Holistic Control Strategy – from molecular design to combination product

Telling a connected story in a BLA

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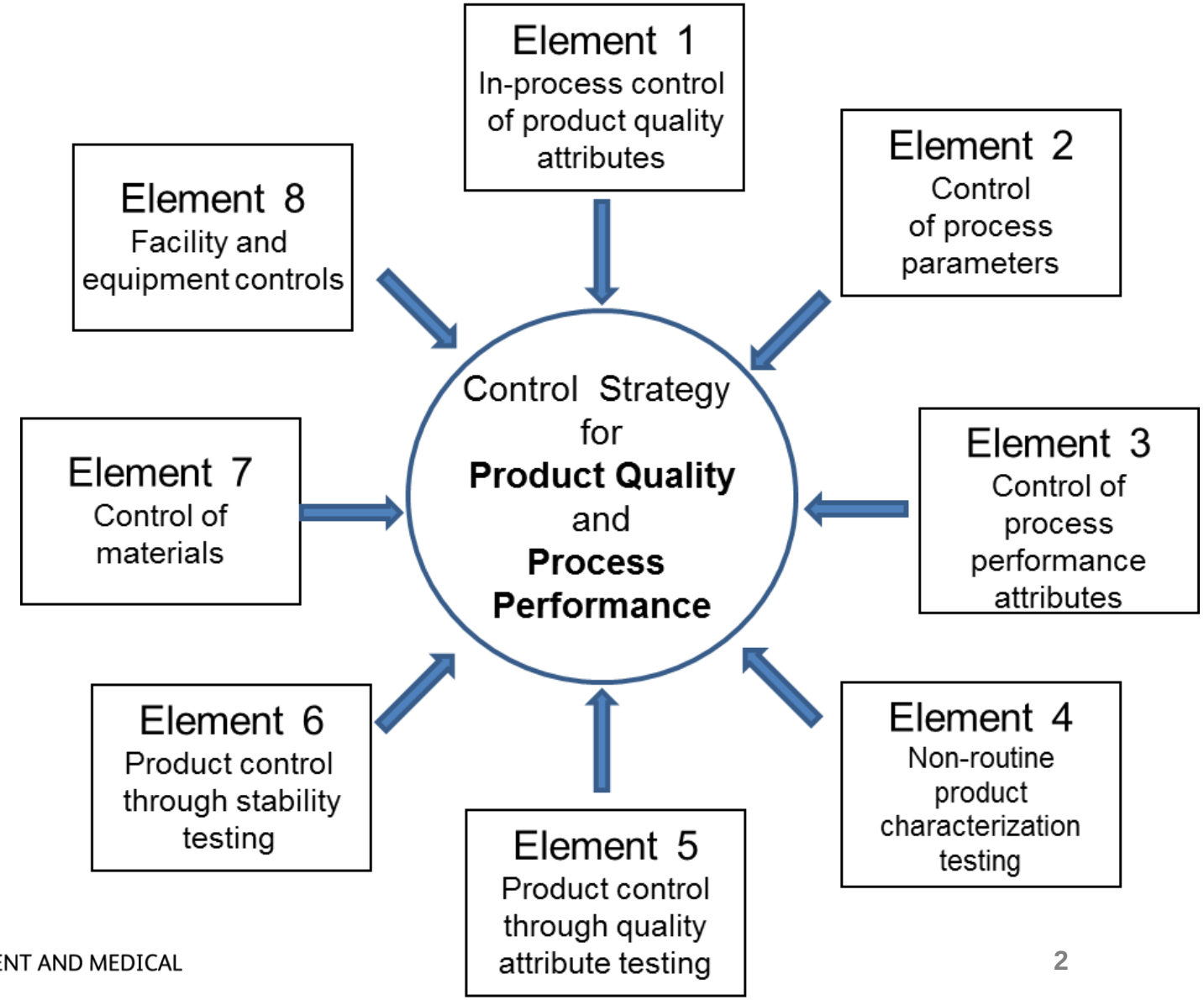
BioTherapeutics Pharmaceutical Sciences
Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

