INDUSTRIALIZZAZIONE E REGOLAMENTAZIONE DI PRODOTTI BIOTECNOLOGICI

Obiettivi formativi
Prospettiva industriale relativa ai requisiti di sviluppo e produzione di prodotti biotecnologici per la cura e la prevenzione di malattie, sia dal punto di vista tecnico che normativo.

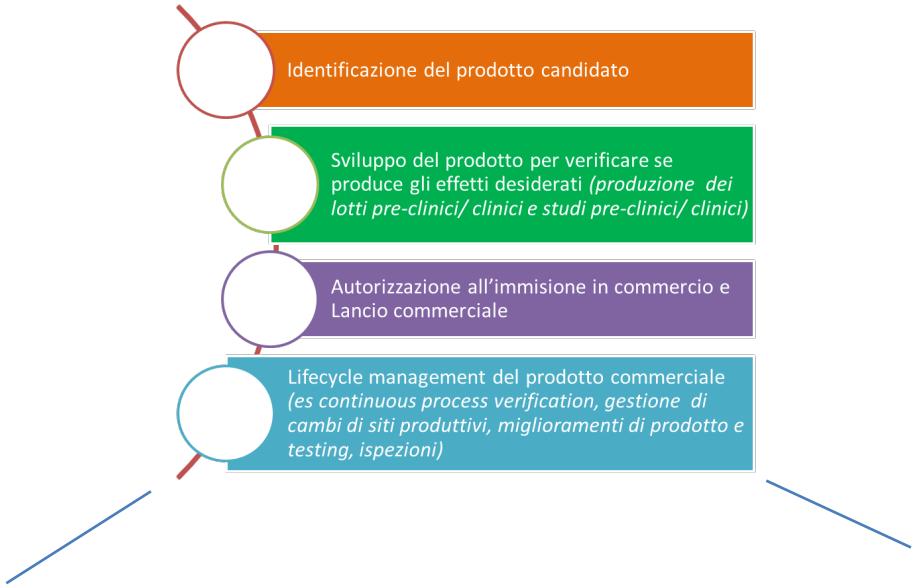
Modalità esame
Scritto

Contatto preferenziale
cri_cam@yahoo.com

Questo corso contiene informazioni a scopo didattico, non correlate in alcun modo a dati rilevanti per GSK Vaccines, e fa riferimento al mio personale punto di vista.

Cristiana Campa

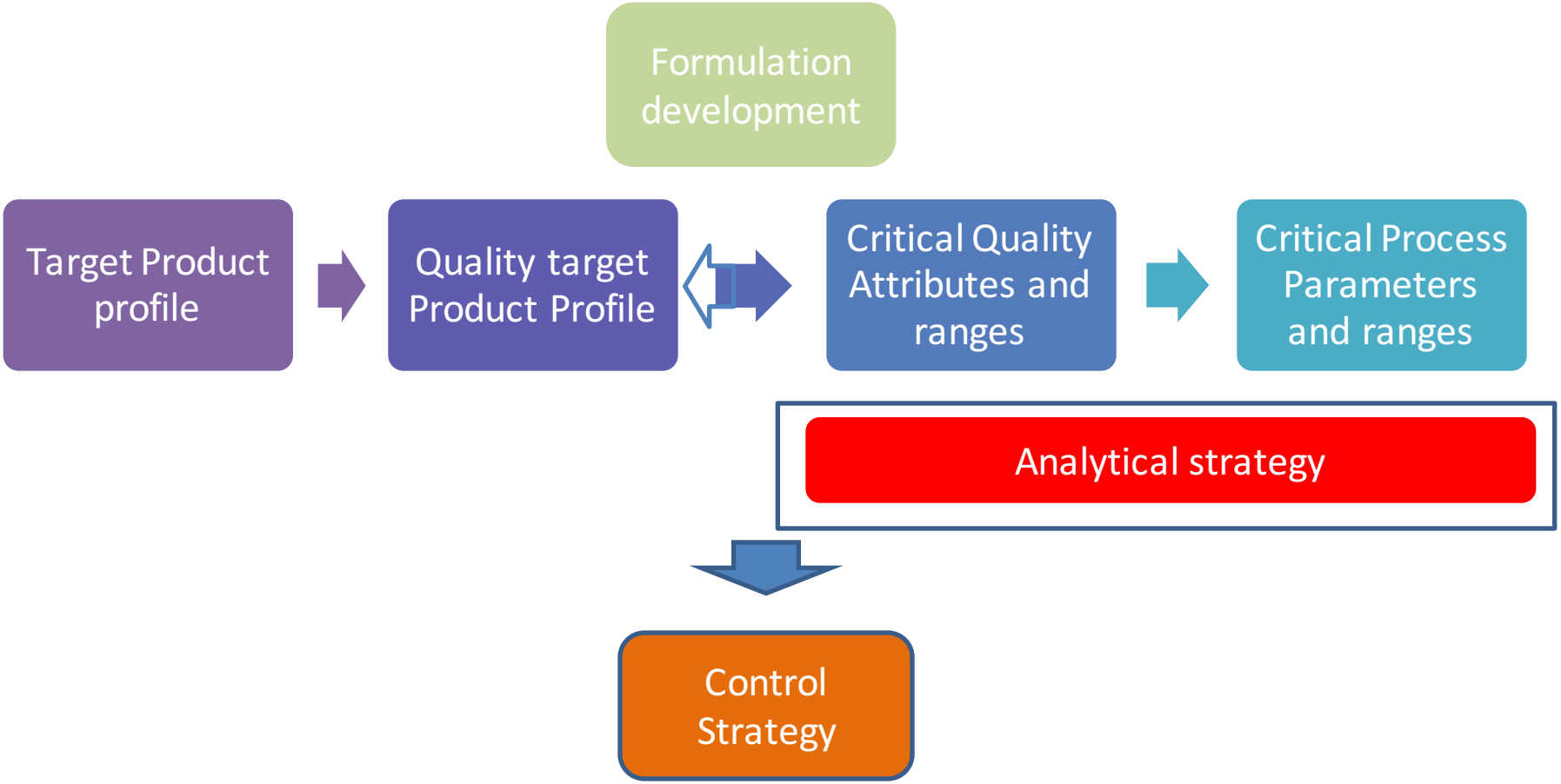
Industrializzazione e requisiti tecnici

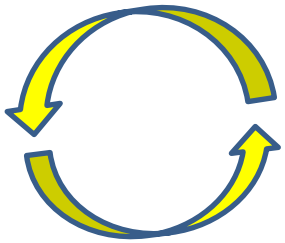


Cosa è necessario per produrre e rilasciare un lotto di prodotto sicuro ed efficace?

