Breakthroughs that change patients' lives

Control Strategy as a Critical Aspect of Manufacturing Innovation

Opportunities and Challenges on the Path to Implementation

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Opportunities for Innovation

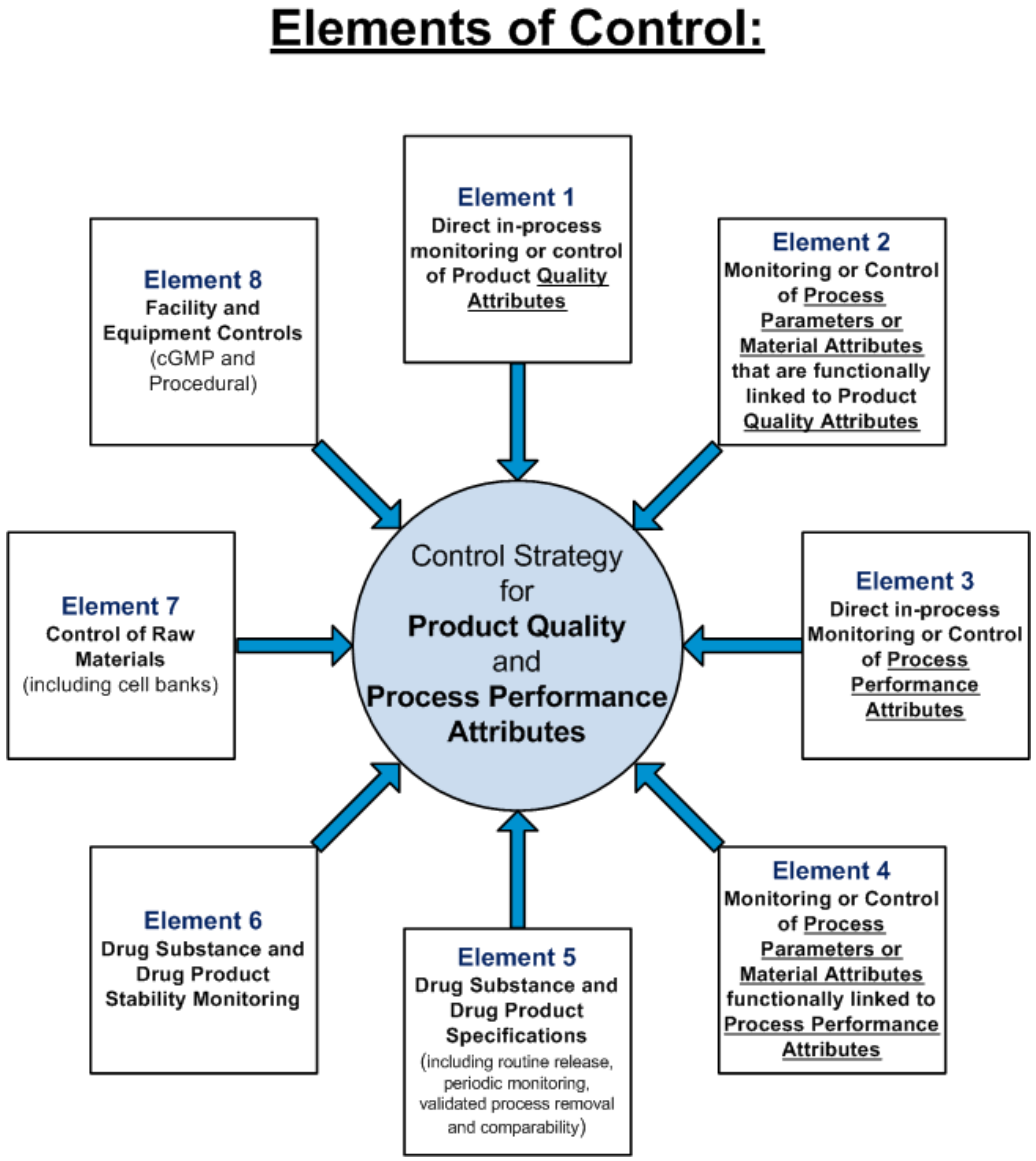
- Advances in biology, engineering, automation, and manufacturing technology
  - Potential to improve quality assurance, supply assurance, productivity, access, etc…
- Ongoing shift to value vs. volume based business models
- Increased focus in oncology segments and rare diseases
- Adaptive trial designs and expedited regulatory pathways in select areas

Innovation Drivers

Process Enabling Technologies	• R&D Productivity - driven by clinical costs • Acceleration - Development as critical path • Efficient, reduced cost commercial processes • Manufacturing flexibility; facility utilization
Product Enabling Technologies	• Market access, regionalization • Customer convenience (devices, storage, shipping) • Novel modalities • Connectivity; diagnostics
Putting the Patient First	• Well-defined QTPP, and Patient Centric Specifications • Control strategy that focuses on product quality, but can afford innovation and changes

What is a Control Strategy?

- 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**.”

