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

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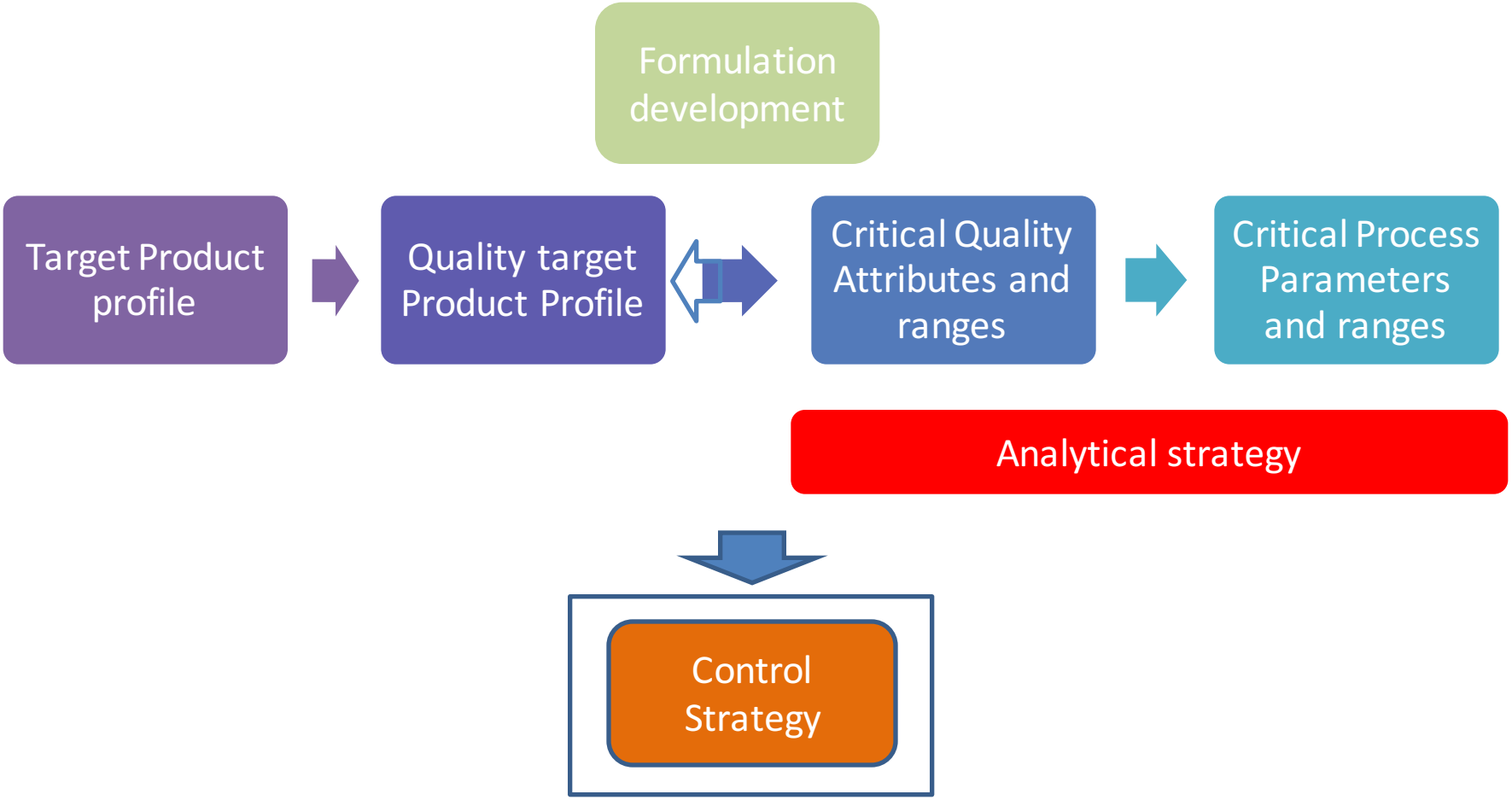
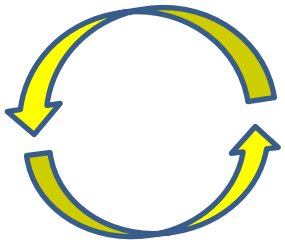
Questo corso contiene informazioni a scopo didattico, non correlate in alcun modo a dati rilevanti per GSK Vaccines, e fa riferimento al mio personale punto di vista.

