
Certified Specialist Programme in Cell Culture Optimization

Regulatory Compliance for Cell-Based Products

Advanced Therapy Medicinal Product (ATMP) – Related terms: cell therapy, gene therapy, tissue-engineered product.

ATMPs are a regulatory category defined by the European Union for medicinal products that are based on genes, cells, or engineered tissues. They are subject to a dedicated regulatory pathway that includes a centralized marketing-authorization application, specific clinical-trial requirements, and post-marketing surveillance. For example, a autologous chondrocyte implantation product is classified as a tissue-engineered ATMP. Practical application involves coordinating with national competent authorities, preparing an extensive dossier that demonstrates quality, safety, and efficacy, and establishing a risk-management plan. Challenges include navigating differing national interpretations of ATMP classification, ensuring traceability of donor cells throughout the manufacturing chain, and meeting the stringent requirements for long-term follow-up data.

Adverse Event Reporting – Related terms: pharmacovigilance, serious adverse event.

Adverse event reporting is the systematic collection, assessment, and communication of any undesirable medical occurrence that follows the administration of a cell-based product. In the United States, sponsors must submit reports to the FDA under 21 CFR 312.32; in the EU, the EudraVigilance system is used. An example is the reporting of unexpected immune reactions after infusion of mesenchymal stromal cells. Practical steps include establishing a robust electronic reporting system, training staff to recognize and document events, and defining timelines for expedited reporting. Challenges arise from the need to differentiate product-related events from underlying disease progression, managing reports across multiple jurisdictions, and ensuring data privacy while maintaining transparency.

ALCOA – Related terms: data integrity, record keeping.

ALCOA stands for Attributable, Legible, Contemporaneous, Original, and Accurate, a set of principles guiding the integrity of data generated during cell-product manufacturing. For instance, each batch record must clearly identify the operator (attributable), be readable (legible), captured at the time of the activity (contemporaneous), stored in its original form (original), and free from errors (accurate). Practical implementation involves electronic batch records with audit trails, regular data-integrity audits, and staff training on proper documentation. Challenges include retrofitting legacy paper-based systems to meet ALCOA, preventing inadvertent overwriting of data, and ensuring that all electronic systems are validated in accordance with regulatory expectations.

Aseptic Processing – Related terms: cleanroom, sterility assurance.

Aseptic processing refers to the series of operations performed under controlled conditions to prevent microbial contamination of cell-based products. It encompasses gowning procedures, use of laminar-flow

hoods, and validated sterilization of equipment. For example, the filling of a cryopreserved cell suspension into vials is conducted inside a Grade A biosafety cabinet within a Grade B background. Practical applications include the development of standard operating procedures (SOPs) that detail air-flow monitoring, personnel training, and environmental monitoring plans. Challenges include maintaining consistent aseptic technique during scale-up, controlling particulate contamination introduced by equipment, and addressing the impact of operator fatigue on aseptic integrity.

Bioburden – Related terms: microbial limit test, sterility testing.

Bioburden is the number of viable microorganisms present on a product or component before sterilization. In cell therapy, bioburden testing is performed on raw materials, containers, and equipment to ensure that the downstream sterilization step is adequate. An example is the quantification of bacterial spores on a single-use bag used for cell expansion. Practical steps involve sampling, plating on appropriate media, and calculating colony-forming units (CFU). Challenges include the low-level detection limits required for high-risk products, variability in sampling techniques, and the need to differentiate between environmental contaminants and process-related flora.

Biosafety – Related terms: containment, risk assessment.

Biosafety encompasses the measures taken to protect personnel, the public, and the environment from exposure to biological agents used in cell-based product development. It includes classification of the work (e.g., BSL-2 for most human cell lines), implementation of containment devices, and emergency response procedures. For example, handling of genetically modified induced pluripotent stem cells (iPSCs) requires a biosafety cabinet and a written biosafety plan. Practical application includes conducting a biosafety risk assessment for each new cell line, training staff on decontamination protocols, and maintaining a biosafety manual. Challenges involve keeping biosafety documentation up to date with evolving regulations, managing cross-contamination risks in shared facilities, and ensuring that all personnel understand the implications of working with potentially tumorigenic cells.

