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.

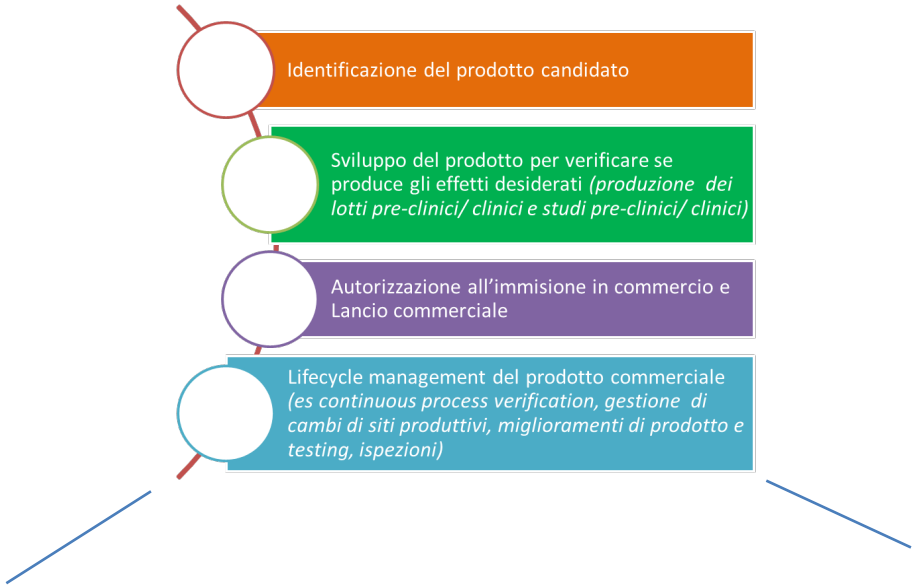
Modalità esame
Scritto

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?

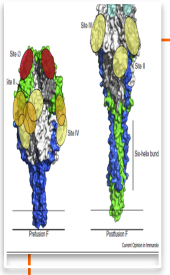
- Conoscere il **Prodotto** e le caratteristiche importanti per la sua efficacia e sicurezza (struttura, formulazione)
- Avere un **Processo** in grado di generare il materiale della giusta qualità in maniera sostenibile (alte rese e riproducibile)
- Avere **Test analitici** in grado di monitorare la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

Industrializzazione e requisiti tecnici

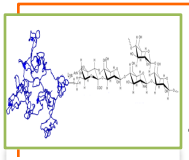
- Quali sono le sfide associate allo sviluppo e alla produzione commerciale di **prodotti biologici**?

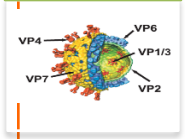
- Quali **strategie** possiamo mettere in campo per supportare lo **sviluppo** e il **lifecycle management** dei prodotti biologici?

Sfide: sviluppo di prodotti biologici



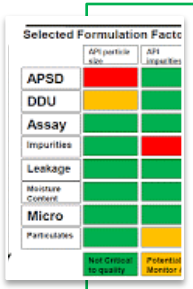
Complex products and processes → difficult characterization





Wide variety of possible product ***categories/ structural*** features, → sometimes limited possibility to leverage information from different products

Analytical strategy: structural and formulation changes → impact on efficacy



Knowledge of **antigen structure, formulation, analytics and process** are instrumental for attribute selection and ranges to be clinically explored

Aggressive timelines : product, process, analytical development (especially in case of disease outbreaks)