Pfizer's Control Strategy Framework – Elements of Control

ICH Q10 definition:

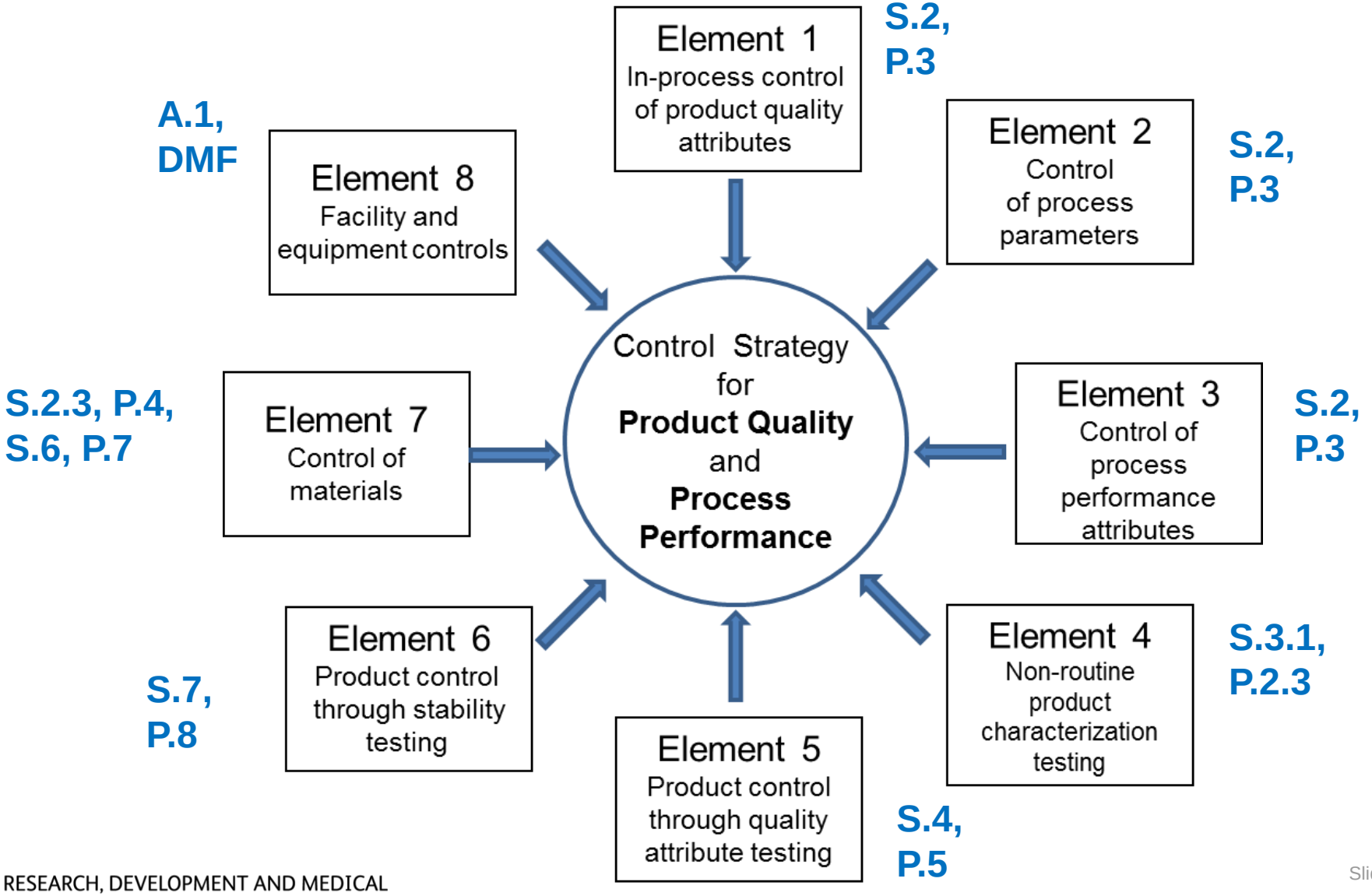
"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include **parameters** and **attributes** related to drug substance and drug product **materials** and **components**, **facility** and **equipment** operating conditions, **in-process** controls, finished product **specifications**, and the associated **methods** and frequency of **monitoring and control**."



