System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
Quality[a)]: • Quality management/ oversight • Personnel training • Documentation & records • Product release • Change management • Deviations/investigations • CAPA (Corrective Action Preventive Action) • Auditing • Quality agreements	Personnel have science background & are trained in routine laboratory practices but should also be made aware of GMP principles. Signed notebook records are kept of production and testing activities. If batches fail, they are studied to increase product and process knowledge. R&D activities are well documented in the notebooks, as well as in periodic development reports. There is a need to document source/ pedigree/ chain of custody of biological starting materials – cell ancestor and any animal materials used to create the initial cell line to the extent feasible (Reference Appendix 1 and in section 3.3.3 of this technical report for more information).	GLP practices are implemented as per regulations in specific global regions EU and FDA GLP Requirements cover the areas of: • Organization and Personnel • Facilities • Equipment • Facility Operation • Articles • Protocol and Conduct • Records and Reports • Disqualification There is a need to document the Tox lot and reference standard material with sufficient diligence to allow comparability to clinical/GMP lots later.	It is expected that a laboratory director with a science background is in charge of the Quality Unit (or equivalent function) and reviews all procedures and documents. Use of batch records are highly recommended but could be generic. The Bulk Drug Substance is released by QA/QP after satisfactory review of the manufacturing and analytical records and data (e.g. Completed batch record, analytical results, COA, environmental and water monitoring data, deviations and changes), as well as compliance to the investigational new drug registration (e.g., IND, IMPD). Manufacturing or testing deviations or unexpected events that do not impact product quality or patient safety should be documented, but could be appended to the executed batch records. Formal deviation and CAPA systems are recommended, albeit a simple and uncomplicated system, with the level of investigation dictated by the severity of the incident. Change management is important during development of a product and the process to catalogues changes and facilitates product / process understanding. A system should be in place at all GMP manufacturing facilities. Auditing/self-assessment is recommended, even though it is not mandated. Testing or manufacturing conducted by a third party should be subject to a written agreement that might outline critical quality expectations but a separate quality agreement may not be required.	Responsibilities are governed by CGMP (e.g., ICH Q7 Eudralex - Volume 4 Good Manufacturing Practice Guidelines, and its Annex 13 by phase of development for some items (e.g., as methods are fully validated or transferred, as master batch records are created). QA/QP responsibilities must not be delegated to another functional area (unless allowable by local law), but may be contracted to a qualified external service providers. QA/QP takes a more active role in directing investigations and approving findings and CAPAs. The reporting structure and hierarchy of the Quality Unit should ensure its ability to be independent from production. (From ICH Q7: There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities). Quality standards (e.g., policies, SOPs) must be reviewed and approved by QA. Even when these standards and procedures have not been formally changed, they should be subject to periodic review in order to ensure that they are still valid and up to date with actual practices. It is recommended that for each phase of clinical development, the relevant summary development reports should be completed to review process development activities and results. The reports should include an evaluation of deviations and unexpected results that are encountered during clinical production, scale up, tech transfer, characterization studies, etc. The Bulk Drug Substance is released by QA/QP after review of the completed batch record, COA, environmental and water monitoring data, deviations and changes, the investigational new drug registration (e.g., IND, IMPD), and any other relevant information available in the product specification file as specified in the procedures for batch release. QA/QP can delegate the release of manufactured intermediates to other qualified personnel upon formalized agreements and acceptance.	

System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
				As clinical development proceeds, more detailed batch records with acceptance criteria or target values should be developed. Master batch records should be used prior to conducting process validation. Deviations should be recorded in the batch records as well as require formal investigations and CAPA. Deviation and investigations are increasingly thorough as clinical development proceeds. By Phase 3 a formal deviation tracking system and a CAPA system should be in place. Clinical materials should not be distributed to external partners of the clinical supply chain until all open deviations, test results, or other documentation are closed and approved by QA/QP. Changes during the initial phases of clinical development should be documented and justified based on the magnitude of the change. Significant changes to the process should be conducted in accordance with a written change management procedure and the IND should be updated accordingly. As clinical development progresses a formal change control program should be developed for Phase 3. Any potential impact of the change on on-going trials should be considered. Changes made during production operations must be reviewed by QA/QP during batch disposition. QA/QP audits should be conducted based upon a risk assessment. Typically, fewer audits are conducted for early phase development operations and compounds. Personnel must be trained on the manufacturing and testing activities in which they are involved and this training must be documented. This will vary by area as well as phase of clinical development. CGMP training must be given on a periodic basis to all personnel involved in CGMP activities. Quality agreement should be in place as manufacturing and testing activities are contracted out. The contracts should be approved by QA/QP. In the initial clinical manufacturing there is very little understanding of the level of cleaning required for the new process and soil stream and thus each soiling and cleaning should be thoroughly examined to determine worst case soiling locations and the capability of the cleaning process to remove it. As experience is gained sampling and testing can be tailed off to minimal verification and after the process is finalized cleaning validation can replace the need for monitoring each production event. Same for reused chromatography media, removal of storage solutions, etc., more testing and assurance is required up front to establish performance parameters, then only critical parameters need to be monitored once established. Process change-over procedure should be defined based on risk assessments and should evolve as additional products are introduced in the facility and as the clinical development program proceeds.

