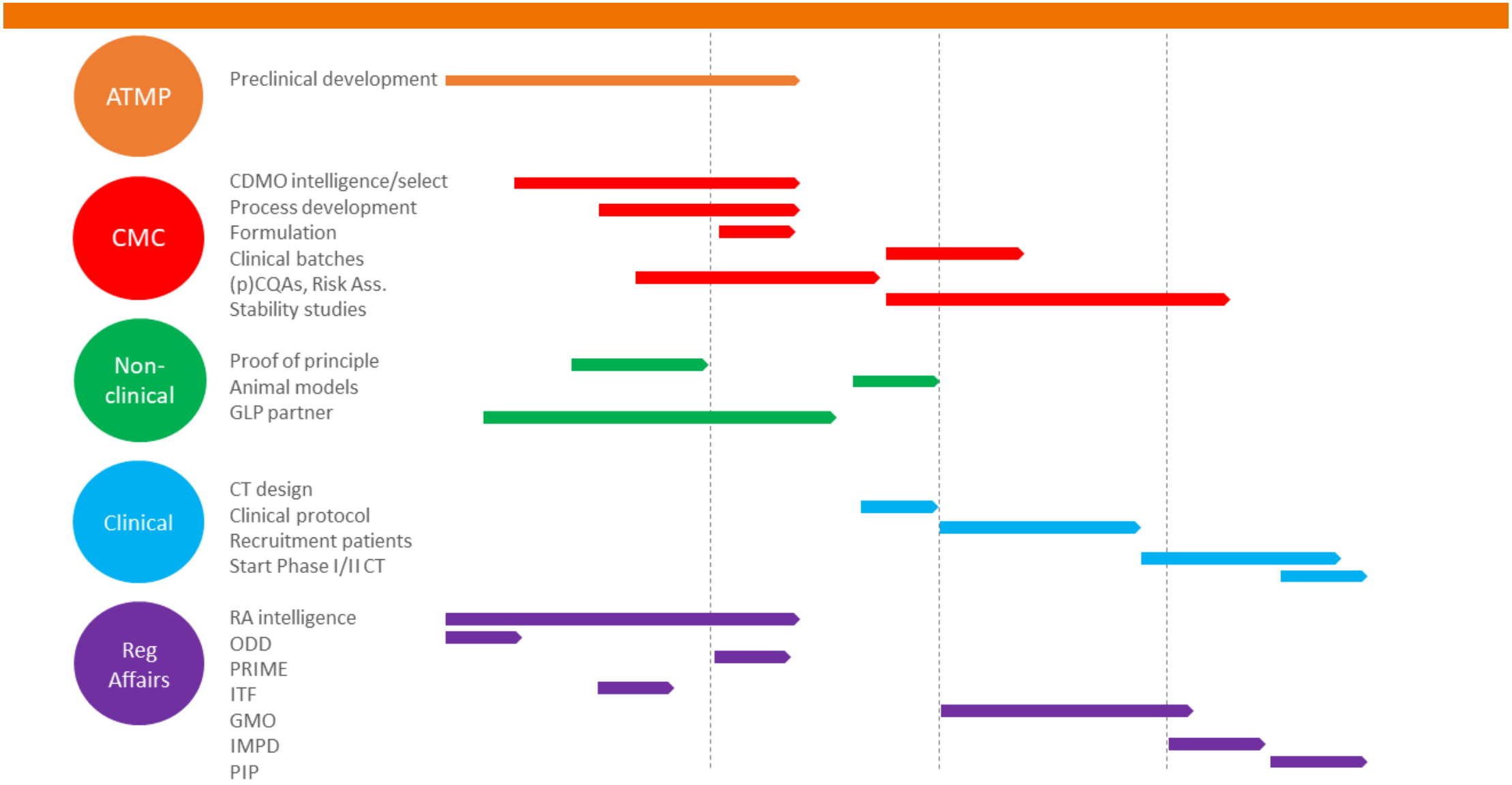
INTEGRATED DEVELOPMENT ROADMAP



SUCCESSFUL ATMP DEVELOPMENT

- Start with the end in mind
- Multidisciplinary integration
- Defining a process & product
- Embed robustness into process and product quality
- Regulatory compliance