Cristiana Campa

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.

Control Strategy (ICH Q11)

In either the traditional or enhanced approach, the control strategy can include an in-process determination that a CQA is within an appropriate limit, range or distribution in lieu of testing the final drug substance.

Any approach other than testing the final drug substance should provide at least the same level of assurance of drug substance quality. […]

When developing a control strategy, **a manufacturer can consider implementing single or multiple points of control for a specific CQA, depending on the risk associated with the CQA and the ability of individual controls to detect a potential problem**.

For example, with sterilised drug substances or biotechnological/biological products, there is an inherent limitation in the ability to detect low levels of bacterial or viral contamination in the drug substance. In these cases, end-product testing is considered to provide inadequate assurance of quality, so additional points of control (e.g., attribute and in-process controls) are incorporated into the control strategy.

Control Strategy (ICH Q11)

A control strategy is a planned set of controls, derived from current product and process understanding that assures process performance and product quality (ICH Q10). Every drug substance manufacturing process, whether developed through a traditional or an enhanced approach (or some combination thereof), has an associated control strategy.

A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));
- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g., release testing).

Control Strategy (ICH Q11)

A control strategy can be developed through a combination of approaches, utilising the traditional approach for some CQAs, steps, or unit operations, and a more enhanced approach for others.

In a **traditional approach** to developing a manufacturing process and control strategy, set points and operating ranges are typically set narrowly based on the observed data to ensure consistency of manufacture. More emphasis is placed on assessment of CQAs at the stage of the drug substance (i.e., end-product testing). **The traditional approach provides limited flexibility in the operating ranges to address variability (e.g., in raw materials).**

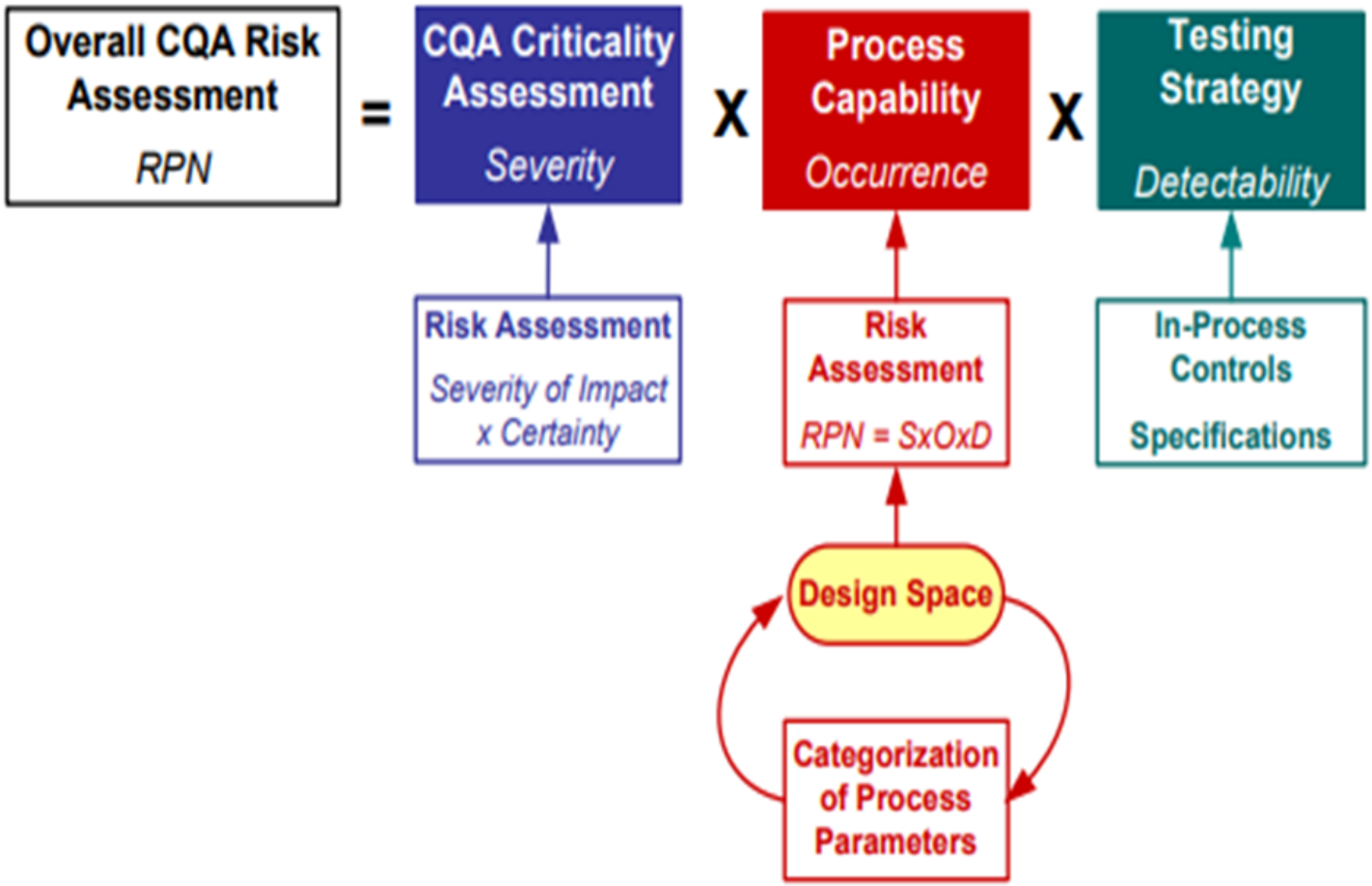
An **enhanced approach** to manufacturing process development generates better process and product understanding than the traditional approach, so sources of variability can be identified in a more systematic way. This allows for the development of more meaningful and efficient parametric, attribute, and procedural controls. The control strategy might be developed through several iterations as the level of process understanding increases during the product lifecycle. A control strategy based ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities) on an enhanced approach can provide for **flexibility in the operating ranges for process parameters to address variability (e.g., in raw materials).**