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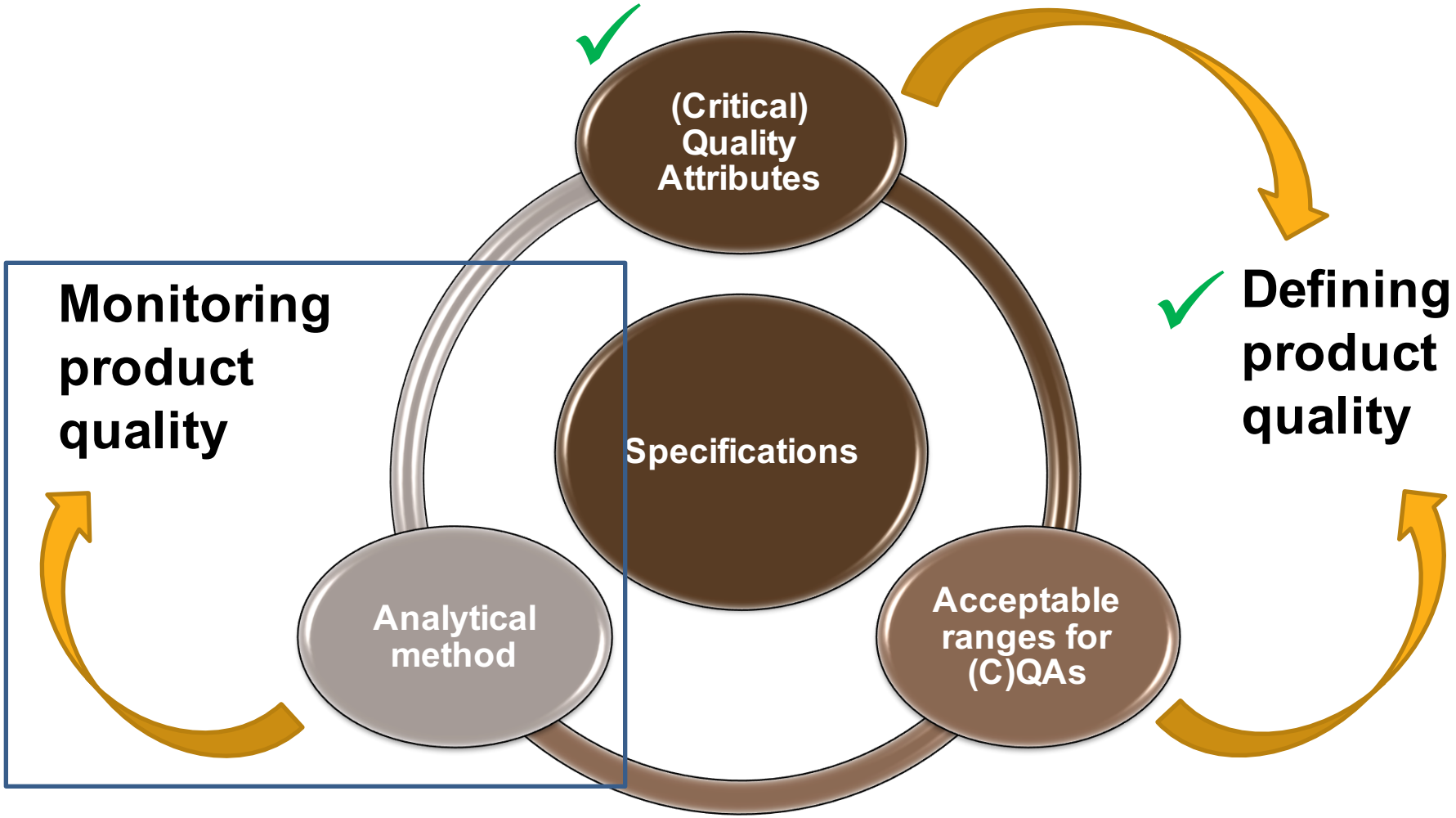
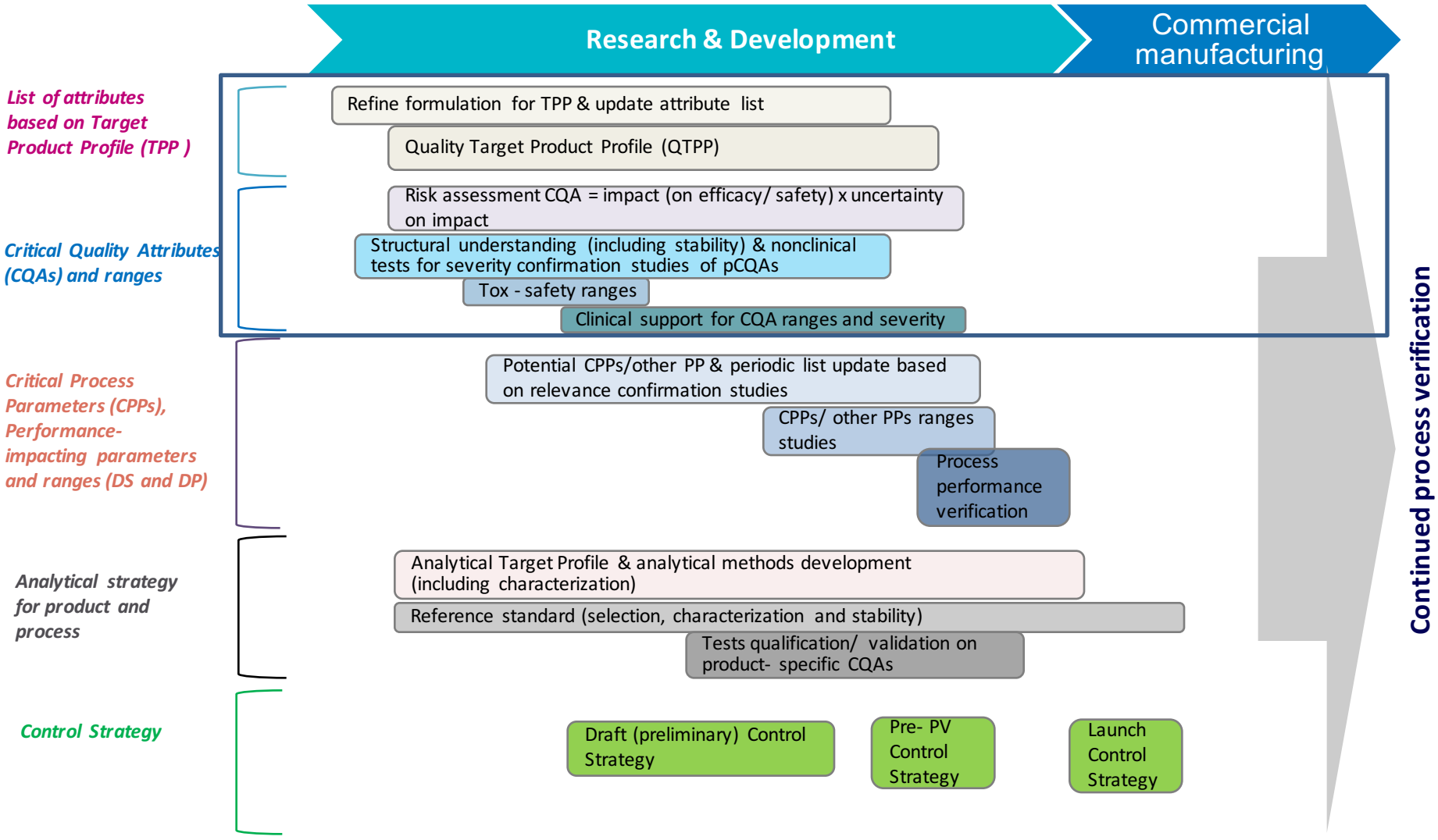
