FORUM

Development Expert Biologics

Required skill set in development, manufacturing, regulatory and analytics

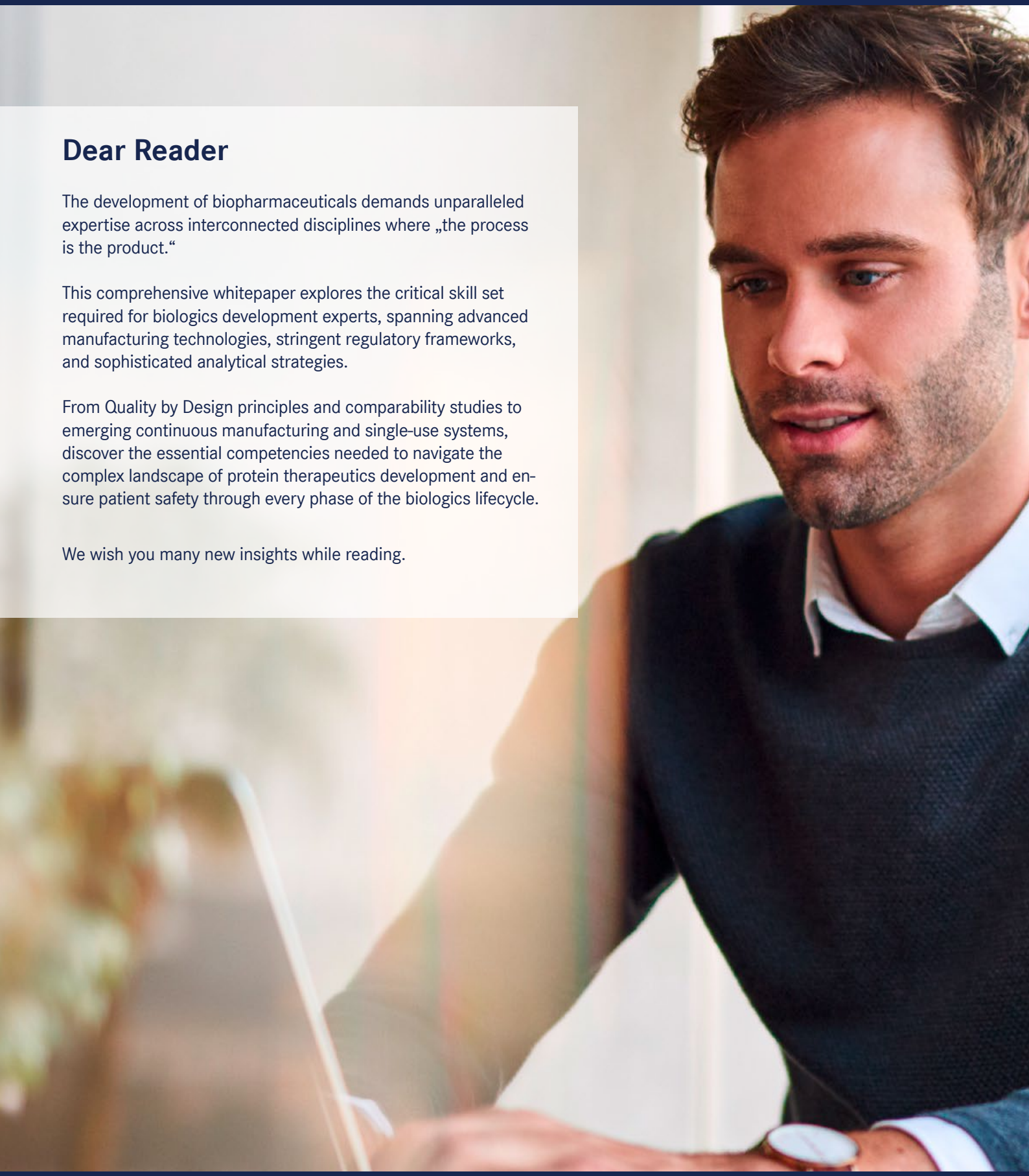
Dear Reader

The development of biopharmaceuticals demands unparalleled expertise across interconnected disciplines where „the process is the product.“

This comprehensive whitepaper explores the critical skill set required for biologics development experts, spanning advanced manufacturing technologies, stringent regulatory frameworks, and sophisticated analytical strategies.