Batch Release – Related terms: certificate of analysis, release criteria.

Batch release is the formal decision, documented by a qualified person, that a manufactured cell-based product meets all predefined specifications and is fit for clinical use. The process involves reviewing analytical test results, sterility data, and documentation of the manufacturing process. For instance, a CAR-T cell product must demonstrate viability >70 %, transduction efficiency >30 %, and absence of microbial contamination before release. Practical steps include compiling a batch record, performing final product testing, and issuing a certificate of analysis (CoA). Challenges include coordinating timely release with clinical schedules, managing deviations that arise during testing, and ensuring that release decisions are auditable and traceable.

Biosimilar – Related terms: comparability, reference product.

A biosimilar is a biologic product that is highly similar to an already licensed reference product, with no clinically meaningful differences in safety, purity, or potency. While most biosimilar discussions focus on proteins, the concept extends to cell-based products that share a common manufacturing platform. An

example is a second-generation allogeneic mesenchymal stromal cell product intended to replicate the clinical profile of an existing approved therapy. Practical applications involve conducting comparative analytical studies, non-clinical functional assays, and possibly a bridging clinical trial. Challenges include establishing sufficient analytical similarity for a complex cell product, navigating regulatory pathways that may differ between regions, and addressing intellectual-property considerations.

Cell Banking – Related terms: master cell bank, working cell bank.

Cell banking is the process of creating and storing cryopreserved cell stocks at defined passage numbers to ensure a consistent source of material for manufacturing. A master cell bank (MCB) is generated from a well-characterized cell line and serves as the ultimate source; a working cell bank (WCB) is derived from the MCB for routine use. For example, an iPSC line is banked at passage 5, with aliquots stored in liquid nitrogen. Practical steps involve validating the cryopreservation protocol, performing sterility and identity testing on each bank, and establishing a retrieval and thawing SOP. Challenges include monitoring genetic stability over time, preventing cross-contamination between banks, and maintaining the cold-chain integrity during transport.

Cell Line Authentication – Related terms: STR profiling, contamination testing.

Cell line authentication is the verification that a cell culture used in production is the intended line and is free from cross-contamination or misidentification. Techniques such as short tandem repeat (STR) profiling, karyotyping, and mycoplasma testing are employed. An example is confirming that a GMP-grade MSC line matches the reference STR profile before batch manufacturing. Practical application includes establishing a schedule for periodic authentication, documenting results in the batch record, and implementing corrective actions if discrepancies are found. Challenges involve the cost and time required for comprehensive testing, the potential for genetic drift during expansion, and the need for rapid turnaround to avoid manufacturing delays.

Clinical Trial Authorization (CTA) – Related terms: investigational new drug, ethics committee.

A CTA is the regulatory approval required to commence a clinical investigation of a cell-based product. In the EU, the CTA is submitted to the national competent authority and includes the investigational medicinal product dossier, protocol, and investigator's brochure. For instance, a Phase I trial of a novel allogeneic NK-cell therapy requires a CTA that demonstrates product safety and manufacturing compliance. Practical steps involve compiling the dossier, addressing queries from the authority, and obtaining ethics-committee approval. Challenges include synchronizing CTA submissions across multiple countries, ensuring the dossier reflects the most current manufacturing data, and managing amendments that arise from protocol changes.

Cleanroom Classification – Related terms: ISO 14644, grade A/B.

Cleanroom classification defines the allowable particulate and microbial load in manufacturing environments. The ISO 14644-1 standard categorizes rooms from ISO 5 (Grade A) to ISO 8 (Grade D), while the EU GMP guidelines use Grades A, B, C, and D. For example, the filling operation for a cell-therapy product is performed in a Grade A environment with a Grade B background. Practical application includes performing regular particle-count monitoring, validating air-flow patterns, and establishing gowning

procedures. Challenges consist of maintaining compliance during equipment changes, controlling ingress of particles during personnel movement, and documenting deviations without compromising product release.

cGMP – Related terms: regulatory compliance, quality system.