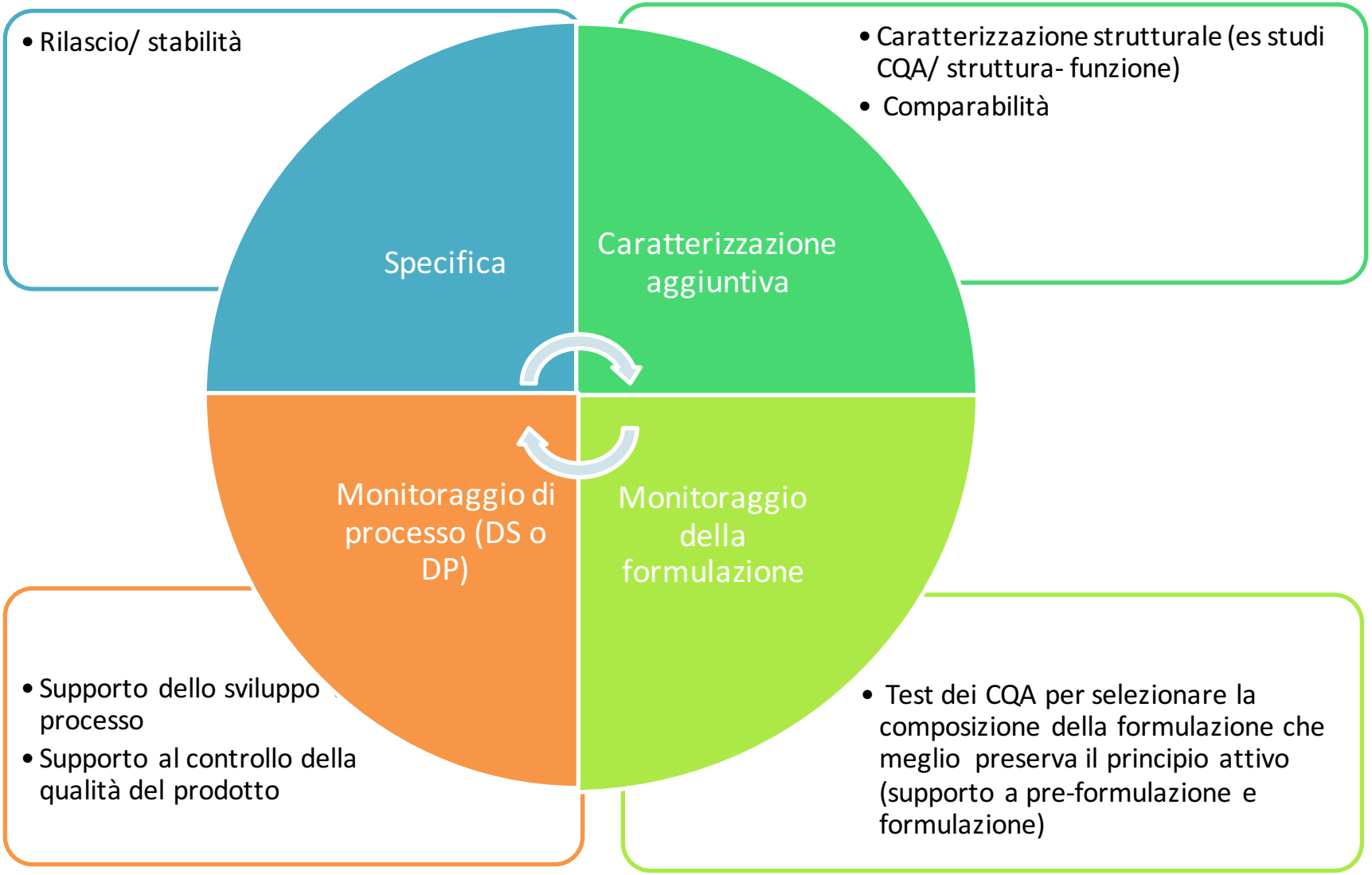