- Conoscere il **Prodotto** e le caratteristiche importanti per la sua efficacia e sicurezza (struttura, formulazione)
- Avere un **Processo** in grado di generare il materiale della giusta qualità in maniera sostenibile (alte rese e riproducibile)
- Avere **Test analitici** in grado di monitorare la qualità del prodotto e le prestazioni del processo

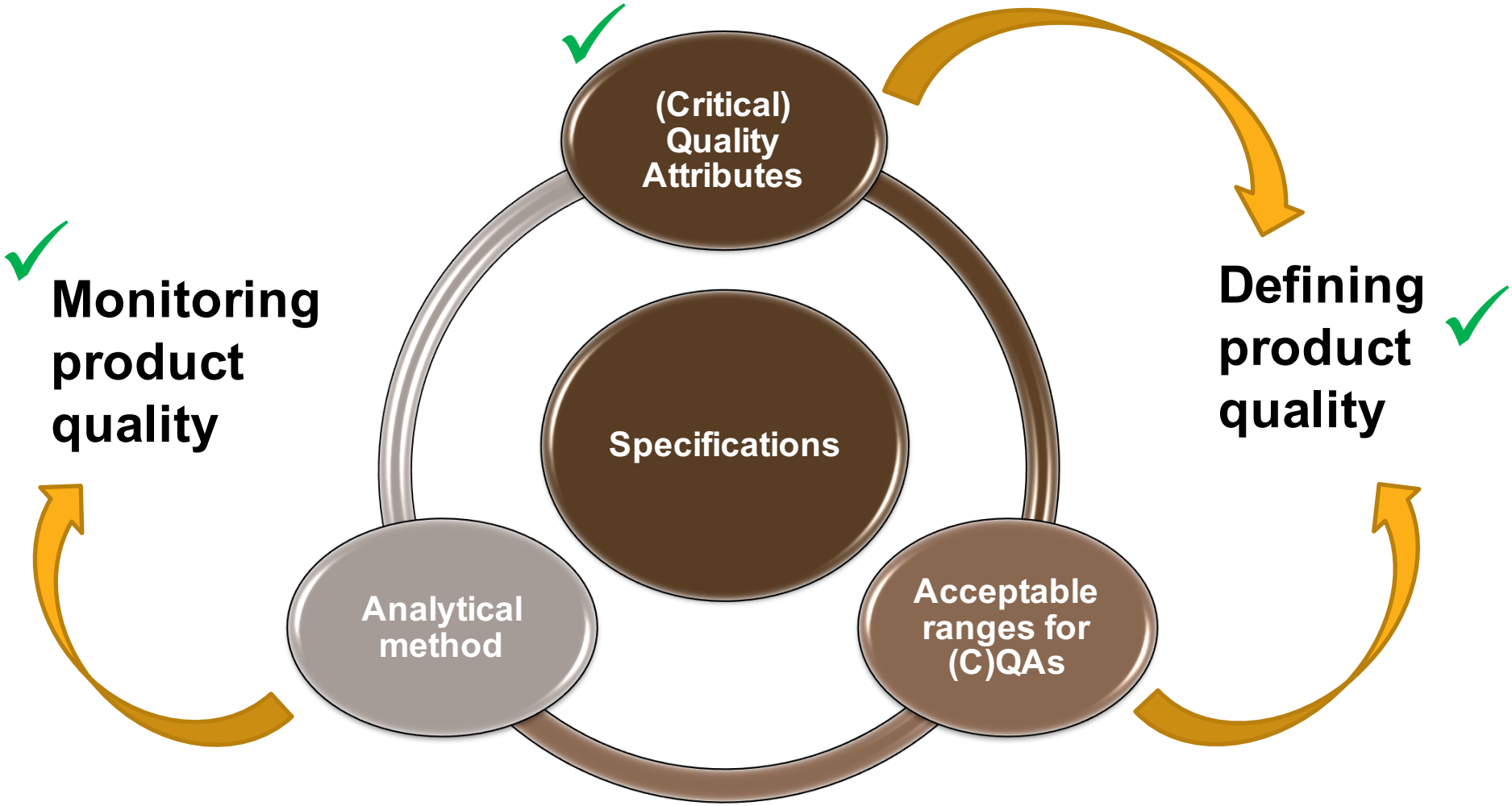
QbD simplified Flow



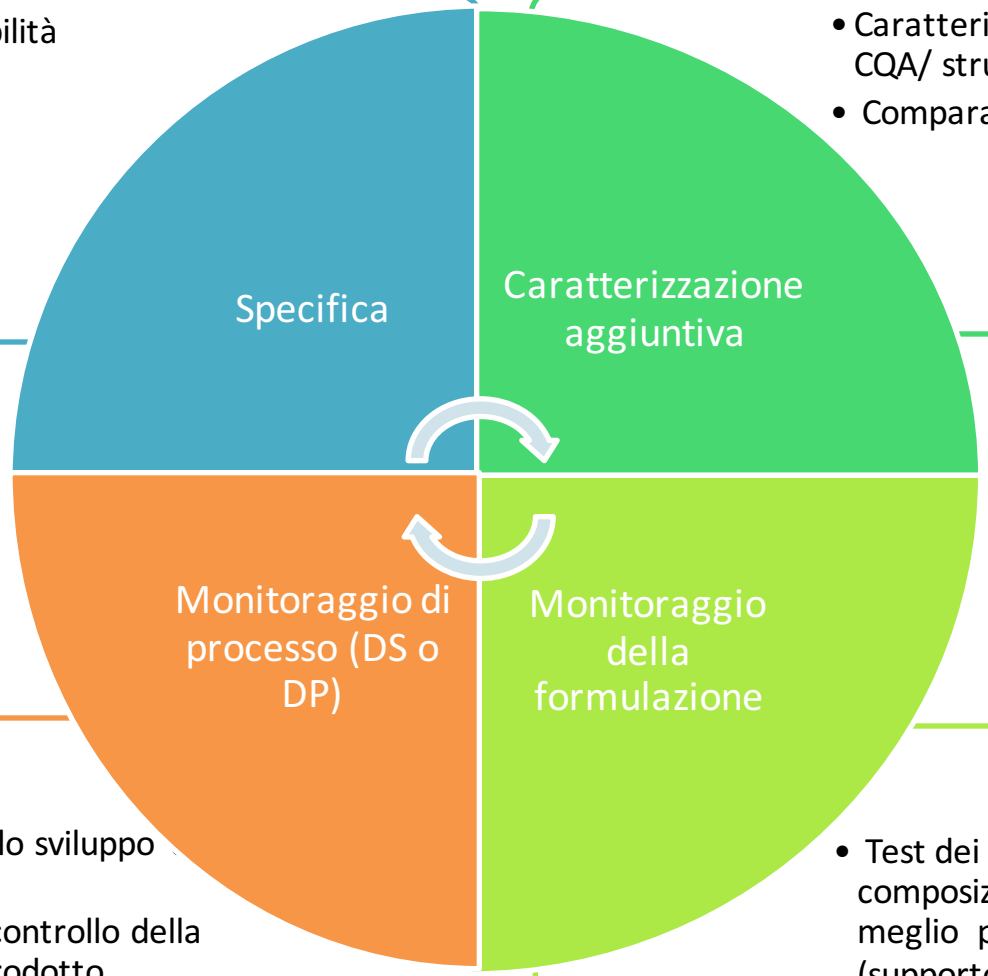


Durante lo sviluppo di un prodotto biologico, ciascun aspetto qui descritto può subire cambiamenti periodici, causati dall'acquisizione di nuova conoscenza su prodotto, processo e/o metodi analitici.