Control Strategy- AMAb Case study

1) The Severity (S) of failure corresponds to the Criticality Level of the CQA which was determined based on the impact to safety and efficacy and the certainty of the knowledge used to establish that impact. A detailed description of the criticality assessment is presented in Section 2 (Design of Molecule and Quality Attributes Assessment). The Criticality Level used for this FMEA was based on the assessment done using Tool #1 and summarized in Table 2.4.
2) The probability of Occurrence (O) or frequency of failure was determined based on process capability analysis to assess the risk that a CQA could exceed its acceptable limits. A description of capability assessment is presented in Section 6.2 (Process Capability).
3) The probability of Detection (D) of failure is based on the proposed testing strategy which includes in-process controls and end-product testing (specifications).

This risk based approach can be used in an iterative fashion to design the overall control strategy.

Control Strategy- AMAb Case study



https://cdn.ymaws.com/www.casss.org/resource/resmgr/imported/A-Mab_case_study_Version_2-1.pdf

Control Strategy- AMAb Case study

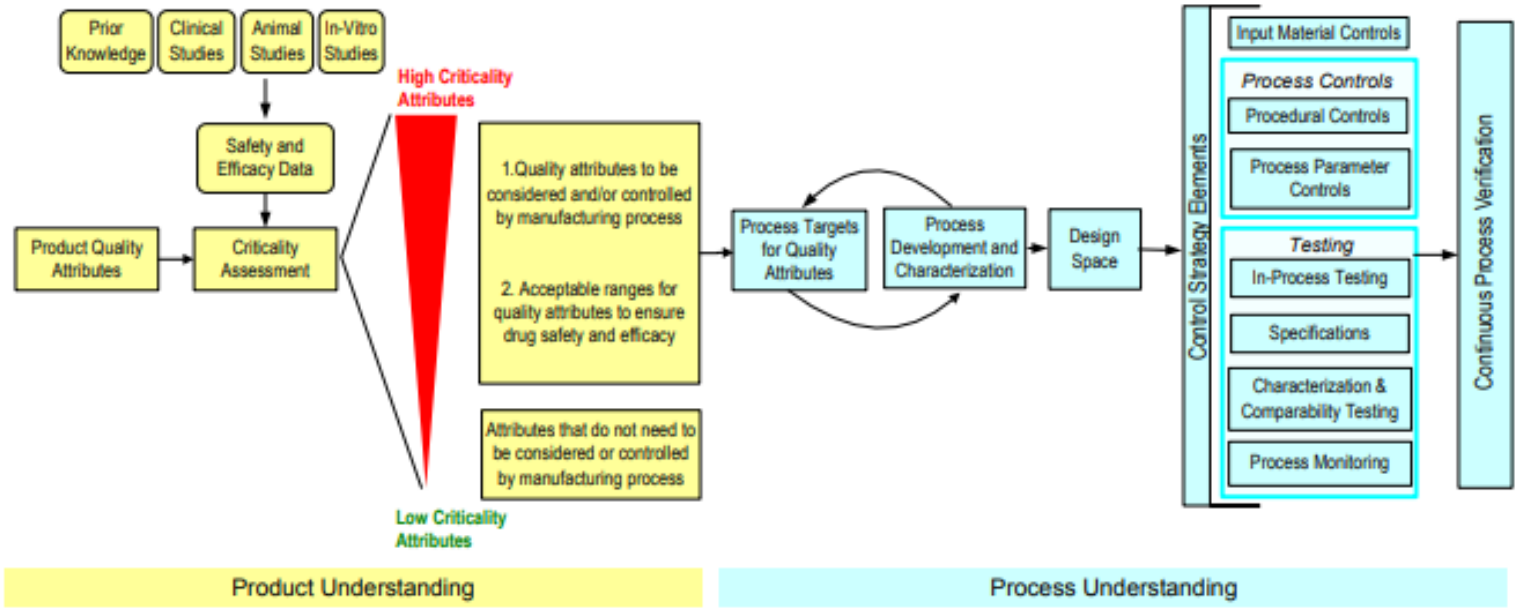


Figure 6.5 The control strategy is based on a rational approach that links process understanding to product quality requirements (product understanding)