(Critical) Quality Attributes
Defining product quality
Specifications
Acceptable ranges for (C)QAs
Analytical method
Monitoring product quality

Knowledge refinement

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



Scopo dei test analitici



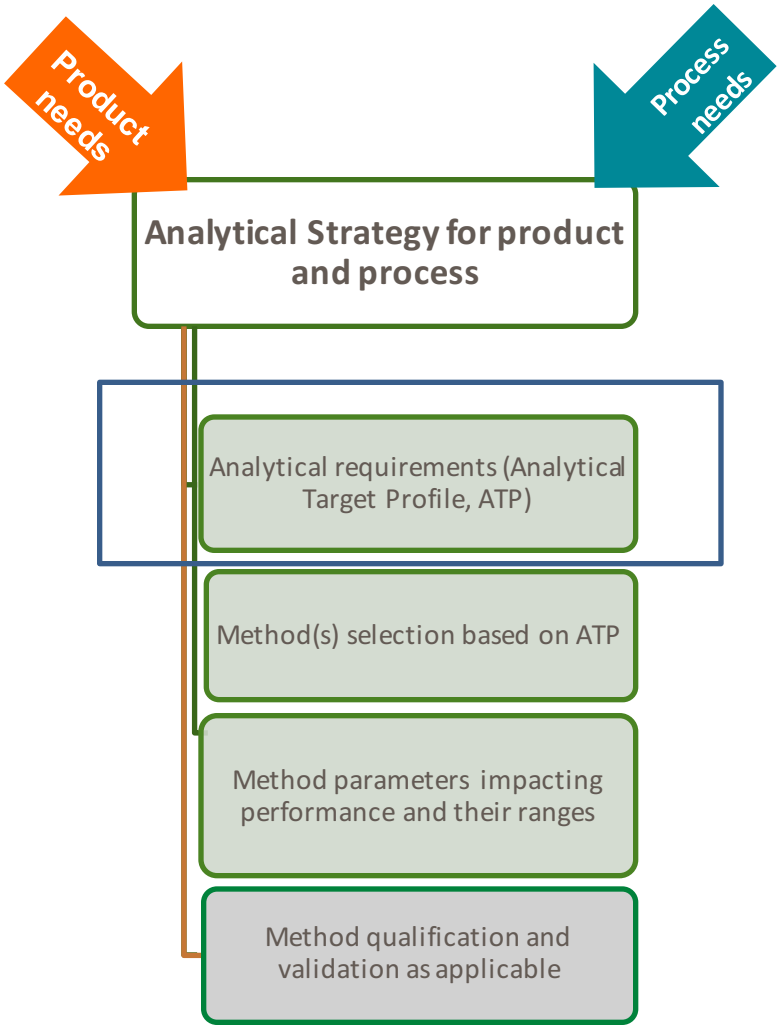
Sviluppo di test analitici secondo approccio QbD

Approccio tradizionale	Approccio QbD
Utilizzo le tecnologie che ho applicato ad altri prodotti; se non funzionano, cerco alternative	In base alla finalità del metodo analitico, pre- definisco le prestazioni che il metodo dovrebbe avere (ad esempio, accuratezza, precisione ecc), e seleziono la tecnologia in grado di soddisfare questi requisiti, dipendenti esclusivamente dalle necessità di testing del prodotto e/ of del processo
Una volta selezionato il metodo, definisco i criteri di validazione in base alle caratteristiche della tecnologia analitica e ai dati ottenuti prima della validazione	Una volta selezionato il metodo, eseguo studi per identificare i parametri critici (ovvero quelli che impattano le prestazioni che ho pre-definito) e i loro ranges, per valutare la robustezza ed assicurare che il metodo sia affidabile. I criteri di validazione saranno allineati con le prestazioni che ho pre-definito, e quindi non dipendenti solo dalla tecnologia scelta
Lo standard di riferimento viene qualificato per l'uso	Lo standard di riferimento viene qualificato per l'uso. Sin dall'inizio dello sviluppo, vengono studiate le condizioni ottimali di stoccaggio degli standard prodotti «in house» e la caratterizzazione può essere utile per la definizione dei CQA e gli studi di comparabilità

Sviluppo di test analitici secondo approccio QbD

Currently, the pharmaceutical industry develops and validates procedures in alignment with ICH and USP guidance. The guidance recommends setting criteria and separately assessing performance characteristics that are good indicators of the performance of an analytical procedure: accuracy, precision, linearity, specificity, sensitivity, and robustness. Although these indicators are important to understand during development, they do not provide a direct measure of the quality, or the error associated with the results generated by the procedure (3). It is common practice to establish default criteria for these validation elements, although the rationale for these criteria is not always transparent. These default validation criteria are often established based on several considerations including product specifications, typical variability of methodology used to characterize drug substances and products, and regulatory feedback. However, they often lose their connection to the ultimate purpose of an analytical procedure, which is generating results upon which decisions are based. Identifying the required output in terms of the final result of the analytical procedure in an ATP statement provides a target for development and helps to ensure that the procedure is developed toward predetermined requirements that are directly linked to the intended use of the procedure and the specifications. Hence, results will be generated during routine testing with an understanding of the TMU associated with them, as well as the effect on decisions made with those results.