Specifiche


(Critical) Quality Attributes
Specifications
Analytical method
Acceptable ranges for (C)QAs
Monitoring product quality
Defining product quality

Scopo dei test analitici



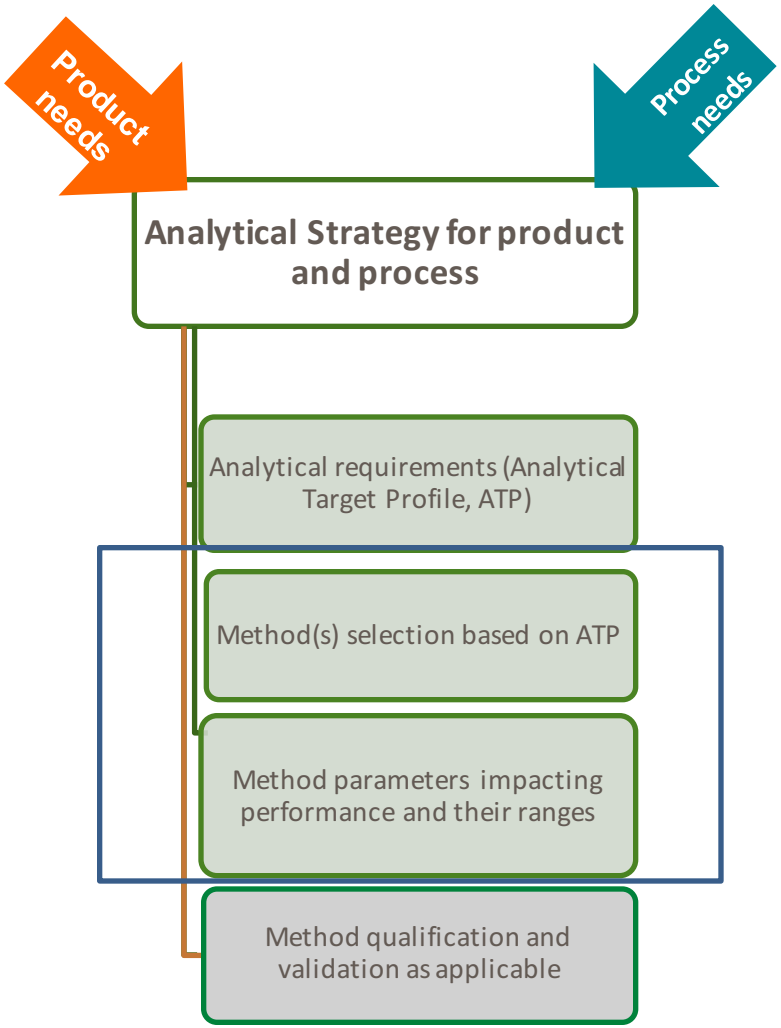
- Rilascio/ stabilità

- Caratterizzazione strutturale (es studi CQA/ struttura- funzione)
- Comparabilità

- Supporto dello sviluppo del processo
- Supporto al controllo della qualità del prodotto

- Test dei CQA per selezionare la composizione della formulazione che meglio preserva il principio attivo (supporto a pre-formulazione e formulazione)

Sviluppo di test analitici secondo approccio QbD



Reference standard strategy

Reference standards can be obtained from:

a. Development/ commercial production lots (in-house standards)
b. Commercial supplier
c. Licensing partner
d. Pharmacopoeias
e. WHO Laboratory for Biological Standards & collaborating centers for biological

Reference standards for vaccines can be used with the following purposes:

a. Calibration for results expression in biological assays,
b. Product- specific calibration for quantitative physicochemical assays,
c. Reference for identity tests,
d. Control samples in analytical sessions,
e. Elucidation of antigen structure to support regulatory submissions,
f. Representative material for analytical methods comparison,
g. Comparator to verify structural changes associated to any process change, as stated in ICH Q5E