System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
Facilities: • Critical utilities • Non critical utilities • Water • Process gases • Segregation/ containment • Maintenance/ sanitation	Appropriate for Laboratory. Use of high quality water (WFI or RO Water plus bioburden-reduction filtration with testing for endotoxin) for cell culture is preferred (as per local regulations and guidance). Creation and banking of cell lines is a critical activity and appropriate segregation/containment needs to be provided for this activity (see also section 3.3.3 and Appendix 1).	R&D or Phase 1 approach may be appropriate based on a risk assessment Bioburden, Bioassay and endotoxin control of material intended for testing in animals would be appropriate.	Facilities should be suitable for the intended use including measures to facilitate cleaning and maintenance, and to prevent cross contamination and contamination of the bulk drug substance. Critical utilities (e.g., those in direct contact with the in-process intermediates or part of the bulk) should be appropriately qualified or monitored to ensure suitability for use in humans. Area classifications and air quality should be consistent with operational requirements (e.g., critical open operations should be performed in an ISO 5 environment such as biological safety cabinet). An effective facility cleaning and sanitization program should be in place. Consideration should be given to establishing an appropriate flow of raw materials, gowned personnel and clean equipment from clean to dirty areas, as well as removal of spent materials, components, equipment and waste. For low bioburden biological drug substance (API) manufacture, consideration should be given to the following: **(a) Upstream production** Cell (bacterial or mammalian) scale up in flasks, roller bottles etc. for open manipulations to be carried out in a biosafety bench with HEPA filters supplying an ISO 7 environment. **(b) Main Production in closed systems such as cell bioreactors and bacterial fermenters which are steam sterilized to be done in an EU Grade D area.** **(c) Downstream processing** Recombinant protein purification by chromatography columns should be carried out in at least ISO 8 clean rooms, depending on the nature of operations. For open operations, a higher classification should be considered. Microbiological control should include 0.2µm filtration at appropriate stages of the purification process.	Facilities should be suitable for the intended use including measures to facilitate cleaning and maintenance, and to prevent cross contamination and contamination of the bulk drug substance. This should include appropriate delineation of controlled manufacturing areas, area segregations and pressure differentials. Critical utilities (e.g., water and HVAC) should be commissioned and qualified through IQ, OQ and PQ programs and maintained as defined in specific facility master plans. Non-critical utilities should be commissioned and maintained in good repair through preventive maintenance programs. Effective facility cleaning and sanitization programs should be developed and implemented by Phase 3. Procedures should be in place prescribing the flow of materials, equipment and personnel in and out of controlled manufacturing areas. An alarm strategy for critical measurements should be in place.	

System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
Equipment: • Qualification • Maintenance • Cleaning G • Calibration • Computerized systems	Equipment can be commercial off the shelf, as applicable. It is maintained, cleaned and calibrated as per vendor recommendations. Computerized systems are as supplied with the equipment.	R&D or Phase 1 approach may be appropriate based on a risk assessment, Calibration and Preventive Maintenance (PM) measurement devices must performed	Equipment should be commissioned, calibrated and monitored as required to ensure fit for use. Equipment used for cell culture/fermentation or bulk fill should be sterilized by a validated process or should use sterile disposable equipment. Records of equipment cleaning and use should be generated and maintained. Computer systems should be qualified for the intended use.	Critical equipment should be fully qualified prior to the initiation of process validation runs. A preventive maintenance, cleaning/sanitization/sterilization and calibration program should in place and fully documented per ICH Q7. Cleaning and sanitization/sterilization processes should be validated prior to conformance lot production. Computer systems for critical GMP equipment should be validated. Alert and action alarm levels for deviations from set points and process parameters should be defined based on risk assessment.	
