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.

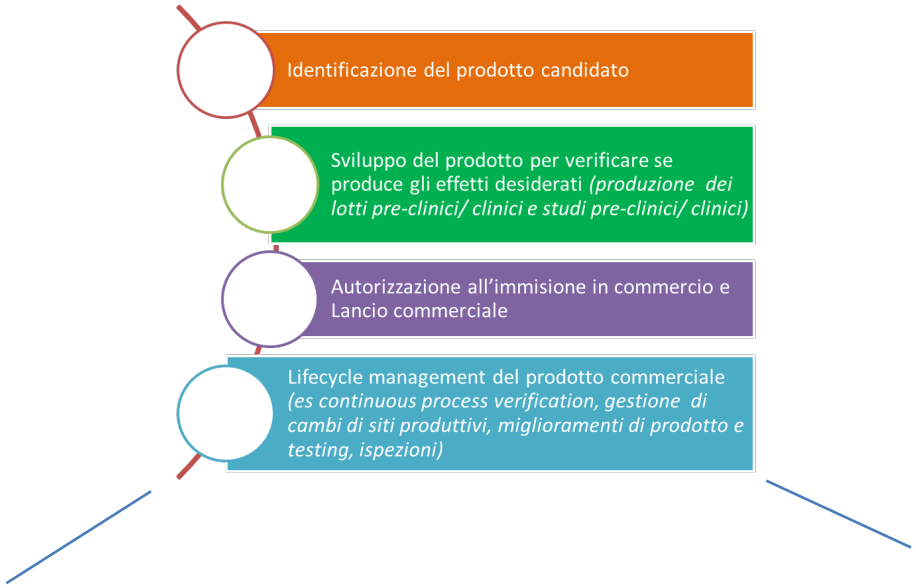
Modalità esame
Scritto

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?

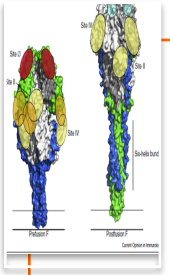
- Conoscere il **Prodotto** e le caratteristiche importanti per la sua efficacia e sicurezza (struttura, formulazione)
- Avere un **Processo** in grado di generare il materiale della giusta qualità in maniera sostenibile (alte rese e riproducibile)
- Avere **Test analitici** in grado di monitorare la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

Industrializzazione e requisiti tecnici

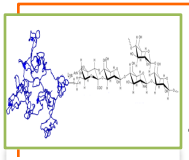
- Quali sono le sfide associate allo sviluppo e alla produzione commerciale di **prodotti biologici**?

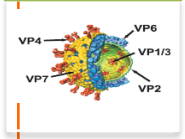
- Quali **strategie** possiamo mettere in campo per supportare lo **sviluppo** e il **lifecycle management** dei prodotti biologici?

Sfide: sviluppo di prodotti biologici



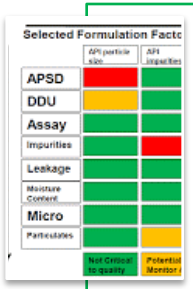
Complex products and processes → difficult characterization





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)

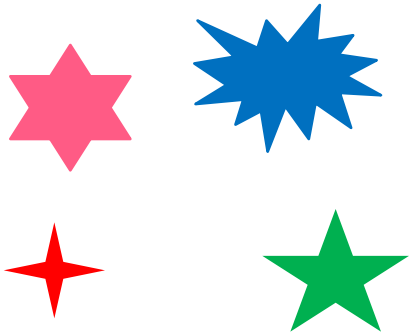
Sfide: esempi dalla lezione precedente (focus su caratteristiche di prodotto)

- Impurezze e product- related substances per prodotti biologici (definizioni ICH Q6B)

- Complessità di vaccini glicoconiugati
  - classificazione dei residui coniugazione
  - complessità e diversità strutturale degli epitopi saccaridici (O- acetilazione)

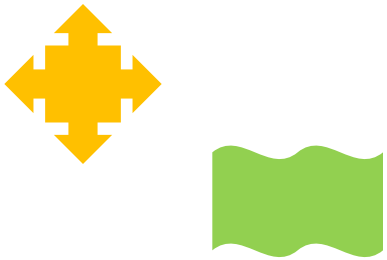
Esempio: vaccini

Antigen(s)



- Complex and multiple ***antigens***
- Different structural ***features*** and ***doses***
- Needed for **specificity of the immune response**

Adjuvant



- Aluminum salts or Adjuvant Systems
- Enhance and modulate **immunogenicity** of the vaccine antigen