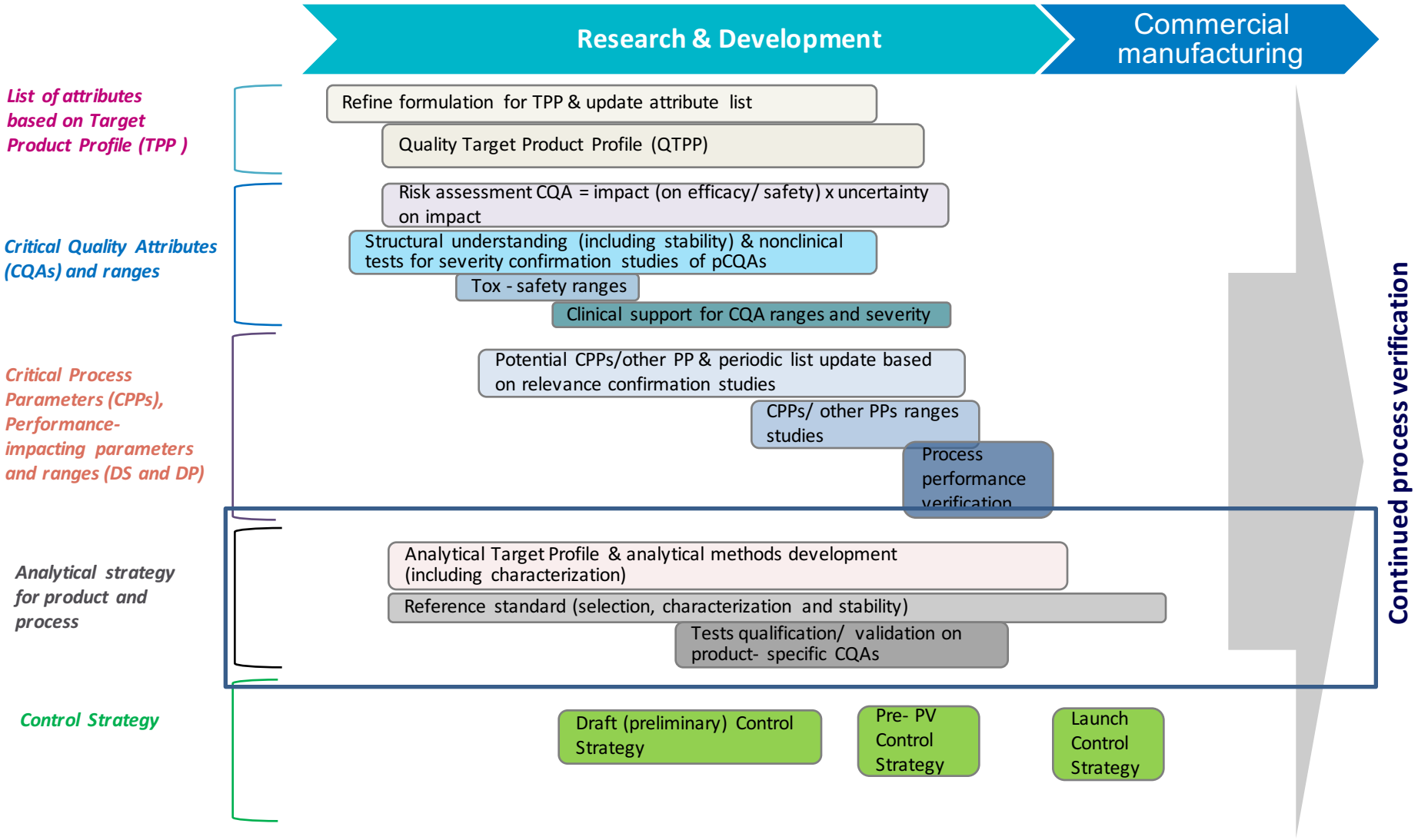
Reference standard strategy

- Characterization of reference material since the beginning of development is necessary for continued screening of antigen structural features potentially impacting vaccine immunogenicity (CQAs) and for the definition of the best analytical approaches for product understanding- analytical methods selection, indeed, should be executed on material representative of the respective lifecycle stage.

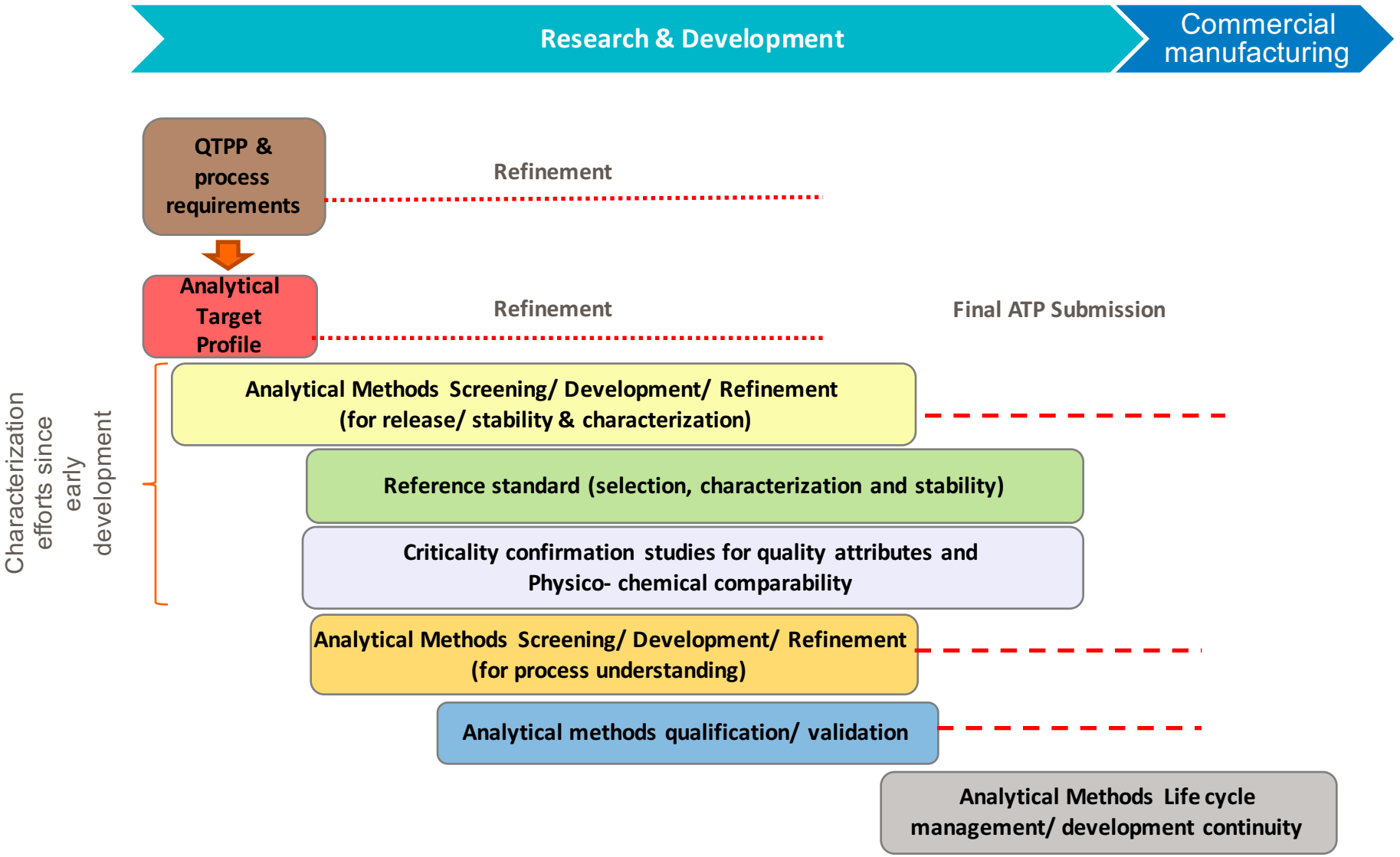
- The achievement of tailored storage conditions for reference standard before Ph III campaign is possible only if studies start early in development (stability verification at various conditions require analyses at different time points which cannot be compressed too much), with proper characterization tools.