Current Good Manufacturing Practice (cGMP) refers to the regulations that ensure products are consistently produced and controlled according to quality standards. For cell-based products, cGMP covers facility design, process validation, documentation, and staff training. An example is the implementation of a cGMP-compliant manufacturing suite for autologous CAR-T cell production. Practical steps involve establishing a quality management system, conducting regular internal audits, and maintaining traceability of all raw materials. Challenges include the high cost of building and qualifying GMP facilities, the need for continuous staff competency assessment, and adapting cGMP principles to rapidly evolving cell-therapy technologies.

cGTP – Related terms: process control, product consistency.

Current Good Tissue Practice (cGTP) is a set of FDA regulations that specifically address the handling of human cells, tissues, and cellular and tissue-based products (HCT/Ps). cGTP requirements include donor screening, record-keeping, and tracking of the product from procurement to distribution. For example, a tissue-engineered skin graft must comply with cGTP for donor eligibility, traceability, and storage conditions. Practical application involves implementing donor-eligibility databases, establishing chain-of-custody documentation, and performing periodic inspections. Challenges revolve around integrating cGTP with cGMP when a product moves from tissue procurement to a manufacturing environment, and ensuring that all personnel understand the distinct regulatory expectations.

Compliance Audit – Related terms: gap analysis, regulatory inspection.

A compliance audit is a systematic, independent examination of an organization's processes and documentation to verify adherence to applicable regulations and internal policies. Audits can be internal or performed by external bodies such as notified bodies in the EU. For instance, an annual GMP audit may review the sterility assurance program for a cell-expansion facility. Practical steps include preparing an audit plan, collecting evidence, reporting findings, and implementing corrective and preventive actions (CAPA). Challenges include maintaining audit readiness amidst frequent process changes, ensuring objective assessment without bias, and addressing audit findings within regulatory timelines.

Certificate of Analysis (CoA) – Related terms: product release, specifications.

A CoA is a document that summarizes the test results of a specific batch of a cell-based product and confirms that it meets predefined specifications. It typically includes identity, potency, sterility, endotoxin, and viability data. For example, a CoA for an autologous stem-cell product will list the cell count, viability percentage, and absence of bacterial contamination. Practical application involves generating the CoA through the quality control laboratory, reviewing it by a qualified person, and attaching it to the batch record before release. Challenges include ensuring that all required tests are completed in a timely manner, preventing transcription errors, and maintaining version control of the CoA template.

Data Integrity – Related terms: ALCOA, electronic records.

Data integrity refers to the completeness, consistency, and accuracy of data throughout its lifecycle. In the context of cell-based product manufacturing, it encompasses raw data capture, electronic record-keeping, audit trails, and secure storage. An example is an electronic batch record system that logs each operator action with a time stamp and prevents unauthorized modifications. Practical steps involve validating software systems, training staff on proper data entry, and performing periodic data-integrity reviews. Challenges include mitigating risks of cyber-security breaches, ensuring that legacy paper records are migrated without loss, and demonstrating compliance during regulatory inspections.

Deviations – Related terms: CAPA, non-conformance.

A deviation is any departure from an approved procedure, specification, or standard operating procedure that could affect product quality. Deviations must be documented, investigated, and, if necessary, corrected. For instance, a temperature excursion in a cell-culture incubator beyond the validated range constitutes a deviation. Practical application includes completing a deviation report, performing root-cause analysis, implementing corrective actions, and updating SOPs where appropriate. Challenges involve distinguishing minor, inconsequential deviations from those that require product hold, ensuring timely investigation, and maintaining a robust CAPA system that prevents recurrence.

Dossier – Related terms: regulatory submission, eCTD.

A dossier is the comprehensive collection of documents submitted to a regulatory authority to obtain marketing authorization for a cell-based product. It includes sections on quality, non-clinical data, clinical data, and risk management. An example is the eCTD (electronic Common Technical Document) dossier for a therapeutic cell line intended for the EU market. Practical steps involve organizing the dossier according to ICH guidelines, ensuring that each module is complete and cross-referenced, and performing internal quality checks before submission. Challenges include managing large volumes of data, coordinating contributions from multiple functional teams, and updating the dossier in response to regulatory feedback.