From Quality by Design principles and comparability studies to emerging continuous manufacturing and single-use systems, discover the essential competencies needed to navigate the complex landscape of protein therapeutics development and ensure patient safety through every phase of the biologics lifecycle.

We wish you many new insights while reading.



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“Development Expert Biologics” – Required skill set in the fields of development, manufacturing, regulatory, and analytics.

A scientific researcher, who works in the field of biologics R&D, requires a holistic and highly specialized skill set. In the following you find a summary of the knowledge a “development expert biologics” needs with a focus on the fields of development and manufacturing (awareness of the special features of the process technologies of galenic development and what to look out for in process changes and comparability studies), regulatory requirements (awareness of the critical quality parameters of biologics and biosimilars and challenges of the non-clinical program), and analytics (know-how in the areas of method validation, stability testing and specification development).

1. Development and manufacturing

Covers the manufacturing process of protein active ingredients, formulation development, comparability studies, and the transition from active substance to finished drug product.

The development and manufacturing of biopharmaceuticals represents one of the most complex and challenging areas in pharmaceutical science, requiring deep expertise across multiple interconnected disciplines. For biologics, the fundamental principle that „the process is the product“ governs all aspects of development due to the inherent complexity of production in living cells, which leads to structural heterogeneity that must be carefully understood and controlled throughout the entire lifecycle.

The manufacturing process of protein active ingredients follows a systematic Quality by Design (QbD) approach that creates essential linkages between the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and Critical Process Parameters (CPPs) to ensure consistent product quality. This systematic approach begins with cell line development and cell banking, which serve as the foundation for all subsequent manufacturing activities and directly impact both product safety and quality. These processes require rigorous characterization protocols to verify authenticity, purity, and stability of the cell substrates.

Viral safety considerations and reduction potential evaluation represent critical safety parameters that must be assessed early in development, often before First-In-Human (FIH) studies commence. These safety measures are achieved through validated downstream processing steps, including sophisticated chromatography and filtration techniques. Additionally, Host Cell Proteins (HCPs) emerge as critical process-related impurities that require minimization and control, typically measured through ELISA methods complemented by orthogonal analytical approaches.

The transition from active substance to protein formulation presents unique challenges, as protein drug products exhibit complex susceptibility to both chemical and physical degradation pathways that can significantly impact safety through immunogenicity concerns and reduce therapeutic efficacy. Formulation development therefore becomes a systematic, data-driven process that critically depends on stability-indicating analytical methods and controlled exposure to various stress conditions to identify optimal formulation conditions.

Excipient selection for protein formulations operates within significant constraints, requiring careful consideration of compatibility profiles, potential degradation pathways such as polysorbate degradation, and established regulatory history for parenteral administration. Manufacturing processes introduce inherent stress factors including shear forces, interface exposure, and cryoconcentration effects that can destabilize protein structures, necessitating careful process design and stringent control measures.

High-concentration formulations present particularly challenging development scenarios, especially regarding increased viscosity and injectability requirements that demand specialized development

approaches and novel delivery systems. Primary packaging materials must ensure comprehensive product protection and compatibility, requiring rigorous testing protocols for extractables and leachables evaluation alongside container-closure integrity assessments.

The manufacturing process from active ingredient to finished drug product involves complex regulatory considerations, particularly for Biologics IMPD (Investigational Medicinal Product Dossier) submissions that face unique quality challenges stemming from complex molecular structures, production in living cells, and inherent structural heterogeneity. Good Manufacturing Practice (GMP) compliance becomes mandatory for all Investigational Medicinal Product (IMP) batches across all clinical phases, necessitating appropriate manufacturing or import authorization and Qualified Person (QP) oversight throughout the development process.