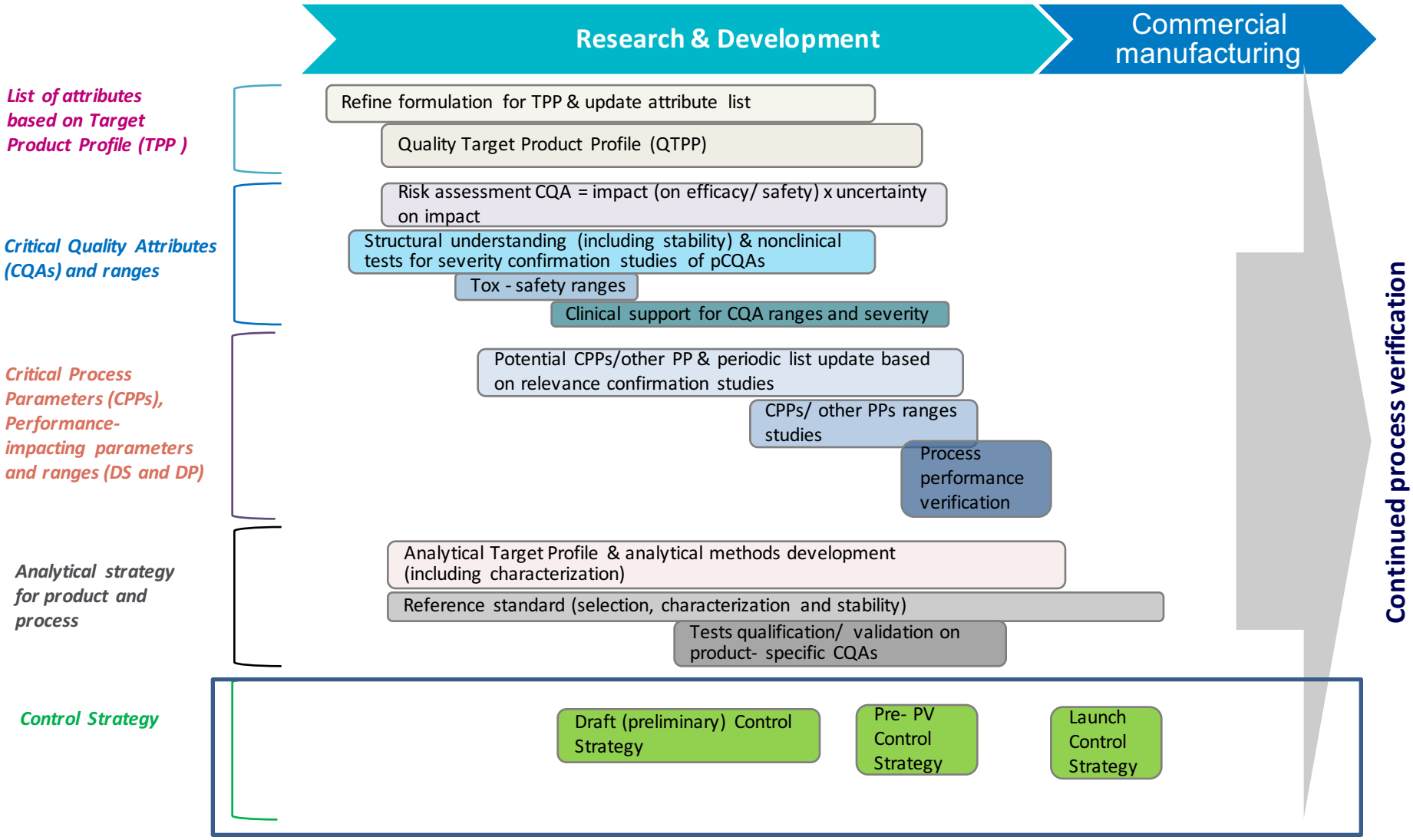
Control Strategy- AMAb Case study

Table 6.4 Control Strategy Elements for A-Mab

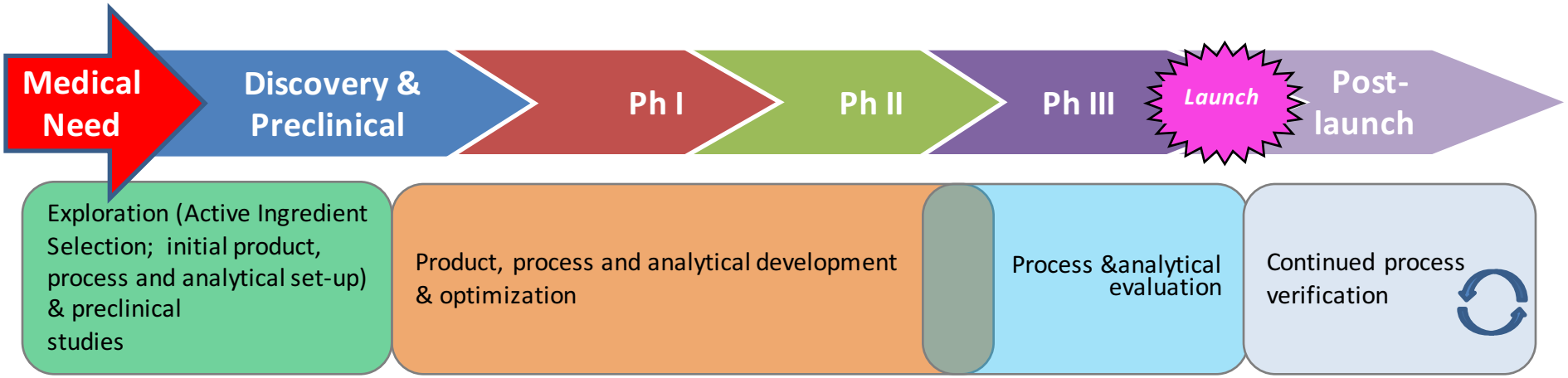
Control Element	Description
Input Material Controls	These are controls pertaining to raw materials, excipients, components etc. used in manufacturing operations, including supplier quality management, raw material qualification and raw material specifications. The case study does not address risk assessment or control strategy supporting input material controls.
Process Control Elements	
Procedural Controls	A comprehensive set of facility, equipment and quality system controls which result in robust and reproducible operations supporting the production of product of the appropriate quality. These controls are supported by a quality risk management system.
Process Parameter Controls	Process parameters that are linked to Critical Quality Attributes (CQAs) and include Critical Process Parameters (CPPs) or Well Controlled Critical Process Parameters (WC-CPPs) that must be controlled within the limits of the design space to ensure product quality. Process parameters linked to process performance (KPPs and GPPs) that must be controlled to ensure process consistency.
Testing Control Elements	
In-process Testing	Measurements typically conducted using analytical test methods or functionality tests to ensure that selected manufacturing operations are performing satisfactorily to achieve the intended product quality. In-process tests include acceptance criteria.
Specification (Lot Release Testing)	Tests with associated acceptance criteria conducted at final lot release on a set of quality attributes to confirm quality of drug substance for forward processing and drug product for distribution. Certain attributes will also be monitored as part of the stability program.
Characterization and/or Comparability Testing	Testing of certain attributes outside of lot release testing for the purposes of intermittent process monitoring or demonstration of comparability. A specific testing plan would be developed based on risk to product quality.
Process Monitoring	Testing or evaluation of selected attributes and/or parameters to trend product quality or process performance within the design space and/or to enhance confidence in an attribute's normal distribution. The frequency of monitoring is periodically reviewed and adjusted based on trends. The process monitoring program may include limits for evaluating data trends.