Materials: • General controls • Receipt and quarantine • Sampling and testing • Storage and expiry • Warehousing procedures • Cell bank maintenance • Supplier qualification • Recordkeeping	No specific practices beyond, a CoA and expiry (if available) check on all incoming items and documentation of use; Storage and expiry as per vendor recommendation. Cell banks are maintained as appropriate (i.e. LN2 tank with vial position recorded in notebook). Storage of the MCB and RS be done in CGMP quality temperature controlled units or that are at least qualified for use and have regular calibration and periodic or continuous temp monitoring	R&D or Phase 1 approach may be appropriate based on a risk assessment but for example, if a tox lot is to be made in the same facility as Phase 1 or clinical materials from other product lines cell lines, some testing is required prior to use in the facility used to produce CTMs.	Good control over materials is required to ensure their proper receipt, storage, release and integrity. The extent of supplier qualification depends both upon the phase of development and upon the criticality of the material. Material is classified through a risk-based approach utilizing process knowledge as it becomes available from process development. In the QC area, critical reagents should be defined and included in the documentation. Vendors should be qualified utilizing a risk-based approach – qualification should be more thorough (e.g., audits vs. questionnaires) for higher risk materials (i.e., that are critical to the process and product quality). Commercial suppliers are identified during later phases. The frequency of vendor reassessment should also be determined using a risk-based approach. Inventory control should be managed to maintain integrity and prevent mix-ups and utilize First In First Out (FIFO) or First Expired First Ordered (FEFO). Vendor COA with ID test can be used to accept incoming raw materials. Storage and expiry as per vendor recommendation. If possible, use of animal/human-derived raw materials should be avoided due to concerns about adventitious agents. Release of raw materials based on a certificate of analysis (CoA) is acceptable if there is an identity test.	Same controls as in Phases 1 and 2. In addition, suppliers should be fully qualified during Phase 3 with risks to supplies identified and mitigated. (it is recommended to have back up suppliers when possible)	

System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
Production: • Production operations • Media • Buffers • Bioreactors • Harvest • Purification • Formulation • Filtration, bulk fill • Hold times • In-process sampling and controls • Pooling criteria • Contamination controls • Cross-contamination controls	Quality by Design Principles could be applied to the development phase and used to begin identifying the design space and control strategy (see ICH Q8 for more detail on this concept). Routine laboratory safety, documentation and quality practices are followed. General laboratory cleanliness practices are employed to minimize bioburden. Procedures and equipment usage are recorded in lab notebooks or electronically; reagents, calibrations and key supplies and samples are tracked in logbooks. At a minimum, there should be area clearance and segregation and labeling of product- dedicated equipment. The source of the cell line and any animal derived materials (FBS etc.) used in the development of the cell line should be researched, documented and/or reserve samples secured. The use of human/animal origin materials should be avoided wherever possible (see also section 3.3.3 and Appendix 1).The R&D team should coordinate early with the Quality Unit concerning the sources, grade and critical characteristics of complex or exotic raw materials to ensure that they can be integrated into GMP raw material quality management systems when required. Reliability of the supplier should also be taken into account.	As per R & D; process and equipment scaled to be sufficient for animal study batch.	Process consists of high quality cell culture, chromatography, filtration and other unit operations. Process and equipment scaled based on size of projected clinical batch. Process-grade equipment, scaled to the batch size, is used. Equipment should be routinely monitored and calibrated. Low bioburden practices (e.g. filtration of buffers, sanitization of columns, etc.) should be implemented. Generic batch records capture most salient process steps and in-process data (e.g. step yields, processing times, column and filter pressures, chromatography loading and elution strategies/parameters, bioreactor conditions, etc.), a sufficient number of IPC should be recorded but acceptance criteria for in-process controls and results are not yet set. Initial acceptance ranges and some early CPPs are being identified. Process flow charts begin to be used to document current process knowledge and this will continue throughout Phase 3. Cell culture media should be filtered through 0.1.1 um filters prior to use to reduce the risk of mycoplasma contamination. Animal derived raw materials should be treated to reduce the risk of contamination by adventitious agents (heat, ionizing radiation, etc.)	Same as Phase 1, but acceptance ranges and presumptive CPPs should be established. Product specific batch records should start to be drafted and implemented. Process understanding utilizing a QbD approach recommended. Preliminary acceptance ranges for IPC should be defined.	Near-final process and equipment choices should be set (but can be at a reduced scale relative to commercial, if warranted). All CPP should be identified and ranges set for manufacturing of registration/ conformance batches based on laboratory studies or a risk analysis prior to the start of the Process Performance Qualification (PPQ) batches. Product specific batch records should be used that include acceptance criteria for in-process controls and results. Stringent low bioburden practices (e.g., filtration of buffers, sanitization of columns, etc.) should be implemented. Alert and action levels should be defined based on risk assessment and identified critical process parameters and/or other.

