Regulatory expectations for Real-Time PAT and Continuous Manufacturing

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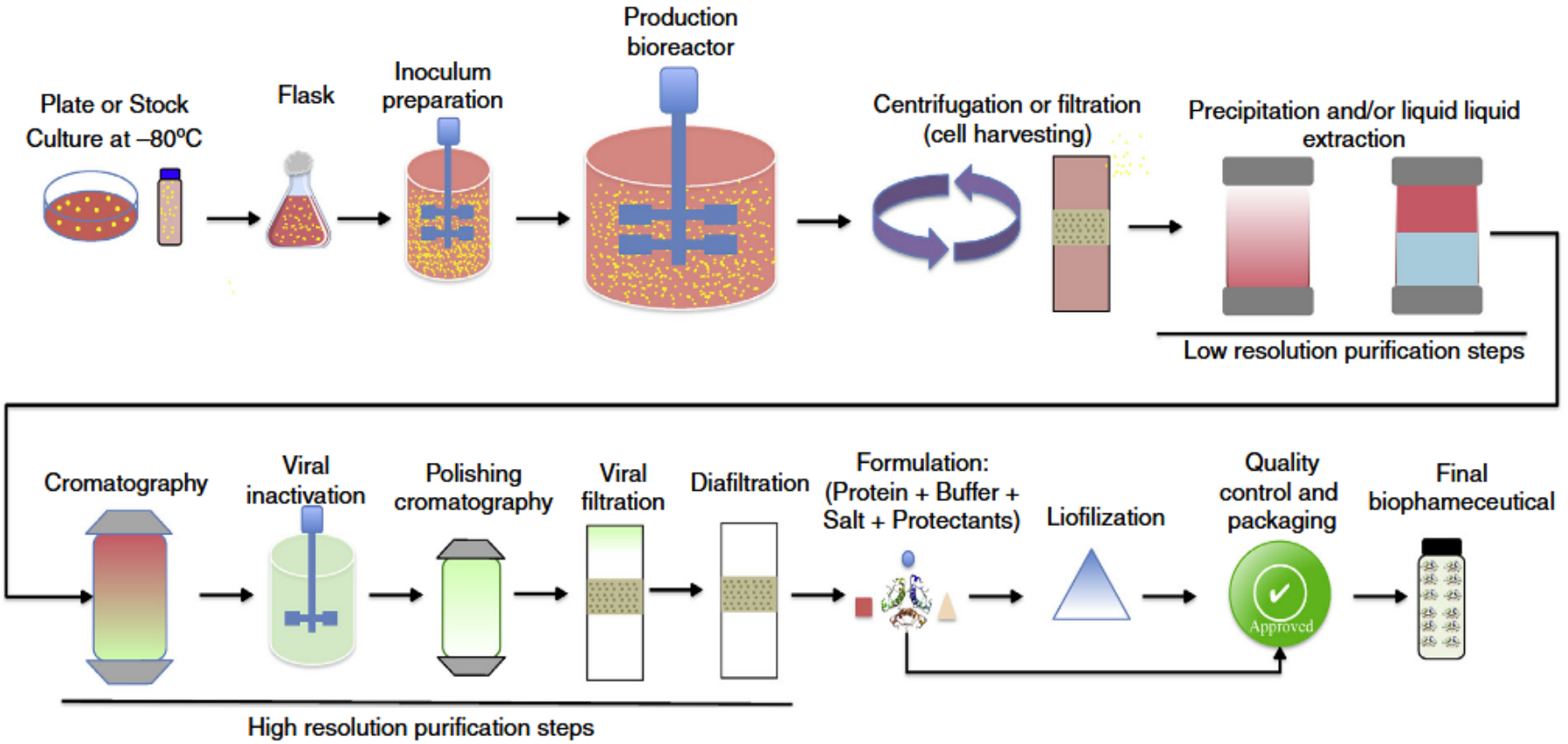
DISCLAIMER: Personal views only: may not necessarily reflect views/opinions of MEB, EMA or EDQM.

Outline

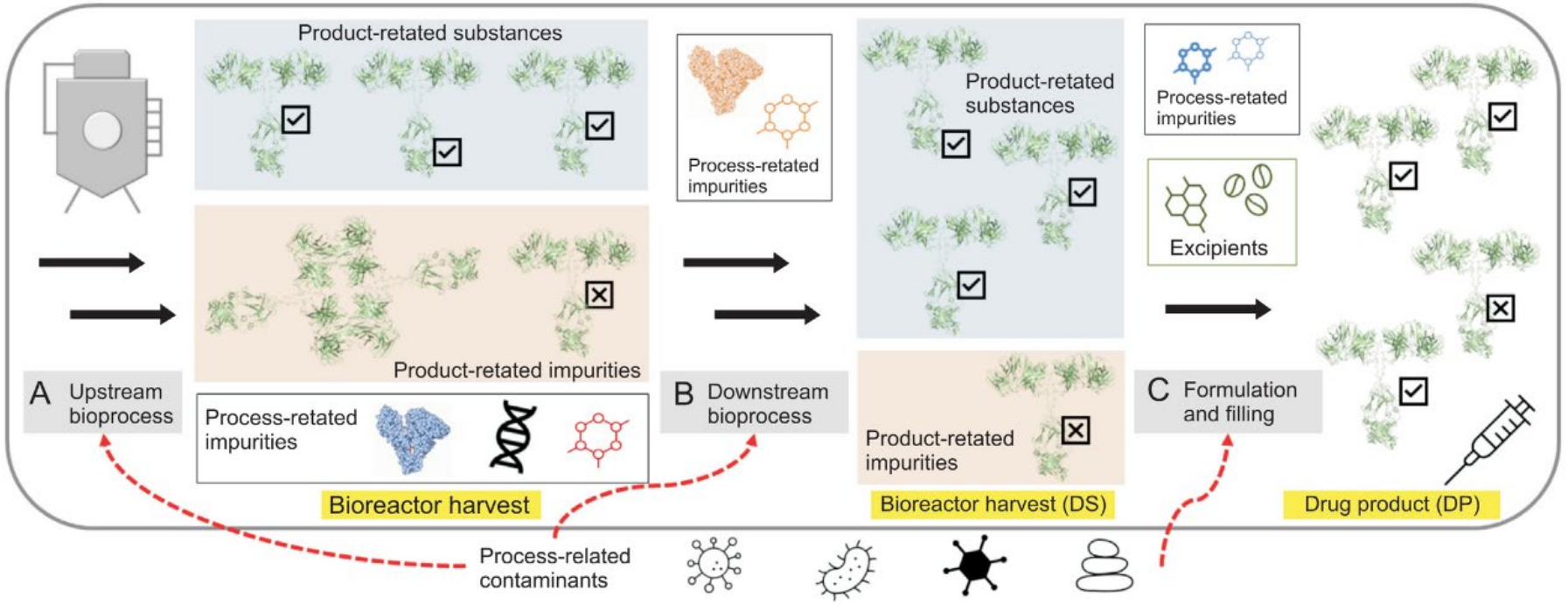
- Process Control & Process understanding (ICH Q8 (QbD), Q9, Q10, Q11)
- PAT in Biopharmaceutical Manufacturing
- Continuous manufacturing & PAT
- Manufacturing models & their validation/verification
- Quality Innovation Group (EMA)
- Take home messages

Biopharmaceutical Manufacturing Process
Process understanding

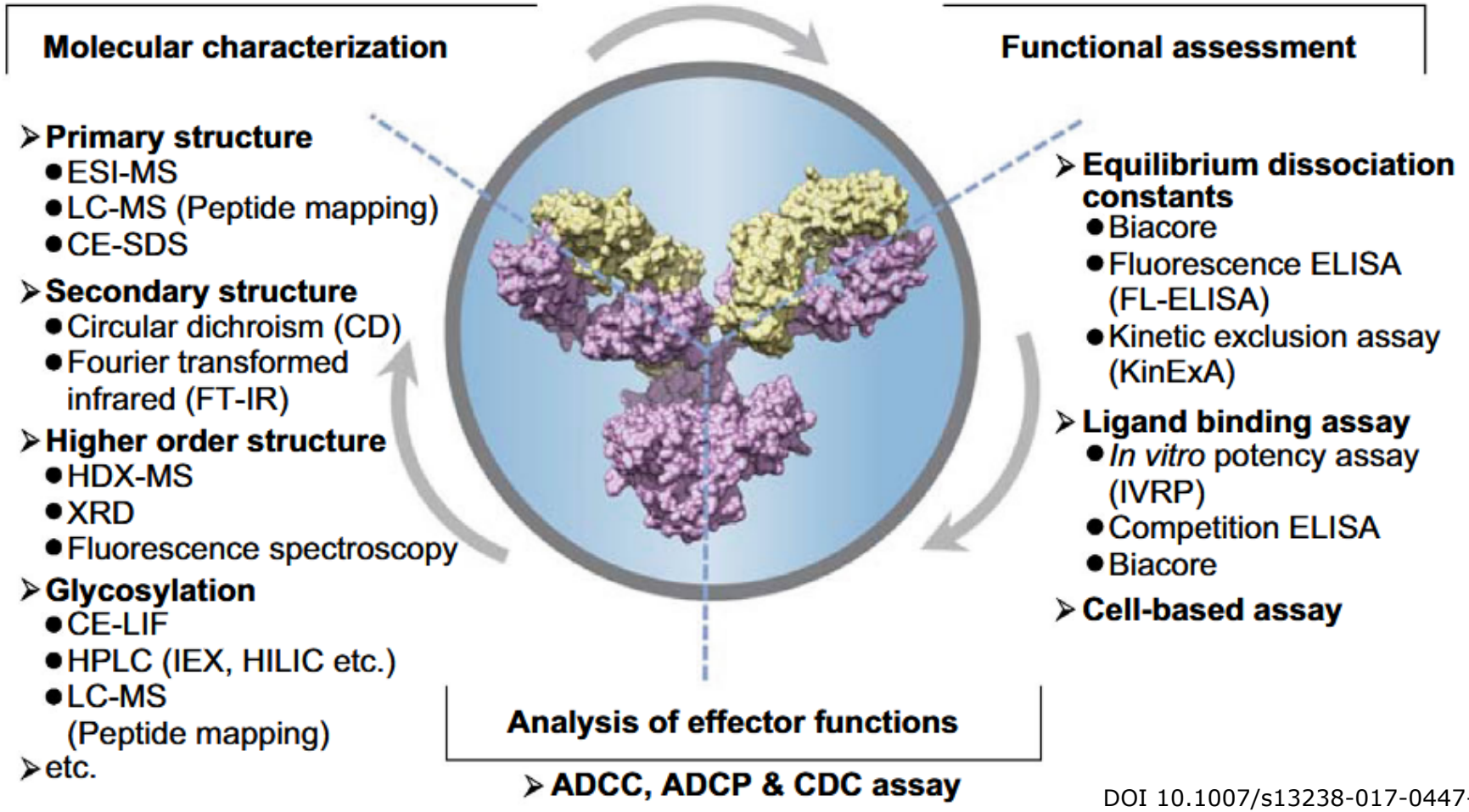


http://dx.doi.org/10.1016/j.bjm.2016.10.007

Characterise Drug Product Critical Quality Attributes

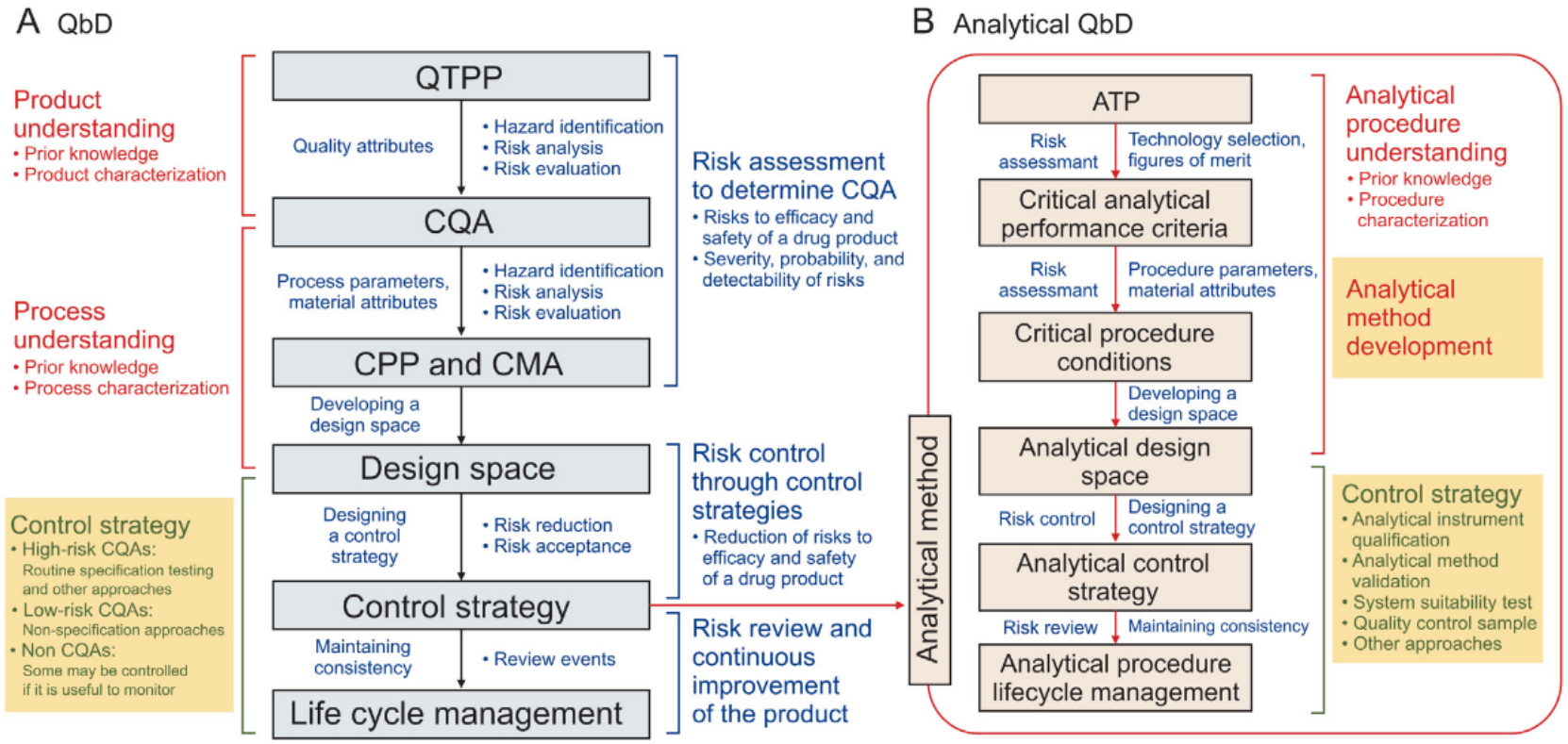


Characterise Drug Substance: Critical Quality Attributes



DOI 10.1007/s13238-017-0447-x

ICH Q8: Quality by Design
Product & Process understanding

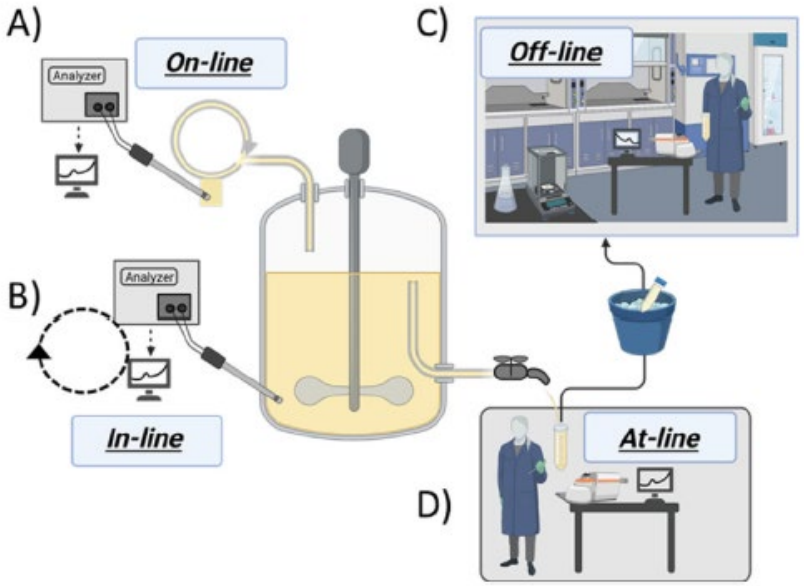


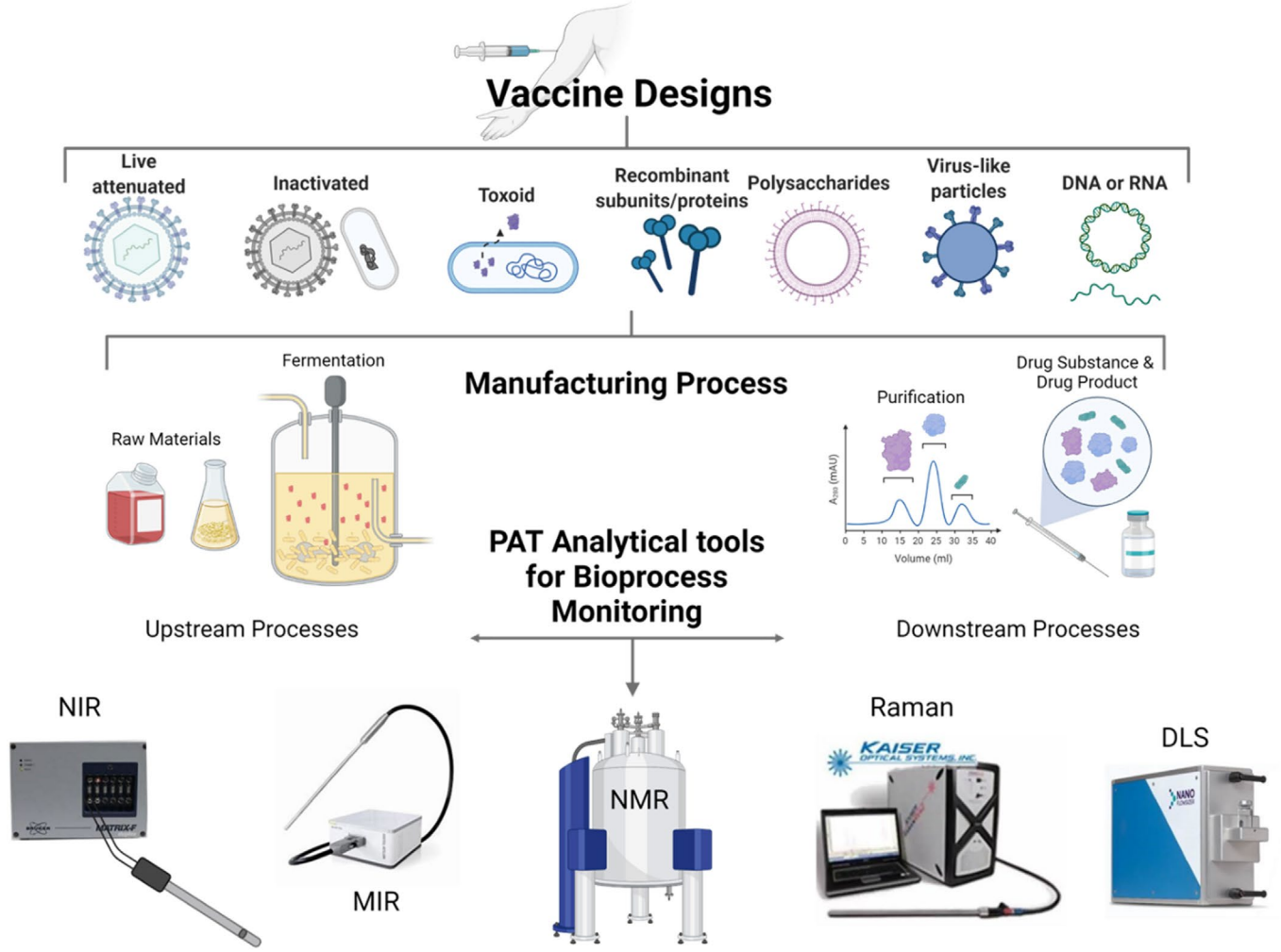
QTPP=Quality Target Product Profile; CQA=Critial Quality Attribute
CPP=Critical Process Parameters; CMA=Critical Material Attribute
ATP= Analytical Target Profile

QbD promise

- risk-based regulatory decisions (reviews and inspections)
- manufacturing process improvements, within approved design space, without regulatory review;
- reduction of post-approval submissions;
- real-time quality control, reduction of end-product release testing.

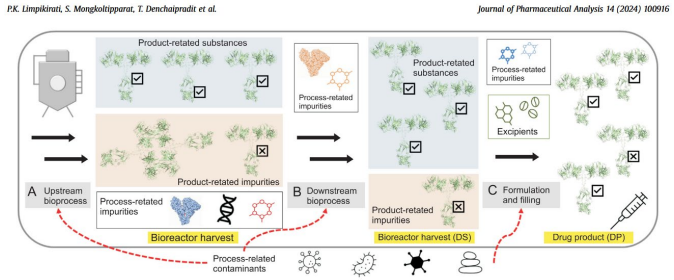
PAT: Real-time (RT) monitoring Process Parameters RT-Release Testing?





Gerzon et al. doi.org/10.1016/j.jpba.2021.114379 0731-7085

PAT: Real-time (RT) monitoring Process Parameters RT-Release Testing?



RAMAN: Monitoring CQA?

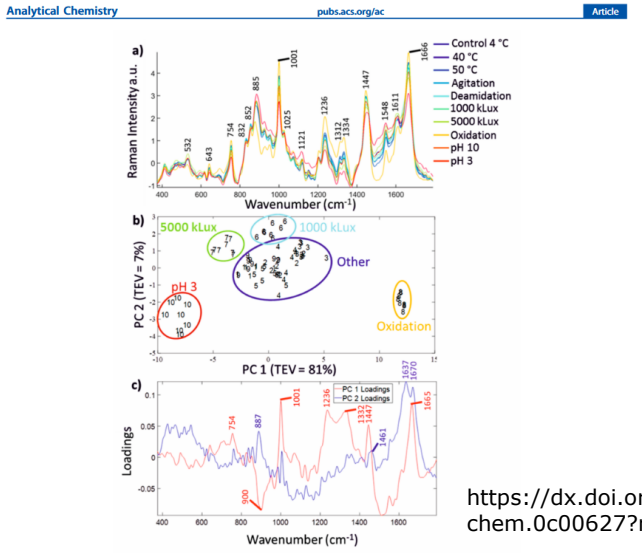
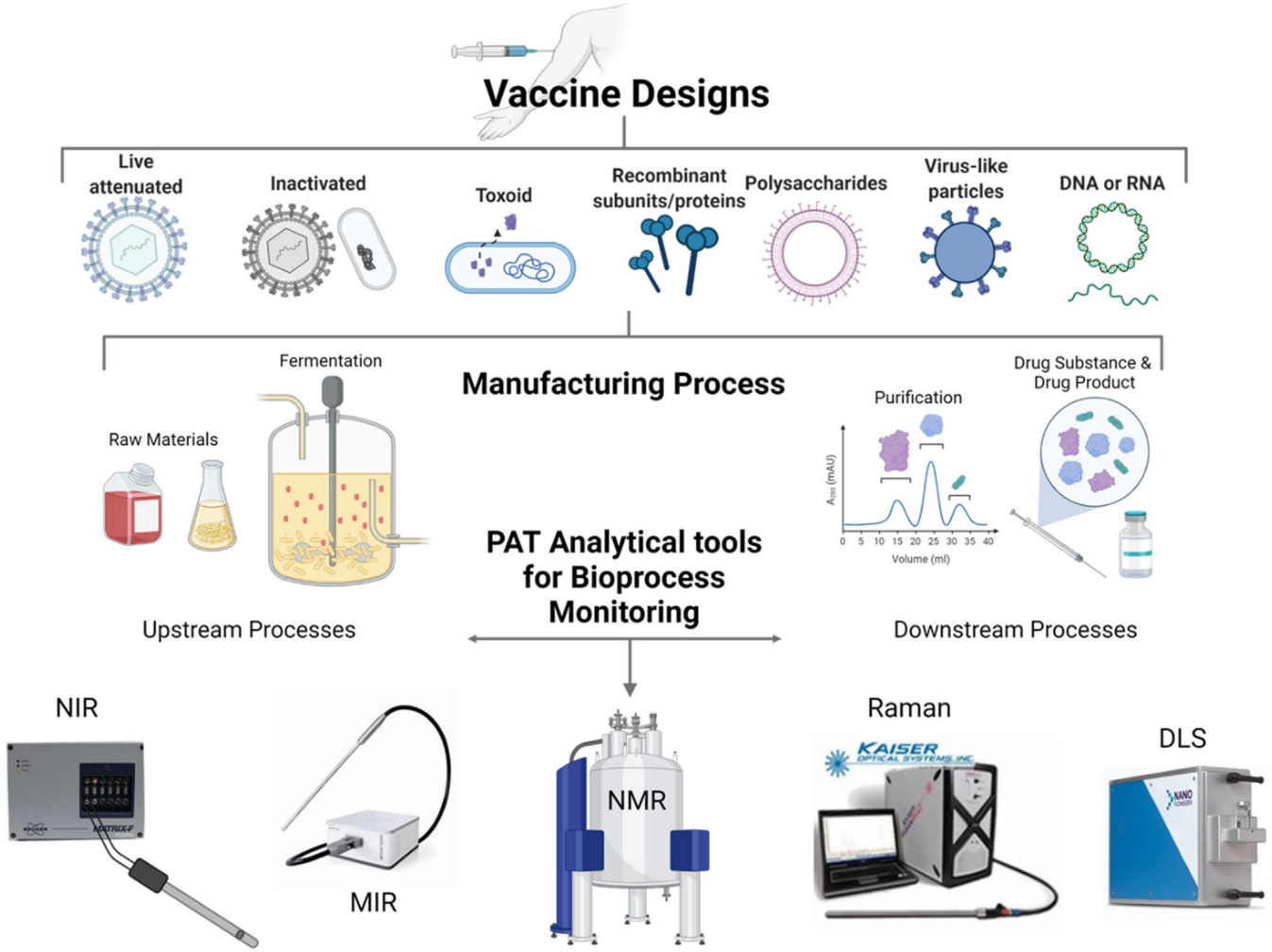


Figure 3. Raman spectra of degraded IgG4 samples with the respective PCA and loading plots. (a) Raman spectra (shown as an average of 8 repeats per condition), (b) PCA (showing 8 replicates individually), and (c) loadings plot showing PC 1 and PC 2. TEV is the total explained variance of each of PCs. (1) Control 4 °C, (2) 40 °C, (3) 50 °C, (4) agitation, (5) deamidation, (6) 1000 kLux·h, (7) 5000 kLux·h, (8) oxidation, (9) pH 10, and (10) pH 3.

https://dx.doi.org/10.1021/acs.analchem.0c00627?ref=pdf

RAMAN: mAb Oxidation/Deamidation



PAT in Biopharmaceutical (Continuous) manufacturing

- NIR /Raman: glucose, ammonium, lactate, glutamate, optical density/ biomass, glycerol, & pH
- Monitor process use models to optimize e.g. yield

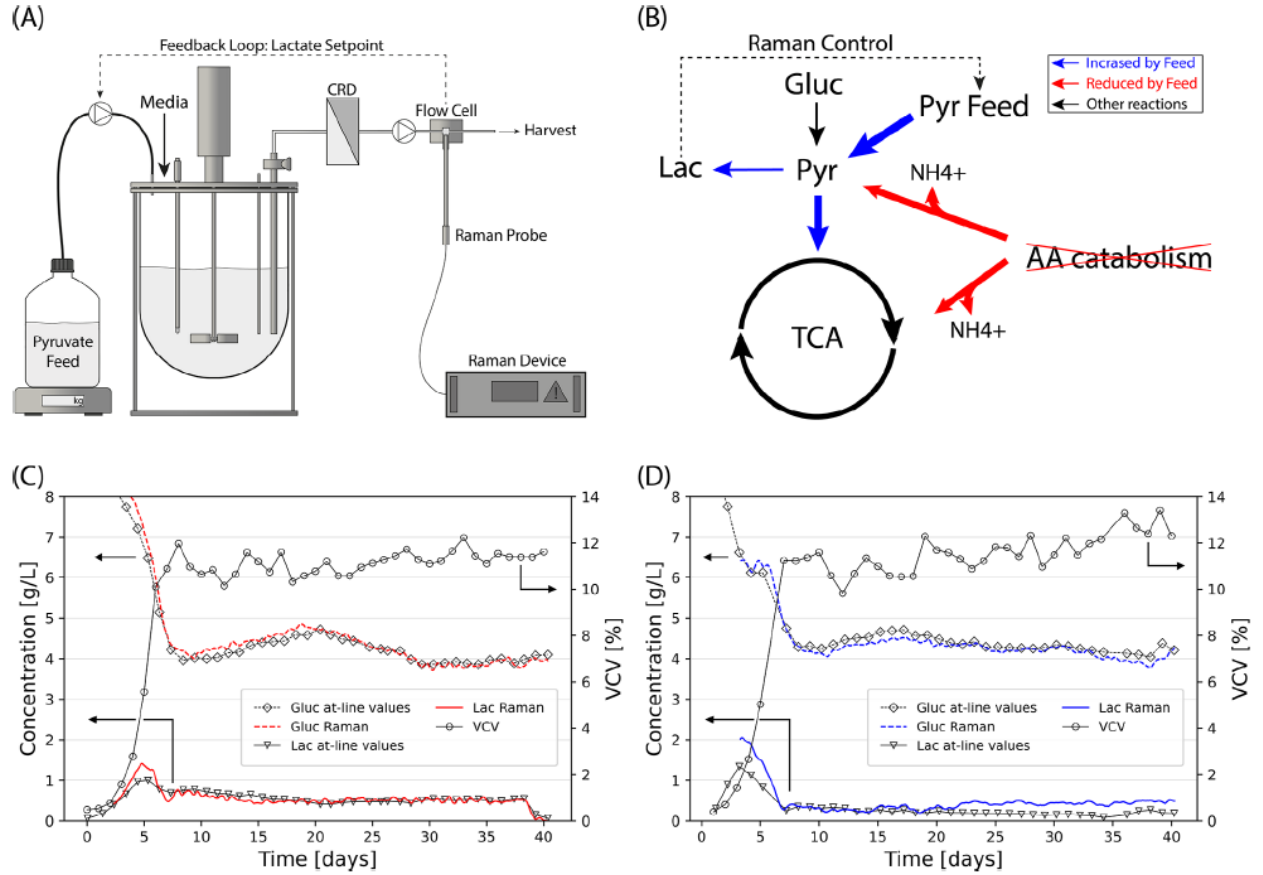


FIGURE 2 Raman-controlled feeding strategy. Schematic setup of perfusion bioreactor with Raman flow cell after cell retention device (CRD) in harvest stream predicting lactate concentration and controlling pyruvate feed addition (A). Simplified metabolic scheme of feeding strategy (B). Real-time Raman predictions and corresponding at-line reference measurements for a perfusion run with 0.7 g L^{-1} lactate setpoint (C) and a perfusion run with a lower lactate setpoint of 0.3 g L^{-1} (D).

Controls Monitoring

Glycosylation

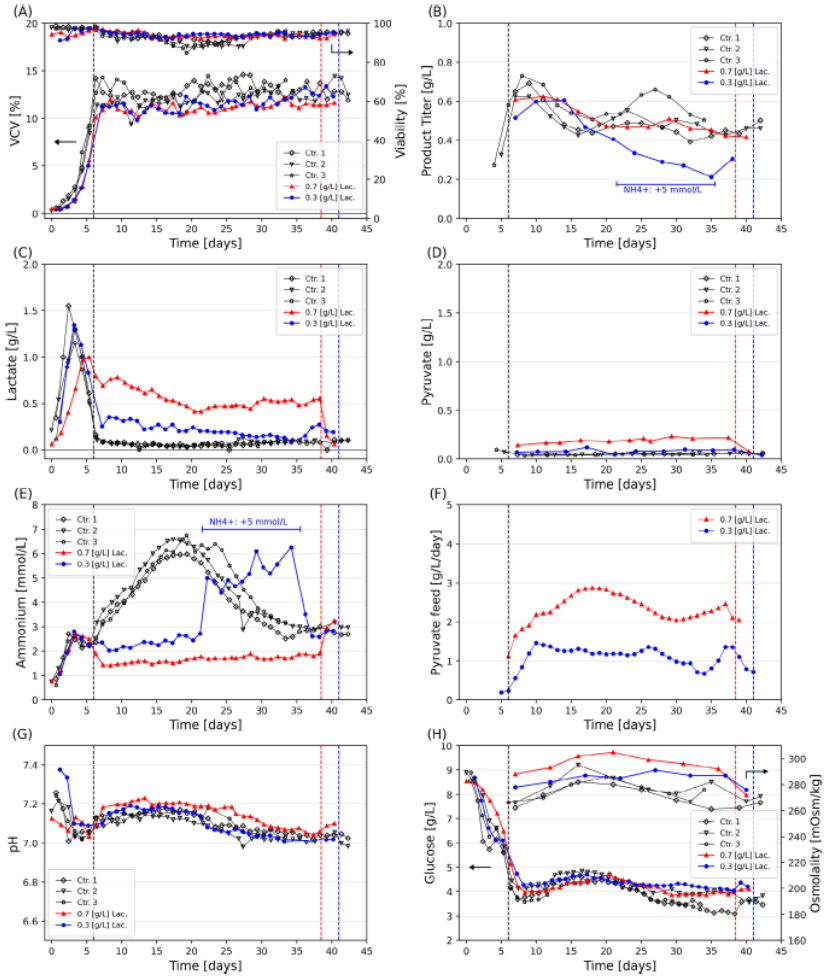


FIGURE 3 Cell culture parameter, nutrient, and metabolite trends for steady-state perfusion cultivations. VCV and viability (A), product titer (B), lactate (C), pyruvate (D), ammonium (E), pyruvate feed rate (F), culture pH (G), glucose and osmolality (H). The vertical black lines represent the start of Raman-controlled pyruvate feeding and the blue and red vertical line represent the end of pyruvate feeding of the respective runs. Blue horizontal lines represent a phase of ammonium addition of 5 mmol L^{-1} to the perfusion media in the perfusion run with 0.3 g L^{-1} lactate setpoint.

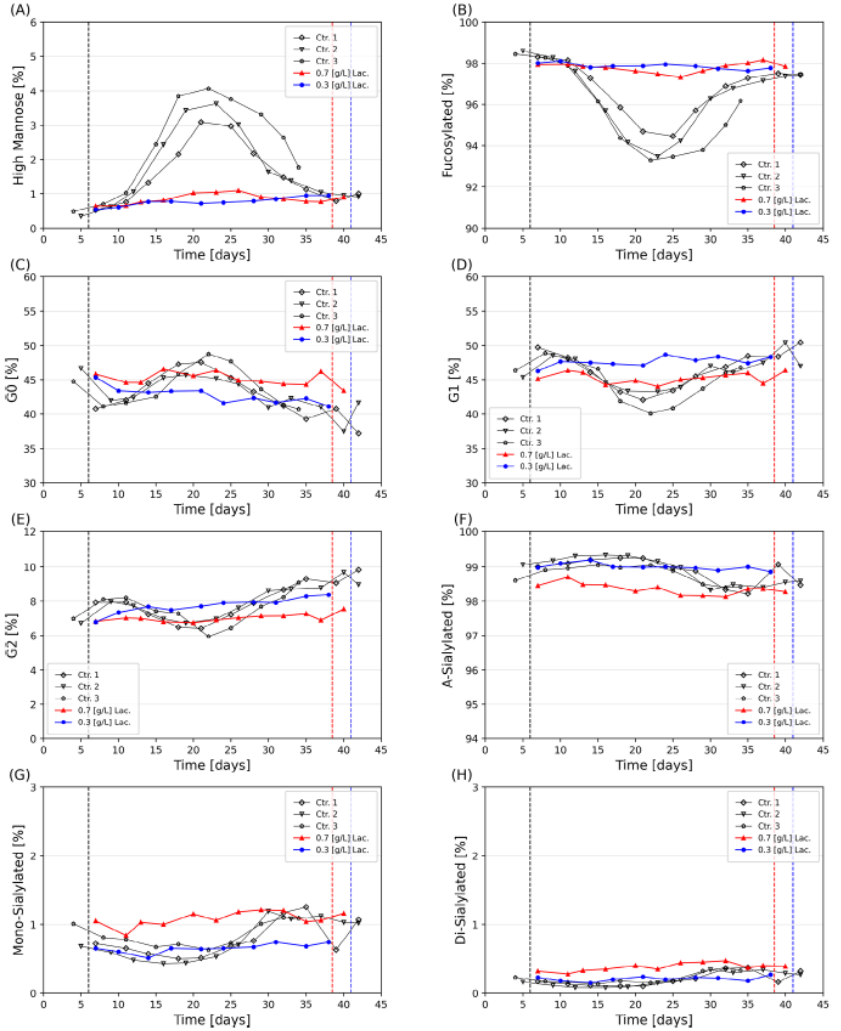


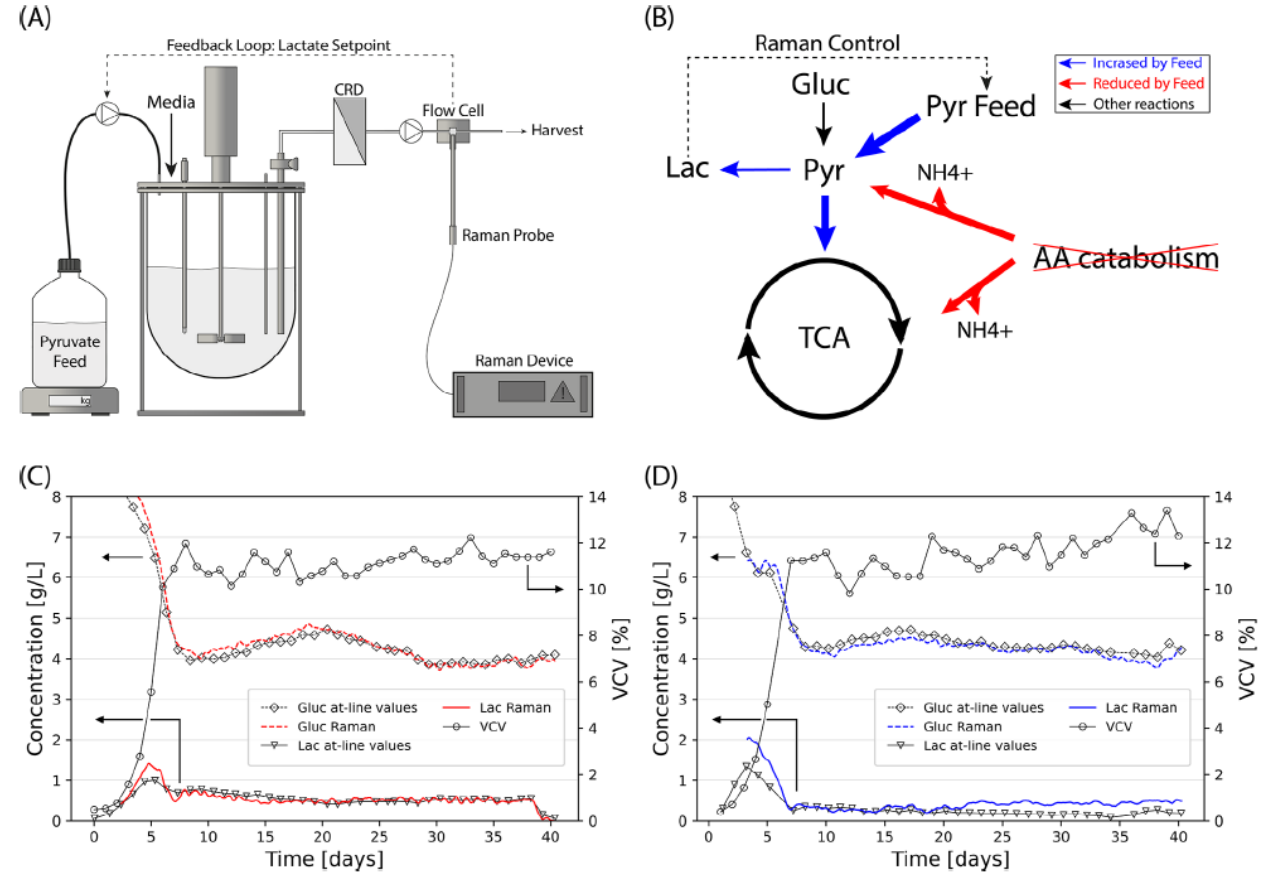
FIGURE 4 Product glycosylation profiles for steady-state perfusion cultivations. High mannose (A), fucosylation (B), G0 (C), G1 (D), G2 (E), a-sialylation (F), mono-sialylation (G), and di-sialylation (H). The vertical black lines represent the start of Raman-controlled pyruvate feeding and the blue and red vertical lines represent the end of pyruvate feeding of the respective runs. Blue horizontal lines represent a phase of ammonium addition of 5 mmol L^{-1} to the perfusion media in the perfusion run with 0.3 g L^{-1} lactate setpoint.

Hoefnagel CASSS-NL 2025

DOI: 10.1002/biot.202300318 Romann et al 2024.

PAT in Biopharmaceutical Continuous manufacturing

- NIR /Raman: glucose, ammonium, lactate, glutamate, optical density/ biomass, glycerol, & pH
- Validate Raman Analysis Results
  - Validate model underlying Raman Spectral Analysis
  - Use Orthogonal method to confirm Raman results



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Development & Validation of PAT technique

EMEA/CHMP/CVMP/QWP/17760/2009 Rev2
Guideline on the use of near infrared spectroscopy

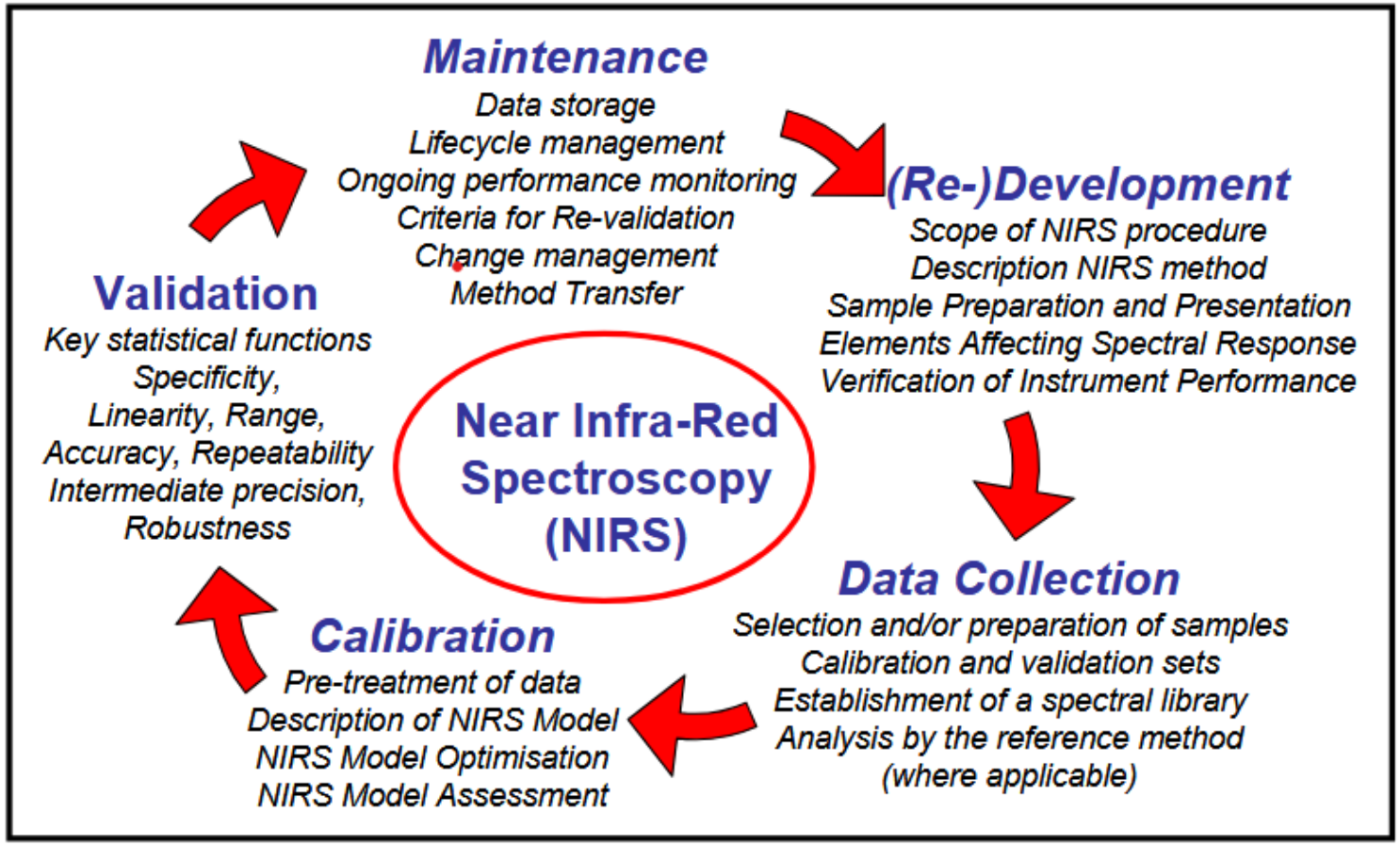


Figure 1. The iterative nature of NIRS

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q13

ICH Consensus Guideline

Continuous Manufacturing (CM) also includes manufacturing approach in which **some unit operations operate in a batch mode** while **others** are integrated and **operate in a continuous mode**

Batch definition: ICH Q7 definition applicable for CM, for both drug substances & drug products

Batch can be defined as:

- Quantity of output material
- Quantity of input material
- Run time at a defined mass flow rate
- Any other scientifically justified approach

Control Strategy: Based on ICH Q7, Q8, Q10, Q11 and Q9 (Quality Risk Management)

State of control (ICH Q10): assurance of continued process performance & product quality

e.g., process parameters, quality attribute may vary within accepted ranges (if non steady state)

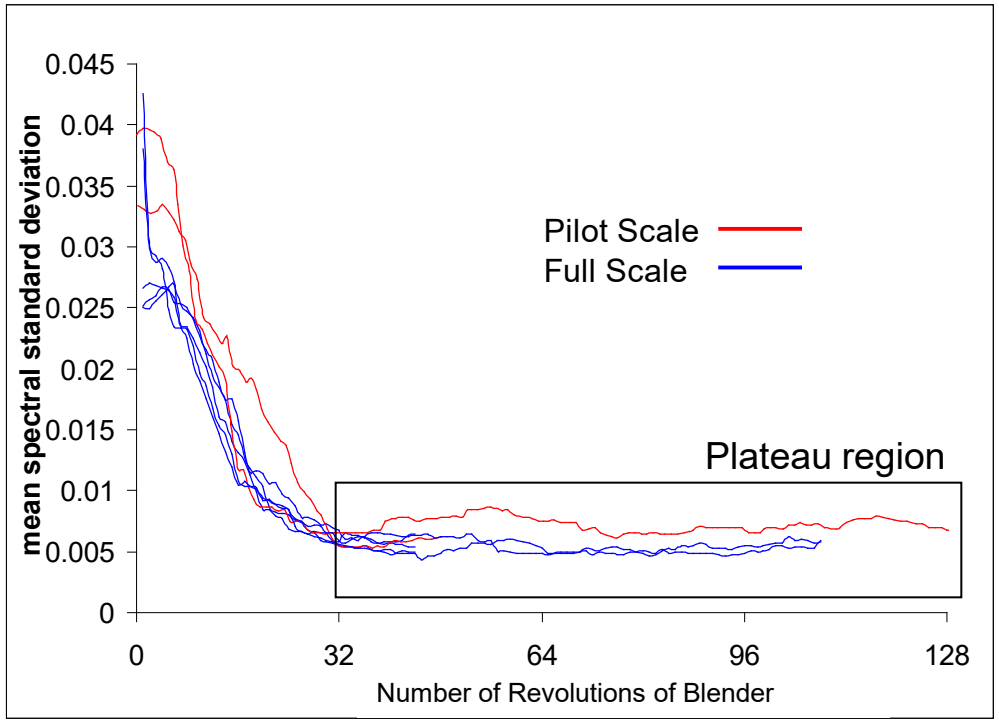
Understand changes over time (cell aging, resin aging), adapt process accordingly

Identify deviations and drifts (identify root cause)

Process control using PAT

Alternative approach: Blend uniformity monitored using a process analyser

- On-line NIR spectrometer used to confirm scale-up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
- Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
  - Assays tablets to confirm uniformity
  - Conducts studies to try to segregate API



Data analysis model will be provided
Plan for updating of model available

Acknowledgement: Adapted from ISPE PQLI Team

ICH HARMONISED GUIDELINE

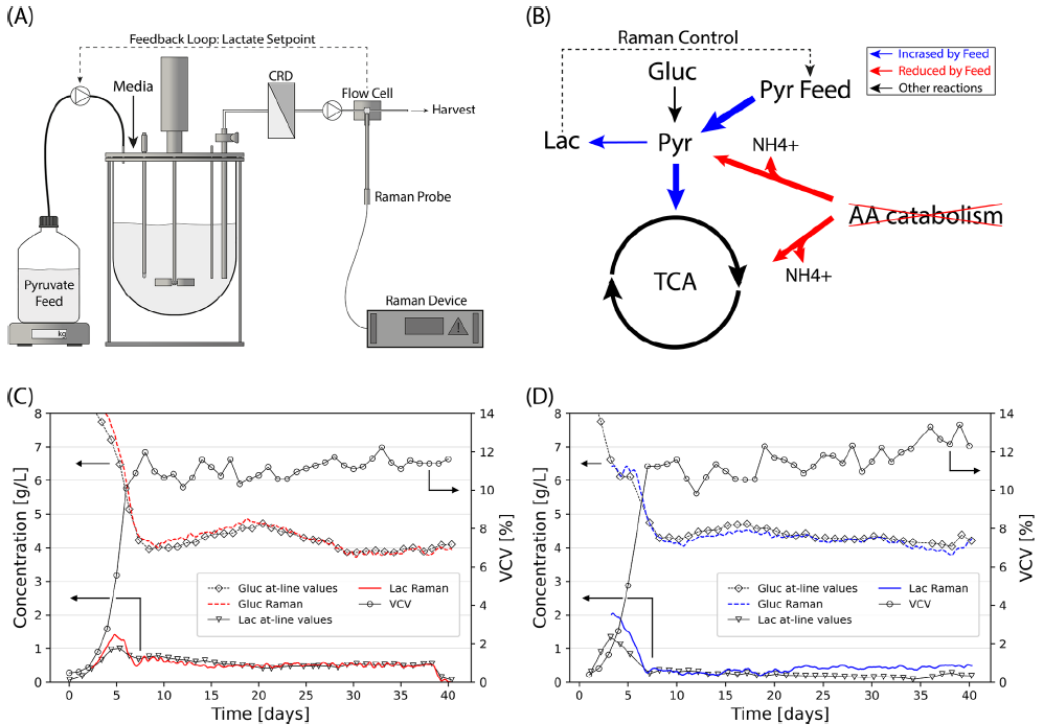
CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q13

ICH Consensus Guideline

Process dynamics:

- Transient events
  - planned (e.g., process start-up, shutdown and pause) or
  - unplanned (e.g., disturbances)
- Characterise process dynamics & impact on Product Quality
  - E.g. Residence Time Distribution (RTD): to determine which fractions to discard (impurities, low DS, other composition)
- PAT process analytical technology
  - Validate technology (confirm Raman Measurement with offline result)



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CM for Biopharmaceuticals

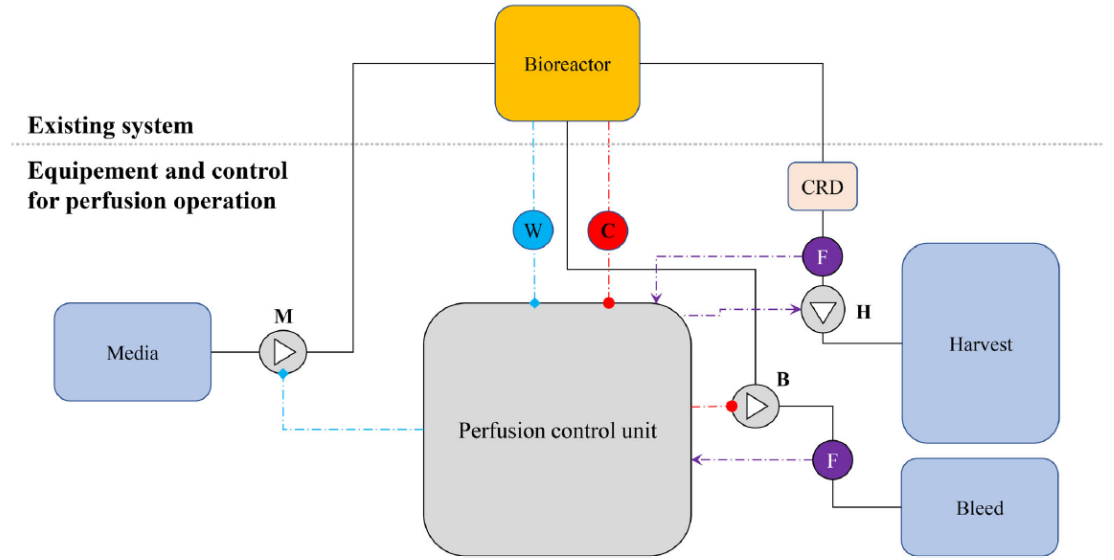
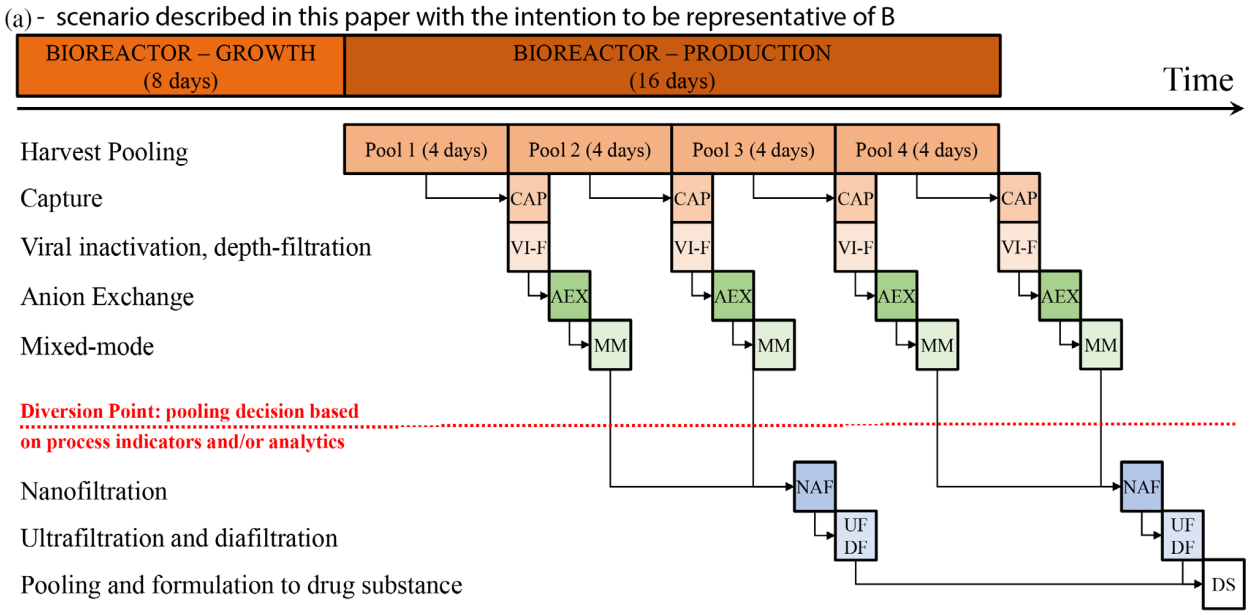
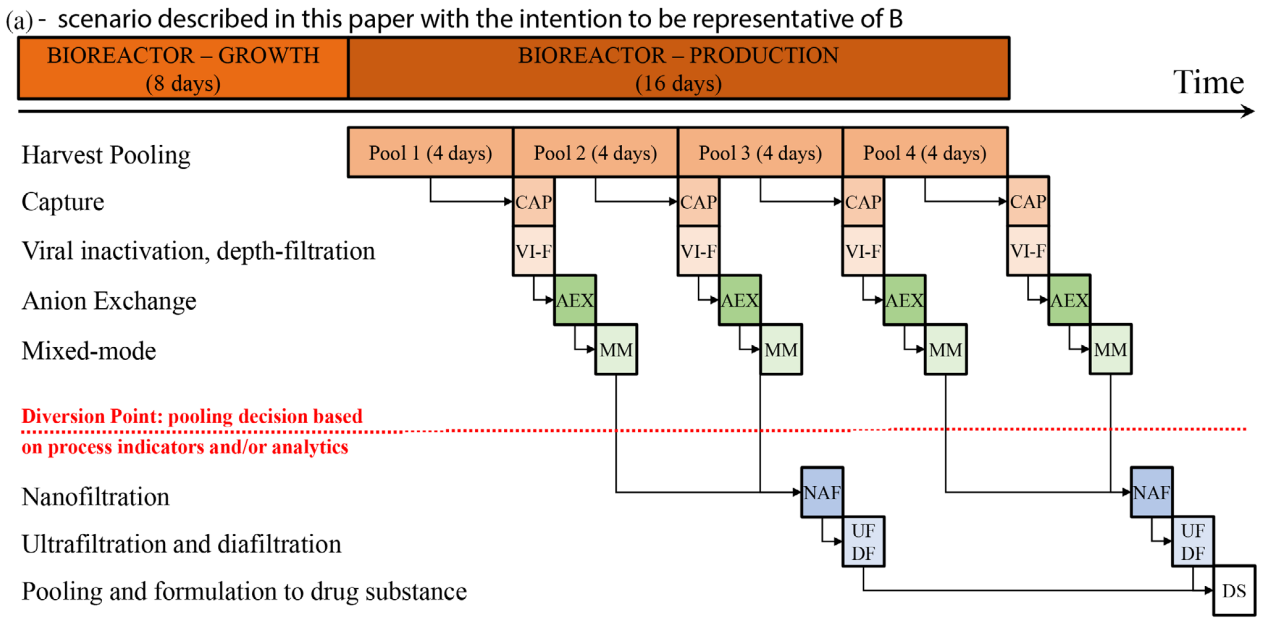


FIGURE 2 Layer of equipment and control added to the existing 200-L bioreactor. M, H, and B are, respectively, media, harvest and bleed flowrates ($L \cdot s^{-1}$). Dotted lines represent the different signals used to control these flowrates. W corresponds to the weight of the bioreactor (kg), C to the biocapacitance signal (pF/cm), and F to flowmeters ($L \cdot s^{-1}$). Signals are centralized in the perfusion control unit that can modulate the pump outputs



Botelho Ferreira et a. https://doi.org/10.1002/btpr.3259

CM for Biopharmaceuticals (2)



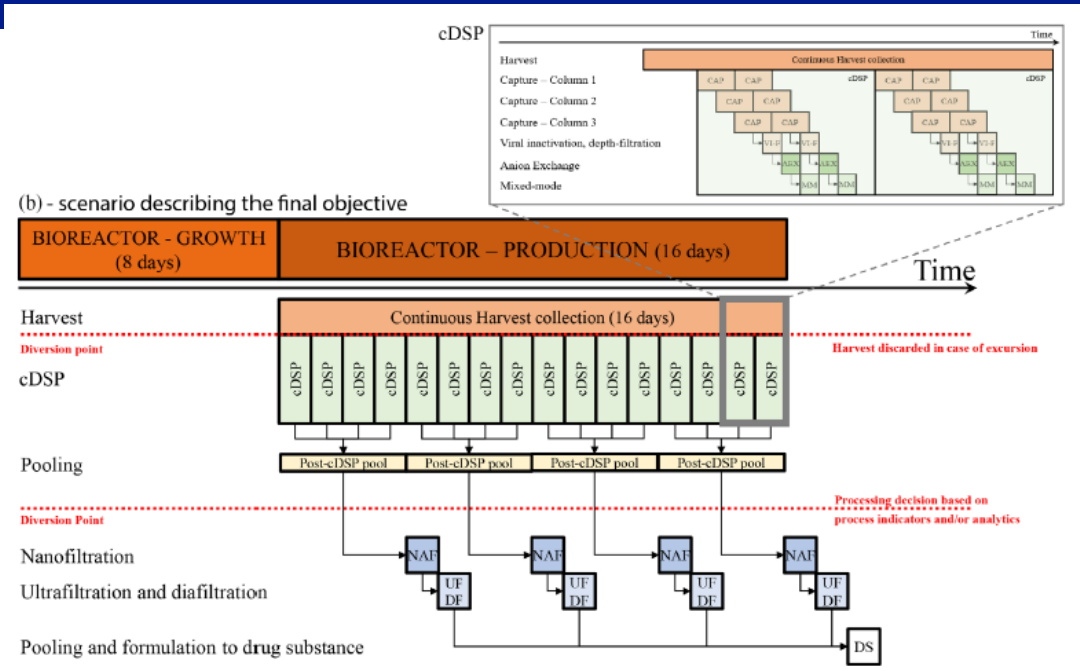


FIGURE 1 Perfusion harvest processing strategy for two scenarios. A: Harvest was pooled for 4 days then captured (CAP), viral inactivated (VI), and depth filtered (F). This was followed by two polishing steps (AEX and MM) operated in flow-through mode. At this point the material was tested for relevant quality attributes and pooled two by two if predefined limits were met. Further steps included NAF, UF, DF, formulation, and the final pooling into the DS. B: Future continuous manufacturing platform at 2000-L. Harvest is continuously collected and purified daily by a cDSP sequence composed of six cycles of capture, two cycles of VI-F, AEX, and MM. Four daily cDSP sequences are pooled before being then further processed to NAF and UF/DF prior to DS

Process dynamics: Process monitoring, Process validation, Process Model validation

- Transient events
  - planned (e.g., process start-up, shutdown and pause) or
  - unplanned (e.g., disturbances)
- Characterise process dynamics & impact on Product Quality
  - E.g. Residence Time Distribution (RTD): to determine which fractions to discard (impurities, low DS, other composition)

Perfusion Upstream Process

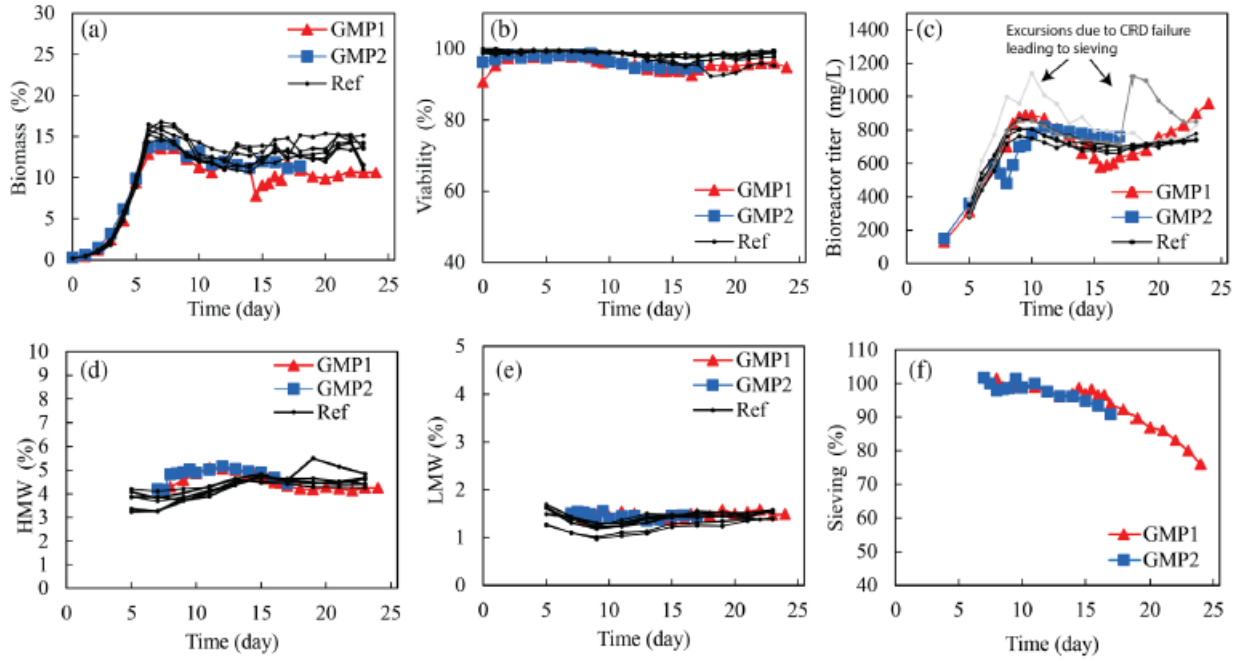
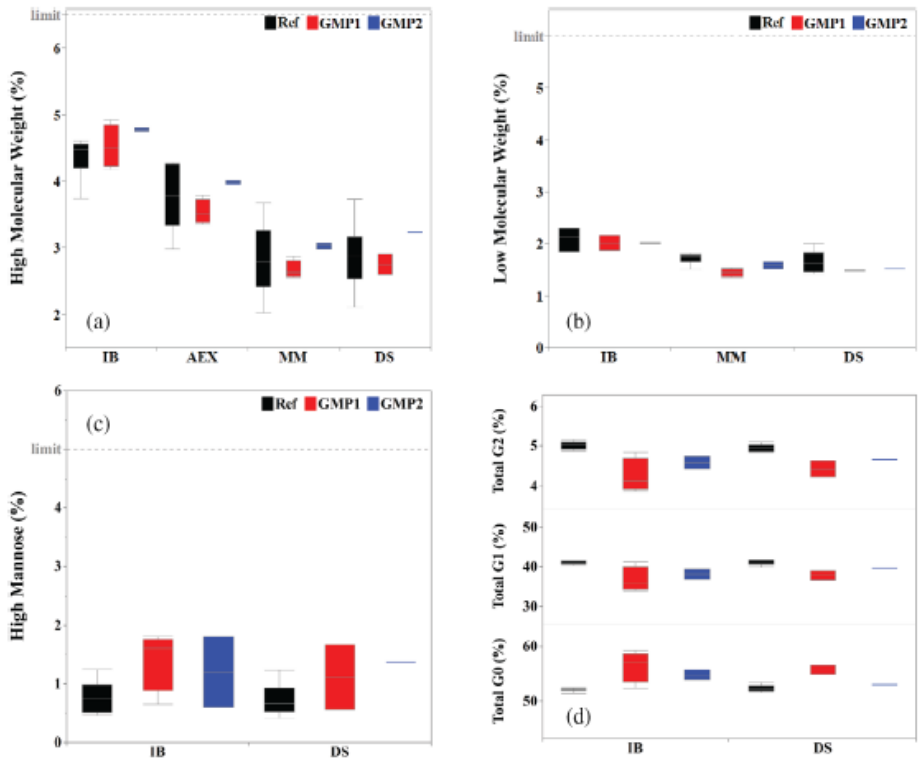


FIGURE 3 Biomass in volume % (a), viability (b), bioreactor titer (c), HMW (d), LMW (e) during both GMP runs (200 L) and from the 6 reference runs (3.5 L bench-scale reactors) and finally sieving (f) measured in the GMP runs. Bioreactor titers of two reference runs were not aligned (gray curves in C) because of CRD failures

Analyisis of Glycans & Impurities in each process step



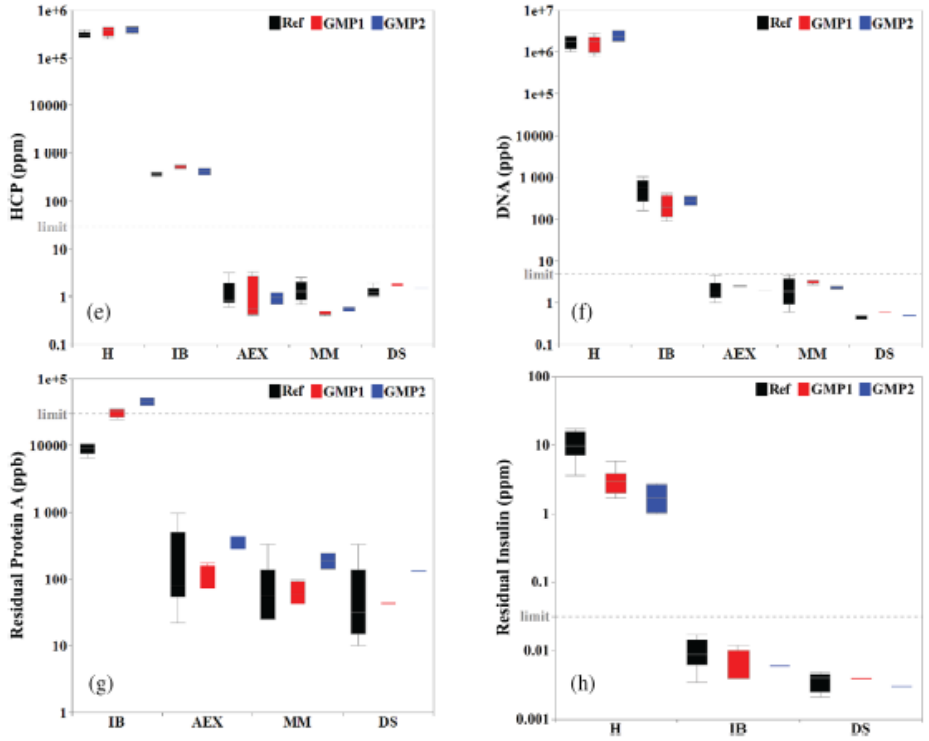


FIGURE 4 Box plots of quality attributes and impurities content in different steps of the process (H, IB, AEX, MM, and DS) with HMW (a), LMW (b), high mannose (c), total G0, total G1 and total G2 galactosylated forms (d), HCP (e), DNA (f), residual protein A (g), and residual insulin (h)

Process Models Regulatory Expectations

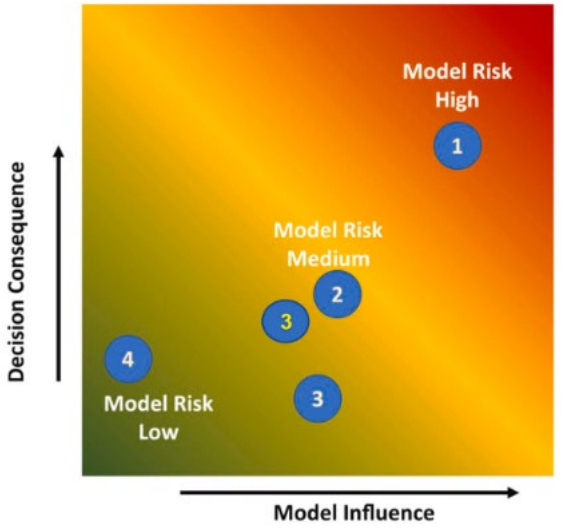
ICH QUALITY IMPLEMENTATION WORKING GROUP POINTS TO CONSIDER (R2)
ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

- Risk-based approach: Criticality of Process Parameters & Quality Attributes
- Does model impact CPP or CQA? (Relation criticality to Control Strategy)
  - E.g. Does optimizing yield impact CPP or CQA?
- Lifecycle of the Control Strategy
  - Development (Well-characterized CQAs?)
  - Continual Improvement (multivariate models: systems to maintain & update model suitability)
  - Changes to model (requires variation of Marketing Authorisation dossier?)
  - Equipment/Process differences between sites

Process Models Regulatory Expectations (2)

- Role of Model
  - Low Impact/Risk (e.g. process development for formulation)
  - Medium Impact:
    - Models assuring quality (other indicators present: e.g. IPCs)
    - Models defining Design Space
  - High Impact Models
    - e.g. Real-time Release Testing Models
    - Models for process control (Depending on Impacted CQAs)
- Developing/Implementing Models
- Type of Model: Mechanistic (1st principle) or Empirical (Data-driven; incl. Machine Learning & AI)
- Prior knowledge, Process understanding, Model understanding

O'Connor et al. 2024
https://doi.org/10.1016/j.ijpx.2024.100274



Process Models Regulatory Expectations (3)

- Model validation
  - Set acceptance criteria for model prediction
  - Comparison of accuracy of prediction
  - Validate using external data set (not used to train the model or otherwise in development)
  - Verify prediction (orthogonal method; if possible)
- Documentation depending on model **impact/risk**
  - **Low**: high level description
  - **Medium**: models assumptions, graphical summary (input/outputs), equation, prediction & measured data, statistics, mitigation measures.
  - **High**: Above + choice of variable selection, appropriateness of data, model validation, model verification **during life-cycle**

Preliminary QIG Considerations regarding Pharmaceutical Process Models

EMA/90634/2024 (22 February 2024)

- Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification?
- Q2. What data is expected in the dossier in terms of model description and scope?
- Q3. What data is expected to be included in the dossier in terms of model validation?
- Q4. What data is expected in the dossier in terms of process model lifecycle

Predictable reg framework
Support EU innovation efforts

Support

EMRN

European medicines regulatory network

Training, guidance

International regulatory convergence

Quality Innovation Group

8 Core experts
(Chemical, Biological, ATMP & GMP)
+ ad hoc experts

Assessment support tailored to technology novelty

Rapporteurs and Assessment Teams

Research Tender, 2025

Academic expertise
Research projects

Support from development throughout lifecycle

Links

EU Innovation network, ITF, National IOs

Point of entry to EMRN
Informed open discussions

Take Home messages

- Develop Process & Product understanding (CPP & CQA)
- Be concious of uncertainties, include mitigation measures
- PAT and Models can contribute to Process understanding & optimisation
- Continuous manufacturing more sustainable, lower cost, more efficient
- Documentation Manufacturing models dependent on Risk/Impact

- Quality Innovation Group (QIG) EMA to support Innovative Techologies in Pharmaceutical manufacturing.

Contact:

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https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp-working-parties-other-groups/quality-innovation-group

Back-up Slides

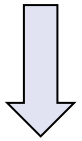
Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification?

- **Intended use of a model**
- Different model uses:
  - Model used to support process development
  - Model used in the control strategy in addition to other related measurements
  - Model used in the control strategy without additional related measurements
- Role of the model in the control strategy (CS), frequency of any additional monitoring, model's performance, potential consequence of an incorrect decision, criticality of the manufacturing operation(s), manufacturing mode, intrinsic risk of the medicine

Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification? *Cont'd*

Contribution of the model to a decision relative to other available evidence,

and the decision consequence



Degree of regulatory oversight

Q2. What data is expected in the dossier in terms of model description and scope?

Model description

- Low-risk: high-level description and discussion regarding model intended use
- Medium-risk: more detailed description, outline of model development
- High-risk: the above + summary of performance metrics and model validity domain

Model scope (similar concept as for NIR chemometric models)

- Low-risk: no formal scope, high-level description as stated above
- Medium- and High-risk: intended use within CS, model type, performance metrics acceptance criteria, validity domain, reference method where applicable ➔ exact content to be justified based on risk

Q3. What data is expected to be included in the dossier in terms of model validation?

- The goal of model validation is to establish the degree to which a model is an **accurate representation** of a process and can **predict** the property(ies) or material quality attribute(s) of interest.
- Focus on **model performance** (e.g., prediction accuracy) and model error, or uncertainty.
- Validation activities are expected to be designed to give confidence in the model for its intended use ➔ driven by risk

Q3. What data is expected to be included in the dossier in terms of model validation? *Cont'd*

- Illustrative examples.
- Overarching role of the manufacturing process validation to show that the process is in a state of control.
- Validity of model at commercial scale (for high-risk models, and for medium-risk on case-by-case); model verification protocol where relevant.
- Continuous model verification/protocol where relevant.

Q4. What data is expected in the dossier in terms of process model lifecycle?

- It is the MAH responsibility to ensure the model is updated as required over its lifecycle to ensure it remains fit for purpose.
- Validity of the model reviewed periodically.
- **Model maintenance protocol** (medium- and high-risk models): expected to set the conditions for changes that can be managed within the PQS or require submission of a variation.
- Extent of model maintenance activities commensurate with model type and model risk.