Molecular Design – Intrinsic properties imparted by sequence

Adapted from: Control Strategy Approach for a Well-Characterized Vaccine Drug Product, Kolhe et. al, **PDA Journal of Pharmaceutical Science and Technology 2019** https://doi.org/10.5731/pdajpst.2018.009415 https://journal.pda.org/content/pdajpst/early/2019/09/13/pdajpst.2018.009415.full.pdf

Map to Module 3



Example 1: Oxidation related variants

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Quality attribute	Risk[3]	Origin	Control Strategy
Identity	Identity	Efficacy, Safety	Intrinsic to the Molecule	(b) (4)
Bioactivity/ Potency	Potency by Binding[4]	Bioactivity, Efficacy, Safety	Intrinsic to the Molecule	
Charge-Related Variants: Basic Variants	(b) (4)	Reduced bioactivity.	Manufacturing process, storage	
Oxidation-Related Variants	?Met or Trp in CDR?	Reduced bioactivity.	Manufacturing process	
	?Met in Fc?	Potential impact to PK.		

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761121Orig1s000ChemR.pdf
Polivy chemistry review, www.fda.gov

Control strategy for oxidation related variants

- molecular design (susceptible residues in sequence)
  - understanding of impact to target binding if in CDR, is it relevant to mechanism of action?
  - Impact to pharmacokinetics? (safety / immunogenicity, patient “harm”)
  - Can susceptible sites be engineered out in the first place?
- Process control of cell culture conditions (temp, time, redox maybe)
- Process controls in purification?
  - (unlikely to be separable, but maybe stainless steel exposure matters)
- is there an analytical method to apply to DS release?
  - Control as “material attribute” at DS level as input to DP process
- can we formulate (anti-oxidant) to mitigate?
- controls around vapor H_2O_2 for isolator decontamination?
- Ozone – E-beam or high voltage leak detection generated?
- control of light exposure through manufacturing steps, pen assembly, final packaging
- labeling statements about light exposure for end-user

Theoretical!

Control strategy for oxidation related variants

- molecular design (sequence) – probably mostly in 3.2.S.3.1
  - understanding of impact to target binding if in CDR, is it relevant to mechanism of action?
  - Impact to pharmacokinetics? (safety / immunogenicity, patient “harm”)
  - Can it be engineered out in the first place?
- Process control of cell culture conditions (temp, time, redox maybe) – 3.2.S.2.6, maybe 3.2.S.2.5
- Process controls in purification? 3.2.S.2.6, maybe 3.2.S.2.5
  - (unlikely to be separable, but maybe stainless steel exposure matters)
- is there an analytical method to apply to DS release? – 3.2.S.4
  - Control as “material attribute” at DS level as input to DP process
- can we formulate (anti-oxidant) to mitigate? – 3.2.P.2.2
- controls around vapor H_2O_2 for isolator decontamination? – (maybe not discussed)
- Ozone – E-beam or high voltage leak detection generated? – 3.2.P.2.3
- control of light exposure through manufacturing steps, pen assembly, final packaging – 3.2.P.2.3
- labeling statements about light exposure for end-user – multiple possibilities