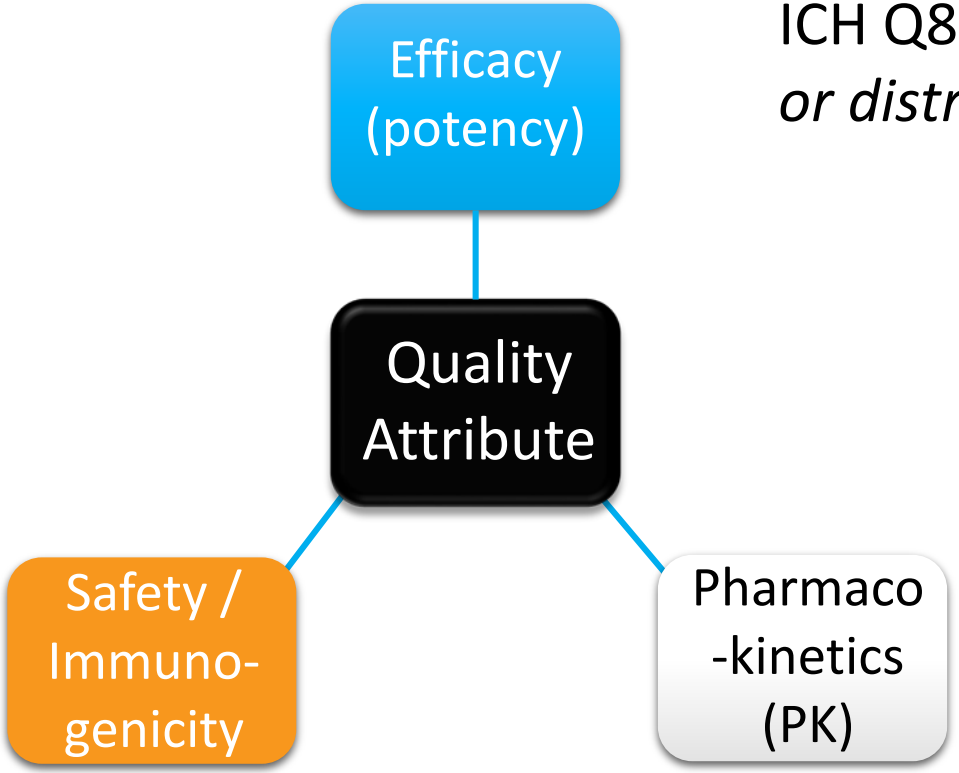


Control Strategy Development

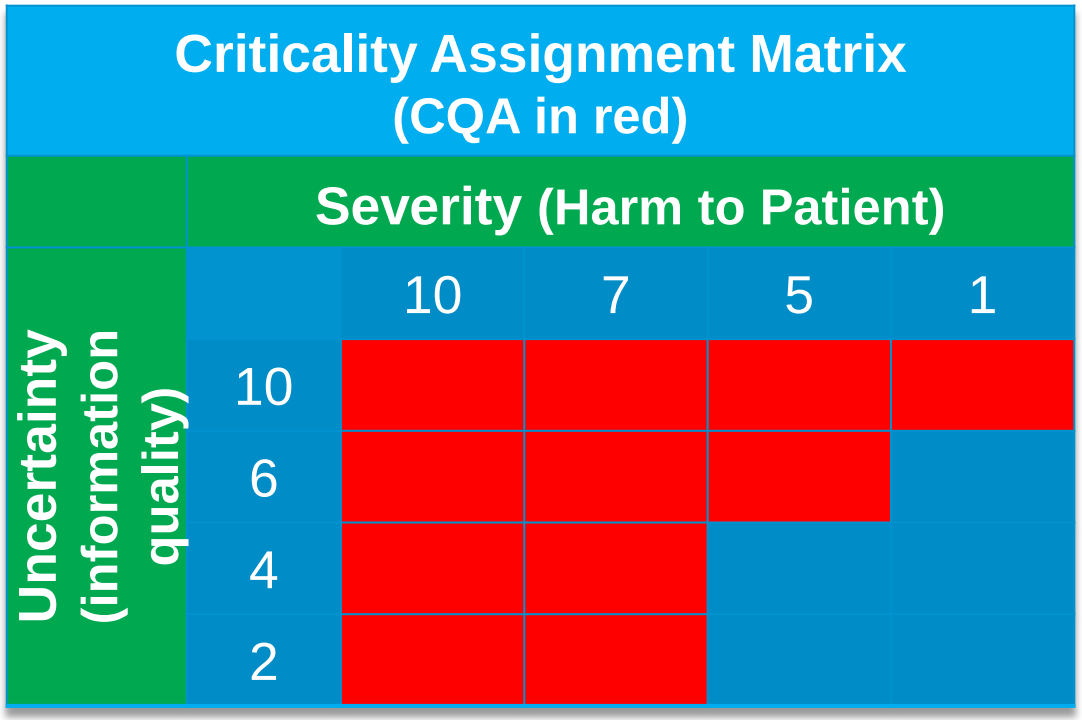
- Starts with molecular design
  - understanding of impact to target binding, is it relevant to mechanism of action?
  - Impact to pharmacokinetics? (safety / immunogenicity, patient “harm”)
  - Can susceptible sites be engineered out in the first place?
- Process control of expression system (temp, time, redox, etc…)
- Process controls in purification?
- Is there an analytical method to apply to release?
- Can we formulate to mitigate liabilities?
- Control through device manufacturing steps, pen assembly, final packaging
- Labeling statements for end-user

Product quality Attributes (PQAs)

Attribute understanding is clinically relevant and is foundational to a good control strategy for biotherapeutic development



ICH Q8R: **CQA**…*should be within an appropriate limit, range or distribution to ensure the desired product quality*



Multiple Control Strategy Elements Impact on quality

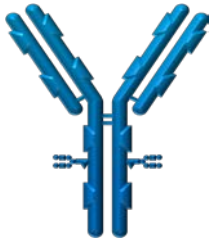
Knowledge of product variants that can impact potency
- Structure-function assessments
- Forced degradation studies

Control of product potency through a combination of process controls and acceptance criteria for physicochemical product quality attributes
- e.g., Purity, post-translational modifications (PTMs)

Confirmation of product potency through release and stability testing
- For drug substance and drug product
- Verification of shelf-life

