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Original Research Article

Regulatory Guidelines and Analytical Strategies in CMC for Monoclonal Antibodies: A Comparative Review of FDA, EMA, and ICH Recommendations

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Abstract:
Monoclonal antibodies (mAbs) now dominate the global biologics landscape, with sustained clinical and commercial impact across oncology, immunology, and infectious disease. Ensuring reliable quality, safety, and efficacy throughout development and lifecycle management depends on a rigorous Chemistry, Manufacturing, and Controls (CMC) framework. This review provides a detailed, comparative synthesis of international CMC expectations for mAbs, anchored in International Council for Harmonisation (ICH) guidelines—Q5A(R2) (viral safety), Q5C (stability), Q6B (specifications), Q8(R2), Q9(R1), Q10, Q11, Q12, and the analytical pair Q14/Q2(R2)—and complemented by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidances. We elaborate practical strategies for CQA-driven product and process understanding; specification setting that integrates clinical relevance, process capability, and assay variability; analytical modernization (ATP-based method development, multi-attribute methods, advanced glycoanalytics); viral safety modernization (molecular detection and orthogonal clearance validation); and Process Analytical Technology (PAT) with elements of real-time release testing (RTRT). We further examine lifecycle agility through Q12 mechanisms (Established Conditions, post-approval change management protocols) and highlight emerging directions—digital CMC models, continuous/hybrid operations, immunogenicity risk integration, and sustainability metrics. Consolidated tables and figures provide at-a-glance operational guidance to support globally harmonized submissions for mAbs.
Keywords: Monoclonal antibodies; CMC; ICH Q5A(R2); Specifications; Analytical lifecycle; PAT; Comparability; Q12; RTRT

Introduction

Monoclonal antibodies (mAbs) have transformed modern therapy across oncology, immunology, and infectious disease by enabling targeted, mechanism-based intervention. The Chemistry, Manufacturing, and Controls (CMC) framework is central to ensuring that mAbs are developed and commercialized with consistent quality, safety, and efficacy across the product lifecycle. Global expectations are anchored in harmonized ICH guidelines—particularly **Q5A(R2)** (viral safety), **Q5C** (stability), **Q6B** (specifications), **Q8(R2)** (pharmaceutical development), **Q9(R1)** (quality risk management), **Q10** (quality system), **Q11** (drug substance development), **Q12** (lifecycle management), and the analytical pair **Q14/Q2(R2)** (procedure development and validation). Regional guidances from the FDA and EMA elaborate on these foundations for biologics and mAbs, including process validation, comparability, and dossier expectations.

This review synthesizes regulatory guidance and practical analytical/manufacturing strategies for mAbs, emphasizing: (i) CQA-driven product and process understanding; (ii) specification setting under **ICH Q6B** with clinical and capability linkage; (iii) analytical modernization (ATP-based development under **Q14/Q2(R2)**, MAM, HCP LC-MS); (iv) **ICH Q5A(R2)**-aligned viral safety mod-

ernization; (v) PAT-enabled control and elements of real-time release testing (RTRT); and (vi) lifecycle agility via **Q12** (Established Conditions, PACMPs). We also outline emerging trajectories (digital CMC, continuous/hybrid operations, and sustainability) and offer practical, figure-based checklists to support submission readiness [1].

Regulatory Landscape: ICH, FDA and EMEA-Scope and Convergence

ICH Guidelines – Harmonize global CMC expectations across regions. Relevant guidelines include **Q8(R2):** Pharmaceutical Development, **Q9:** Quality Risk Management, **Q10:** Pharmaceutical Quality System, **Q11:** Development and Manufacture of Drug Substances [2,3].

FDA Guidance – Provides recommendations on product development, process validation, analytical method qualification, comparability studies, and post-approval changes. Guidance documents such as "Quality Considerations for Biotechnological Products" and "CMC for Gene Therapies" are critical references [4].

EMA Guidance – Focuses on similar areas as the FDA, with additional emphasis on European-specific dossier requirements, environmental risk assessment, and pharmacovigilance integration. Key documents include "Guideline on Biotechnology-Derived Pharmaceuticals" and "Guideline on Quality of Gene Therapy Medicinal Products [5]."