System	R & D	Toxicity Studies	Phase 1 [b, c, d]	Phase 2 [b, c]	Phase 3 [d]
Laboratory: • General controls • Testing intermediates and bulk • Validation of analytical methods • Expiry and retest dating • Reserve and retention samples	Quality by Design Principles should be applied to the selection, development and qualification of appropriate assays. Expiry and storage of assay reagents can be set as per vendor recommendations. Reserve samples should be sufficient to bridge equivalency to subsequent batches.	Testing as per R & D, but includes tests for attributes that can confound animal testing (e.g. such as contaminant and impurities that may generate erroneous results: MAP/HAP and LAL).	Lot, in-process and stability testing as per regulatory dossier is implemented. Typically the minimal approach would be to have sufficient stability data in for the bulk storage to justify its retest date. OOS results are investigated with QA/QP involvement focusing on root cause. Analytical instrumentation calibrated and on a suitable PM schedule. Vendor equipment packages demonstrate that scientifically sound results are produced. System suitability tests are advised to be part of the testing methods. Initial method qualification for most assays should be initiated; safety-critical assays may need to be validated (e.g. sterility, virus). Lab equipment, balances and pipettes should be routinely calibrated on a PM schedule. Expiry and storage of assay reagents is set as per vendor recommendations. Reserve samples are sufficient to bridge equivalency to subsequent batches. Assays procedures and results are recorded in analytical batch records or a LIMS system; samples, reagents, calibrations and key supplies are tracked in logbooks. Analytical results, or at a minimum the CoA, are reviewed by QA/QP.	Same as Phase 1, but method qualification at a more advanced stage At this stage, attention should be given to assuring specificity of process residue testing and the development of host cell specific reagents (proteins and DNA) as standards for use in testing later. Process intermediates and bulk drug substance samples from early lots should be secured and frozen to support subsequent in depth characterization that might be required later if project progresses to pivotal trials.	Lot, in-process and stability testing as per regulatory dossier is implemented. OOS investigation should comply with out of specification regulatory requirements for the appropriate global region(s). Analytical assay validation activities should be at an advanced stage or complete (before registration stability lost are manufactured) lots). Laboratory equipment, balances and pipettes should be routinely calibrated on a PM schedule. Complex analytical equipment (e.g. HPLC, Mass-Spec, etc.) may need to be qualified. Expiry and storage of assay reagents and samples is set as per vendor recommendations, scientific knowledge and/or experimental data. Reserve samples are sufficient to bridge equivalency to subsequent batches. Assays procedures and results are recorded in analytical batch records or a LIMS system; samples, reagents, calibrations and key supplies are tracked in logbooks. Analytical batch records and logbooks are reviewed by QA/QP.
Packaging/Labeling: • General controls • Packaging materials • Label issuance & control • Packaging and labeling operations	Considerations should be applied to the selection of the appropriate packaging for shipping, and to the clear labeling of containers used for the drug substance. Choice of containers must be technically assessed in order to reduce the likelihood of contamination, leaking, breakage, etc.	As per R& D, in addition, the test articles must be stored according to the required conditions (such as to protect the bulk/drug substance from light, etc.).	Bulk protein containers are labeled with material ID, lot number and date. Care should be taken to prevent labels from falling off or smearing under freeze or thaw conditions. Containers use materials certified by vendors as non-interactive for standard aqueous solutions. The labeling operation should be controlled to prevent mislabeling and recorded in a batch record. Samples of the final bulk should be available for testing, without the need to access the primary bulk containers.	Bulk Packaging components must be demonstrated to be suitable for their intended use. This requires that the components have an approved specification or test data indicating that they are compatible with the bulk API and will not impact its stability, safety or purity. Bulk container labeling operations should be controlled to prevent mix-ups and recorded in the batch record.	