Visual representation of ICH Q10

Control of quality Through Process Controls



Quality Attribute

PTMs
- N-linked Glycosylation

Purity
- Intact IgG / Fragments

Process Control

- Cell culture process design & parameter control
- Media composition

- Purification process design & parameter control
- Formulation design

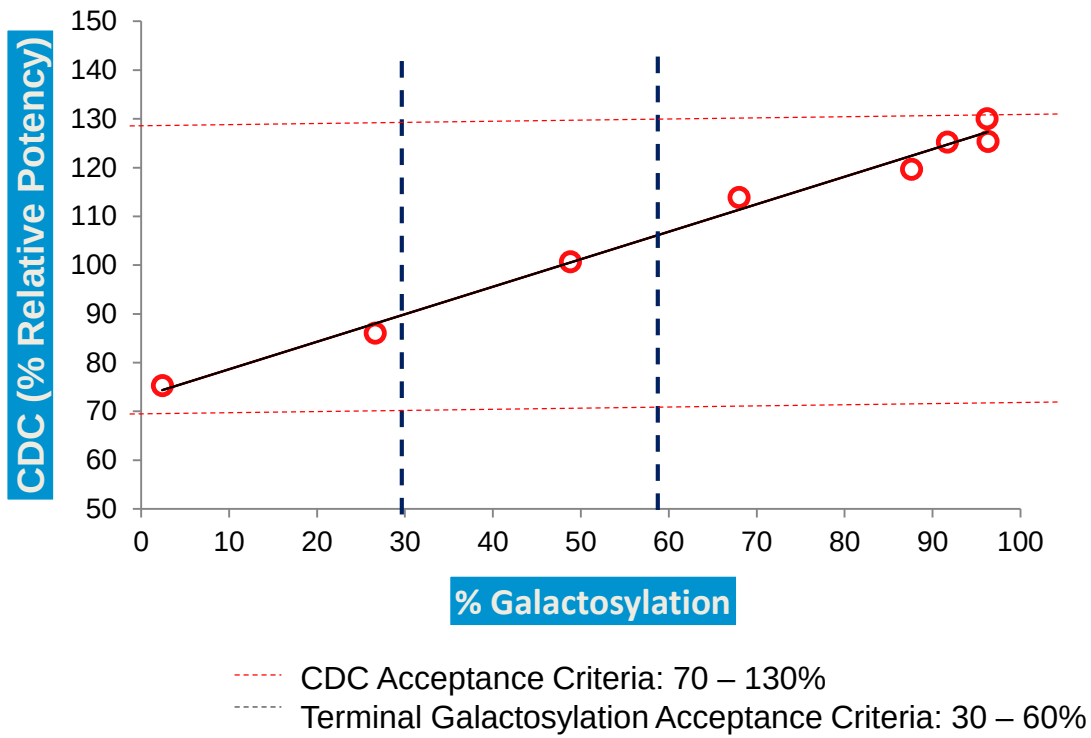
Analytical Control

- N-linked glycan method with acceptance criteria for DS release

- CE method with acceptance criteria for Intact IgG, fragments for DS, DP

Targeted and precise control of product

Structure – Function Relationships: - Cytotoxicity vs. Galactosylation



- Structure function study demonstrates correlation between Fc-galactosylation and CDC activity
- Changes in CDC activity in response to Fc-galactosylation is small

Analytical Control Strategy includes

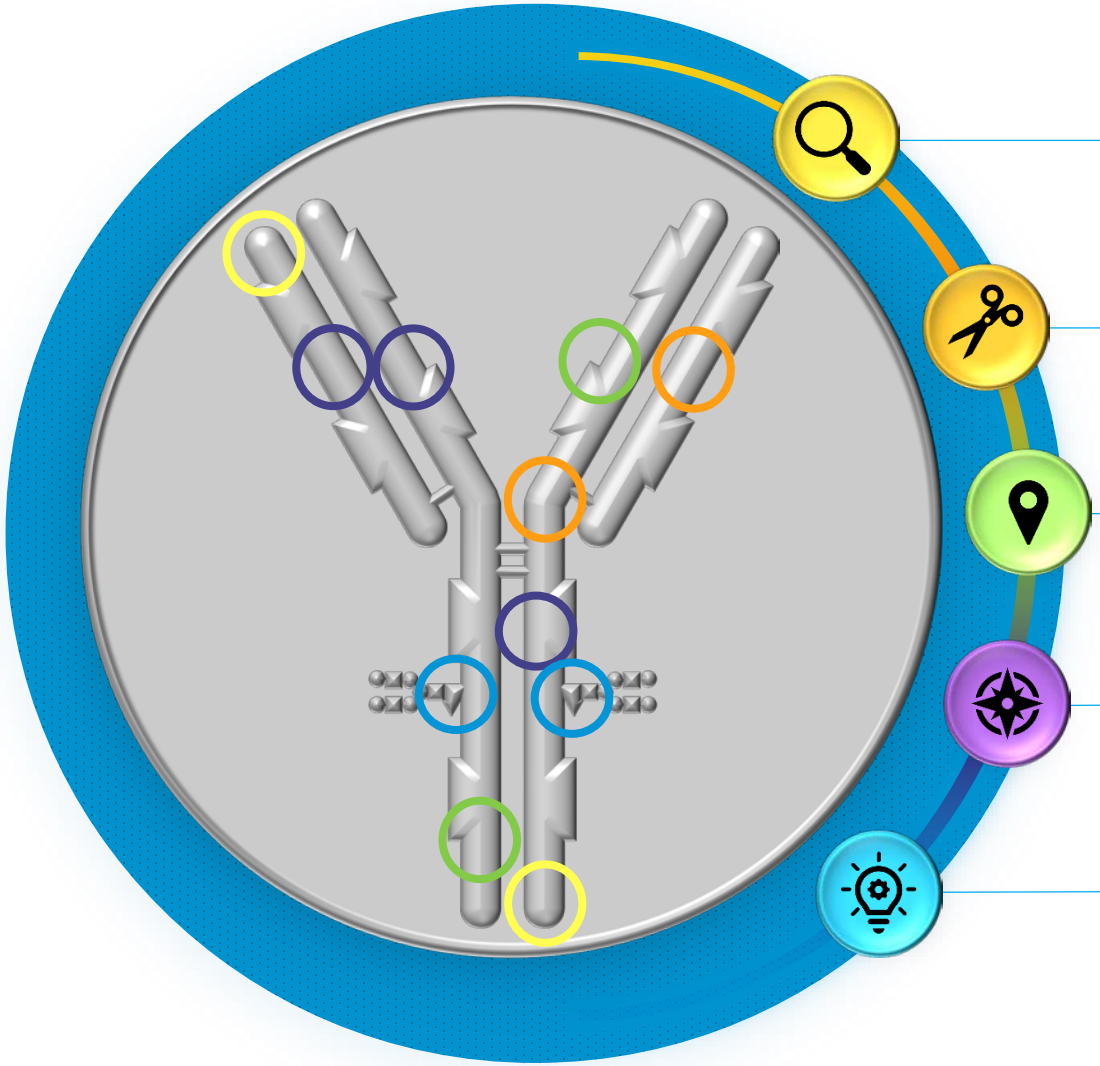
- N-linked glycan method (DS release)
  - Acceptance criteria for terminal galactosylation
- CDC bioassay (DS, DP release, stability)
  - Acceptance for potency

CDC = Complement Dependent Cytotoxicity

Multi-Attribute Method (MAM)

- **A liquid chromatography/mass spectrometry (LC/MS)-based method**
  - Used to analyze multiple product quality attributes - simultaneously
  - Allows for automated monitoring and quantitation of known attributes
  - Detects new peaks (impurity method)
  - Introduced by Amgen (2013)
  - Current state: early and late stage development support: attribute monitoring for stability studies and bioprocess optimization/changes
  - Future state of MAM: QC release and stability

Simultaneous PQA Monitoring Using MAM



Peptide Mapping using Multi-Attribute Method

- Allows monitoring of:
  - Glycosylation
  - Sequence variants/misincorporations
  - Aglycosylation; 2nd/3rd *N*-glycosylation sites
  - *O*-glycosylation
  - All methionine and tryptophan oxidation

MAM is a single mass spectrometry (MS)-based method for simultaneous analysis of multiple PQAs. It allows for monitoring and quantitation of known quality attributes and detection of new peaks.