Knowledge refinement

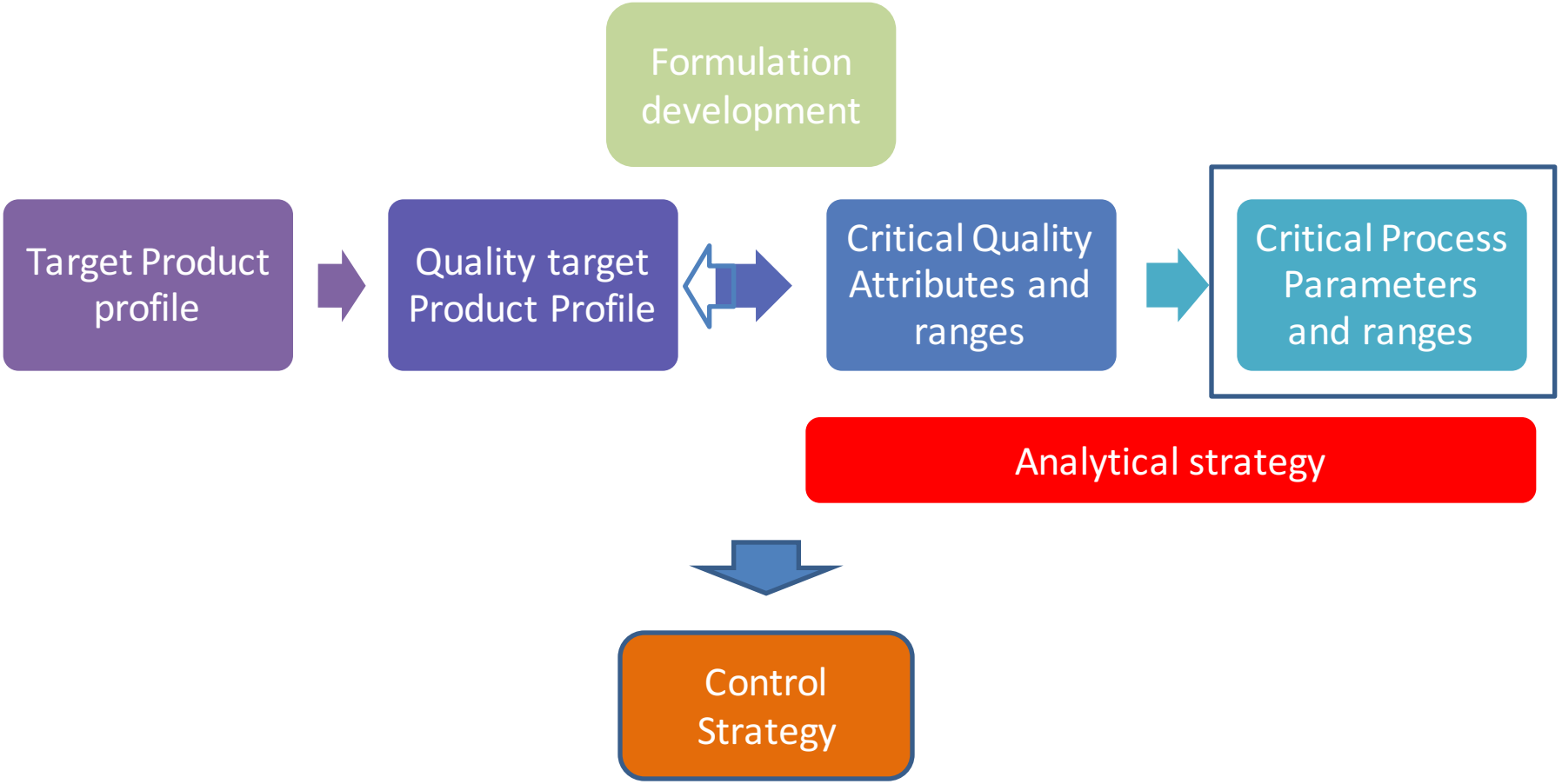
Smart activities planning taking into account complexity & diversity of biologics (eg vaccines)

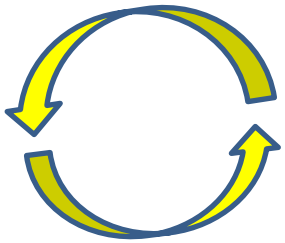


Analytical strategy refinement- detail



QbD simplified Flow





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Critical Process Parameter (ICH Q8)

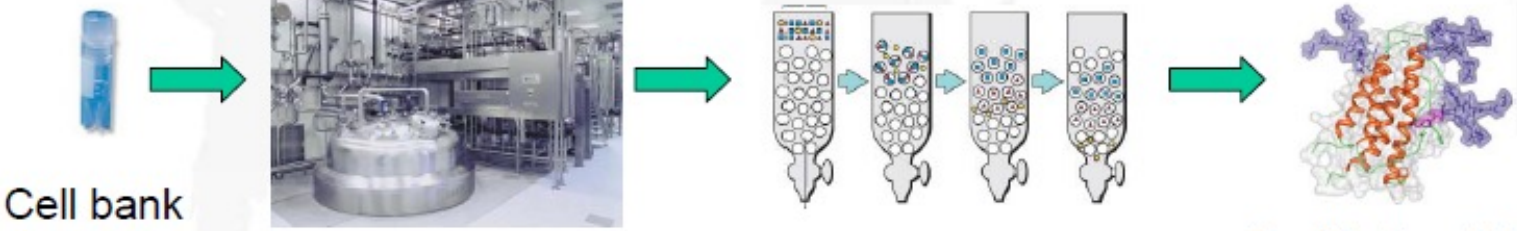
A process parameter **whose variability has an impact on a critical quality attribute** and therefore should be monitored or controlled to ensure the process produces the desired quality.

Come si valutano i Parametri Critici per processi biologici?

Processi per prodotti biologici

ICH harmonisation for better health

Manufacturing process



Cell bank

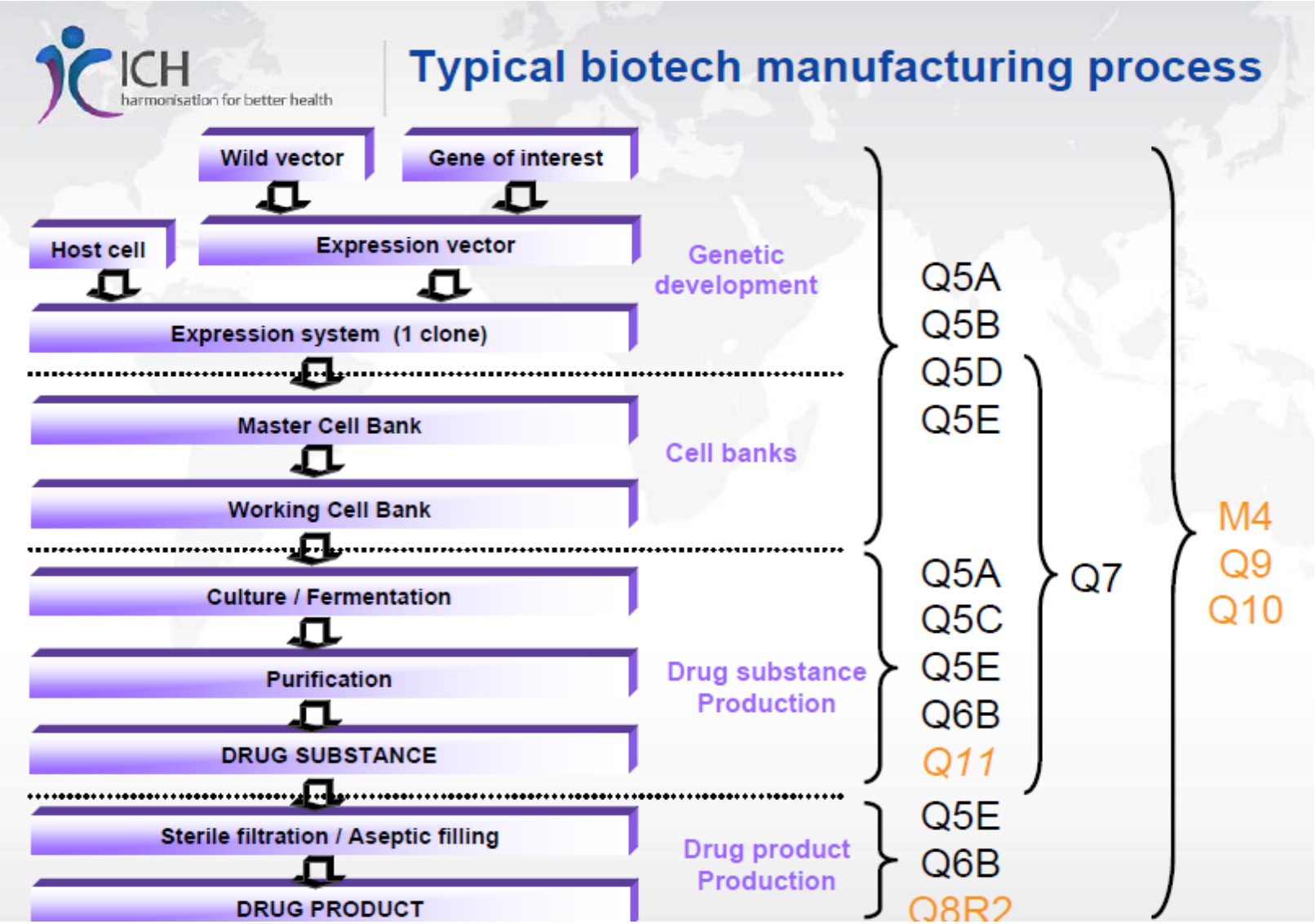
Fermentation

Purification

Purified protein

Drug Substance

Processi per prodotti biologici



Esempio: Freeze- drying

- "To dry (as food) in a frozen state under high vacuum conditions for preservation"