Eg. Light exposure / impact on oxidation

- S.3.1 – forced degradation light exposure
- S.6 – photostability of DS
- P.2.2, P.2.3 – photoexposure studies in formulation development, manufacturing process development, automated visual inspection
- P.2.4 – photoexposure in packaging development
- P.2.6, P.8 – light exposure during dose administration (compatibility) testing (end user)
- P.3.5 – manufacturing process validation with hold times, visual inspection parameters
- P.5 – routine test methods
- P.7 – container closure, eg. amber vials
- P.8 – photostability of DP +/- packaging

- Which residues oxidize when exposed to light?
  - What “kind” of light?
  - Are we using concurrent accelerated temperatures?
- Is there an impact to potency, pharmacokinetics, or safety/immunogenicity?
- Do we have analytical tools to monitor oxidation? (of protein, never mind excipients)
  - Routine release or stability limits needed?
- What light exposure can we routinely expect in “real life”?
  - Manufacturing process
  - Storage
  - End-user

How do we connect all these together, to show process / product understanding, to present an assessment of risk that is relevant to the “real world”, and to defend a proposed control strategy as appropriate?

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Oxidation-Related Variants		Reduced bioactivity.	Manufacturing process	?
		Potential impact to PK.		

What is the best way to succinctly communicate all this in one cell of a table?

Should we make this a map that simply points at the relevant sections, or is a text based summary better?

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761121Orig1s000ChemR.pdf
Polivy chemistry review, www.fda.gov

Example 2: combination product QAs

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy
Extractable volume DP	Accurate dosing	Fill volume was identified as CPP that is controlled within pre-established limits to ensure accurate dosing. (b) (4) [redacted]	(b) (4) [redacted]
Break-out force, gliding force	Accurate dosing		

Pre-filled syringe only, have one P section.

If autoinjector, often have an additional P section specific to AI.

Complicates where / how to describe combination product aspects holistically.

→ Structure of dossier impacts story telling.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761105Orig1s000ChemR.pdf
Skyrizi chemistry review, www.fda.gov

Control Strategy for Glide (Extrusion) Force

- Understanding requirements – how much force is too much?
  - User population
  - Autoinjector design – spring force / electromechanically driven
- Viscosity
  - Molecular design – intrinsic property of molecule
  - Concentration of protein/API
  - Formulation excipients
- Syringe (cartridge) – control of components
  - Needle inner diameter
  - Plunger / barrel lubrication
  - (back pressure relevant to in vivo injection)
- Test methods –
  - speed relevant to time (duration of injection)
  - Variability, reporting of results
- Design Verification
  - Reliability
  - Confidence in assessment
- Stability
- Process Validation
- Routine Controls

Control Strategy for Glide (Extrusion) Force

Understanding requirements – how much force is too much? – P.2 Intro - QTPP

- User population – P.2.4
- Autoinjector design – spring force / electromechanically driven – P.2.4

- Viscosity
  - Molecular design – intrinsic property of molecule - ??
  - Concentration of protein/API – P.2.2
  - Formulation excipients – P.2.2
- Syringe (cartridge) – control of components
  - Needle inner diameter – P.2.4, P.7
  - Plunger / barrel lubrication – maybe P.2.4
  - (back pressure relevant to in vivo injection) - ??

- Test methods –
  - speed relevant to time (duration of injection) – P.2.4, P.5
  - Variability, reporting of results – P.2.4, P.5

- Design Verification
  - Reliability – P.2.4
  - Confidence in assessment – P.2.4

- Stability – P.2.4, P.8
- Process Validation – P.3.5
- Routine Controls – P.3, P.5

EU draft guideline: https://www.ema.europa.eu/en/quality-requirements-drug-device-combinations

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Break-out force, gliding force	Accurate dosing		?

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In Conclusion

- Control Strategies for specific Quality Attributes often encompass several different elements.
- The narrative of the control strategy is largely spread out across many sections in Module 3.
- Is a comprehensive QOS the “right” place to bring the holistic story together? How can we summarize succinctly into a table without losing the connectivity of the holistic narrative?
  - (for discussion! ☺)

Thank you!!
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