Administered Vaccine

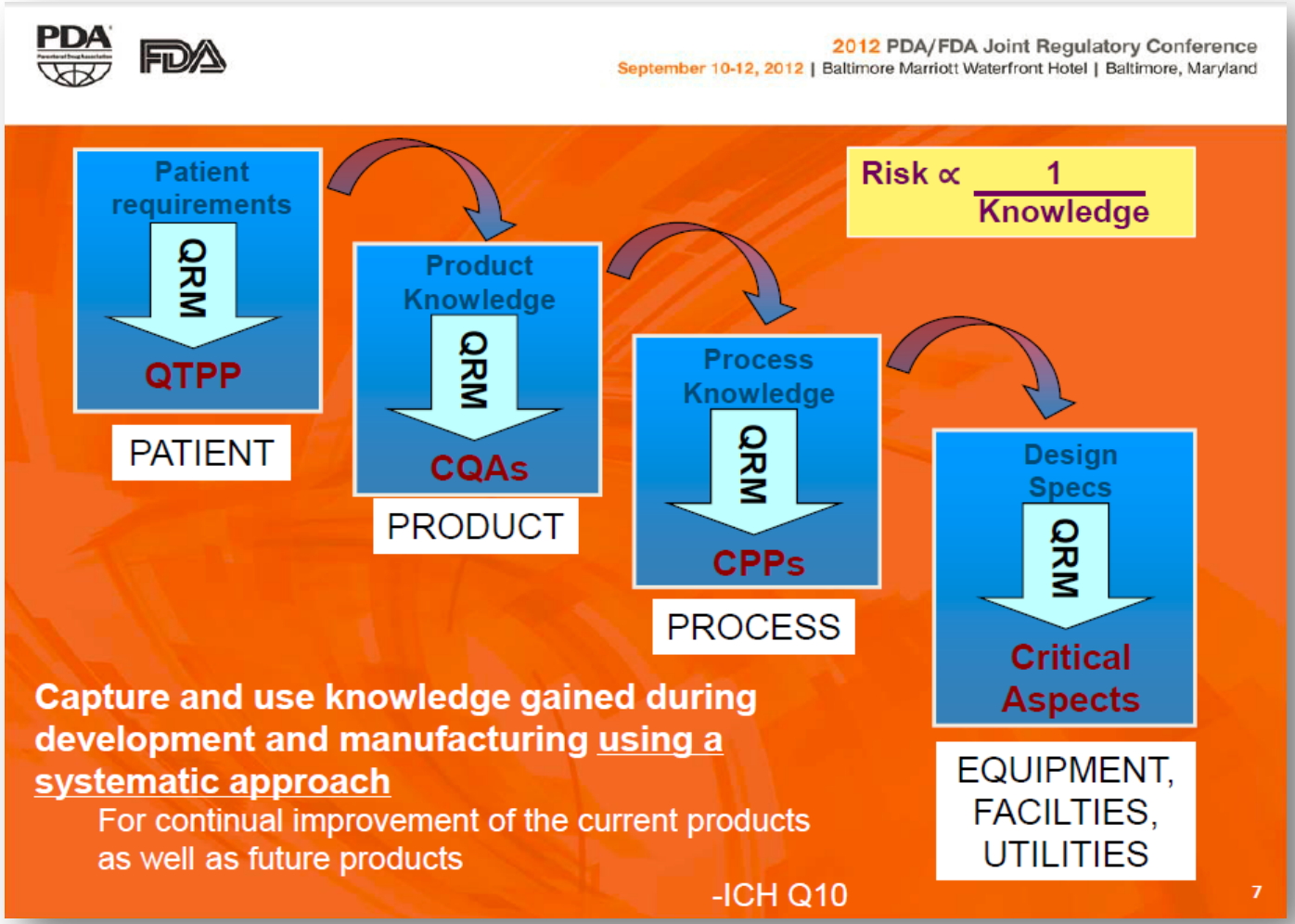
- All components in an appropriate ***buffer***
- Potential ***reconstitution*** before administration
- ***Vial*** or ***syringe*** (formulation, patient needs)

Complessità dei vaccini vs MAbs

Monoclonal antibodies	***Vaccines***	***Implications***
Often well-characterized	*Often difficult to characterize*	*Less definitive analytical comparability pathways* *Less ability to monitor product quality in mid-process*
Clear link to mechanism of action (MoA) and/or biomarker surrogate for clinical performance	*Difficult to establish clinical potency surrogates*	*Challenging to improve process post-licensure*
Consistent process and product	*Sometimes more complex, less predictable process/product*	*Variability over product/process life cycle*
Therapeutic patient population	*Prophylactic patient population*	*"Process is product" philosophy to assure quality*
Well-understood process; good detectability for test methods	*Less understood process; difficult to measure attribute changes*	*Empirical process models for linking parameter inputs to quality outputs* *More stringent threshold for reporting manufacturing changes*