Cell line and cell bank characterization represents a critical component of the IMPD, requiring comprehensive evaluation of identity, purity, sterility, stability, and adventitious agents to ensure quality and safety of starting materials. FIH trials demand heightened quality requirements, including stringent evaluation of strength and potency, confirmation of representativeness of toxicological batches, and proven compatibility with clinical administration systems to mitigate unforeseen biological actions.

Comparability studies emerge as fundamental requirements for biopharmaceuticals due to the „process is the product“ principle and the practical impossibility of achieving identical molecular structures following process changes. ICH Q5E serves as the guiding regulatory framework for demonstrating „high similarity“ rather than identity between pre- and post-change products, ensuring no adverse impact on quality, efficacy, or safety profiles. A comprehensive comparability exercise involves structured design elements including thorough risk analysis, detailed process and in-process control comparisons, extensive analytical characterization using sensitive and orthogonal methods, and robust stability studies encompassing accelerated, stressed, and real-time conditions. The rigor required for comparability studies increases progressively with clinical development phases, with full ICH Q5E application expected by Phase III and Marketing Authorization Application stages.

2. Regulatory requirements

Encompasses IMPD requirements, non-clinical aspects for both biologics and biosimilars, and updates on the regulatory landscape including new manufacturing approaches and regulatory tools.

The regulatory landscape for biologics development is characterized by stringent requirements that ensure patient safety while facilitating efficient development pathways. The EU Clinical Trials Regulation (EU) No 536/2014 significantly harmonizes clinical trial application and assessment processes across Member States through a single portal and coordinated review system, streamlining regulatory procedures while maintaining high safety standards.

Strict GMP compliance is required for all IMPs used in clinical trials from Phase I onwards, necessitating appropriate manufacturing or import authorizations and QP oversight. The IMPD must be a comprehensive, phase-dependent submission detailing quality, non-clinical, and clinical aspects according to the Common Technical Document (CTD) format, with specific emphasis on biological product requirements. Robust cell bank characterization, control of raw materials, and validated adventitious agent (viral) safety evaluation are mandatory quality requirements for biological IMPs, even for early-phase trials.

Non-clinical development for biologics aims to provide critical data for safe and efficacious human use, covering pharmacology, pharmacokinetics, and toxicology, guided primarily by ICH S6(R1). Selection of a pharmacologically relevant animal model is paramount for non-clinical studies of biologics, as activity and responses can be highly species-specific. Immunogenicity (ADA formation) in animal studies is a significant concern for biologics; while not predictive for humans, it must be assessed for its impact on PK/PD and for interpreting observed adverse effects. Off-target toxicity, typically assessed via tissue cross-reactivity studies on human tissue panels, is a crucial safety

evaluation for biologics. Dose selection for FIH studies for biologics increasingly emphasizes the Minimal Anticipated Biological Effect Level (MABEL) approach, alongside NOAEL, to define the safest biologically active starting dose.

The regulatory landscape for biosimilars presents unique challenges, as these complex biological products require demonstration of „high similarity“ to a reference product across quality, safety, and efficacy, distinguishing them significantly from small-molecule generics. A comprehensive, stepwise comparability exercise, involving head-to-head analytical, non-clinical, and clinical comparisons using sensitive and orthogonal methods, is central to biosimilar development. Glycosylation is a critical quality attribute for monoclonal antibodies (mAbs) due to its significant impact on biological function, stability, and immunogenicity, and must be carefully evaluated for similarity. While amino acid sequence, posology, and route of administration must be identical, other differences in formulation or excipients must be justified based on their impact on similarity.