ECTD – Related terms: electronic submission, regulatory portal.

The electronic Common Technical Document (eCTD) is the standardized format for electronic submission of regulatory dossiers. It provides a hierarchical folder structure that facilitates review by authorities. For example, a cell-therapy manufacturer submits its marketing-authorization application via the EMA's online portal using the eCTD format. Practical application includes using validated eCTD publishing software, ensuring proper metadata tagging, and maintaining version control of documents. Challenges involve aligning internal document management systems with eCTD requirements, handling large multimedia files (e.g., videos of manufacturing steps), and responding to technical queries from the authority regarding file integrity.

EU Clinical Trials Regulation – Related terms: CTR, clinical trial application.

The EU Clinical Trials Regulation (EU) No 536/2014 replaced the Clinical Trials Directive and introduced a centralized portal for trial applications, safety reporting, and results dissemination. It aims to streamline the approval process for cell-based therapies across member states. For instance, a multinational trial of an

allogeneic stem-cell product must submit a single application through the EU portal, which then routes the dossier to each national authority. Practical steps include preparing a harmonized trial protocol, establishing a risk-management plan, and ensuring that the investigational medicinal product dossier complies with both GMP and clinical-trial requirements. Challenges involve coordinating timelines across countries, managing differing interpretations of the regulation, and ensuring that post-trial access provisions are addressed.

FDA 21 CFR Part 1271 – Related terms: HCT/P, IND.

Title 21 CFR Part 1271 is the FDA regulation that governs human cells, tissues, and cellular- and tissue-based products (HCT/Ps). It outlines requirements for donor screening, registration, good tissue practice, and reporting. For example, a company developing a gene-edited T-cell product must register as an HCT/P establishment and comply with Part 1271 in addition to filing an IND. Practical implementation includes establishing a donor-eligibility database, performing sterility testing, and maintaining records of all product movements. Challenges involve integrating Part 1271 requirements with cGMP, addressing the dual regulatory oversight (FDA and OHRP), and ensuring that all personnel are aware of the specific obligations for HCT/Ps.

Good Manufacturing Practice (GMP) – Related terms: quality system, process validation.

GMP is a set of regulations that require manufacturers to ensure that products are consistently produced and controlled according to quality standards. In cell-based product manufacturing, GMP covers facility design, equipment qualification, personnel training, and documentation. An example is the qualification of a bioreactor used for large-scale expansion of CAR-T cells. Practical steps involve establishing a quality management system, performing regular internal audits, and maintaining traceability of all raw materials and intermediates. Challenges include the high capital investment needed for GMP-compliant facilities, the need for continuous staff competency assessment, and adapting GMP principles to rapidly evolving technologies such as genome editing.

GMP Inspection – Related terms: regulatory audit, site visit.

A GMP inspection is an on-site evaluation performed by regulatory authorities to assess compliance with GMP regulations. Inspectors review documentation, observe manufacturing processes, and interview personnel. For instance, a US FDA inspection of a cell-therapy manufacturing site may focus on aseptic technique, equipment qualification, and batch release procedures. Practical preparation includes conducting mock inspections, ensuring that all records are up to date, and addressing any identified observations promptly. Challenges involve maintaining inspection readiness despite ongoing process changes, managing the logistical impact of inspector presence, and responding to inspection findings within stipulated timelines.

GxP – Related terms: quality assurance, regulatory compliance.

GxP is an umbrella term that encompasses all “good practice” quality guidelines and regulations, where “x” can represent laboratory (GLP), clinical (GCP), manufacturing (GMP), and other domains. In the context of cell-based products, GxP ensures that each stage—from research to clinical deployment—meets quality and

safety standards. For example, GLP governs non-clinical studies that support a IND filing, while GCP governs the conduct of clinical trials. Practical application involves aligning SOPs across functional areas, establishing cross-functional training programs, and integrating data from multiple GxP domains into a unified quality system. Challenges include maintaining consistency across disparate GxP requirements, avoiding duplication of effort, and ensuring that data integrity is preserved throughout the product lifecycle.