Quality by Design (QbD)

"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management in order to ensure the quality of the product" (ICH Q8 (R2))



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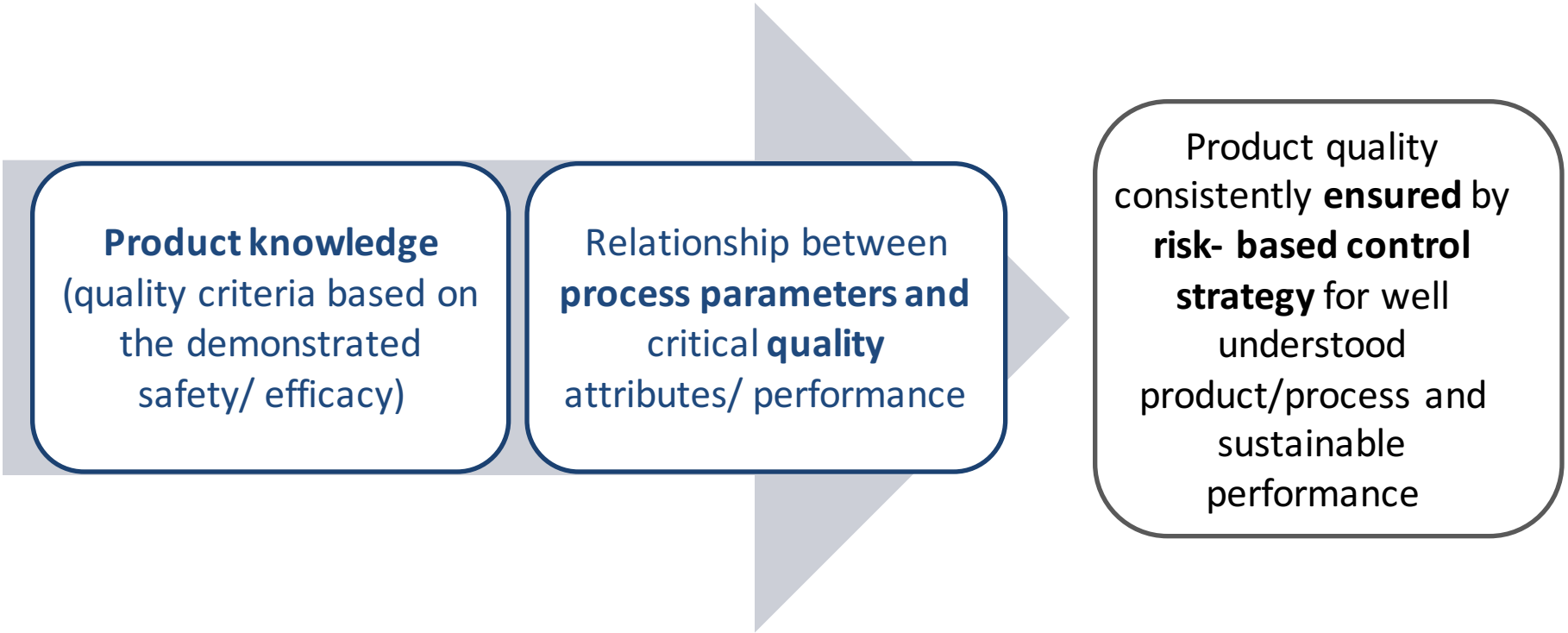
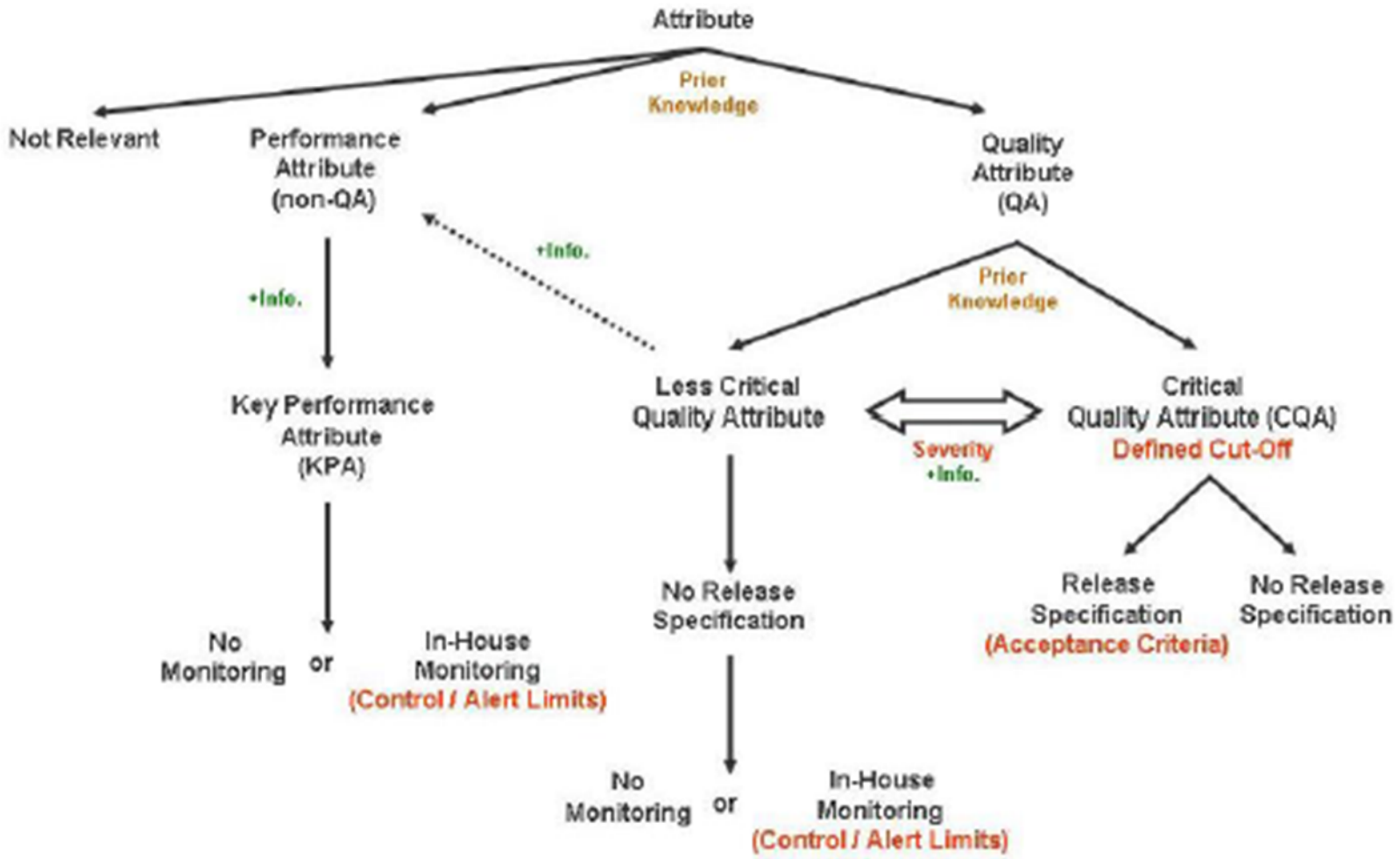