Sviluppo di test analitici secondo approccio QbD



Analytical Target Profile (ATP)

A fundamental component of the lifecycle approach is establishing a predefined objective that stipulates the performance requirements for the analytical procedure. This is captured in the ATP.

The ATP states the required quality of the results produced by a procedure in terms of the acceptable error in the measurement; in other words, it states the allowable TMU associated with the reportable value.

Because the ATP describes the quality attributes of the reportable value, it is applied during the procedure lifecycle and connects all of its stages.

PF42(5) Stimuli to the Revision Process: Analytical Target Profile. Structure and Application Throughout The Analytical Lifecycle

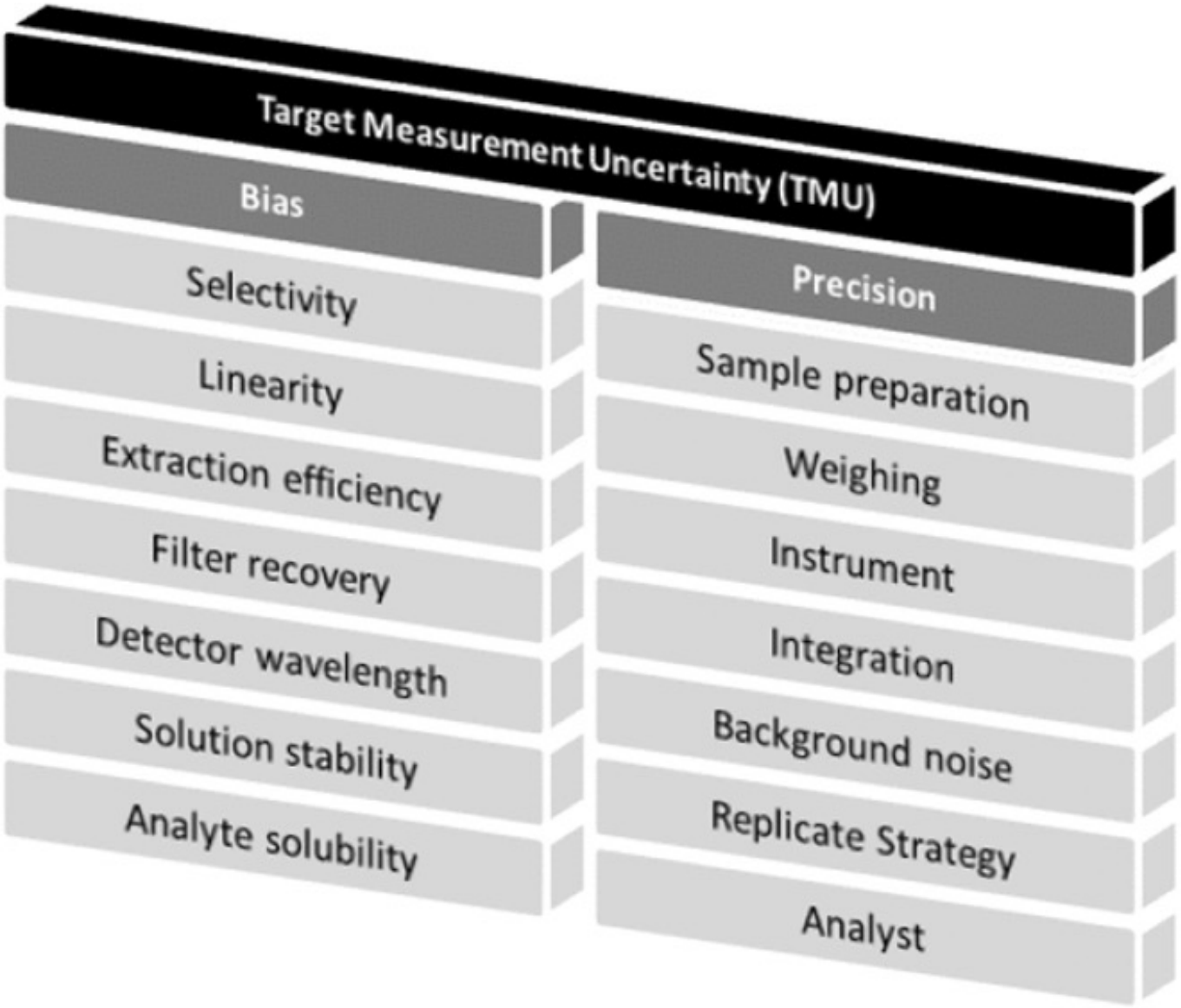
STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle

Kimber L. Barnett,[a] Pauline L. McGregor,[a] Gregory P. Martin,[a] David J. LeBlond,[a] M. L. Jane Weitzel,[a] Joachim Ermer,[a] Steven Walfish,[a] Phil Nethercote,[a] Gyongyi S. Gratzl,[a] Elisabeth Kovacs[a],[b]

Analytical Target Profile (ATP)- riporta la TMU (total measurement uncertainty)



Analytical Target Profile (ATP)- possibili approcci riportati in USP stimuli article

example 1: atp #1

The procedure must be able to accurately quantify [drug] in the [description of test article] in the presence of [x, y, z] with the following requirements for the reportable values: Accuracy = 100% ± D% and Precision ≤ E%.

Note that [x, y, z] are the specified impurities and excipients.

example 2: atp #2

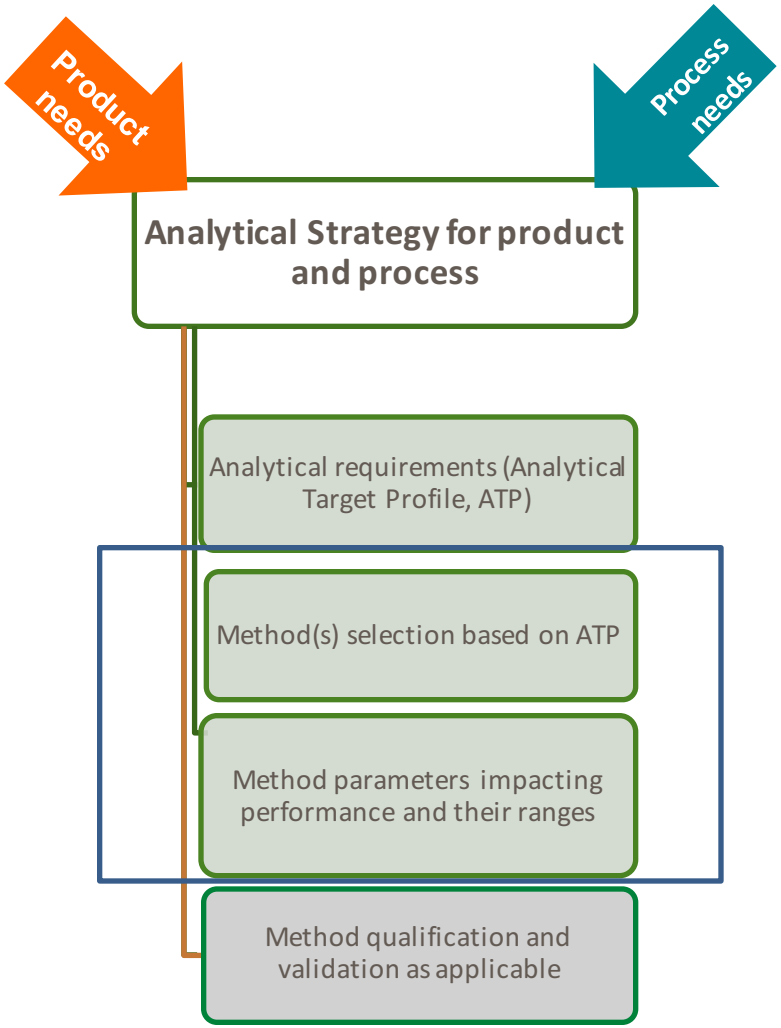
A simplified version of the ATP that was described in the initial Stimuli article of PF 39(5) is shown below as ATP #2. This example contains criteria for TMU (±C%) and is directly linked to the results generated by the procedure.