(Webster Dictionary)

- " ... a means of drying, achieved by freezing the wet substance and causing ice to sublime directly to vapor by exposing it to a low partial pressure of water vapor"

(Sterile Pharmaceutical Manufacturing - Applications for the 1990's)

Identificazione dei Critical Process Parameters e dei loro ranges

1- lista degli step di processo e valutazione del possibile impatto su uno o più CQA

2- lista dei parametri per ciascuno step critico

3- identificazione dei potenziali parametri critici (ad esempio mediante matrice causa & effetto)

4- conferma sperimentale di criticità dei parametri mediante studi univariati e/o multivariati

5- definizione dei ranges ottimali dei parametri critici (Proven Acceptable Range/ Design Space) e utilizzo di risk assessment più complessi (es FMEA) (late development/ commercial)

Esempio: DP process development, A-Vax Case study

Step	Process
1	Addition of WFI, buffer, sucrose, and polysorbate to obtain final desired concentration Volume to be between 50% and 60% of final drug product formulation Adjustment of formulation pH to desired condition
2	Mixing of buffer components to ensure homogeneity
3	Thaw of individual antigen components in specified water bath Dilution calculation of antigens to ensure proper amount added to formulation tank Addition of antigens to conjugate blend tank Volume between 50% and 40% of final batch
4	Addition of conjugate blend to final formulation tank Mixing of product to ensure homogeneity Filtration of final formulated bulk through 0.22 um PVDF membranes; two filters in sequence Filtered FFB filled into respective vials and half-stoppered for lyophilization
5	Lyophilization of A-VAX vaccine Sealing and inspection
6	Packaging of A-VAX vaccine Lyophilized A-VAX vaccine combined with aluminum-containing diluent

Identificazione dei Critical Process Parameters e dei loro ranges

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Esempio: Cause & effect matrix, A-Vax Case study

Scoring of Process Parameters	
Impact Score	Ranking Criteria
10	Strong relationship known based on available data and experience
7	Strong relationship is expected
5	Not-so-strong relationship expected or unknown
1	Known to not have a relationship

CQAs

Parametri di processo

Cause-and-Effect Matrix

Process Parameters	Potency	Purity	Identity	Dose	pH	Moisture	Appearance (Lyo)	Appearance (Recon)	Recon Time	Endotoxin /LAL	Sterility	General Safety	Sub-Visible Particulates	Adsorption	Formulation Composition	Score
Raw Material (DS)	10	10	10	5	5	1	1	5	1	5	5	5	5	10	5	83
Raw Material (Buffer)	1	5	1	1	10	7	7	7	5	5	5	5	1	7	10	77
Raw Maerial (Vial/Stopper)	1	1	1	1	1	10	5	5	1	5	10	1	5	1	1	49
DS Thaw/ Handling	5	5	1	1	1	1	1	1	1	1	1	1	5	5	1	31
Formulation Compounding & Mixing	10	1	1	10	5	5	5	1	5	5	5	1	5	7	7	73
Filtration	5	5	1	5	1	1	1	1	1	1	10	1	7	5	1	46
Filling	7	1	1	10	1	1	5	1	5	5	5	1	7	5	1	56
Lyophilization	1	5	1	1	1	10	10	5	10	5	5	1	5	1	1	62
Capping	1	1	1	1	1	5	1	1	1	1	7	1	1	1	1	25
Visual Inspection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
	42	35	19	36	27	42	37	28	31	34	54	18	42	43	29	

Esempi study

Table 6-3: Impact Assessment of Attributes: Main Effect Ranking

Impact Description	Impact Definition	Main Effect Ranking Based on Impact on Attributes	
		Critical Quality Attribute (CQA)	Low-Criticality Quality Attribute or Process Attribute
No Impact	Parameter is not expected to impact attribute – impact not detectable	1	1
Minor Impact	Expected parameter impact on attribute is within acceptable range	4	2
Major Impact	Expected parameter impact on attribute is outside acceptable range	8	4

Table 6-4: Impact Assessment of Attributes: Interaction Effect Ranking

Impact Description	Impact Definition	Interaction Effect Ranking Based on Impact on Attributes	
		Critical Quality Attribute (CQA)	Low-Criticality Quality Attribute or Process Attribute
No Impact	No parameter interaction; not expected to impact attribute – impact not detectable	1	1
Minor Impact	Expected parameter interaction; impact on attribute is within acceptable range	4	2
Major Impact	Expected parameter interaction; impact on attribute is outside acceptable range	8	4

Esempio: Risk ranking and filtering, A-Vax case study

Severity score = Main effect x interaction effect

The severity score provided the basis for determining whether process parameters required additional multivariate or univariate analysis or whether prior knowledge provided adequate characterization of the parameters. This assessment was used to rank parameters within individual unit operations. No attempt was made to estimate interactive effects of parameters across multiple unit operations.

Table 6-5: Severity Score as a Function of Main and Interactive Rankings

		Main Effect Ranking			
		1	2	3	4
Interaction Effect Ranking	8	8	16	32	64
	4	4	8	16	32
	2	2	4	8	16
	1	1	2	4	8