Knowledge refinement

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



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

Quality by Design (QbD)

Change in regulatory expectations

"Quality by Control" & strict compliance

"Quality by Design" - science & risk based development

Some references

- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ICH Q11: Development and Manufacture of Drug Substances (chemical entities and biotechnological/ biological entities)
- FDA Guidance for Industry Process Validation: General Principles and Practices (2011)

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Quality by control & strict compliance

- Relatively fast development with reduced costs
- Clinical trials with few lots, with similar quality characteristics

- Quality criteria based on manufactured lots results, analytical methods and stability, not on demonstrated impact on efficacy/ safety
- Specification attributes choice mainly based on current knowledge on similar products
- Impact of process parameters on product quality is not systematically investigated; ranges boundaries are not explored

Quality by control & strict compliance

Issues

- High number of variations after product registration
- Risk of recalls due to poor product knowledge
- Risk to waste good lots due to the limited information on specifications boundaries
- Risk of submission delays requested
- Regulatory agencies questioning product and process controls applied to ensure lot- to- lot consistency and to fulfill stringent specification limits

Quality by Design (QbD)

"Quality by Design" - science & risk based development

"….quality cannot be tested into products; i.e. quality should be built in by design"

- Quality by design means:
  - Designing and developing products and processes during the development stage to **consistently ensure a predefined quality** at the end of the manufacturing process*…
    - Product and process understanding
    - Process control
    - Quality risk management
  - Applying the principles of QbD to enhance the quality of science and engineering in product and process development

* as described in ICH Q8, Q9, Q10, Q11; FDA guidance on process validation (2011), PDA &ISPE technical docs....

Quality by Design

Change in regulatory expectations

From ICH Q8 (R2), Appendix 1. Differing Approaches to Pharmaceutical Development

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

Argomenti	Letture consigliate (oltre agli appunti delle lezioni)
Impurezze prodotti biologici	• http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf
Quality by Design, aspetti generali	• ICH Q8 (R2), Part II e Appendix 1 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf
Product Understanding, Quality Target Product Profile e Critical Quality Attributes	• ICH Q8 (R2), Part II http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf • A-VAX case study, Capitolo 2 (CQA) www.ispe.org/2013-biotech-conference/a-vax-applying-qbd-to-vaccines.pdf oppure https://www.slideshare.net/shivang47/qbd-model-case-study-of-vaccine-avax
Stability per prodotti biologici	ICH Q 5C http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf https://admin.ich.org/sites/default/files/inline-files/ASEAN_Intro_ICH_GCG.pdf
Preformulazione e formulazione	• ICH Q8 (R2), Part I, sezione 2.2 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

Argomenti	Letture consigliate (oltre agli appunti delle lezioni)
Process Understanding e Critical Process Parameters	• ICH Q8 (R2), Part II http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf • A-VAX case study, Capitolo 7 (sezione 7.4, matrice Causa- effetto); Capitolo 6 (sezioni 6.4 e 6.5, Risk Rank and Filtering e FMEA, rispettivamente) www.ispe.org/2013-biotech-conference/a-vax-applying-qbd-to-vaccines.pdf
Process Understanding e Critical Process Parameters (inclusa discussione ranges e definizione Design Space)	• ICH Q8 (R2), Part II http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf • A-VAX case study, Capitolo 6 (sezione 6.5, FMEA) www.ispe.org/2013-biotech-conference/a-vax-applying-qbd-to-vaccines.pdf • ICH Q9, Annex I (risk assessment tools citati in A-VAX, v sopra) https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf • Practical considerations on multivariate studies http://www.bioprocessintl.com/wp-content/uploads/bpi-content/BPI_A_100806AR03_O_98037a.pdf