Non-clinical development for biosimilars follows a stepwise approach, focusing on demonstrating „biosimilarity“ rather than conducting de novo safety and efficacy studies. Extensive in vitro studies, covering target binding and functional activity, are paramount for biosimilar non-clinical comparability and are often more sensitive in detecting subtle differences than in vivo studies. In vivo non-clinical studies are generally not required if quality and in vitro comparability studies are satisfactory and raise no safety concerns, leading to a tailored program on a case-by-case basis if needed.

Recent regulatory developments include the implementation of Continuous Manufacturing (CM) for biologics, which offers efficiency benefits but presents new challenges in batch definition, control strategy (including adventitious agents), and process validation compared to traditional batch processing. The implementation of Single-Use Systems (SUS) provides flexibility but necessitates rigorous vendor qualification and comprehensive assessment of extractables/leachables to ensure product quality and safety. QbD and Process Analytical Technologies (PAT) are crucial for achieving comprehensive process understanding and control, enabling advanced strategies like Real Time Release Testing (RTRT).

Post Approval Change Management Protocols (PACMPs) and Established Conditions (ECs) are regulatory tools under ICH Q12 that enable proactive and flexible management of post-marketing changes for approved products, with recent EU changes aiming for broader applicability to biologicals. Drug-Device Combination Products have specific regulatory requirements under new EU Medical Devices Regulations, particularly for integral devices, necessitating conformity assessment and functional/compatibility testing.

3. Biopharmaceutical analytics

Details analytical strategies for clinical IMPs, method development and validation, stability studies, ICH Q14 principles, and specifications development.

Analytical strategies for biologics represent a critical foundation for ensuring product quality, safety, and efficacy throughout development and commercial manufacturing. These strategies are systematically governed by ICH Q6B and EMA guidelines, which define specifications and qualification requirements for biological products. QbD principles, especially Analytical Target Profile (ATP) and QTPP, are fundamental for developing robust analytical methods that meet the unique challenges of biological products.

Analytical rigor increases progressively throughout clinical development phases, from GLP requirements for toxicology studies to full GMP standards for consistency lots and clinical trial material. Assay validation is a phased, risk-based process, requiring suitability confirmation for early phases and full validation for later stages. Reference standards are indispensable for method calibration, validation, and product characterization, necessitating thorough characterization and stability assessment to ensure reliable analytical performance.

Analytical method validation is defined by ICH Q2 as demonstrating „fitness for the intended purpose“ across various performance characteristics such as identity, assay, biological activity, and

purity. Key validation parameters include specificity, accuracy, precision (repeatability, intermediate, reproducibility), range, and quantification/detection limits. Specificity and selectivity are crucial to ensure a method unequivocally measures the analyte without interference from other components. Robustness, the method's capacity to remain unaffected by small variations, should be assessed during the development phase to ensure reliable performance under normal use conditions.

Stability studies represent a critical component of analytical development, as proteins are susceptible to various physical (e.g., aggregation) and chemical (e.g., oxidation, deamidation) degradation pathways that must be understood and monitored. Forced Degradation Studies (FDS) are crucial early in development to identify degradation pathways, formulate products, and develop stability-indicating analytical methods. Stability studies are a regulatory requirement (ICH Q1A-E, Q5C), performed throughout development and for marketing authorization, to define product shelf life and storage conditions.

ICH Q14 introduces Analytical Method Lifecycle Management, promoting a systematic, risk-based approach to analytical procedure development and validation. The ATP is a core concept that prospectively defines the objectives and performance criteria of an analytical procedure, guiding its development. Knowledge management (including prior knowledge) and quality risk management are integral to designing robust analytical procedures and making informed decisions throughout the lifecycle. Robustness evaluation, conducted during development, explores the impact of deliberate parameter variations to ensure reliable method performance under normal use.

Specifications are critical quality standards for drug substances and products, defining tests and acceptance criteria to ensure suitability for intended use, and are linked to the manufacturing process, stability, and clinical studies. CQAs, identified through risk assessment, must be included in specifications and are crucial for ensuring product quality related to safety and efficacy. Comprehensive characterization using state-of-the-art and orthogonal analytical methods is essential to establish relevant specifications for complex impurities (e.g., HCPs, aggregates) and biological activity. Specifications are justified by clinical data, batch history, and statistical evaluation, and often undergo tightening post-authorization as process understanding improves. In-process controls (IPCs) are vital for monitoring manufacturing consistency and can sometimes justify waiving certain tests at later stages of development.

Conclusion

Top priorities of a “development expert biologics”

In the following are listed the top priorities concerning the skills of a “development expert biologics”, integrating scientific, technical, and regulatory expertise, from foundational understanding to advanced application.

Experience with emerging technologies and material science

- Knowledge of continuous manufacturing and single-use systems to understand their benefits, challenges, and regulatory implications for biologics manufacturing.
- Understanding of extractables/leachables (E/L) assessment is critical for primary packaging materials and single-use systems to ensure product quality and patient safety.
- Familiarity with drug-device combination products, including their specific regulatory requirements and quality control considerations.

Strong risk management and problem-solving capabilities

- The ability to identify, assess, and mitigate risks across all stages of biologics development is essential for navigating complex scientific and regulatory challenges, and for proactive problem-solving.
- The capability to troubleshoot analytical and manufacturing issues based on a deep scientific and technical understanding of bioprocesses and protein properties.

Proficiency in designing and interpreting comparability and stability studies

- A deep understanding of ICH Q5E for comparability studies is essential for justifying process changes throughout development and ensuring continued product quality, safety, and efficacy.
- Expertise in designing and executing stability studies (real-time, accelerated, forced degradation) which is crucial for understanding degradation pathways, determining shelf life, and supporting formulation and process development.

Comprehensive RA knowledge for biologics development

- A strong grasp of EU Clinical Trials Regulation (EU CTR) 536/2014 and IMPD requirements is critical for successful clinical trial applications and progression.
- In-depth understanding of GMP requirements for Investigational Medicinal Products (IMPs) ensures compliance from early phases onwards, including manufacturing and import authorizations.
- Awareness of specific quality requirements for First-In-Human (FIH) trials, including dose justification (MABEL approach), material representativeness, and compatibility with administration systems.

Understanding of non-clinical development and its CMC interfaces

- Familiarity with non-clinical study design for biologics (ICH S6, S9) is essential to understand how pharmacology, pharmacokinetics, and toxicology data inform clinical development and patient safety.
- Specific awareness of immunogenicity considerations for biologics, including its assessment in non-clinical studies and potential impact on PK/PD and safety interpretation.
- The ability to effectively interface with non-clinical and clinical teams to ensure material consistency, align study designs, and interpret safety findings throughout development.

Mastery of biologics CMC and QbD principles

- A deep understanding of protein structure, heterogeneity, and degradation pathways is essential for anticipating and mitigating quality issues from early development through to the final product.
- Expertise in upstream and downstream processing principles and their impact on Critical Quality Attributes (CQAs) which forms the core of „the process is the product“ for biologics.
- Proficiency in applying QbD methodologies including defining Quality Target Product Profile (QTPP), identifying CQAs and Critical Process Parameters (CPPs), and utilizing risk management to build quality into the product and process from the outset.

Advanced knowledge of analytical method development, validation, and characterization

- The ability to develop and validate „stability-indicating“ and highly sensitive/orthogonal analytical methods is critical for comprehensive characterization, impurity detection (e.g., Host Cell Proteins (HCPs), aggregates), and biological activity assessment.
- Expertise in applying ICH Q2 and ICH Q14 principles, especially for phased assay validation, robustness evaluation, and establishing analytical target profiles and analytical procedure control strategies.

Other offers

Practical regulatory affairs and vigilance knowledge

Our regulatory courses and conferences provide practical information on the fundamentals and trends in marketing authorisation, regulatory maintenance and post-marketing surveillance. More information.

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