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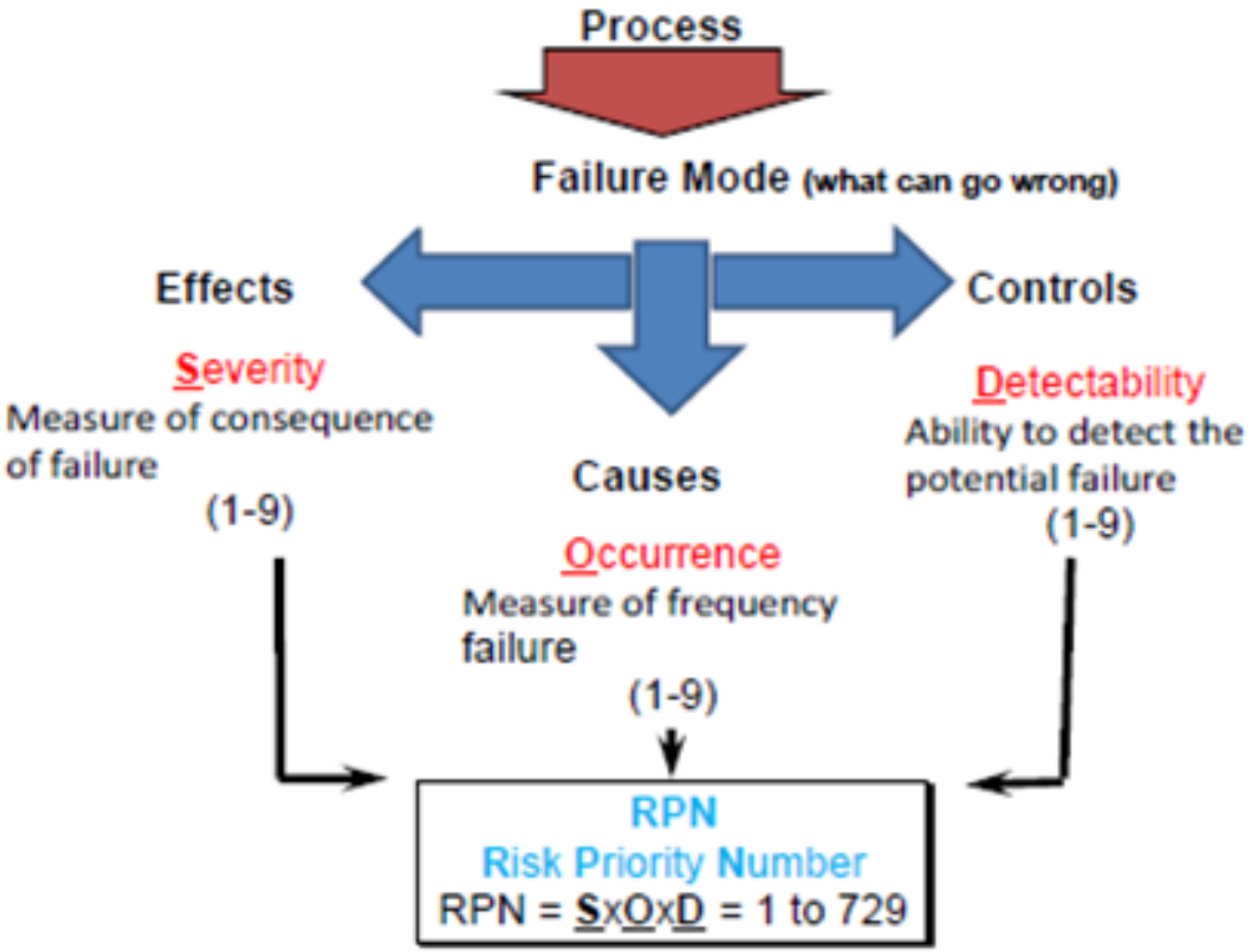
Esempio: FMEA, A-Vax Case study