Argomenti	Letture consigliate (oltre agli appunti delle lezioni)
Analytical strategy guidata dal QbD	• USP Stimuli articles (appendici escluse) su Analytical Target Profile e Analytical Control Strategy ○ https://www.researchgate.net/publication/308467600_Analytical_target_profile_Structure_and_application_throughout_the_analytical_lifecycle ○ https://www.researchgate.net/publication/308478035_Analytical_control_strategy ○ http://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/s201784.pdf • ICH Q6B http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf

Argomenti	Letture consigliate (oltre agli appunti delle lezioni)
Product Understanding e specifiche di prodotto	• ICH Q6B, Capitoli 1-3 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf • Nota: su impurezze, v anche slides lezione 20 marzo
Reference Standard strategy	• ICH Q6B, sezione 2.2 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf
Comparabilità	• ICH Q5E http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

Argomenti	Letture consigliate (oltre agli appunti delle lezioni)
Control Strategy	• ICH Q8 (R2) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf • ICH Q10 (Glossary) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf • A-Mab Case Study (sezioni 6.1, 6.3, 6.6.1) http://c.ymcdn.com/sites/www.casss.org/resource/resmgr/imported/A-Mab_Case_Study_Version_2-1.pdf

Quality by Design (QbD)

Industry implementation status

Pharmaceutical industry has been implementing QbD principles for years

Example Case Study on Monoclonal Antibody

- **A-Mab**: a Case study in Process development, CMC Biotech Working Group, published by ISPE, version 2.1, Oct. 2009

Vaccine industry only recently is implementing QbD. The first case study in this field was published in May 2012.

Case Study - Carbohydrate/Protein Conjugate Vaccine

- **A-VAX**: Applying Quality by Design Principles to Vaccines, CMC-Vaccines Working Group, placed in the public domain May, 2012, by the PDA

COVID- 19, vaccini

- https://media.nature.com/original/magazine-assets/d41573-020-00073-5/d41573-020-00073-5.pdf

Diversity of technology platforms (eg RNA/DNA, viral vectors, recombinant proteins, VLP …)

"Many of these platforms are not currently the basis for licensed vaccines, but experience in fields such as oncology is encouraging developers to exploit the opportunities that next-generation approaches offer for increased speed of development and manufacture."-

Each category has specific advantages and challenges

> "The novel platforms based on DNA or mRNA offer great flexibility in terms of antigen manipulation and potential for speed
> Vaccines based on viral vectors offer a high level of protein expression and long-term stability, and induce strong immune responses
> Finally, there are already licensed vaccines based on recombinant proteins for other diseases, and so such candidates could take advantage of existing large-scale production capacity."

"For some platforms, adjuvants could enhance immunogenicity and make lower doses viable, thereby enabling vaccination of more people without compromising protection. "

COVID- 19, vaccini

- https://media.nature.com/original/magazine-assets/d41573-020-00073-5/d41573-020-00073-5.pdf

"The approaches being applied for COVID-19 development — which involve a **new virus target** and often **novel vaccine technology platforms** and **novel development paradigms** as well — are likely to increase the risks associated with delivering a licensed vaccine, and will require careful evaluation of effectiveness and safety at each step. In order to assess vaccine efficacy, COVID-19 specific animal models are being developed, …requiring international coordination to ensure that sufficient laboratory capacity is available."

"Many of the lead developers are small and/or inexperienced in large-scale vaccine manufacture. So, it will be important to ensure coordination of vaccine manufacturing and supply capability and capacity to meet demand."

"Strong international coordination and cooperation between vaccine developers, regulators, policymakers, funders, public health bodies and governments will be needed to ensure that promising late-stage vaccine candidates can be manufactured in sufficient quantities and equitably supplied to all affected areas, particularly low-resource regions"

Altre risorse condivise a lezione (per informazione)

TPP COVID-19 vaccines, WHO

https://www.who.int/blueprint/priority-diseases/key-action/WHO_Target_Product_Profiles_for_COVID-19_web.pdf

EMA/ FDA workshop early access approaches

https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough

Altre risorse condivise a lezione (per informazione)

Treatment and Vaccine tracker- COVID
https://milkeninstitute.org/covid-19-tracker

mRNA vaccine platform example
https://www.youtube.com/watch?v=qJlP91xjvsQ&feature=emb_title

Adeno vaccine platform example
https://www.ema.europa.eu/en/documents/presentation/presentation-case-study-3-use-platform-technologies-adenovirus-vectored-vaccines-session-2-mark-van_en.pdf

EMA updates on COVID
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-whats-new