Table 1: Comparative CMC expectations for monoclonal antibodies across FDA, EMA, and ICH [6,7,8,9]

Topic	FDA (key guidance, year)	EMA (key guidance, year)	ICH anchor	mAb-specific note
Analytical lifecycle	Analytical Procedures & Methods Validation for Drugs and Biologics (2015); Q14 adoption (2023)	EMA CMC guidance page; Q14 local adoption (2023)	Q14 (2023), Q2(R2) (2023)	ATP-driven method development and lifecycle control required.
Potency assays	Potency guidance for mAbs targeting viral proteins (2023) – stresses biologically relevant, cell-based assays	mAb quality guideline (2007, updated reflections) – mechanism-based potency justification, orthogonal methods	No single potency doc; Q6B (1999) provides general specification principles	Emphasis on mechanism-of-action–linked potency; dual assays expected.
Comparability	Guidance for Industry: Q5E-based comparability (2004); Comparability Protocols for Human Drugs & Biologics (2022)	Revised mAb guideline emphasizes deeper characterization for comparability	Q5E (2004)	Comparability packages must integrate orthogonal analytics and, if relevant, clinical bridging.
Stability & specifications	ICH Q5C & Q6B adopted in FDA guidances; Specification guidance (Q6B alignment, 1999)	mAb quality guideline with detail on stability/specification setting	Q5C (1995), Q6B (1999)	Spec rationales must integrate clinical relevance, process capability, and variability data.
Viral safety	Guidance on Viral Safety Evaluation of Biotech Products (aligned to Q5A)	Reflection Paper on Viral Safety (2005) + mAb guideline	Q5A(R2) (2023)	Shift to molecular/in vitro detection, validated clearance studies, reduced in vivo reliance.
Post-approval changes / lifecycle	Comparability Protocols guidance (2022); Q12 implementation emerging	EMA applies Q12 with local variation; encourages PACMP use	Q12 (2019)	PACMPs, Established Conditions, and PLCM documents increasingly expected for global submissions.
Lifecycle management	Q12 adoption; ECs + PACMPs	Q12-aligned with regional implementation	Q12 (2019)	Established Conditions in Module 3; PLCM documents.
Impurities (HCP/DNA)	HCP ELISA; residual DNA qPCR; orthogonal	Similar expectations in EMA	Q6B; Q14/Q2(R2)	Trend-based HCP profiling; numeric

	LC–MS			spec for DNA/Protein A.
Immunogenicity linkage	Quality–immunogenicity considerations	Biosimilar/quality–clinical linkage papers	Q6B, Q11, Q12	Tighten specs on attributes with plausible immunogenicity mechanisms.

Methodology

A structured and integrative literature review was conducted to systematically evaluate global regulatory guidelines and analytical strategies in Chemistry, Manufacturing, and Controls (CMC) for monoclonal antibodies (mAbs), with emphasis on harmonization across International Council for Harmonisation (ICH), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA) frameworks. This review follows a structured narrative approach with elements of systematic literature identification.

Literature Sources and Data Collection: A comprehensive search was performed across multiple scientific and regulatory databases, including PubMed, Scopus, and Google Scholar, to identify peer-reviewed publications relevant to monoclonal antibody development, CMC strategies, and analytical methodologies.

In addition, primary regulatory documents and guidance were retrieved from official sources, including:

- ICH guidelines (Q5A(R2), Q6B, Q8(R2), Q9(R1), Q10, Q11, Q12, Q14, Q2(R2))
- FDA guidance documents on biologics and analytical procedures
- EMA guidelines on biotechnology-derived products and monoclonal antibodies

These sources were prioritized to ensure alignment with current global regulatory expectations.

Search Strategy

The literature search was conducted using predefined keywords and Boolean operators to maximize relevance and coverage. Key search terms included:

- "monoclonal antibodies" AND "CMC"
- "ICH Q6B" OR "specifications biologics"
- "analytical method validation" AND "Q2(R2)"
- "Q14 analytical procedure development"

Search queries were iteratively refined to capture emerging trends such as multi-attribute methods (MAM), digital CMC, and continuous manufacturing.

Inclusion Criteria: Publications and documents were included based on the following criteria:

- Published between January- 2015 and September-2024 , with inclusion of foundational guidelines where necessary
- Peer-reviewed journal articles, regulatory guidance documents, and authoritative industry reports
- Studies focusing on CMC development, analytical characterization, regulatory expectations, or manufacturing of monoclonal antibodies
- Literature providing practical insights, case studies, or comparative regulatory perspectives

Exclusion Criteria

The following sources were excluded:

- Non-English publications
- Studies not directly relevant to biologics or CMC frameworks
- Outdated literature not aligned with current regulatory or technological advancements
- Publications lacking scientific rigor or regulatory applicability

Data Extraction and Thematic Analysis

Relevant information from selected sources was systematically extracted and categorized into key thematic domains aligned with the objectives of this review:

- Regulatory frameworks and harmonization (ICH, FDA, EMA)
- Critical Quality Attributes (CQAs) and specification setting (ICH Q6B)
- Analytical method lifecycle and validation (Q14/Q2(R2))
- Advanced analytical platforms (e.g., MAM, LC–MS, glycoanalytics)
- Lifecycle management and post-approval changes (ICH Q12)

A comparative analysis approach was applied to identify similarities, differences, and convergence across regulatory expectations.

Critical Appraisal and Synthesis: Selected literature was critically evaluated for scientific quality, regulatory relevance, and practical applicability. Emphasis was placed on:

- Alignment with current regulatory frameworks
- Strength of analytical and manufacturing evidence

- Applicability to real-world CMC development and submissions

Findings were synthesized to provide a regulatory-science-driven perspective, integrating both established practices and emerging trends such as digital CMC, continuous manufacturing, and advanced analytics.

Limitations of the Review: This review is limited by the availability of publicly accessible regulatory information and published literature. Proprietary industry data and confidential regulatory submissions were not included. Additionally, rapid advancements in analytical technologies and regulatory expectations may lead to evolving practices beyond the scope of this review.

CMC for Monoclonal Antibodies: Core Elements: A robust CMC strategy for mAbs integrates product and process knowledge to control CQAs. Core domains include: (i) molecular characterization (primary structure, post-translational modifications), (ii) higher order structure, (iii) glycosylation and Fc-function, (iv) charge and size variants, and (v) potency and impurities. Orthogonal analytics and statistically justified acceptance criteria are essential to link assay outputs to clinical performance and process capability.

Molecular and product characterization [10, 11]

- **Primary structure & PTMs:** Intact mass, peptide mapping LC-MS/MS; identification/quantitation of deamidation, oxidation, glycation, C-terminal Lys, N-terminal pyro-Glu.
- **Higher order structure:** Circular dichroism, DSC, HDX-MS (emerging), orthogonal methods for conformational integrity.
- **Glycosylation:** 2-AB/2-AA labeled N-glycan profiles by HILIC-FLD, released glycan MS, glycopeptide LC-MS; sialylation, fucosylation, galactosylation linked to Fc-mediated function.
- **Charge and size variants:** icIEF for charge heterogeneity; CE-SDS (NR/R) and SEC-HPLC for fragments/aggregates; AUC (as orthogonal).
- **Specifications and release (ICH Q6B)**

Specification setting should be consistent with ICH Q6B and informed by product-specific knowledge. Given the inherent heterogeneity of biologics, specification justifications integrate process capability, clinical relevance, and assay variability. Acceptance limits for attributes such as size variants or charge heterogeneity should be supported by stability data, PK/PD linkages, or historical clinical safety/efficacy information. Routine QC relies on validated methods (identity, potency, purity, aggregates, host-cell impurities), while high-resolution assays (e.g., LC–MS peptide mapping) are applied in characterization and stability studies.

Analytical Strategies: Lifecycle, Validation and Modern Platforms : Analytical characterization of monoclonal antibodies must align with ICH Q2(R2) and Q14, emphasizing lifecycle control of methods through the Analytical Target Profile (ATP). Validation should establish accuracy, precision (repeatability and intermediate precision), specificity, sensitivity, linearity, range, robustness, and system suitability [12,13].

Established assays include:

- **Mass spectrometry (MS):** intact/reduced mass, peptide mapping, and glycan profiling.
- **Capillary electrophoresis (CE):** CE-SDS for purity, icIEF for charge heterogeneity, and cZE for identity.
- **Chromatography:** SEC-HPLC for aggregates, HIC for variants, and RP-HPLC for fragments.
- **Bioassays:** mechanism-of-action–reflective potency assays with appropriate reference standards and statistical criteria for parallelism.
- **Binding kinetics:** SPR or BLI for affinity/kinetics, used in comparability and potency support.
- **Impurities:** host-cell proteins (ELISA with LC–MS orthogonal profiling), residual DNA (qPCR/dPCR), and Protein A (ligand-binding assays).

Advanced approaches are increasingly applied [14]:

- **Multi-attribute method (MAM):** LC–MS peptide mapping enables simultaneous monitoring of multiple CQAs (e.g., deamidation, oxidation, glycoforms).
- **Next-generation glycoanalytics:** MS-based methods, exoglycosidase arrays, and FcγRIIIa binding as surrogates for ADCC-relevant afucosylation.
- **Process analytical technology (PAT):** Raman, NIR, and UV–Vis spectroscopy with multivariate models to support real-time release testing (RTRT).
- **Subvisible/submicron particles:** Flow imaging microscopy and resonant mass measurement to differentiate proteinaceous particles from silicone oil in prefilled syringes.

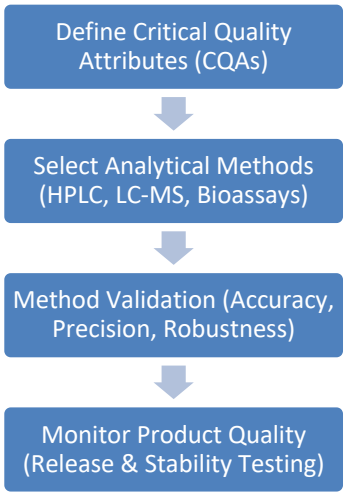


Figure 1 Mapping of critical quality attributes (CQAs) to analytical methods and Life cycle stages

Specifications and acceptance criteria: Specification setting for monoclonal antibodies should be consistent with ICH Q6B and informed by product-specific knowledge. Given the inherent heterogeneity of biologics, specification justifications must integrate process capability, clinical relevance, and assay variability. Acceptance limits for attributes such as size variants or charge heterogeneity should be supported by stability data, pharmacokinetic/pharmacodynamic (PK/PD) correlations, or historical clinical safety and efficacy information. Routine quality control testing should rely on validated methods for identity, potency, purity, aggregates, and host-cell impurities, while high-resolution assays (e.g., LC–MS peptide mapping) may be applied in characterization and stability studies to provide additional assurance [3,4].

Manufacturing Strategies in CMC: The manufacturing of advanced therapeutics involves complex processes that require stringent quality control and risk management. Both upstream and downstream processes must be optimized to ensure consistent product quality. Upstream Process includes cell culture development and optimization for biologics, bioreactor selection and control strategies, monitoring of critical process parameters (CPPs) to maintain CQAs. Downstream Process includes purification and formulation, sterility and stability considerations, scalability and comparability studies for commercial production [15, 17].

Emerging Trends in Manufacturing:

- **Continuous Manufacturing:** Reduces variability and increases efficiency
- **Single-Use Bioreactors:** Decrease contamination risk and cleaning validation
- **Integration of PAT and QbD:** Real-time monitoring and control for robust processes

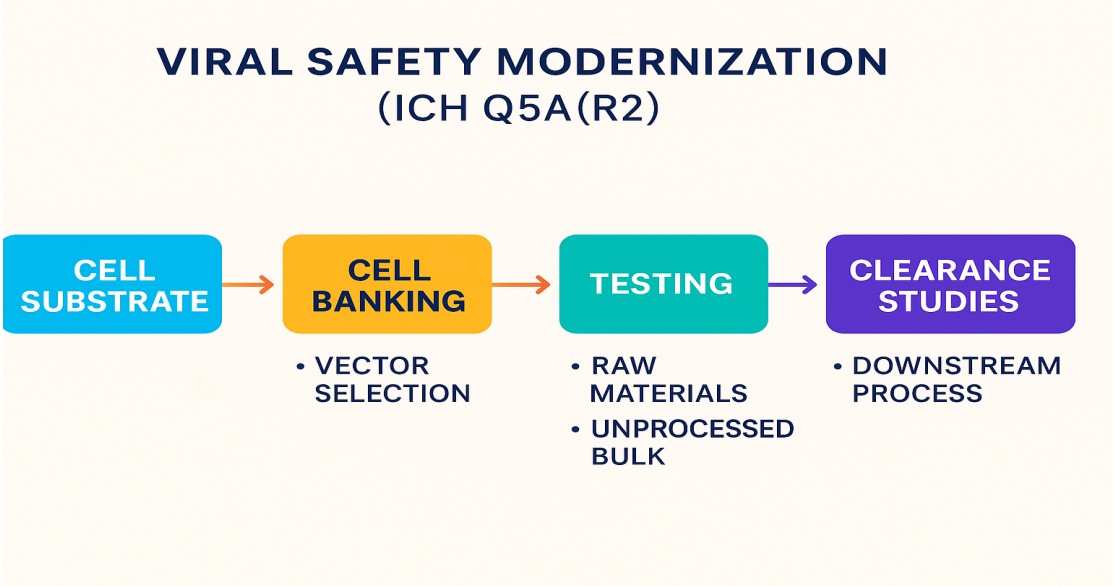
Challenges and Opportunities

Despite significant advances in CMC strategies for advanced therapeutics, several challenges remain that impact development, regulatory compliance, and commercialization.

Key Challenges:

- **Regulatory Divergence:** Differences in requirements across regions can complicate global submissions and delay approvals.
- **Analytical Complexity:** Characterization of large molecules, gene therapies, and novel modalities requires sophisticated, time-consuming analytical methods.
- **Manufacturing Scale-Up:** Translating lab-scale processes to commercial scale without compromising product quality remains difficult.
- **Post-Approval Changes:** Managing lifecycle changes, comparability studies, and risk-based modifications requires meticulous planning.

Viral Safety and Adventitious Agents (ICH Q5A(R2)) [16]: ICH Q5A(R2) emphasizes a risk-based, multilayer strategy: (i) qualified cell substrates with endogenous/adventitious virus testing and genetic stability; (ii) raw materials controls (supplier qualification, animal-origin risk management); (iii) in-process monitoring of bulk harvests (including retrovirus for rodent cells); and (iv) orthogonal viral clearance validation with model viruses chosen for enveloped/non-enveloped and DNA/RNA diversity. Modernization recognizes molecular methods (NGS, qPCR/dPCR) as orthogonal tools and reduces reliance on in vivo assays, while reinforcing robust, worst-case, scaled own viral clearance demonstrations.



Flow-chart Viral Safety Modernization: Viral Clearance Studies includes model virus selection it should cover a range of enveloped vs non-enveloped, DNA vs RNA, and small vs large viruses. Commonly used models are Xenotropic murine leukemia virus (retrovirus, enveloped RNA) and, Minute virus of mice (MVM; parvovirus, small non-enveloped DNA) [20].

Adventitious Agent Testing: Master and Working Cell Banks (MCB/WCB) must undergo rigorous testing to ensure the absence of microbial and viral contaminants. These assessments include bacterial and fungal contamination checks, mycoplasma detection using culture-based and PCR methods, adventitious virus testing through in vitro assays across multiple cell lines, in vivo inoculation studies, and molecular techniques, as well as retrovirus evaluation via reverse transcriptase assays, electron microscopy, and PCR. In addition, each bulk harvest lot, or as scientifically justified, should be tested for adventitious viruses before proceeding to downstream purification. Post-production monitoring relies on routine in-process controls (IPCs), which include testing for bioburden, mycoplasma, and relevant viral markers. Regulatory expectations under ICH Q5A stress the importance of a robust, redundant strategy, recognizing that no single barrier alone can guarantee viral safety. Consequently, sponsors are required to provide comprehensive viral safety assessments of cell lines and raw materials, validation data supporting effective viral clearance, detailed protocols and results for adventitious agent testing, and risk assessments addressing novel raw materials and cell substrates [18,19].

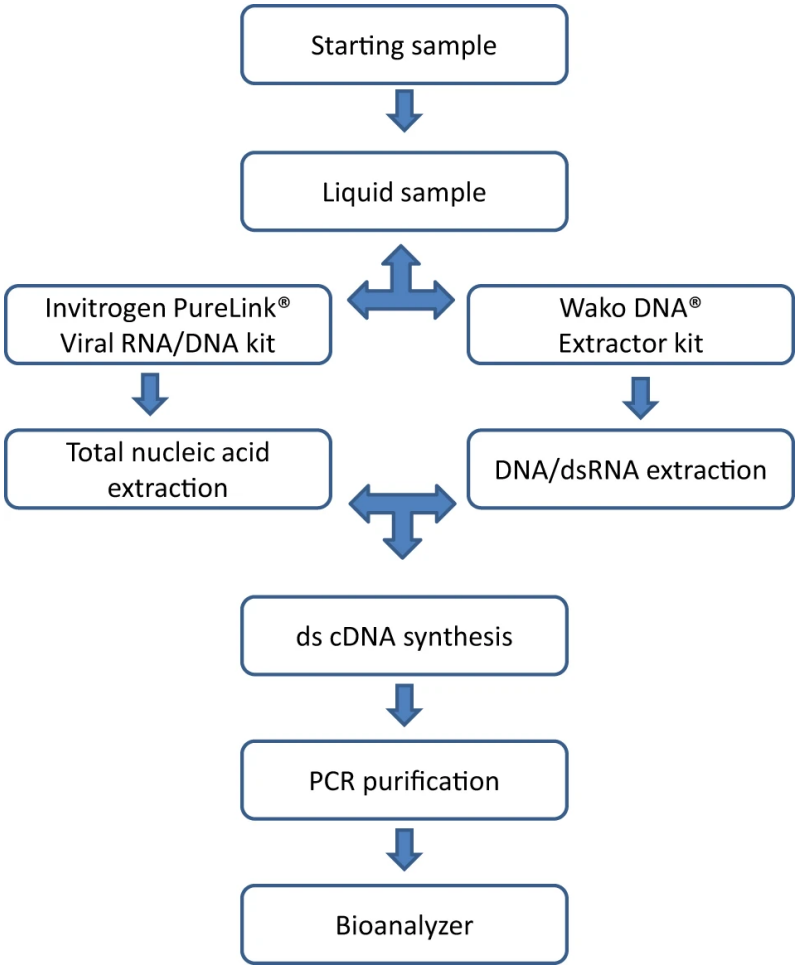


Figure 2: General overview of Viral nucleic acid extraction protocol

Practical Considerations for mAbs: Most monoclonal antibodies (mAbs) are produced in Chinese Hamster Ovary (CHO) cells, which, while not known to harbor human pathogens, may contain endogenous retrovirus-like particles. These must be carefully monitored using reverse transcriptase assays, electron microscopy, and validated viral clearance steps. A typical viral clearance strategy for mAbs involves multiple orthogonal steps, including low-pH viral inactivation following Protein A elution, virus filtration using membranes with pore sizes of 20–50 nm, and additional log reduction achieved through chromatography methods such as anion exchange (AEX) and cation exchange (CEX). On the regulatory front, increasing global convergence is anticipated through ICH Q12, Q14, and Q2(R2), which collectively emphasize lifecycle management, risk-based analytical development, and method lifecycle control. For sponsors, this shift carries significant implications: dossiers should clearly distinguish Established Conditions (ECs) from supportive data, with ECs linked to predefined acceptable ranges and monitoring plans; Analytical Target Profiles (ATPs) should be developed early, ensuring that validation characteristics are directly tied to clinical and CMC risks; and proactive use of Post-Approval Change Management Protocols (PACMPs) is encouraged to streamline common changes such as resin substitutions, site transfers, or potency assay updates [18].

Analytical Modernization: Transitioning from Single-Attribute Assays to Information-Rich Platforms: The analytical landscape for monoclonal antibodies is shifting from reliance on numerous single-attribute assays toward integrated, information-rich platforms. Multi-Attribute Method (MAM), based on LC–MS peptide mapping, is progressing beyond characterization and is now being considered for release-adjacent or even release testing of selected critical quality attributes (CQAs). Similarly, intact and subunit mass spectrometry, along with advanced glycoanalytics such as FcγRIIIa surrogate binding panels, are being adopted to provide functionally relevant insights into product quality. Orthogonal host-cell protein (HCP) control strategies are also evolving, with LC–MS profiling increasingly used to complement or qualify process-specific ELISAs and to bridge results during process changes. For successful implementation, it is critical to define which CQAs are amenable to MAM and which require continued orthogonal or functional testing. Sponsors must also establish bridging packages to ensure continui-

ty when replacing legacy assays with MS-based readouts, while bioassay variability should be managed through statistical process control, robust lifecycle planning of cell banks, and parallelism criteria tailored to fit-for-purpose contexts [19,20].

Real-Time Release Testing (RTRT) and PAT in Bioprocessing: Alongside assay modernization, the adoption of Process Analytical Technology (PAT) and real-time release testing (RTRT) is expanding in both upstream and downstream operations. Spectroscopic techniques such as Raman, NIR, and UV–Vis, coupled with soft sensors and mass balance models, are increasingly employed to predict critical parameters such as titer, impurity profiles, and viral inactivation kinetics. Selective migration of RTRT into routine practice is expected, particularly for parameters with strong mechanistic linkages to product quality. To satisfy regulatory expectations, developers must demonstrate clear traceability from critical process parameters (CPPs) to CQAs, supported by well-defined design spaces or control strategies. Robust fallback plans are also essential—specifying which conventional tests will apply if a PAT signal fails. Finally, model governance requires careful documentation of recalibration triggers and maintenance strategies within continued process verification (CPV) frameworks.

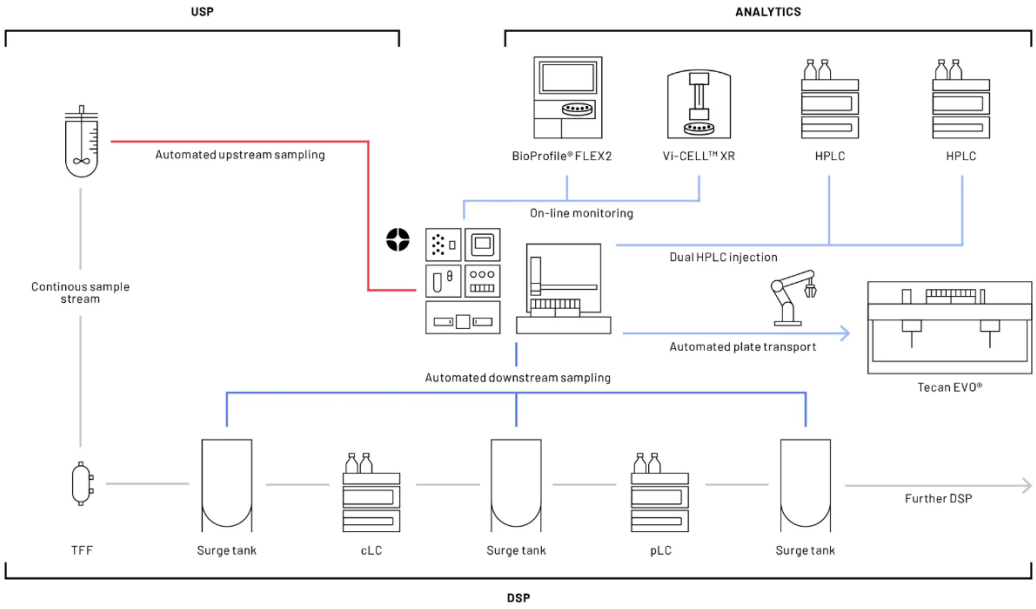


Figure 3: Advanced real-time monitoring in bioprocess, use of PAT across upstream and downstream unit operations, automated sampling, and data feedback loops

Immunogenicity Risk Integration into CMC: An emerging trend in CMC strategy is the closer integration of critical quality attribute (CQA) drift with immunogenicity risk assessment. Shifts in attributes such as glycan afucosylation, aggregate formation, or specific host-cell protein species are increasingly being correlated with potential clinical immunogenicity signals. This integration is supported by in silico epitope prediction tools as well as targeted innate and adaptive immune assays conducted in vitro. To manage these risks, developers are encouraged to establish cross-functional risk registers that explicitly link attribute variability to clinical outcomes, tightening specifications when mechanistic or empirical evidence supports an immunogenicity concern. For biosimilar development, additional measures such as expanding age- and lot-specific regional reference sampling can help capture immunogenicity-relevant variability across diverse patient populations [21,22,23,24].

Continuous and Hybrid Manufacturing: Manufacturing strategies are also evolving toward continuous and hybrid models, combining batch and continuous operations. Regulatory frameworks now provide guidance for continuous capture and polishing steps, supported by real-time monitoring, reduced pool sizes, and enhanced exception management. Successful implementation requires well-defined diversion and segregation protocols, as well as clearly specified real-time release gates. Developers must demonstrate state-estimation accuracy and a robust understanding of residence time distribution across the process. Furthermore, maintenance and calibration schedules must be aligned with validated steady-state performance criteria, supported by ongoing PAT monitoring to ensure process consistency and control [25,26,27,28].

Conclusion

Monoclonal antibodies have become a cornerstone of modern medicine, offering highly specific and effective therapeutic options across oncology, immunology, and infectious diseases. Ensuring their quality, safety, and efficacy depends on a robust Chemistry, Manufacturing, and Controls (CMC) framework that integrates global regulatory expectations, advanced analytical strategies, and modern manufacturing approaches. ICH guidelines—anchored in Q5A(R2), Q6B, Q8(R2), Q9(R1), Q10, Q11, Q12, Q14, and Q2(R2)—along with complementary FDA and EMA guidance, provide the foundation for harmonized global oversight. At the same time, sponsors must address practical challenges such as regulatory divergence, analytical complexity, and lifecycle agility.

This review highlights critical themes shaping the current and future CMC landscape for monoclonal antibodies: CQA-driven product and process understanding; specification setting aligned with ICH Q6B and clinical relevance; analytical modernization through information-rich platforms such as MAM and advanced glycoanalytics; PAT-enabled process control and real-time release testing (RTRT); and risk-based viral safety strategies under ICH Q5A(R2). Emerging areas—including digital CMC, continuous and hybrid manufacturing models, and sustainability metrics—are expected to transform regulatory interactions and industry practices over the next decade.

Moving forward, success will depend on proactive integration of regulatory science with technological innovation. Industry stakeholders must embrace data-driven, risk-based approaches to method development, viral safety, immunogenicity risk management, and lifecycle control while fostering early and transparent dialogue with regulators. Ultimately, convergence on harmonized frameworks and adoption of next-generation analytical and manufacturing technologies will be key to accelerating development, ensuring global access, and sustaining the high quality of monoclonal antibody therapeutics for patients worldwide.

References

1. Ecker DM, Jones SD, Levine HL. The therapeutic monoclonal antibody market. mAbs. 2015;7(1):9–14.
2. ICH Q5A(R2). Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. International Council for Harmonisation; 2023.
3. ICH Q6B. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. International Council for Harmonisation; 1999.
4. FDA. Analytical Procedures and Methods Validation for Drugs and Biologics—Guidance for Industry. Silver Spring, MD: U.S. Food and Drug Administration; 2015.
5. EMA. Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products. EMA/CHMP/BWP/157653/2007. London: European Medicines Agency; 2007.
6. ICH Q2(R2). Validation of Analytical Procedures. International Council for Harmonisation; 2023.
7. ICH Q14. Analytical Procedure Development. International Council for Harmonisation; 2023.
8. FDA. Analytical Procedures and Methods Validation for Drugs and Biologics—Guidance for Industry. Silver Spring, MD: U.S. Food and Drug Administration; 2015.
9. ICH Q6B. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. International Council for Harmonisation; 1999.
10. Berkowitz SA, Engen JR, Mazzeo JR, Jones GB. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov. 2012;11(7):527–540.
11. Goyon A, Cecchini D, Zhang K. Characterization of therapeutic monoclonal antibodies at multiple levels by liquid chromatography and mass spectrometry. Anal Chem. 2021;93(1): 382–402.
12. Rogstad S, Faustino A, Ruth A, Keire D, Boyne M, et al. Multi-attribute method (MAM) for characterization, quality control testing, and comparability. mAbs. 2019;11(7):1189–1201.
13. Reusch D, Tejada ML. Fc glycans of therapeutic antibodies as critical quality attributes. Glycobiology. 2015;25(12):1325–1334.
14. Sharma DK, Oma P, Polozova A, et al. Subvisible particle characterization in protein biotherapeutics: current status and emerging technologies. AAPS J. 2019;21(6):107.
15. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol. 2009;27(1):26–34.
16. Gottschalk U. Process scale–down models: strategies for viral clearance studies in biopharmaceutical process validation. Biotechnol Prog. 2005;21(2): 478–484.
17. Shukla AA, Gottschalk U. Single-use disposable technologies for biopharmaceutical manufacturing. Trends Biotechnol. 2013;31(3):147–154.
18. Rogstad S, Faustino A, Ruth A, Keire D, Boyne M, et al. Multi-attribute method (MAM) for characterization, quality control testing, and comparability. mAbs. 2019;11(7):1189–1201.

19. Reusch D, Tejada ML. Fc glycans of therapeutic antibodies as critical quality attributes. Glycobiology. 2015;25(12):1325–1334.
20. Sharma DK, Oma P, Polozova A, et al. Subvisible particle characterization in protein biotherapeutics: current status and emerging technologies. AAPS J. 2019;21(6):107
21. Rosenberg AS. Effects of protein aggregates: an immunogenicity perspective. AAPS J. 2006;8(3):E501–E507.
22. Jawa V, Cousens LP, Awwad M, Wakshull E, Kropshofer H, De Groot AS. T-cell dependent immunogenicity of protein therapeutics: preclinical assessment and mitigation. Clin Immunol. 2013;149(3):534–555.
23. Shankar G, Shores E, Wagner C, Mire-Sluis A. Scientific and regulatory considerations on the immunogenicity of biologics. Trends Biotechnol. 2006;24(6):274–280.
24. van Beers MMC, Jiskoot W, Schellekens H. On the role of aggregates in the immunogenicity of recombinant human interferon beta in patients with multiple sclerosis. J Interferon Cytokine Res. 2010;30(10):767–775.
25. Rathore AS, Bhambure R, Ghare V. Process analytical technology (PAT) for biopharmaceutical products. Anal Bioanal Chem. 2010;398(1):137–154.
26. Konstantinov KB, Cooney CL. White paper on continuous bioprocessing. Biotechnol Bioeng. 2015;112(9):1832–1843.
27. Zydney AL. Continuous downstream processing for high value biological products: A review. Biotechnol Bioeng. 2016;113(3):465–475.
28. FDA. Guidance for Industry: Quality Considerations for Continuous Manufacturing. U.S. Food and Drug Administration; 2019.