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] so that the reportable values fall within a TMU of ± C%.

The ATP inputs for [analyte], [description of test article], and [x, y, z] can be specified.

C describes the acceptable TMU. It considers the acceptable difference between the measured value and the target value and can be established based on a fraction of the specification range.

Sviluppo di test analitici secondo approccio QbD



Identificazione dei Critical Method Parameters e dei loro ranges

1- lista degli step del metodo e valutazione del possibile impatto su uno o più performance indicators dell'ATP

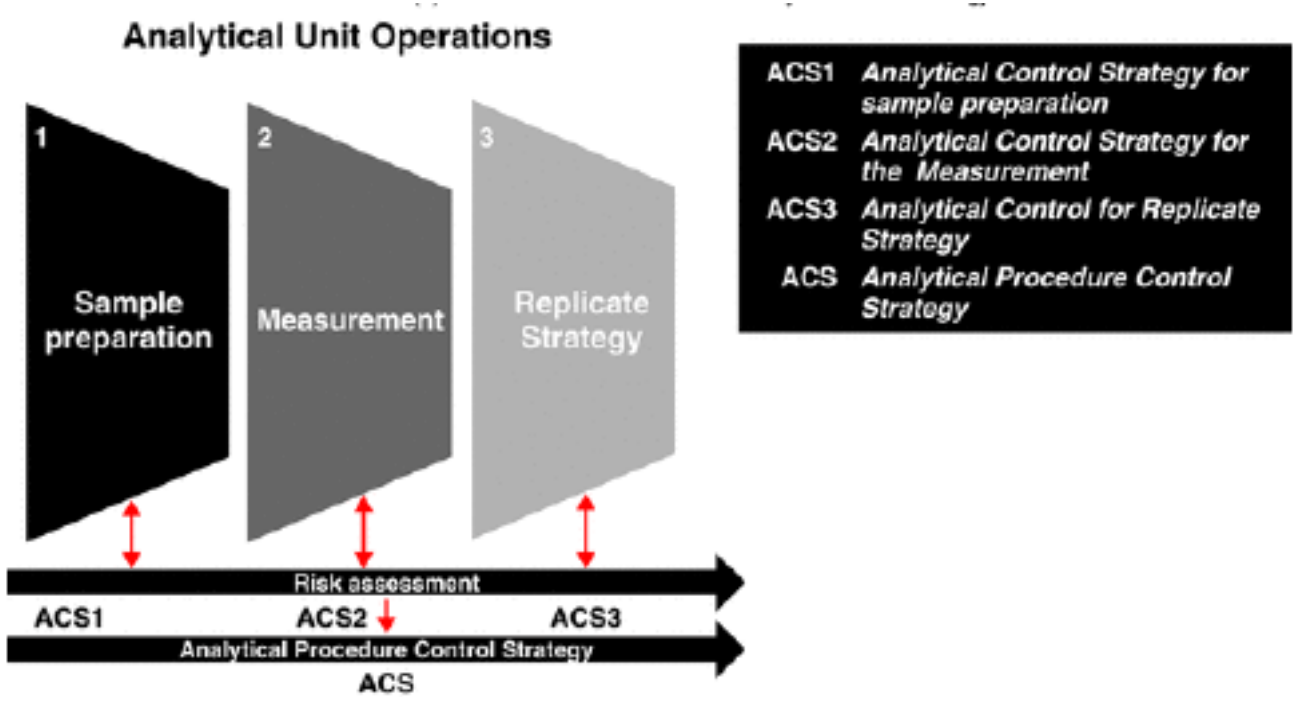
2- lista dei parametri per ciascuno step critico

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

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

5- definizione dei ranges ottimali dei parametri critici (Method Operable Design Region)

Sviluppo di test analitici secondo approccio QbD



STIMULI TO THE REVISION PROCESS

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Analytical Control Strategy

Elisabeth Kovacs, Joachim Ermer, PhD, Pauline L McGregor, PhD, Phil Nethercote, PhD Rosario LoBrutto, PhD, Gregory P Martin, MS, Horacio Pappa, PhD

Figure 5 e 7, Tabella 1

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.