HEPA Filtration – Related terms: air quality, cleanroom.

High-Efficiency Particulate Air (HEPA) filters remove at least 99.97 % of particles $\geq 0.3 \mu\text{m}$ in diameter and are critical components of aseptic processing environments. In cell-therapy manufacturing, HEPA filters are used in laminar-flow hoods, HVAC systems, and isolators to protect product sterility. For example, a Grade A laminar-flow cabinet is equipped with a HEPA filter that provides unidirectional airflow over the work surface. Practical steps include routine filter integrity testing, scheduled replacement, and monitoring pressure differentials. Challenges include ensuring filter performance after installation, preventing filter bypass during maintenance, and documenting compliance with filter-validation protocols.

Harmonized Standards – Related terms: ISO, EN.

Harmonized standards are technical specifications adopted by the European Commission that provide a presumption of conformity with EU legislation. Standards such as ISO 14644 (cleanroom classification) and ISO 13485 (medical device quality management) are frequently referenced in cell-therapy regulations. For instance, compliance with ISO 13485 supports the quality system requirements for a cell-based medicinal product. Practical application involves selecting appropriate standards during product development, performing gap analyses, and integrating standard-derived procedures into the quality management system. Challenges include keeping pace with updates to standards, interpreting the scope of each standard in relation to specific cell-therapy processes, and demonstrating that compliance is maintained throughout the product lifecycle.

Informed Consent – Related terms: patient enrollment, ethical review.

Informed consent is the process by which a trial participant voluntarily agrees to partake in a clinical study after being fully informed of the purpose, procedures, risks, and benefits. For cell-based therapies, consent documents must also address issues such as cell source, potential genetic modifications, and long-term follow-up. An example is a consent form for a patient receiving an autologous stem-cell infusion, which outlines the collection of bone-marrow aspirate and the possibility of unforeseen adverse events. Practical steps include drafting clear consent language, obtaining approval from an ethics committee, and maintaining a signed copy in the trial master file. Challenges include ensuring comprehension across diverse patient populations, updating consent documents when protocol amendments occur, and managing re-consent for long-term follow-up studies.

IND – Related terms: investigational new drug, FDA submission.

An Investigational New Drug (IND) application is the regulatory submission required in the United States to begin clinical testing of a new cell-based product. The IND includes preclinical data, manufacturing information, and the clinical protocol. For example, a company developing a gene-edited T-cell therapy

submits an IND that details the vector design, cell processing steps, and safety data from animal studies. Practical application involves compiling the CMC (Chemistry, Manufacturing, and Controls) section, addressing FDA questions, and obtaining clearance before enrolling the first patient. Challenges include aligning IND timelines with manufacturing scale-up, addressing FDA concerns about vector safety, and ensuring that any changes to the manufacturing process are reflected in supplemental INDs.

International Council for Harmonisation (ICH) – Related terms: guidelines, QRM.

The ICH is a global organization that develops harmonized guidelines for the development and registration of pharmaceuticals, including cell-based products. Key guidelines relevant to regulatory compliance are Q7 (Good Manufacturing Practice for Active Pharmaceutical Ingredients), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System). For instance, applying ICH Q9 helps a cell-therapy manufacturer assess risks associated with donor variability. Practical steps include adopting ICH-based SOPs, training staff on guideline intent, and integrating ICH principles into the quality system. Challenges involve interpreting guidance intended for small-molecule drugs in the context of complex biologics, and ensuring that local regulatory authorities accept the ICH-based approach.

Joint Research Center (JRC) – Related terms: EU scientific support, standardization.

The European Commission's Joint Research Center provides scientific and technical support to EU policy makers, including the development of standards for advanced therapies. The JRC may publish reference methods for cell-based product characterization or assist in the creation of EU-wide databases for donor screening. For example, the JRC contributed to the development of a harmonized protocol for measuring potency of mesenchymal stromal cells. Practical application includes consulting JRC publications during method development and participating in collaborative projects coordinated by the JRC. Challenges include aligning internal validation data with JRC-published methods and navigating the time required for consensus-building among multiple stakeholders.

Karyotype Stability – Related terms: genetic integrity, cell line monitoring.

Karyotype stability refers to the maintenance of a normal chromosome complement in a cell line over successive passages. In cell-based product manufacturing, monitoring karyotype is essential to ensure that the therapeutic cells have not acquired deleterious chromosomal abnormalities that could affect safety or efficacy. An example is performing G-banding analysis on a batch of induced pluripotent stem cells before release. Practical steps include establishing a schedule for karyotype testing, defining acceptance criteria (e.g., $\leq 5\%$ of cells with abnormalities), and documenting the results in the batch record. Challenges include the time-intensive nature of cytogenetic analysis, the possibility of sub-clonal changes that escape detection, and the need to balance thoroughness with manufacturing timelines.

Lot Release – Related terms: final product testing, qualified person.

Lot release is the formal approval by a qualified person that a manufactured lot of a cell-based product meets all required specifications and is ready for distribution. It involves reviewing analytical data, sterility results, and compliance with the manufacturing record. For instance, a lot of allogeneic MSCs must demonstrate viability $>80\%$, identity markers CD73+, CD90+, CD105+, and negative microbial cultures

before release. Practical application includes compiling a release dossier, signing the release certificate, and updating the inventory system. Challenges include coordinating release timing with clinical site needs, handling out-of-specification results without delaying patient treatment, and ensuring traceability of each released lot.

Manufacturing Release – Related terms: product release, quality control.

Manufacturing release is the comprehensive process of confirming that a cell-based product, from raw material receipt through final packaging, complies with all quality attributes defined in the product specification. It encompasses in-process controls, final product testing, and documentation review. An example is the release of a cryopreserved CAR-T cell product after confirming transduction efficiency, sterility, and endotoxin levels. Practical steps involve finalizing the batch record, performing a final review by the quality assurance department, and issuing a certificate of analysis. Challenges include managing the tight window between product release and patient infusion, integrating multiple testing platforms, and maintaining a robust audit trail for each release decision.

Microbial Limit Test – Related terms: bioburden, sterility testing.

The microbial limit test determines the presence and quantity of microorganisms in a non-sterile product or component. In cell-based manufacturing, it is applied to raw materials such as media, supplements, and containers. For example, a microbial limit test on a batch of serum-free medium may involve inoculating the medium onto agar plates and incubating for 7 days. Practical application includes selecting appropriate media, establishing acceptance criteria (e.g., $\leq 10 \text{ CFU mL}^{-1}$), and documenting results in the batch record. Challenges involve detecting low-level contamination, differentiating between environmental contaminants and product-related flora, and ensuring that testing does not delay the manufacturing schedule.

Non-clinical Studies – Related terms: toxicity testing, pharmacodynamics.

Non-clinical studies provide pre-clinical data on the safety and biological activity of a cell-based product before human exposure. They typically include in-vitro potency assays, animal toxicology, and biodistribution studies. For instance, a mouse model may be used to assess tumorigenicity of genetically modified MSCs. Practical steps involve selecting appropriate models, defining study endpoints, and complying with GLP standards. Challenges include the limited predictive value of animal models for human cell therapies, ethical considerations of using large-animal studies, and the need to generate sufficient data to satisfy regulatory expectations while preserving limited cell material for clinical use.

Nucleic Acid Testing (NAT) – Related terms: viral screening, donor testing.

NAT is a molecular method used to detect viral genomes (e.g., HIV, HBV, HCV) in donor blood or tissue samples. In cell-based product manufacturing, NAT is performed on donor material to mitigate the risk of pathogen transmission. For example, a donor's peripheral blood mononuclear cells are screened by PCR for hepatitis B surface antigen DNA. Practical application includes establishing a validated NAT assay, defining the detection limit (e.g., 10 IU mL^{-1}), and integrating results into the donor eligibility database. Challenges involve maintaining assay sensitivity, handling false-positive results, and ensuring that NAT results are available before cell processing begins.

Ongoing Stability – Related terms: shelf-life, real-time testing.