Come definire le caratteristiche del prodotto rilevanti per la sicurezza e l'efficacia di un prodotto biologico?



A-VAX Case study

Esempio: A-Vax Case study

The exact mechanism by which *X. horrificus* bacteria causes cooties disease is not known, but anticapsular polysaccharide (Ps) antibody levels (humoral response) and an enhanced cellular response correlate with a significantly reduced incidence of invasive *X. horrificus* infection. These humoral and cellular responses are similar to those observed in surviving individuals who fully recovered from the disease.

Five *X. horrificus* strains, each composed of a unique polysaccharide serotype (1, 2, 3, 4, or 5), account for about 80% of the total disease. A-VAX is indicated for the active immunization of 2-month-old to 60-month-old babies for prevention of cooties-related illnesses caused by *X. horrificus*, and the vaccine is designed to elicit antibodies to *X. horrificus* capsular Ps.

A-VAX is a pentavalent vaccine that has finished Phase 2 clinical trials and contains the capsular Ps of *X. horrificus* serotypes 1-5, individually linked to a recombinant, non-infectious VLP and adjuvanted with an aluminum salt. The mechanism by which A-VAX stimulates the cellular and humoral immune response is not fully understood; however, prior knowledge supports the assumption that only the Ps-VLP conjugate can initiate a protective immune response to Ps in this age group. Ps 1-4 are more immunogenic than Ps 5 (no neutralizing monoclonal antibody [Mab] is available for Ps 5). A murine challenge-protection model is available for each of the serotypes. However, no *in vitro* model exists that can be correlated with human protection for serotype 5.