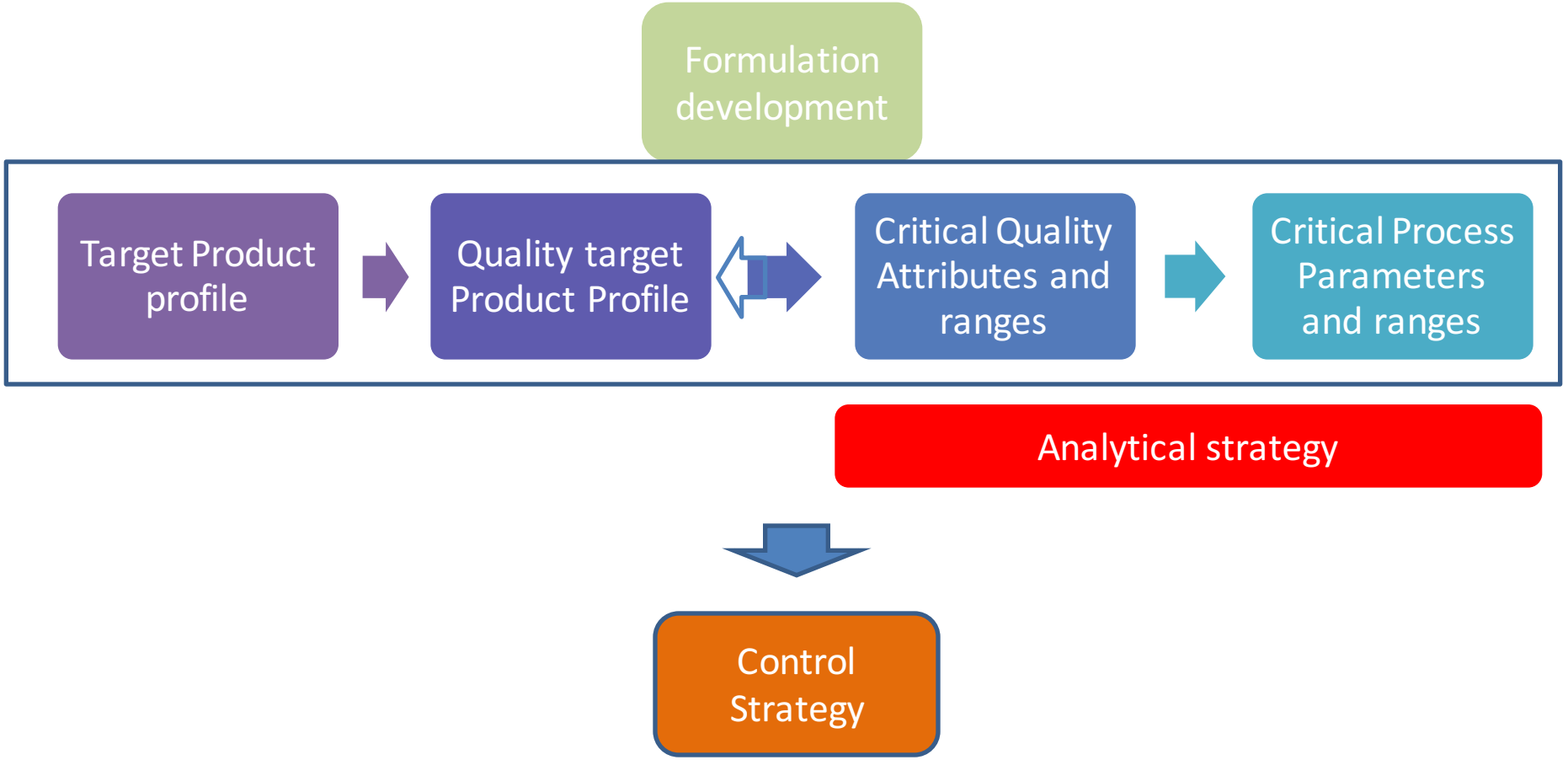


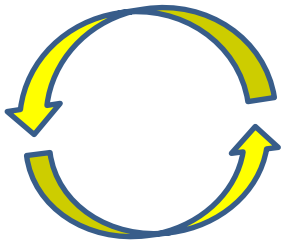
Esempio: FMEA, A-Vax Case study

Table 6-9: FMEA Scoring Guidelines

Score	Severity	Occurrence	Detection
9 "HIGH risk"	Process failure potentially impacting one or more critical product quality attributes leading to product rejection	*> 20% (very frequent)*	*No way to detect excursion. Not tracked or alarmed.*
7	Potential impact on product quality or consistency (e.g., product related substances). Investigation needed prior to product release.	*~ 5-20% (frequent)*	*Difficult to detect excursion, and not until after it has impacted the process.*
5	No impact on product quality, but deviation from manufacturing procedures requires justification. Likely deterioration in process performance (e.g., yield or operability).	*~ 1-5% (occasional)*	*Excursion can be detected, but not until after it has impacted the process.*
3	No impact on product quality. Potential for minor deterioration in process performance (e.g., yield or operability).	*< 1% (rare)*	*Excursion is usually detected and corrected prior to impacting the process.*
1 "LOW risk"	No impact to product quality or process performance.	*0% (never observed)*	*Excursion is obvious and always detected prior to impacting the process.*

QbD simplified Flow





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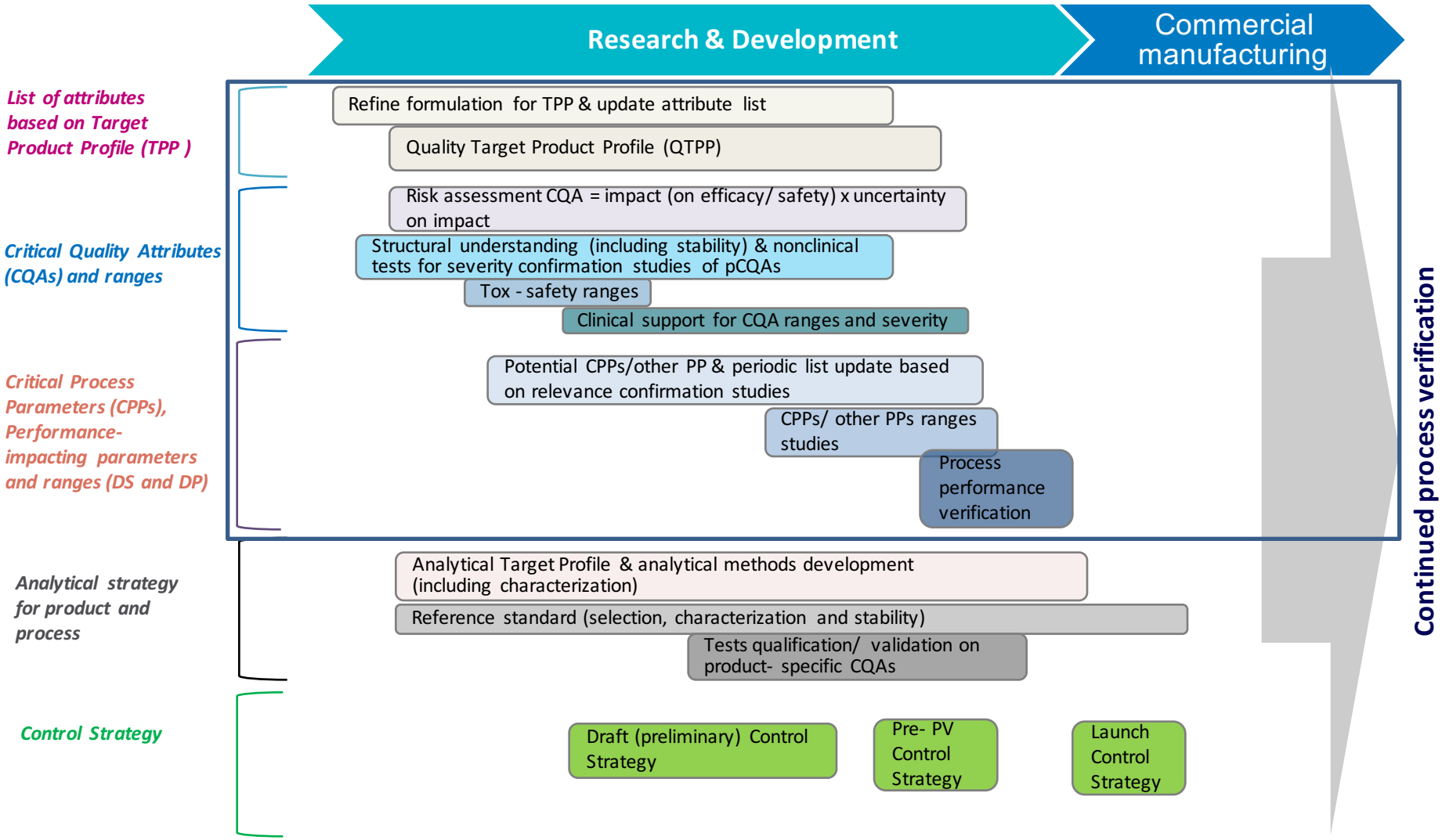
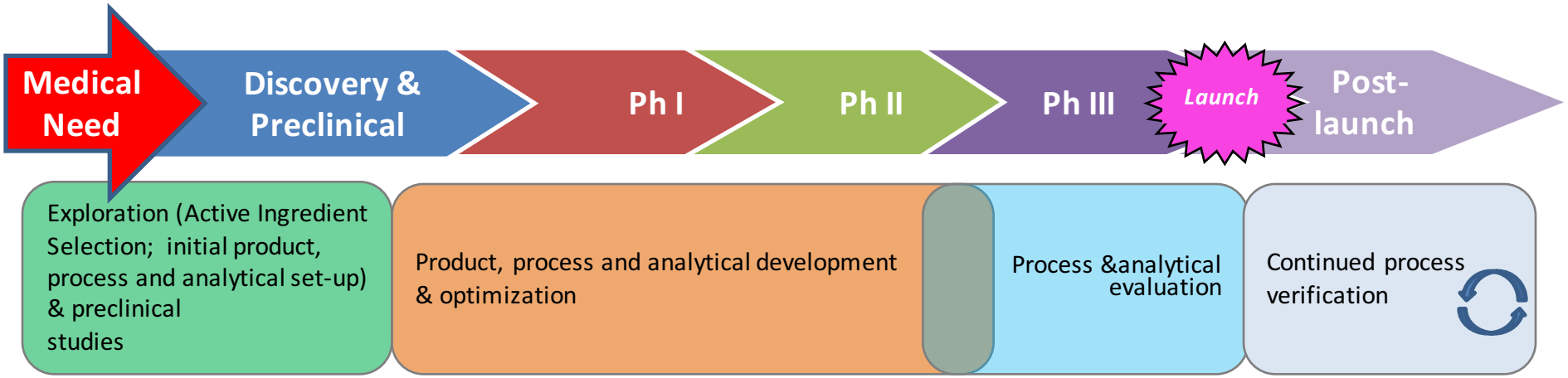


CICLO DI VITA DI UN PRODOTTO FARMACEUTICO (CMC perspective)



Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf