ECA Foundation
Fostering harmonisation of GMP/GDP regulations

ECA Good Practice Guide – GMP Auditors Reference Handbook

– Attachment 3: Audit Areas and Criteria –

A guidance document by the ECA Foundation
Version 4.0; April 2026

Contents

A. Pharmaceutical Quality System

A company's pharmaceutical quality system (PQS) should describe the procedures and controls in place to ensure reliable operations across the organisation.

The PQS should ensure all operations follow current GMP requirements and local regulatory expectations and comply with licensing requirements.

Audits of the PQS are detailed in various guidelines, but especially in chapter one of the EU-GMP guidelines. Examples of what to look for when auditing the PQS are indicated in this chapter.

Aspect	**Possible details to evaluate**
Structure of the PQS	Consistency across the process?
	Are all processes clearly defined?
	Are elements of the PQS reviewed and approved by management and the Quality Unit?
	Are responsibilities clearly defined?
Regulatory status	Is the company operating within its authorised licences?
Company organisation	Is an organisational diagram in place illustrating roles and responsibilities of key roles?
	Is the company staffed appropriately?
	Is the Quality Control Unit operating independently of production?
Release system	Who is responsible for batch confirmation, certification and release?
	Who actually performs batch confirmation, certification, and release, and can decisions be made independently of other management functions?
	Is all relevant documentation and information related to each batch available at the point of review, confirmation, certification and release?
	Are the functions involved appropriately resourced to ensure a full overview?
Deviation handling	Is there a clear definition of a deviation and how deviations are classified (e.g. incident, minor, major, critical)? Note: different organisations may use different terms when referring to these processes, and this is acceptable as long as the definitions are clear and all processes are covered.
	Who is responsible for investigating and reporting deviations?

Aspect	Possible details to evaluate
	Who is responsible for reviewing and approving the investigation report?
	Who assesses the impact of the deviation on the final batch before confirmation, certification and release?
	Are flow charts available for associated processes?
	What actions are taken when serious deviations are reported, and how are actions justified and documented?
	Are all personnel trained in the processes?
	How many deviations are overdue, and how are they treated (deviation, extension, etc.)?
Corrective and Preventive Action (CAPA)	Are there clear definitions of the terms used (e.g. corrections, corrective actions and preventive actions)?
	Are CAPAs defined when needed? And if no CAPA is opened, how is this justified / documented?
	How are effectiveness checks realised?
	Is the Quality Unit involved in defining, closing and approving CAPAs?
	Are all personnel trained in the processes?
Root cause analysis (RCA)	Is the RCA process clearly defined in a procedure?
	Has the organisation defined and provided useful RCA tools?
	Are RCA processes logical and scientifically sound, and have the potential root causes and contributing factors been identified?
	Are the defined CAPAs based on root causes?
	How is the Quality Unit involved in defining, closing and approving an RCA?
	Are all personnel trained in the processes?
	Are there any repeated RCAs (e.g. 'human error') reported with no clear corrective action to resolve the issue?
Change Control	Are types of changes and relevant responsibilities defined?
	Is the process / are further batches halted until the change is fully implemented (when appropriate)?
	Is an impact analysis available for the change and each action that leads to the change, and is there a requirement

Aspect	Possible details to evaluate
	for an effectiveness check for each change / action? If not, how is this justified?
	How many changes are overdue? How are they handled (deviation or extension, etc.)?
	Is the Quality Unit involved in closing and approving a change?
	Are all personnel trained in the processes?
Supplier management	Does the audit programme define the frequency of audits? A company may use a risk-based approach, as described in chapter 3 of this guide. An auditor should check this approach and the associated documentation.
	Are the audits performed as defined in the programme?
	Are the audits performed by trained auditors?
	How is supplier performance monitored and linked to the qualification?
	Do the responsible positions (QP, Purchasing) have access to relevant data and audit reports? Are they aware of possible deficiencies and the corrective actions agreed upon?
	Is there a formal assessment of the impact on product quality when serious deficiencies are reported?
	Are quality agreements in place for every outsourced activity? Is the Quality Unit involved (e.g. in review and approval)?
Training system	Is there a GMP / GDP training programme for new employees?
	Is training recorded, and is it possible to track staff training to the tasks they performed?
	How is training realised (online, classroom, shop floor)?
	Who trains, and what are the requirements to become a trainer?
	How are effectiveness checks done and documented?
	How are personnel disqualified for processes, if necessary? How is disqualification recorded and communicated?
Internal audits	Is there an SOP in place to describe the IA process?
	Is there an annual plan / schedule in place?

Aspect	Possible details to evaluate
	Does the company adhere to the schedule, and how are overdue IAs addressed?
	Who is performing IAs and how are the auditors trained?
	Are the actions arising incorporated into the Corrective and Preventive Action (CAPA) system?
Document management	Is there a version control for each GMP-relevant document including unique number and version number?
	Are documents distributed and tracked appropriately?
	Is the documentation hierarchy clear, and are documents structured?
	Are the documents reviewed periodically as defined in the Document Management procedure, or earlier if required?
	Is there a link between the Change Control and Document Management procedures to ensure documents are reviewed and updated if impacted by a change?
Quality Risk Management (QRM)	Is there a QRM procedure in place, and is it applied appropriately?
	Which QRM tools are used, and are they appropriate?
	Are all personnel trained in the processes?
Management review	Does the management review process follow ICH Q10 requirements?
	Is the management review conducted regularly based on a pre-defined agenda covering all relevant quality-related activities of the organisation?
	Are key personnel involved?
	Is the protocol / report signed off by management?
	Are the actions arising incorporated into the CAPA system?
Product Quality Review (PQR)/ Annual Product Review (APR)	Are Quality Reviews in place, and are they conducted regularly?
	How is the QP involved?
	Is the protocol / report signed off by management?
	Are the actions arising incorporated into the corrective and preventive action (CAPA) system?
Recall system	Is there an SOP in place to describe the recall system?

Aspect	Possible details to evaluate
	Are roles and responsibilities in a recall process clearly defined?
	Who makes the final decision on a recall?
	In case of a recall, who is informed, including the local regulatory authority?
	How are the activities documented?
	Who makes the final decision on a recall?
Complaint handling	How are complaints received by the company?
	Are they investigated appropriately (see deviations, RCA, CAPA, etc.)?
	Are appropriate actions taken (CAPA)?
	How is feedback provided to the complaint provider?

B. Equipment / Utilities / Systems

Aspect	Possible details to evaluate
Qualification	How is equipment designed, qualified, monitored and maintained?
	Is equipment qualified before use and re-qualified after any significant changes or repairs?
	Is equipment identified unambiguously?
	How are cleaning processes defined, and are they validated?
	How is equipment labelled?
Maintenance	Is a maintenance programme in place?
	Are maintenance plans (for individual equipment) in place?
	Are pre-defined frequencies complied with?
Logbooks	Are logbooks available?
	Are they regularly checked by personnel who can draw conclusions and, for example, adapt maintenance plans?
Outsourcing	Are maintenance / calibration activities outsourced, and are contracts in place?

Aspect	Possible details to evaluate
	Do external partners have to comply with the auditees' SOPs, and, if so, how are they kept up-to-date?
Status labelling	Is the status (clean / to be cleaned) clearly identified?
	Are holding times for clean / dirty equipment defined?

C. Warehouse and Logistics

Aspect	Possible details to evaluate
Storage	How are the product and its components stored before, during and after the process?
	What are the storage time limits and conditions for each stage?
	How are the storage areas controlled and monitored?
Transport	How are the personnel, material, waste and product flows managed in each area?
	What are the transportation methods and routes used for each item (unidirectional flow)?
	How are the transportation conditions controlled and monitored?

D. Premises

Aspect	Possible details to evaluate
Warehouse	How is access controlled?
	What is the status and maintenance condition of the facility (holes and cracks in walls and floors, broken windows, rusty equipment, etc.)?
	Are there water or solvent stains that might be caused by incoming water during the rainy season or leakages in pipes / vessels?
	What is the overall quality of starting materials (missing labels, rusty or damaged drums, insufficient sampling and quality control tests)?
	Is a status labelling of materials defined and adhered to?
	Are cleaning processes in place and controlled?

Aspect	Possible details to evaluate
	Are there API drums from third parties which might just be re-labelled?
	Are areas, rooms, and key equipment qualified and key processes validated?
	Are medicinal products stored directly on the ground (making sufficient cleaning impossible)?
	Is there adequate separation between the receipt, dispatch and storage areas?
	Is there a defined room capacity for cool rooms, and is this qualified and controlled?
Outer premises	Is there a fence or other protective measures against unauthorised access?
	How are visitors registered?
	Is there CCTV coverage of the outer area?
	How are incoming and outgoing trucks registered?
	Is there any outside storage or stacking of materials, and if so, how is it justified and controlled?
External (contracted) premises	Do contracted premises exist?
	Do contracted premises have their own certification?
	How are these premises qualified and monitored?
	Are transportation activities between sites validated and monitored?
Pest control	Is there an adequate system in place?
	Is there an unregulated usage of biocides?
	What happens if animals are caught?

E. Environmental Conditions

Aspect	Possible details to evaluate
Storage conditions	How are storage conditions maintained in different climatic conditions (heat in summer, cold periods in winter, rain periods)
	Are seasonal variations taken into consideration during qualification and validation activities?
	Is the equipment used to control or monitor environmental conditions calibrated at defined intervals based on a risk assessment?
	How are (temperature) deviations managed?
Mapping Note: For small premises consisting of a few square meters, an assessment of potential risks (e.g. heaters) can be conducted and temperature monitors positioned accordingly.	Was an initial temperature mapping carried out before the warehouse was put into use?
	Was temperature mapping performed under representative conditions?
	Are temperature monitoring devices located according to the results of the mapping exercise (positioned in the areas that experience extreme fluctuations)?
	Is the mapping exercise repeated according to the results of a risk assessment or whenever significant modifications are made to the facility or the temperature controlling equipment?
	Have all relevant areas been mapped?

F. Handling of Goods

Aspect	Possible details to evaluate
Returned goods Note: for medicinal products requiring specific temperature storage conditions such as low temperature, returns to saleable stock can only be made if there is documented evidence that the product has been stored under the authorised conditions throughout the entire storage period. If any deviation has occurred, a risk assessment has to be performed to determine the integrity of the product.	If returned to stock, has it been demonstrated by the customer that products have been transported, stored and handled in compliance with their specific storage requirements?
	If returned to stock, have they been examined and assessed by a sufficiently trained and competent person authorised to do so?

Aspect	Possible details to evaluate
Dispensing and intermediate storage areas	Are there multi-purpose drums for internal transport and storage?
	Is there a risk of mix-ups (labelling of raw materials and intermediates)?
	How is (cross-)contamination of drums avoided (dust, multiple use, cleaning)?
Storage of solvents	Which solvents are used and how are they stored (focus on toxic solvents)?
	How are tanks and pipes identified / labelled?
	How is the recovery and testing of solvents performed?
	How is (cross-)contamination of storage tanks avoided?

G. Processes

Aspect	Possible details to evaluate
Qualification and validation	Is there a list of critical equipment?
	Is there a validation master plan (VMP)?
	Is the company's approach to qualification and validation correctly described?
	Are there proper documentation requirements for the risk assessment, validation plan, protocol, report?
	How often is re-qualification realised, and how is it justified?
	Are worst-case and bracketing approaches applied and justified?
	Are deviations treated appropriately in the various systems?
	Is there a process in place to disqualify equipment, etc.?
	Is there a possibility to use non-validated equipment / processes?
	How are the qualification and validation results recorded and analysed?

H. Quality Control

Auditing a quality control laboratory involves evaluating various areas such as, but not limited to, the laboratory facility, including stability chambers, sample management, equipment calibration and maintenance, result creation and reporting, OOS/OOE/OOT investigations and storage of reagents and reference substances.

Aspect	**Possible details to evaluate**
Laboratories	How are the rooms classified, qualified and maintained?
	How is the equipment classified, qualified, calibrated and maintained?
	Is there sufficient space for the preparation of samples and reagent with good labelling control / documentation practices?
	How are waste and leftovers dealt with?
	Are equipment logbooks available, and do they include entries on at least the following: operations performed (including product), maintenance (planned / breakdown / calibration), checks and verifications, and cleaning?
	Maintenance of analytical equipment
Equipment calibration	In-house calibration: Are personnel trained (training plan and records should be clear)? Traceability of the standard used.
	External calibration: • Is the service provider qualified / approved? • How is equipment transported? • How does the contractor transport and store the standards? • Traceability of the standard used.
	Does the calibration certificate include the following? • Equipment identification • Results (pass / fail) – incl. specification • Uncertainty measurements • Traceability to international standard of measurement • Limitation on use (if any) • Date of calibration

Aspect	Possible details to evaluate
	• Signature of the accepting calibration company, if outsourced • Next due date for calibration
	Does the calibration label include the following? Equipment identifier Date of calibration performed Date of expiry / Date of next calibration Performed by
	Are out of limit / specification results investigated according to an SOP, including notification / information and an impact assessment on prior tests / results?
Reference substances / standards (RS)	Are reference substances / standards correctly labelled, have an expiry date and indicate purity on the label or CoA?
	From where do RS originate?
	Is there a certificate for each RS?
	Are storage conditions for the RS adhered to?
	Is there a usage log for each RS?
	How are expiry dates handled?
Out of specification, out of trend and out of expectation results (OOS, OOT, OOE)	Do processes comply with GMP requirements and instructions / SOPs?
	How are such results investigated, recorded and reported?
	Was all glassware and instrumentation retained in the state it was used until results were deemed acceptable to report?
	Is re-measurement only allowed using the approved protocol which specify the purpose and intent of the test? It should not be used to "fix" the result.
	Is re-testing only allowed after both laboratory and production investigations have been completed and both have been deemed inconclusive?
	Is re-sampling only allowed if evidence is available indicating that the original sample was not taken correctly or compromised before analytical testing started? This should be done following the same procedure as the original sample.

I. Microbiology

When auditing microbiological laboratories, it is essential to ensure that processes and methods comply with marketing authorisation and meet necessary standards and requirements.

By following a systematic approach and thoroughly examining key areas such as laboratory facilities, documentation, personnel, sample management, culture media, reference cultures, sterilisation indicators, method validation, major equipment, environmental monitoring and record keeping, auditors can ensure the laboratory's quality management system is well-established and meets necessary requirements.

Note: this is a highly specialised subject, therefore the auditor conducting a full audit of these facilities should have adequate knowledge of microbiology and microbiological test methods or consult with / bring an expert.

Aspect	**Possible details to evaluate**
Sample receipt	Is there a dedicated area assigned for receipt of samples?
	How does the company prevent sample mix-ups?
	Are storage conditions observed where necessary? Sample receipt requires adherence to defined storage requirements and may include frozen (-80°C) or cold (5°C), a defined time before cold storage and adherence to correct labelling.
	Do sampling processes comply with GMP requirements and instructions / SOPs? How is it documented (at minimum are the lot number, expiry date, storage conditions and the test(s) required)?
	How are the samples labelled?
	How is traceability ensured?
	Where are the samples stored?
Sample preparation	Do processes comply with GMP requirements and instructions / SOPs? How are they documented?
	Are balances checked regularly within appropriate ranges and masses, ensuring that they are situated on stable platforms, are clean and unaffected by environmental conditions? Is volumetric glassware of the correct grade used, washed and stored?
Documentation	Are laboratory notebooks assigned to specific individuals, version controlled and appropriately stored and archived?
	Are results sheets pre-printed, and what is the procedure for this? What is the reconciliation process of pre-printed sheets?

Aspect	Possible details to evaluate
	Are specifications consistent with the dossier and / or quality agreement?
Data and reporting	How is raw data defined?
	Are test results independently checked to ensure there are no errors?
	Is system suitability testing performed before the start of the test?
	How are reports reviewed and approved?
	Who has the authority to approve reports, and how is this defined?
	How is data transferred to the certificate of analysis (CoA)?
	How is it ensured that CoAs meet customer requirements / specifications?
	Are IT, computer system validation and data integrity requirements being met?
Microbiology laboratory tour	How are access, gowning and changing rooms managed and checked?
	Is the size, housekeeping and cleanliness of the laboratory adequate?
	Are there dedicated areas for sample and culture media preparation, incubation, reference microbial cultures, bio-hazardous waste collection, endotoxin and sterility testing, sampling and material storage (e.g. freezers)?
	Is equipment labelled, qualified and maintained? Are logbooks available, and do they confirm these activities?
Personnel	How is protective gowning practised, including hygienic hand washing (e.g. the use of antimicrobial soap and duration), disinfection and drying?
	Are garments for the laboratories dedicated to the micro lab fresh and sterilised, non-shedding and with no external pockets? Do garments for sterility testing (sterile zone) include closed footwear, a hair net, gloves, a mask and goggles?
Sample management	How are contaminated biohazardous samples, used culture media, containers, plates and tubes decontaminated?
	How is it ensured that the correct media is used for testing?

Aspect	Possible details to evaluate
Culture media, including reference and working cultures	Is there an SOP for media preparation, and how are the processes validated?
	Have heat / cold shock studies for assessment of media transportation been performed?
	Which tests are run for identity and purity (genotypic analysis)?
	How is identity and purity confirmed for incoming cultures?
	How long can the working culture be used under the defined storage condition, and how was this defined?
Indicators for sterilisation / biological indicators (BI)	Which BI is used, and from where was it purchased?
	Is the supplier qualified and regularly audited, and did the supplier audit cover the verification of the D-value claimed by the supplier?
	Is the bacterial population (and purity) confirmed for every BI lot?
Review procedure on microbial identification	Are standard solutions of strains suitable, available and controlled?
	Is the database suitable (with representative organisms used within the lab facility)?

J. Evaluating Testing Process & Methods

Aspect	Possible details to evaluate
Sterility testing	Are procedures for testing and transferring sterility samples and media into the test environment in place (including media usage, incubation time, closure integrity), and do they comply with requirements?
	What actions are taken after a sterility failure?
Bacterial endotoxin testing	Are there procedures in place for preparation of a standard endotoxin stock solution and for preparation of test solutions?
	Is the test method validated appropriately, and how often is validation / re-validation checked?
	How is test sensitivity confirmed with a new LAL reagent lot?
Microbial limit testing	Is there a procedure in place for a growth promotion test?

Aspect	Possible details to evaluate
	Is media use effective (media should not only recover the target microorganism, but also other inhibitors)?
	Is the incubation process sufficient (correct temperature, duration and conditions)? How are the conditions defined?

K. Evaluating major Equipment and Instruments

Aspect	Possible details to evaluate
Autoclave	Is the sterilisation autoclave separated from the decontaminating autoclave?
	Is the autoclave qualified, including calibration of sensors, a timer, type of thermocouples, etc.?
	Are sterilisation processes validated?
Incubator	Is air equally distributed (incl. during the heat-up phase)?
	How are details like door opening (causing a temperature drop) handled and documented?
	Is there a log for temperature / humidity excursions?
	Is the incubator qualified, including temperature / humidity sensors, a timer, a gas supply and an alarm?
	Was mapping performed for the location of the probes?
Water bath	How is the water level monitored?
	What quality of water is used (only distilled water should be acceptable)?
	How is closure integrity of samples controlled?
	How are samples labelled?
	How are samples cleaned after removing them from the water bath and before testing?
	How are the samples dried?
Biosafety cabinet	Where is it placed, and how is cabinet seal integrity controlled?
	How are filter integrity tests and glove integrity tests performed?
	Is the decontamination process appropriate (including frequency, monitoring, verification)?

Aspect	Possible details to evaluate
	How is the decontamination agent chosen, controlled and verified?

L. Utilities

Aspect	Possible details to evaluate
Air and gas quality	How are specifications for the quality of the gases used defined?
	How is the air and gas quality ensured in each area?
Air supply	Do air supply systems provide adequate filtration, ventilation, humidity, temperature control, air speed, number of air exchanges per hour and unidirectional flow (in laminar flow compartments)?
	Do they meet the microbial and particulate limits for each grade?
	Do they have regular testing and (re-)validation?
Compressed air	How is the compressed air quality ensured for pneumatic purposes?
	Does it meet the requirements for purity, dryness, pressure and flow rate?
	Does it have regular testing and validation? How were the specifications set?
Steam	How is the steam quality ensured for sterilisation purposes?
	Does it meet the requirements for purity, dryness, pressure and temperature?
	Does it have regular testing and validation? How were the specifications set?
Other gases (N2, etc.)	How are other gases used in the process quality controlled?
	Do they meet the requirements for purity, dryness, pressure and flow rate?
	Do they have regular testing and validation? How were the specifications set?

M. Maintenance

Aspect	Possible details to evaluate
Maintenance and repair	Are rooms maintained properly, employing suitable cleaning and disinfection agents and procedures?
	Are rooms qualified before use and re-qualified after any significant changes or repairs?
Equipment maintenance	Is there a procedure in place describing what the company expects from preventative maintenance?
	Who is authorised to realise it, and how is it documented?
	Is there a clear definition for replacement parts and final assessment / review of the impact of any parts? Is there a handover process from an engineer to the laboratory?
	How is it ensured that the equipment is performing as before and if its validated status is maintained?
	Is there a clear description of what parts are in the programme and how often?
	Are personnel qualified to perform the tasks in question?
	How is the glassware washer maintained (drains check, sieve, signs of wear, cleaning of trolleys and jet nozzles)?

N. Non-sterile and sterile Solid Dosage Forms Production Area

Solid dosage forms come in various styles such as powders, granules, tablets, capsules and suppositories. Each form has its own unique characteristics and administration methods. Therefore, it is important to consider these characteristics when auditing facilities involved in the manufacture and testing of such products.

Sterile dosage forms are products that are intended to be administered bypassing the patient's digestion system, making them a potentially life-threatening source of infections if they are contaminated with microorganisms and pyrogens. Usually they are administered by injection, infusion, implantation or inhalation. To ensure the quality and safety of these products (sterility), auditors need to ask key questions and focus on certain areas during an audit.

When auditing the production of these dosage forms, it is important to pay attention to the specific requirements relating to the product. This includes ensuring that the raw materials used in production meet the required specifications, the processes follow the established validated processes and that the finished product is fully produced (and tested) in line with the Marketing Authorisation (MA) and cGMP requirements.

If an auditor has access to the relevant technical sections (Module 2, 3) of the product Marketing Authorisation (MA), the auditor can check the manufacturing documentation against these documents to identify any non-compliance issues.

To review the manufacturing process, the auditor may select a batch based on one of the following:

- A batch that was reported in a non-compliance investigation or a deviation / complaint / OOS, etc.
- A batch that was impacted by significant change (equipment, procedures, layout, etc.)
- A re-processed or reworked batch
- A rejected batch
- Other considerations (new product, volume, specificity, etc.)
- Or simply selection of one of the last three batches manufactured recently.

Alternatively, auditors can review a proposed batch by the auditee, but this may not guarantee a representative document. Auditors should check if there is a system controlling the 'blank' batch records and check if that is controlled by the change control procedure. The auditor can then check the compliance of this template with the validation documentation or MA. Then the selected batch record should be checked to ensure the process is followed correctly.

When auditing without having access to the MA, auditors can use process validation as a starting point. If there is no access to the MA and the process validation, an auditor can review the manufacturing process as per the evaluation focus areas.

Aspect	**Possible details to evaluate**
Audit with Marketing Authorisation (MA)	Does process validation (batch size, scale up, yield) follow the defined master formula?
	Do executed batch records correspond to the master batch records (including packaging)?
	Do critical IPC test results and acceptance limits match with pre-defined IPC checks and acceptance limits?
	Do QC test methods, incl. IPC, comply with validated methods?
	Do QC test results comply with product specifications?
	Is the holding time of bulk product(s) documented and justified?
	Was the equipment used for manufacturing also used during validation (type, model, including packaging)?
	Are listed suppliers of starting materials qualified?
Audit without marketing authorisation (MA)	Process validation in comparison with master batch records • Manufacturing process flow • Equipment and rooms • Starting / Raw materials

Aspect	Possible details to evaluate
	• Sampling • IPC checks • Acceptance criteria • Environmental conditions • Cleaning process
Audit without Marketing Authorisation (MA) or process validation	Check overall GMP compliance

O. Particulars for sterile Dosage Forms

Aspect	Possible details to evaluate
Room design	Are rooms designed to follow a clean room cascade, preventing contamination from lower-grade areas to higher-grade areas?
	How are the (air over-) pressure cascades established and controlled? Do they prevent the ingress of contaminants from lower-grade areas to higher-grade areas? Do they account for the different activities and operations in each area?
	How are the rooms classified, qualified and maintained?
	Do they comply with the relevant standards and regulations, such as Annex 1 and the US FDA aseptic guide?
	Are rooms easy to clean and disinfect?
	Are the rooms free from drains in grade A and B areas (as they can be a source of microbial contamination)?
Monitoring	Are the rooms monitored regularly for microbial and particulate counts using appropriate methods and locations?
	How are rooms, environment, surfaces monitored?
	What methods and instruments are used for monitoring?
	How often and where are the samples taken?
	How are the results recorded and analysed?
Contamination control	How is contamination and degradation of the product and its components prevented?
	Are there adequate cleaning and sterilisation processes and procedures in place?

Aspect	Possible details to evaluate
	Are cleaning and sterilisation processes validated?
Personal hygiene	How are personnel adequately monitored and controlled?
	Do personnel follow strict hygiene and gowning requirements for each area and perform their tasks correctly and consistently following standard operating procedures (SOPs) based on applicable GMPs? How is this ensured?
	Do personnel undergo regular media fill tests to demonstrate their aseptic skills?
	When (i.e. based on which criteria) are qualified personnel dis-qualified to continue working in the aseptic environment?
	How is it ensured that personnel minimise their interventions and movements in critical areas where aseptic operations take place?
Aseptic process simulation	How are media fills performed to simulate the aseptic filling process according to specifications and instructions?
	What are the media fill methods, materials and frequency used for each product type and container size?
	How are the media fill results recorded and analysed?
Filling	How is the product filled into the final containers, and does it comply with GMP requirements and instructions / SOPs?
	Are filling processes validated appropriately and re-validated after any significant changes or modifications?
	What are the filling methods, equipment and parameters used for each product type and container size? Do they comply with GMP requirements, process validation and MA?
	How are the filling accuracy, uniformity and sterility ensured and verified?
	Are filling processes simulated using media fills to demonstrate aseptic performance?
Lyophilisation	How is the product lyophilised, and does it comply with GMP requirements and instructions / SOPs?
	What are the lyophilisation methods, equipment, and parameters used for each product type and container size? Do they comply with GMP requirements, process validation, and MA?
	How are the lyophilisation cycle, temperature, pressure, and duration controlled and measured?

Aspect	Possible details to evaluate
	How are the lyophilised product characteristics, such as appearance, moisture content and reconstitution time, ensured and verified?
Crimping and container closure integrity (CCI)	Do the processes employed comply with GMP requirements and instructions / SOPs?
	What are the crimping methods, equipment and parameters used for each product type and container size? Do they comply with GMP requirements, process validation and MA?
	How are the crimping quality, uniformity and integrity ensured and verified?
	How is the container closure integrity (CCI) tested and validated for each product type and container size?
Sterile filtration	Do filtration processes comply with GMP requirements and instructions / SOPs?
	What are the filtration methods, equipment and materials used for each product type and container size?
	How are the filter integrity, efficiency and compatibility ensured and verified?
Sterilisation	Do sterilisation processes comply with GMP requirements and instructions / SOPs?
	What are the sterilisation methods, equipment and materials used for each product type and equipment?
	How are the sterilisation efficacy, uniformity and compatibility ensured and verified?
Sterilisation of containers Note: Most companies speak about "Depyrogenation", when "Sterilisation" of containers is the target. Depyrogenation is something that happens when glass containers undergo thermal treatment for sterilisation. Containers may be "free from pyrogens" – but this does not necessarily mean that they are sterile!	Do the sterilisation processes used comply with GMP requirements and instructions / SOPs?
	What are the sterilisation methods, equipment and materials used for each item?
	How are the sterilisation efficacy, uniformity and compatibility ensured and verified?
Visual inspection	Do visual inspection processes comply with GMP requirements and instructions / SOPs?
	What are the visual inspection methods, equipment and materials used for each product type and container size?
	How are the visual inspection results recorded and analysed?

P. Auditing a Packaging Company

All criteria regarding the Pharmaceutical Quality System are relevant!

The list below summarizes major aspects, but is not comprehensive and does of course not reflect specific process requirements.

Aspect	**Possible Details to Evaluate**
Information on the printed packaging material	Compliance with the marketing authorisation – how is it ensured?
	Responsibility for label and leaflet design Communication with the company responsible for packaging
	Procedure for approval of the printed information and design including braille Specimen of printed materials
	Procedure to ensure that the correct combination of version numbers of label / cardboard box / leaflet is ensured
	Variable data control Serialization code control
Suppliers/Manufacturers of packaging materials	Qualification
	Audited/Checked printed materials – very important: avoiding of mix-up!
	Approved suppliers, regular assessment
	Way of transfer of information to be printed on the packaging material? Electronic? Secured? Safeguards protect from modification the information e.g. variable data
Packaging Instructions	Conformity with Packaging Instructions / Master Packaging Record
	Approval by Client/MAH/Responsible
	Assurance of compliance with Marketing authorisation
Storage area	Qualification Access control Environmental monitoring, cleaning Dedicated locations (quarantine, blocked/restricted, waste)
	Incoming material check
	Material / Inventory management system, CSV

Aspect	Possible Details to Evaluate
	Identification of the individual units stored (label rolls, packages of patient leaflets)
	Storage of retained samples of packaging materials
QC	Specifications in place?
	Test procedures in place?
	Sampling incl. retain sample instructions – based on which criteria?
	Microbiological monitoring
	Equipment and process for checking correctness of printed information (e.g. electronic systems), relevant for all characters and languages
	Parameters to be tested (e.g. Alu/paper/plastic type, adhesive material, colour intensity, numbers/letters/text style, closure) Tamper Evidence features
	Release/rejection of packaging materials Final release / Certification according to Finished Product Specification file
Packaging equipment	Qualification Maintenance, regular checkup, logbook Prevention of cross-contaminations
	CSV for the Control Systems
	Access Control: Often, a system is switched on by one person (log-on with user name and PW), but multiple persons use the equipment
	Automated systems / In-line control in place for presence of labels, package inserts
	Level of precision of the inspection systems e.g. reading window of monitors, electronic code reader, label counter, scale (what can the sensor recognize) Sampling/In-Process-Control procedure, recording
	Manual packaging operation, control
	Release of packaging line for operation, checklist
Line Clearance	Clear instruction with the locations that have to be inspected?

Aspect	Possible Details to Evaluate
	Photos should be part of the instruction
	Line clearance instruction available as check-list? 4-eye principle in place
	Handling the line clearance to new packaging material when the bulk material remains on the line (e.g. ampoules packaged for different countries) Precautionary instructions to avoid mix up, substitutions
	How is the continuous supervision ensured? (breaks, equipment down-time)
Connection of packaging systems to other IT-systems	Download of information regarding batch number / expiry date / manufacturing date / serialization code – or manual entry?
	In case of manual entry: 4-eye-principle
	Are all the relevant documentation and information related to each batch available at the point of review, confirmation, certification, and release?
	Are the functions involved appropriately resourced to ensure full overview?
	Lot tracing of packaging materials
Label / printed packaging material identification and reconciliation	Assembling and verification of packaging materials to use for a batch packaging
	Reconciliation system in place, in cases, where not all packaging systems are able to unequivocally identify the identity of printed packaging material?
	How are returned quantities calculated / verified (coded / un-coded?
	Waste management
	Management of retained samples of pre-printed materials
Packaging process	Approved validation of packaging process Monitoring of critical process parameters / IPC checks Handling of cut-labels Control of over-printing carried out off-line Re-labelling process
	Handling of rejected material

Aspect	Possible Details to Evaluate
	In-line-control instruments should be checked for proper function before and after the packaging process
	Availability of defect lists
	Identification of defects / counting / limits per defect
	Training of personnel to identify defects / test kits

Q. Water and Sanitisers

Aspect	Possible details to evaluate
Water	What quality of water is used for which purpose?
	How are the water samples taken (where and when; rationale)?
	Where are the sampling points (rationale)?
	Which sample containers are used (glass, sterilised, labelled, identified; rationale)?
	What is the max. time of storage prior to testing? Is it controlled?
Sanitiser	What sanitisers are used and for what purpose (type and temperature)?
	How are sanitising solutions prepared, approved and stored?
	How is effectiveness checked and verified?
	How are contact time and drying method and time controlled?

R. Utilisation of Artificial Intelligence (AI) in Auditing

Part 1: General Remarks and Pre-Requisites

Part 2: AI Tools in Audit Preparation, Implementation and Follow-up

Part 3: Auditing Artificial Intelligence Providers and AI Applications

Note: When using AI tools in audit preparation or when auditing AI applications and implementation always refer to the current applicable legislation.

1. General Remarks and Pre-Requisites

Several AI applications can be used:

- AI as a Service (AIaaS / Cloud AI)
- Built into computer code (Embedded AI / On device AI / In app AI)
- Company-specific AI solutions (On prem / Self hosted / Private AI infrastructure)
- Hybrid (On-prem / self-hosted combined with Cloud AI etc.)

When using AI tools, organisations should establish clear policies governing the use of AI applications.

1.1. Risks of open AI Applications

The use of AIaaS / Cloud AI applications may introduce risks, including:

- Data privacy breaches
- Disclosure of sensitive information
- Biased or inaccurate outputs
- Intellectual property concerns
- Potential security vulnerabilities

A key concern is the risk to confidentiality when internal or external data are processed using public AI systems. Information entered into such systems may be stored or processed in ways that could expose sensitive data beyond the organisation's control. Therefore, careful data management and adherence to internal policies are essential when using AI tools. Consider using internal AI tools with enhanced data security control. It is recommended to use Company-specific AI solutions only.

1.2. Limitations of Artificial Intelligence

Although Artificial Intelligence (AI) tools can support various auditing activities, they also have significant limitations that must be understood by auditors.

AI systems generate responses based on statistical pattern recognition and training data, rather than on actual knowledge or regulatory responsibility. As a result, outputs may be incomplete, outdated, biased or factually incorrect.

AI-generated information must therefore never be considered authoritative without verification (Human in the loop, human oversight.

Typical limitations include:

- Hallucinations: AI tools may generate plausible but incorrect statements or references.
- Lack of regulatory context: AI systems may not fully reflect the latest regulatory requirements or jurisdiction-specific expectations.
- Bias in training data: Outputs may reflect biases present in the data used to train the model.
- Systems can demonstrate deterioration under pressure with increasing complexity.
- AI tools tend to agree with the user in their outputs.

Consequently, AI tools should be considered supporting instruments. Auditors remain fully responsible for:

- interpretation of regulatory requirements
- evaluation of audit evidence
- classification of audit observations
- final audit conclusions

AI may assist in structuring information and generating ideas, but professional judgement remains essential.

2. AI Tools in Audit Preparation, Implementation and Follow-up

These tools may support various audit-related activities, including:

- Audit planning
- Audit preparation
- Development of audit checklists
- Review of documents
- Preparation and structuring of audit reports

2.1. Examples of Using AI for Audit Preparation and Planning

Example 1 — AI-Supported Pre-Audit Document Review and Gap Analysis

AI tools can be used to review and/or summarise documentation — such as SOPs, deviation reports, training records and distribution logs — in order to identify missing, outdated or inconsistent elements before the audit begins.

This can support early identification of potential compliance gaps and help organisations address issues prior to the audit.

A possible AI prompt could be:

Review all supply chain and applicable GxP documentation, including SOPs, training records, deviations and distribution logs. Identify outdated documents, missing training acknowledgements, documentation gaps or inconsistencies. Summarise the identified risks and recommend corrective actions to be implemented prior to the audit.

Example 2 — Predictive Risk Assessment for Prioritisation of Supplier Audits

AI tools may also be used to analyse historical audit findings, supplier performance data, CAPA records and distribution deviations in order to identify potential future GxP risks.

This analysis may support risk-based prioritisation of supplier or third-party logistics (3PL) audits.

A possible AI prompt could be:

Analyse the last 24 months of supplier and logistics data, including audit reports, CAPA trends, complints, temperature excursion history and delivery performance. Identify suppliers or 3PL partners with increasing GxP compliance risk and rank them according to audit priority. Provide reasons for prioritisation and recommend specific audit focus areas for each supplier.

2.2. Examples of AI Use in Document Compliance Review

During an audit process, AI tools may assist in reviewing internal or externally provided documentation to identify potential compliance gaps or areas requiring further clarification.

Such an initial assessment may help auditors identify potential risk areas and formulate targeted questions during the audit.

Example prompts for reviewing operating procedures against existing regulations, when trained accordingly and access to current regulations is guaranteed:

- *Which specific regulatory clauses are addressed by this SOP, and are any required elements missing?*
- *Which sections of the current EU or ICH GMP/GDP guidance directly apply to the activities described in this SOP?*
- *Does the SOP provide sufficient detail to meet current regulatory expectations for the described process?*
- *Are critical control points and Quality Risk Management principles documented as required under current GMP or GDP guidance?*

Example prompts for reviewing procedures against emerging regulations

- *Does the SOP already reflect changes proposed in draft revisions of EU GMP or GDP regulations?*
- *How does this SOP compare with regulatory expectations described in current consultation documents or concept papers?*
- *Which elements of this SOP may no longer be compliant once the proposed regulatory updates are implemented?*

2.3. Verification of AI-Generated Outputs by Auditors

Whenever AI tools are used during audit preparation, execution or reporting, the outputs must be critically assessed and verified by the auditor.

Verification is necessary because AI systems may produce incorrect, incomplete or misleading information.

Auditors should therefore apply a systematic verification approach, which may include:

- Confirming regulatory references against official guidelines and regulations (e.g. EU GMP Guidelines, ICH Guidelines, GDP Guidelines).
- Cross-checking AI-generated information with internal procedures and documentation. Checking interfaces of AI tools with other systems (e.g. with MES systems or production equipment).
- Ensuring that AI-generated summaries accurately reflect the source material.
- Reviewing AI-generated audit questions or observations for technical correctness and relevance.
- Ensuring that conclusions remain independent from AI-generated interpretations.

It is good practice that AI-generated text should not be directly copied into audit reports without appropriate review and modification.

The responsibility for the content of the audit report always remains with the lead auditor and the auditing organisation.

3. Auditing Artificial Intelligence Providers and AI Applications

As Artificial Intelligence becomes increasingly integrated into pharmaceutical operations, auditors may also need to assess AI-supported systems used within GxP-relevant processes.

Examples of such systems may include:

- AI-supported deviation management tools
- AI-based predictive maintenance systems
- AI-supported document management systems
- AI-assisted batch record review systems
- AI-supported supply chain monitoring tools

When auditing such systems, the auditor should focus on both the provider and the application within the GxP environment.

Important audit aspects may include:

Governance and Responsibility

- Clear definition of responsibilities for development, implementation and maintenance of the AI system
- Oversight by qualified and trained personnel and quality functions
- Defined procedures for approval and change management

Data Integrity and Data Quality

- Quality and origin of training data
- Controls preventing data manipulation or corruption
- Traceability of data used by the AI system

Set-up and Transparency

- How was the AI application trained?
- How long were parallel tests carried out (human vs. AI)– and what were the results?
- Ability to explain how the system generates its outputs
- Documentation of algorithms, model development and updates
- Understanding of system limitations

Performance Monitoring

- Evidence that the AI system is qualified for its intended use
- Defined performance metrics and acceptance criteria
- Ongoing monitoring of system performance

Risk Management

- Application of Quality Risk Management principles (ICH Q9) to AI implementation
- Identification of potential failure modes
- Mitigation measures and fallback procedures

Change Management

- Controls for model updates, retraining and software changes
- Assessment of impact
- Documentation and approval of changes

In GxP environments, the use of AI systems should follow the same fundamental principles that apply to computerised systems and automated processes, including validation, documentation and quality oversight.

Auditors should therefore assess whether AI applications are implemented within an appropriate pharmaceutical quality system and remain under adequate control throughout their lifecycle.

3.1. Practical Checklist for Auditing Artificial Intelligence Systems

When auditing Artificial Intelligence (AI) systems used in GxP-relevant processes, auditors should assess whether the system is appropriately controlled within the pharmaceutical quality system and the computerised system lifecycle.