Esempio: A-Vax Case study

Come definire le caratteristiche rilevanti per la sicurezza e l'efficacia di questo prodotto complesso?

«Critical Quality Attributes»

A CQA is "a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." (ICH Q8(R2))

Input for CQAs

- **The Target Product Profile (TPP)** is generally accepted as a tool for setting the strategic foundation for drug development – "planning with the end in mind". It is a summary of the drug development program described in the context of prescribing information goals. It is currently primarily expressed in clinical terms such as clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, overdosage, etc.

- **Quality Target Product Profile (QTPP)** is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug/vaccine product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTPP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label.

[L. X. Yu. Pharm. Res., 25 (4), 781 (2008)]

Esempio: TPP, A-Vax Case study

Product attribute	Target
Dosage form	Sterile product lyophilized, single use. To be reconstituted with aluminum phosphate diluents.
Dose	50 µg each of polysaccharides from serotypes 1–4 and 5 µg polysaccharide 5, each individually conjugated to VLP and adsorbed to 300 µg aluminum as aluminum phosphate adjuvant following reconstitution.
Label volume	0.5 mL filled (actual fill volume will be greater than the label volume to account for losses)
Concentration	100 µg/mL of active polysaccharide for serotypes 1–4 and 10 µg/mL for serotype 5
Mode of administration	IM
Dose administration	3 doses administered 2 months apart (preferably two, four, and fix months or based on pediatric vaccine schedule)
Dose volume	0.5 mL nominal dose
Viscosity	1–3 cP
Container	Single-dose vial (ISO2R vial, clear, Type I glass), latex-free stopper, and flip-off seal
Shelf life	≥ 3 years at 2—8°C VVM14 required for developing world and emerging-market supply (14 days at 37ºC, and 90 days at 25ºC)
Secondary packaging and shipping	Allowed shipping-excursion temperature 2–40°C for three days in a carton (10 vials/carton)

Esempio: CQA, A-Vax Case study

A questionnaire-based severity analysis was performed to identify potential CQAs. Each quality attribute was assessed for:

i. level of impact on clinical performance (safety and efficacy, see Table 2-5: Impact Scores)
ii. level of uncertainty associated with this prediction of the impact (see Table 2-6: Uncertainty Scores)

In this case study, we define (very high) uncertainty as a situation where the current state of knowledge about an attribute is such that the consequences, extent, or magnitude of a change event is unpredictable, and credible probabilities cannot be assigned to possible outcomes.

The quality attributes that have "severity" scores ≥25 are initially categorized as "critical"

Severity = Impact × Uncertainty

Quality attributes slightly below the cutoff value are further evaluated and discussed to confirm their level of criticality. The ≥25 cutoff limit is justified even if all the uncertainty is removed from the evaluation, because any parameter with a potential high impact will still remain a potential CQA. Furthermore, the quality attributes with only moderate impact can be considered critical if there is high uncertainty.

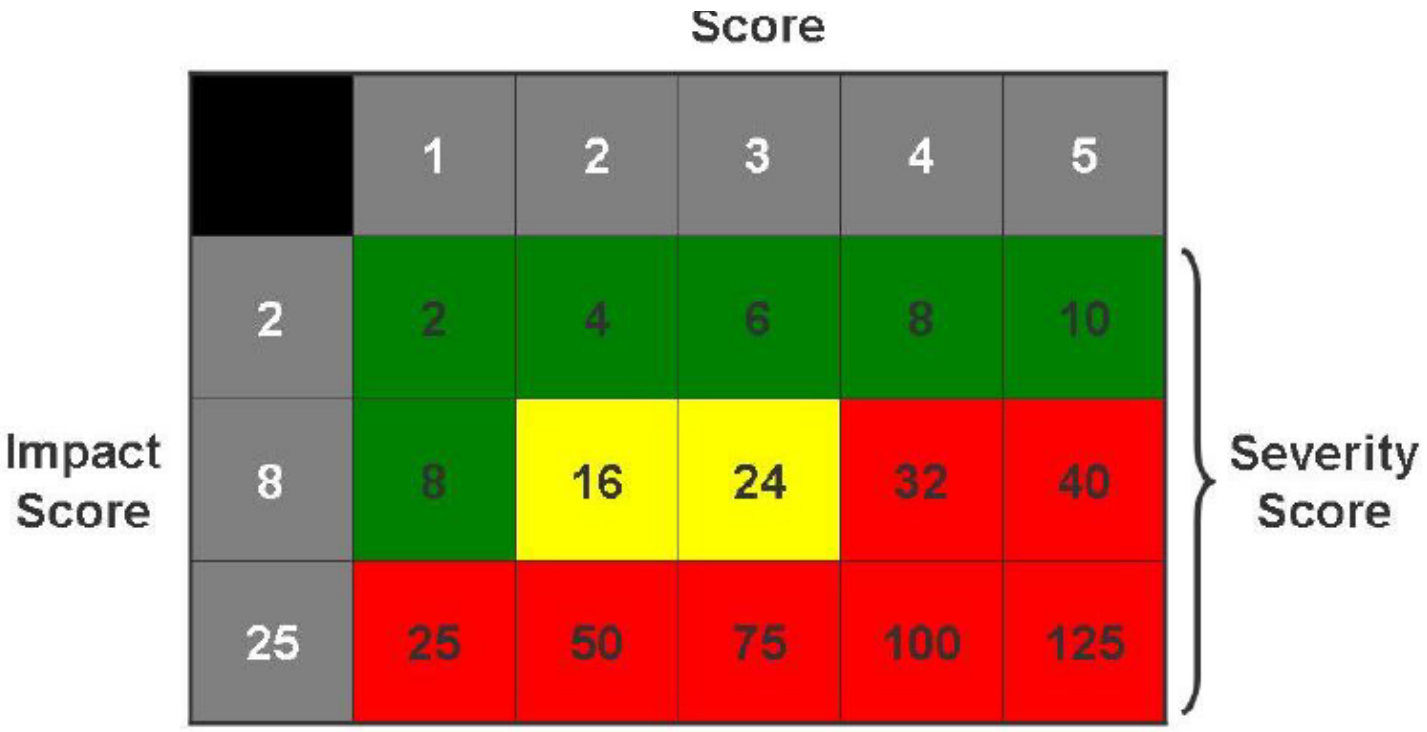
Esempio: CQA, A-Vax Case study

Impact Score	Efficacy	Safety and Tolerability (Adverse Events, AEs)
Very High 25	Significant Change	**Severe** AE prevents normal, everyday activities (e.g., prevent attendance at school/kindergarten/day-care center, requiring medical attention or advice). Significant increase in severity and/or frequency.
Moderate 8	Moderate Change	**Moderate** Sufficiently discomforting to interfere with normal everyday activities. Moderate but detectable increase severity and/or frequency over placebo.
Minimal 2	Minor to No Change	**Mild** Easily tolerated, causing minimal discomfort and not interfering with everyday activities. Similar to placebo.

Esempio: CQA, A-Vax Case study

Score	Uncertainty
Very High 5	No information available
High 4	*External* information available from literature on related vaccine(s)
Moderate 3	Data from *internal* laboratory or nonclinical studies with this antigen:adjuvant complex, or *internal* data extrapolated from related vaccine(s)
Low 2	Supportive data from *clinical studies* with this antigen:adjuvant complex
Minimal 1	Published limits widely accepted by regulatory and scientific community

Esempio: CQA, A-Vax Case study



Per i prodotti biologici, l' identificazione dei CQAs è un processo che può protrarsi nel tempo durante lo sviluppo, man mano che vengono acquisite conoscenze sul rapporto tra le caratteristiche strutturali e la funzione del prodotto

Esempio: CQA, A-Vax Case study

Quality/Product Attribute	Method	I*	U*	S*
Potency				
Serotypes 1-4 (correlation)	mAb-based Competitive ELISA (adsorbed)	25	2	50
Serotype 5 (no correlation)	Rate Nephelometry (desorbed)	8	2	16
Animal Model (confirms correlation)	Murine Serology (adsorbed)	25	2	50
Th1/Th2 Profile	Cytokine-panel ELISAs (adsorbed)	25	2	50
Purity (desorbed Ps-VLP)				
Peptidoglycan Level	Calculated	8	3	24
Monomer	Reducing CGE	25	2	50
Complexes/Aggregates	Non-reducing CGE	25	2	50
Product-derived Impurity (desorbed Ps-VLP)				
Fragments	Reducing CGE	8	3	24
Complexes/Aggregates	Non-reducing CGE	25	3	75
Process-derived Impurity				
Activation and Conjugation Reactants	Calculated	8	5	40
Structure/Function (Charac.) (adsorbed Ps-VLP unless indicated)				
VLP Structure	Cryo-TEM	8	5	40
Ps/VLP/Adjuvant Ratio	Calculated	8	5	40
VLP Linear and Conformational Epitopes	mAb-based ELISA (desorbed)	8	5	40
Ps Size Distribution	HPSEC-MALLS-RI	25	5	125
Size of Aggregates	DLS (desorbed)	25	5	125
Extent of Conjugation (as Ps-VLP, free Ps, and free VLP)	Reducing CGE	25	3	75
Other				
Quantity (as Protein Content)	Calculated	25	2	50
Quantity (as Ps Content)	Calculated	25	2	50
Fill Volume in Container	Compendial	25	1	25
Endotoxin	Compendial	25	1	25
Completeness-of-Adsorption (Adsorption to Al)	mAb-based ELISA (adsorbed)	25	5	125
Aluminum Content	ICP or AA	25	1	25

Reconstituted A-VAX (adjuvant + Ps- conjugate) initial

Esempio: CQA, A-Vax Case study

Quality/Product Attribute	Method	I*	U*	S*
Potency				
Serotypes 1-4 (correlation)	mAb-based Competitive ELISA (adsorbed)	25	2	50
Serotype 5 (no correlation)	Rate Nephelometry (desorbed)	8	2	16
Animal Model (confirms correlation)	Murine Serology (adsorbed)	25	2	50
Purity (desorbed Ps-VLP)				
Peptidoglycan Level	Calculated	8	3	24
Monomer	Reducing CGE	25	2	50
Complexes/Aggregates	Non-reducing CGE	25	2	50
Product-derived Impurity (desorbed Ps-VLP)				
Fragments	Reducing CGE	8	3	24
Complexes/Aggregates	Non-reducing CGE	25	3	75
Process-derived Impurity				
Activation and Conjugation Reactants	Calculated	8	5	40
Structure/Function (Charac.) (adsorbed Ps-VLP unless indicated)				
VLP Structure	Cryo-TEM	8	5	40
Ps/VLP/Adjuvant Ratio	Calculated	8	5	40
VLP Linear and Conformational Epitopes	mAb-based ELISA (desorbed)	8	5	40
Ps Size Distribution	HPSEC-MALLS-RI	25	5	125
Size of Aggregates	DLS (desorbed)	25	5	125
Extent of Conjugation (as Ps-VLP, free Ps & free VLP)	Reducing CGE	25	3	75
Other				
Quantity (as Protein Content)	Calculated	25	2	50
Quantity (as Ps Content)	Calculated	25	2	50
Fill Volume in Container	Compendial	25	1	25
Endotoxin	Compendial	25	1	25
Completeness-of-Adsorption (Adsorption to Al)	mAb-based ELISA (adsorbed)	25	5	125
Aluminum Content	ICP or AA	25	1	25

* Impact = I, Uncertainty = U, and Severity = S (see Equation 2-1 and Table 2-7).