Ongoing stability studies assess the quality of a cell-based product over its intended storage period under defined conditions. They provide data to support shelf-life claims and determine appropriate storage temperatures. For example, a cryopreserved NK-cell product may be stored at – 150 °C and periodically tested for viability, phenotype, and cytotoxic activity over 12 months. Practical steps include establishing a stability protocol, selecting appropriate time points, and using validated analytical methods. Challenges include the long duration of stability studies, the need for sufficient product quantity to support testing, and the potential for degradation mechanisms that are not apparent until later time points.

Process Validation – Related terms: IQ, OQ, PQ.

Process validation demonstrates that a manufacturing process consistently yields a product meeting its predetermined specifications. It typically comprises Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). For a bioreactor-based expansion of T-cells, IQ confirms equipment installation, OQ verifies that the bioreactor operates within specified parameters, and PQ demonstrates that the process produces cells with the required phenotype and potency. Practical application involves defining critical process parameters (CPPs), establishing acceptance criteria, and documenting results in a validation report. Challenges include the inherent variability of biological systems, the need to re-validate after equipment changes, and ensuring that validation data remain relevant over the product's lifecycle.

Quality Risk Management (QRM) – Related terms: ICH Q9, risk assessment.

QRM is a systematic approach to identifying, evaluating, and controlling risks to product quality. ICH Q9 provides the framework for implementing QRM in pharmaceutical development and manufacturing. For cell-based products, QRM may be applied to assess risks associated with donor variability, process deviations, or storage conditions. An example is a risk-assessment matrix that scores the likelihood and impact of contamination events during aseptic filling. Practical steps include forming a cross-functional risk team, using tools such as Failure Mode Effects Analysis (FMEA), and documenting risk-mitigation actions. Challenges involve quantifying risks for complex biologics, maintaining risk registers over time, and ensuring that risk assessments are proportionate to the product's risk profile.

Qualified Person (QP) – Related terms: product release, EU regulation.

A Qualified Person is a legally designated individual in the EU who is responsible for certifying that each batch of a medicinal product complies with the marketing-authorisation requirements before it is released to the market. The QP must hold appropriate qualifications and experience in pharmaceutical manufacturing. For a cell-therapy product, the QP reviews batch records, analytical data, and GMP compliance before signing the release certificate. Practical application includes maintaining a register of QPs, providing ongoing training, and ensuring that the QP is independent of the manufacturing team. Challenges involve the scarcity of qualified personnel with both clinical and manufacturing expertise, managing QP responsibilities across multiple product lines, and meeting the regulatory requirement that the QP be present on-site during release activities.

Regulatory Submission – Related terms: dossier, marketing authorization.

A regulatory submission is the formal package of documents submitted to a health authority to obtain marketing authorization for a cell-based product. It includes sections on quality (CMC), non-clinical data, clinical data, and risk management. For example, a company prepares a Common Technical Document (CTD) for submission to the FDA (as an IND) and to the EMA (as an MA). Practical steps involve coordinating contributions from R&D, manufacturing, and clinical teams, ensuring that all data are up-to-date, and meeting electronic submission requirements. Challenges include synchronizing timelines across regions, addressing divergent data expectations, and managing post-submission queries that may require additional studies.

Risk Assessment – Related terms: hazard analysis, mitigation.

Risk assessment is the process of identifying potential hazards, evaluating their likelihood and impact, and determining appropriate control measures. In the context of cell-based products, risks may relate to donor screening, process deviations, or product transport. An example is assessing the risk of temperature excursions during shipment of a cryopreserved product and implementing insulated containers with temperature loggers. Practical application includes using tools such as FMEA or HACCP, documenting the assessment in a risk-management file, and reviewing the assessment periodically. Challenges involve quantifying risks for low-frequency events, integrating risk assessments into the overall quality system, and ensuring that mitigation strategies are feasible and cost-effective.

Release Criteria – Related terms: specifications, batch release.

Release criteria are the predefined specifications that a cell-based product must meet before it can be released for clinical use. They typically include identity markers, potency assays, viability, sterility, endotoxin levels, and storage conditions. For a CAR-T cell product, release criteria may require $\geq 30\%$ transduction efficiency, viability $\geq 70\%$, and negative sterility test. Practical steps involve establishing these criteria during