Analytical Testing in Biotherapeutic Development

- Release and Stability Testing
  - Compendial Testing
  - Content
  - Product-related species
  - Process-related species
  - Potency and efficacy
- Characterization Testing
  - Primary and Higher-Order structure
  - Orthogonal assessments

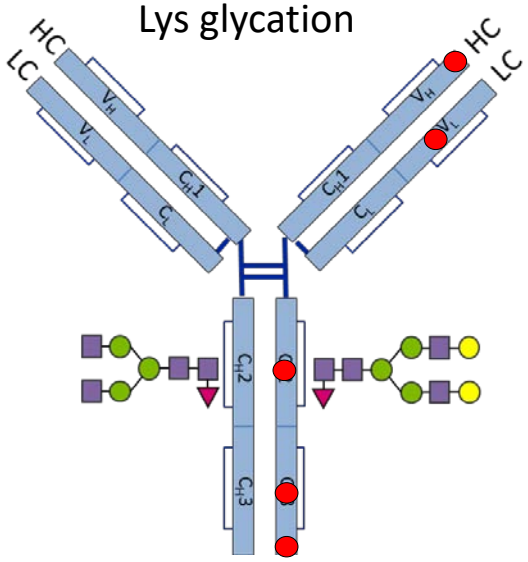
Quality Attribute	Method	DS	DP
Appearance	Compendia	√	√
Moisture, Particles, Osmolality, Reconstitution Time			√
pH		√	√
Protein Concentration	UV	√	√
Charge Isoforms	iCE	√	√
Heavy Chain + Light Chain	CGE (reducing)	√	√
Fragments	CGE (reducing)	√	√
Monomer	CGE (nonreducing)	√	√
High Molecular Mass Species	HPLC SEC	√	√
Peptide Profile / Identity	Peptide Mapping	√	√
Relative Potency	Binding ELISA	√	√
Glycan Fingerprint	HPLC	√	
Endotoxin		√	√
Bioburden (DS),Sterility (DP)		√	√
Impurities (HCP, ProA, DNA)	ELISA, qPCR	√	

Charge Variants: Global to Local

- **iCE provides global charge variant information, but no specific information on identification or location of attributes**

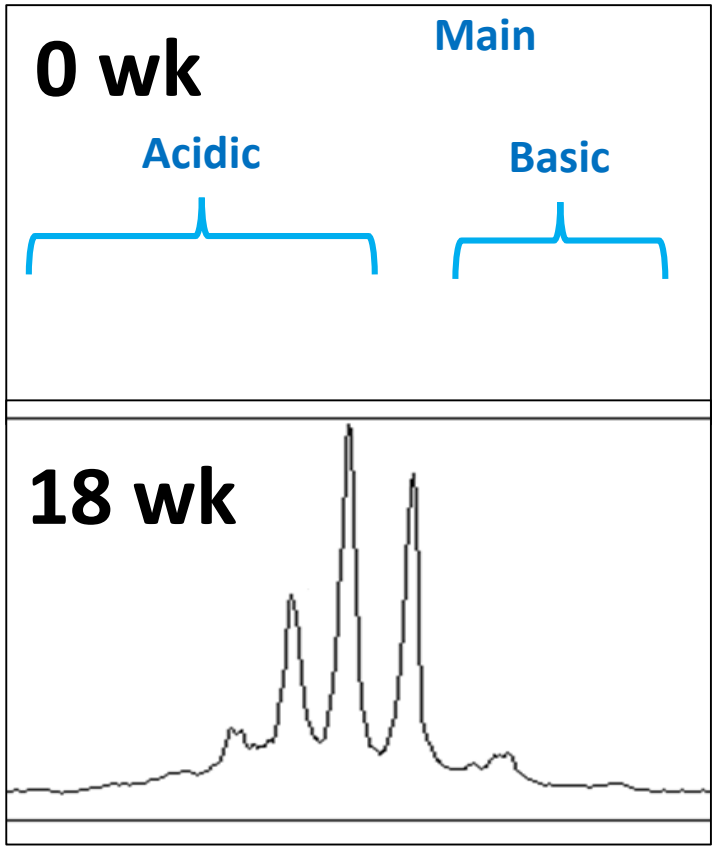
Examples of Charge Variants

Asn deamidation
Sialylated N-Glycans
N-terminal pyro Glu
C-terminal Lys
C-terminal amidated Pro
Lys glycation