Reconstituted A-VAX (adjuvant + Ps- conjugate)
Second iteration

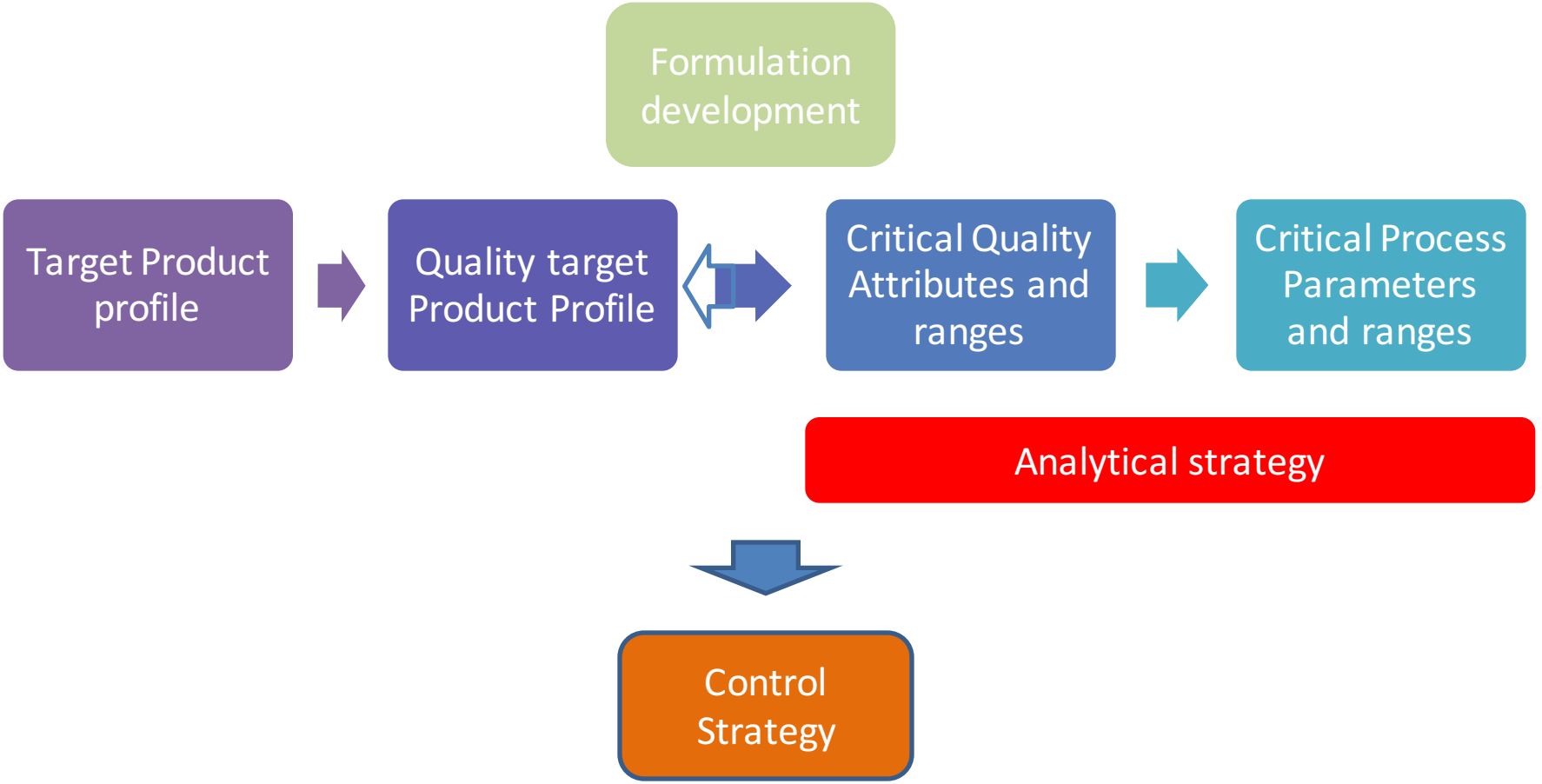
Esempio: CQA, A-Vax Case study

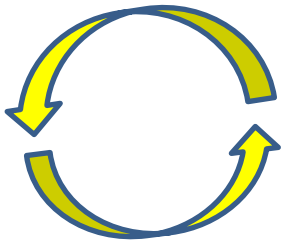
Quality/Product Attribute	Method	I*	U*	S*
Potency				
Serotypes 1-4 (correlation)	mAb-based Competitive ELISA (adsorbed)	25	2	50
Animal Model for Type 5	Murine Serology (adsorbed)	25	2	50
Purity (desorbed Ps-VLP)				
Peptidoglycan Level	Calculated	8	3	24
Monomer	Reducing CGE	25	2	50
Complexes/Aggregates	Non-reducing CGE	25	2	50
Product-derived Impurity (desorbed Ps-VLP)				
Complexes/Aggregates	Non-reducing CGE	25	3	75
Process-derived Impurity				
Activation and Conjugation Reactants	Calculated	8	5	40
Structure/Function (Charac.) (adsorbed Ps-VLP unless indicated)				
VLP Structure	Cryo-TEM	8	5	40
Ps/VLP/Adjuvant Ratio	Calculated	8	5	40
VLP Linear and Conformational Epitopes	mAb-based ELISA (desorbed)	8	5	40
Ps Size Distribution	HPSEC-MALLS-RI	25	5	125
Size of Aggregates	DLS (desorbed)	25	5	125
Extent of Conjugation (as Ps-VLP, free Ps, and free VLP)	Reducing CGE	25	3	75
Other				
Quantity (as Protein Content)	Calculated	25	2	50
Quantity (as Ps Content)	Calculated	25	2	50
Fill Volume in Container	Compendial	25	1	25
Endotoxin	Compendial	25	1	25
Completeness of Adsorption (Adsorption to Al)	mAb-based ELISA (adsorbed)	25	5	125
Aluminum Content	ICP or AA	25	1	25

* Impact = I, Uncertainty = U, and Severity = S (see Equation 2-1 and Table 2-7).

Reconstituted A-VAX (adjuvant + Ps- conjugate)
Third iteration

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.