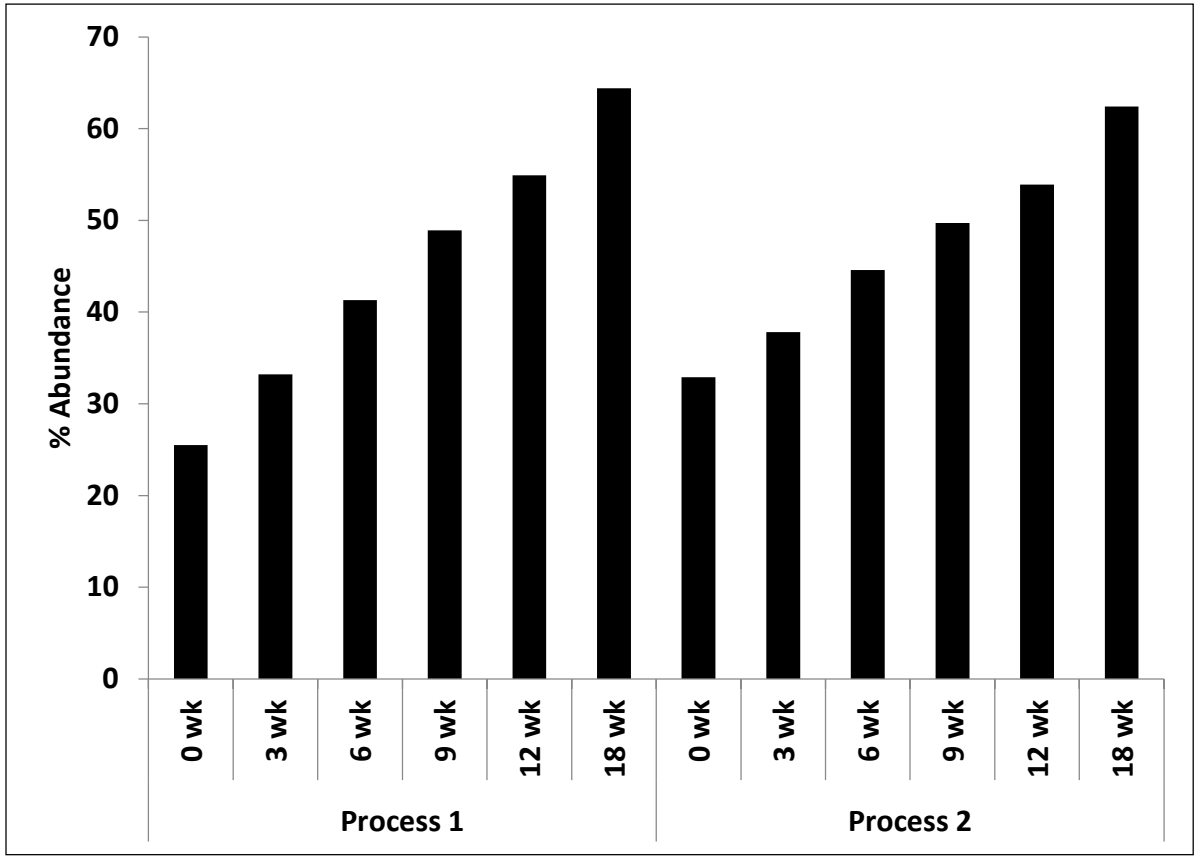


Drug Substance Batches Subjected to 40° C Stress for 18 Weeks

iCE Profile



Acidic Species by iCE



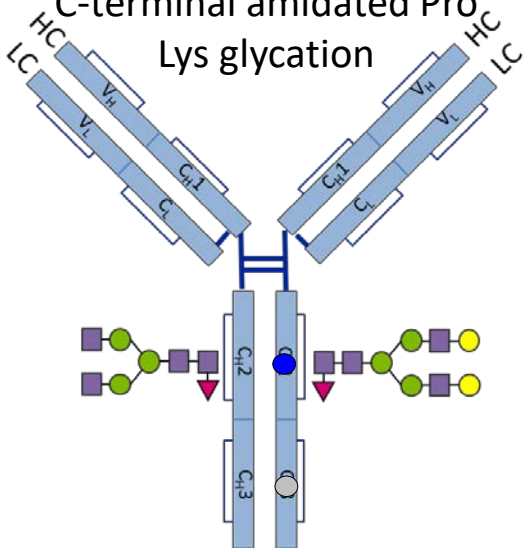
Pfizer | Breakthroughs that change patients' lives

Charge Variants: Global to Local

- **Increase in acidic species by iCE trends with increase observed by MAM**
- **MAM provides ID and site-specificity for each acidic PQA**

Examples of Charge Variants

Asn deamidation
Sialylated N-Glycans
N-terminal pyro Glu
C-terminal Lys
C-terminal amidated Pro
Lys glycation



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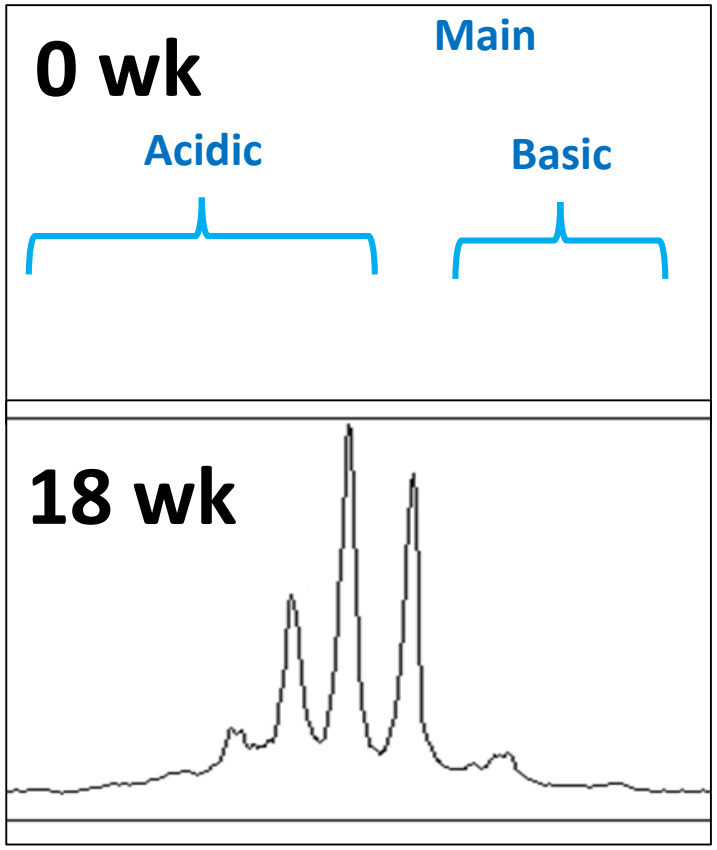
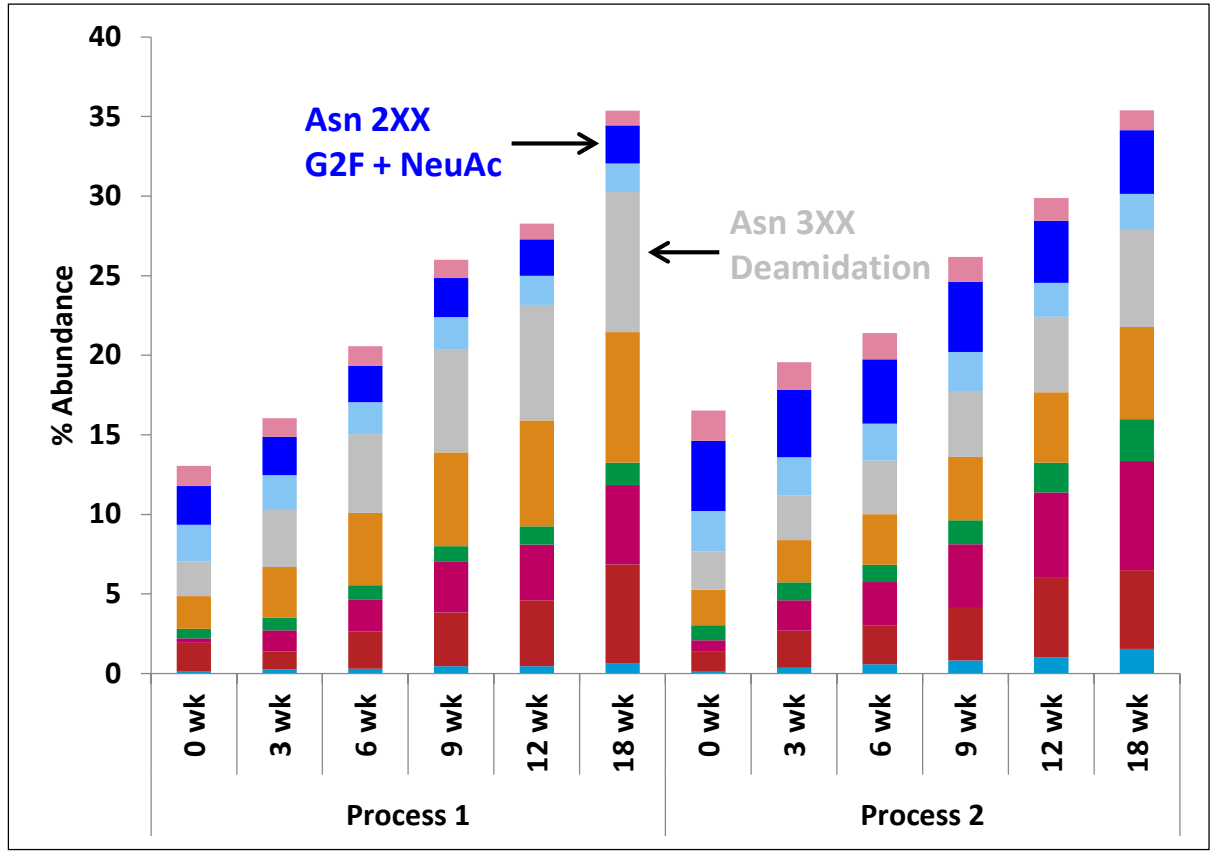


Acidic Species by MAM



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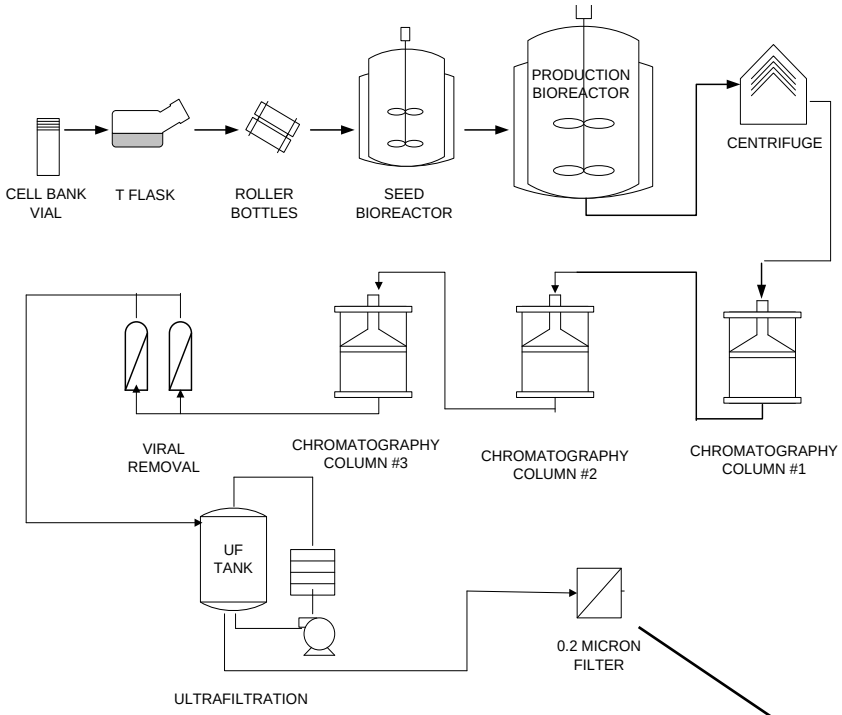
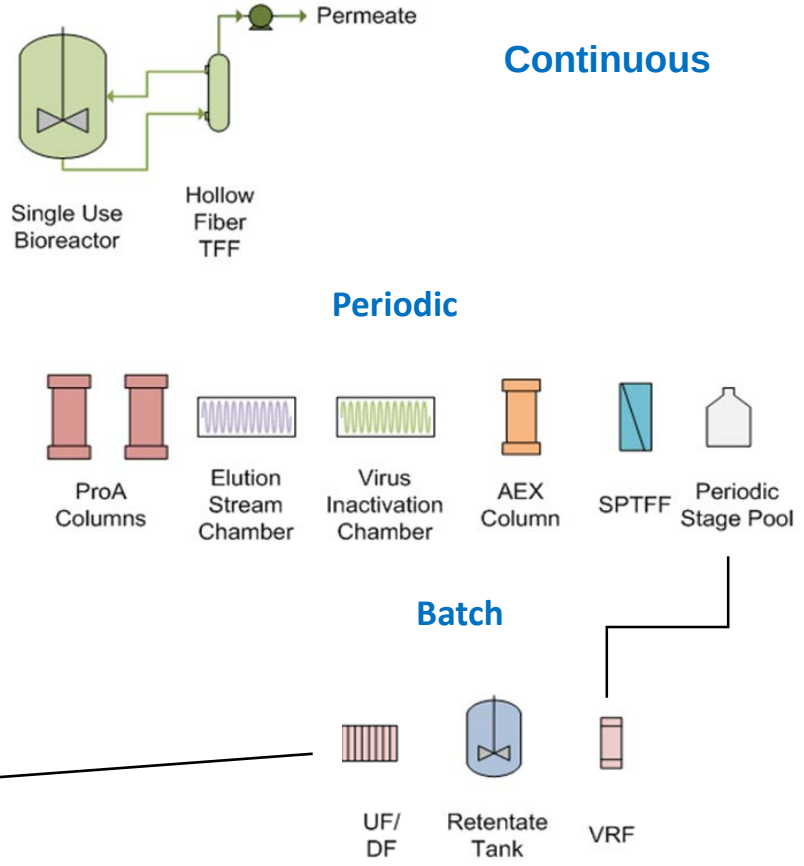
Same Drug Substance: Different Process

Typical Biologics Manufacturing Process:
Discrete Unit Operations

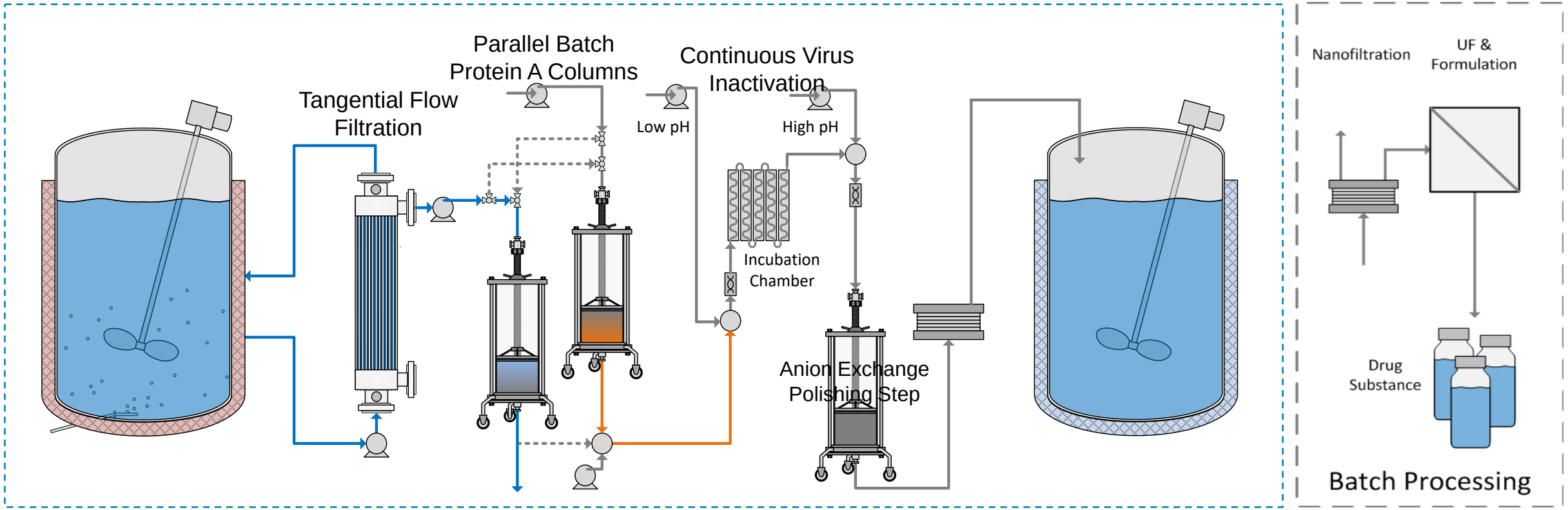


Next Gen Manufacturing Process iSKID):
3-Stage Hybrid System



Same Drug Substance

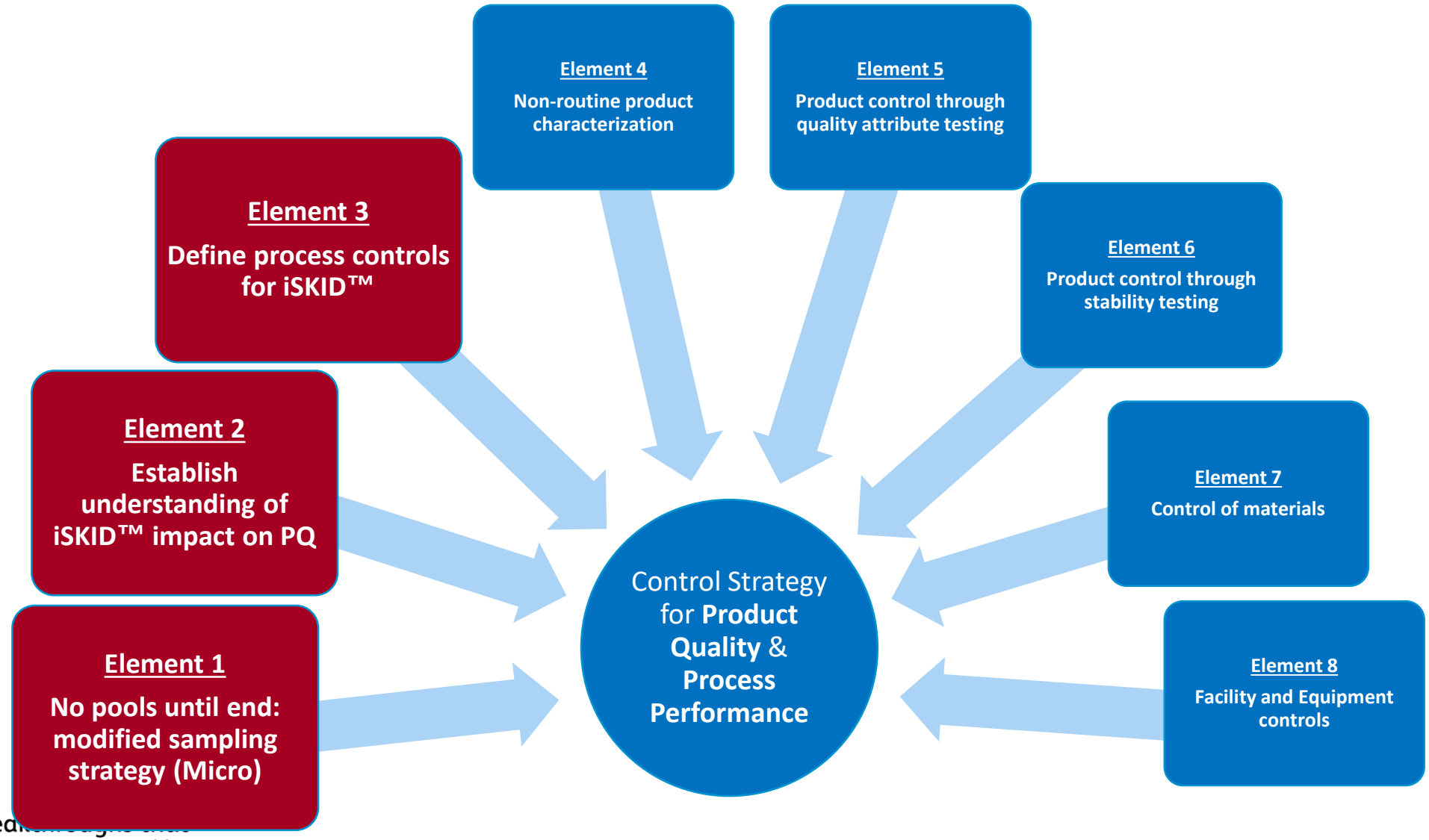
iSKID Manufacturing System



Fully automated and disposable system

- Highly productive short duration perfusion: 2-3 week cadence
- “Simple” downstream design – Continuous, periodic, batch
- Buffer and media concentrates

iSKID Will Require a Modified Control Strategy



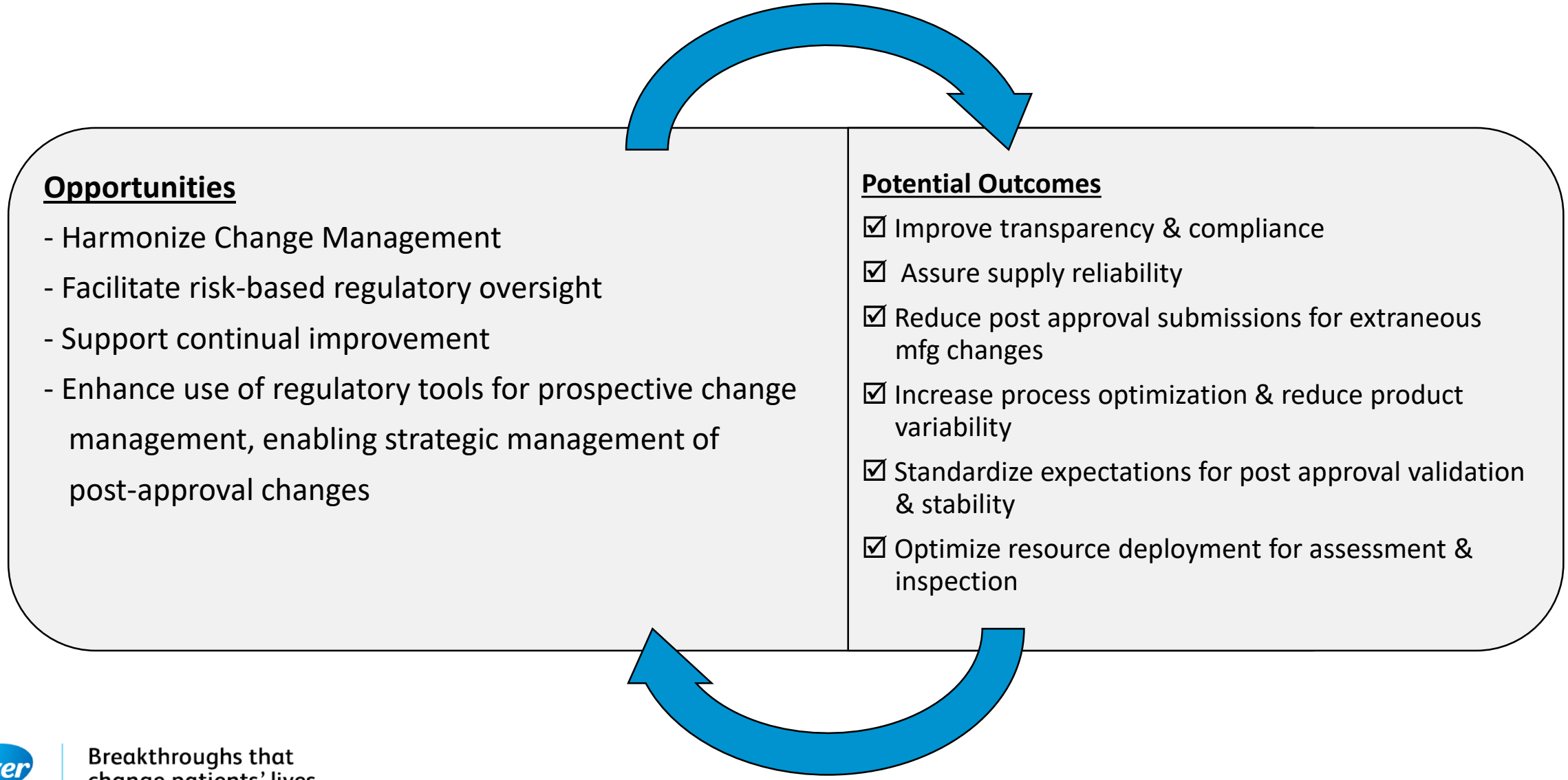
iSKID™ Benefits

- iSKID™ expands development and manufacturing capacity
  - Short duration perfusion: highly productive and efficient
  - Simple downstream process: easy to develop and control
- Appropriate for low volume, high value products
- Scalable to accommodate increase in demand
- Enhanced Cost & Capacity Profile
  - Facility friendly
- Integration and automation facilitates improved operational excellence
- Innovation affords focus on quality and supply demands

Global Harmonization

- ❑ Simultaneous global development and filing
- ❑ Mutual recognition or join review of marketing applications
- ❑ Improved post-approval change implementation
- ❑ Reduced supply chain complexity
- ❑ Reduced drug shortages
- ❑ Reduced administrative costs for industry and BOH
- ❑ Increased patient access to medicines

Regulatory Pathways for Innovation:
- ICH Q12 could be Transformational



Concluding Statements

- Development of a holistic control strategy is the core of development and commercialization of products
- Innovation has made a profound impact on our process and product knowledge, and ability to control product quality
- New analytical, manufacturing, and distribution technical innovations will have a direct impact on patients lives, through increased access and value
- Introducing innovation and technology remains a challenge in a global setting
  - Pfizer develops one control strategy for global submissions. We submit the same set of data for every region.
  - Work through the query process with a goal of achieving global alignment
  - Challenges to any element of a control strategy (even by one country) results in manufacturing to the “lowest common denominator”
- Novel control strategies will be necessary to face the challenges ahead for the industry

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