The following questions may support auditors in structuring the assessment:

Governance and Responsibility

- Does application comply with the current applicable legislation and guidance?
- Is there a clear owner of the AI system within the organisation?
- Are responsibilities for development, control, maintenance and oversight clearly defined?
- Is the Quality Unit appropriately involved in the approval and oversight of the system?

Intended Use and Scope

- Is the intended use of the AI system clearly defined and documented?
- Are the boundaries and limitations of the system clearly understood by users?
- Is the system used only within the defined scope?

Data Management and Data Integrity

- What data sources are used to train or operate the AI system?
- Is the quality and integrity of the input data ensured?
- Are mechanisms in place to prevent data manipulation or corruption?

Model Development and Implementation

- Has the AI model been developed and implemented for its intended use?
- Are acceptance criteria and performance metrics defined?

- Is there evidence that the model performs consistently and reliably?

Set-up and Transparency

- Can the organisation explain how the AI system generates its outputs or recommendations?
- Are limitations of the model documented and understood?

Risk Management

- Has a Quality Risk Management (QRM) assessment been performed for the AI system?
- Are potential failure modes and risks identified and mitigated?

Change Management and Lifecycle Control

- How are model updates, retraining or software changes controlled?
- Is the impact of changes on the system assessed and documented?

Monitoring and Continuous Oversight

- Is the performance of the AI system regularly monitored?
- Are deviations or unexpected outputs investigated?

Human Oversight

- Are qualified personnel responsible for reviewing and approving AI-generated outputs?
- Is it ensured that critical decisions are not made solely by the AI system?

This checklist should be used as a supporting tool. The depth of the assessment should always be adapted to the criticality of the AI system and its impact on product quality, patient safety and data integrity.

S. How to audit a medical Cannabis Grower

Auditing a medical Cannabis grower introduces several new concepts at the edges of GMP such as hydroponic cultivation systems, Good Agricultural Collection Practice (GACP) and increased demand for site and product security measures. Some authorities inspect both, GACP and GMP, but others solely inspect GMP. The scope in the criteria below is mainly limited to GMP considerations.

Some authorities regard Cannabis flowers as APIs, whereas others treat them as intermediate products, and others as medicinal products, i.e. requiring batch certification by a qualified person. It is an evolving area, with uncertainties on both, manufacturers' and inspectors' side.

Laboratory testing Cannabis products frequently needs several test laboratories and these are often contractors as sites have no or very basic laboratory facilities.

Relevant sections of Eudralex Vol 4 should be followed and include non-sterile production topics plus relevant annexes such as Annex 7 (Manufacture of Herbal Medicinal Products), Annex 11 (Computerised Systems) and Annex 15 (Qualification and Validation).

Most sites have sophisticated plant monitoring measures to satisfy narcotics regulations.

In case of involvement of external service providers, e.g. laboratories or irradiation facilities, these should also be covered by the audit activities.

Cannabis products can present substantial patient risks from Aflatoxins, Ochratoxins and microbial contaminants. Cultivators and manufacturers should ensure that the finished product specification is appropriate (Ph. Eur. Monograph) and results are being adequately monitored.

Aspect	**Possible details to evaluate**
Fundamental questions for preparation	What is the site's determined cut-off between GACP and GMP? – It should be ensured that all operations starting with drying (trimming, curing, packaging) are performed in a GMP area, clearly separated from the GACP part of the facility.
	Is there a formal QMS for GACP?
	Are plants bought in, or grown at the site?
	Is the site activity limited to flower growing, or are there additional activities such as extraction and formulation?
	What narcotics licences are held or applied for?
	Does the company use hydroponics or soil growing?
	What laboratories are used for chemical and microbial testing?
	Is there 24/7 security with manned presence and a security plan?
Goods received and storage	Are growth media received with suitable certification?
	Are chemical nutrients suitably labelled and stored to prevent degradation?
	Do the company adequately address TSE risks in all potential product-contact items?
	Are any printed materials received and suitably checked and securely stored?
Facility design	Are rooms classified to expected GMP standards for non-steriles?
	Are suitable pressure cascades maintained and monitored?
	Are air inlets and outlets located to achieve suitable sweeping and absence of stagnant areas?
	What filtration standards are applied to both incoming and recirculated air?
	Is a suitable area provided for cleaning equipment and solutions?

Aspect	Possible details to evaluate
Clothing	Is a suitable changing area provided with adequate space and washing facility?
	What measures are in place to protect workers and inspectors from light radiation - eye protection, special clothing and sunscreen?
	Are any external laundry facilities audited and approved?
Fertigation controls	Is there an automated system controlling key parameters such as solution preparation, irrigation, temperatures, light and gas levels?
	Has the system been formally validated and approved?
	Request and examination calibration records of key sensors.
	What controls are in place to stop unauthorised changes or optimisation?
Pest controls and fungus risks	What pest control measures are in place and how is their efficacy challenged?
	What measures are in place to reduce/discourage fungal growth?
Harvesting, drying, trimming and curing	How is flowering monitored to determine a suitable and consistent point for harvesting?
	Are machines used for bucking and trimming?
	Is there sufficient instrumentation on automatic machines?
	Is there an adequate procedure for cleaning and sanitising machinery?
Packaging and labelling	Is the packing process manual or is machinery required?
	What containers are used for the product – are these bought in or is a local pouch produced?
	Is there any use of nitrogen in the packing process and, if so, is this subject to point-of-use filtration?
	Are suitable in-process checks conducted during packing?
	If pouches are used, what checks are carried out for pinholes and integrity of the seal?
	Are product labels printed fully in house, or just variable data such as the batch number and expiry date added locally?
QC testing	Are the water sources evaluated for pesticides, heavy metals and micro levels?

Aspect	Possible details to evaluate
	Is there an adequate environmental monitoring programme in place?
	Does the company check for the absence of aspergillus in the finished product?
	Does the company monitor and trend levels of aflatoxins and ochratoxins in the finished product?
	Is there a requirement for the absence of salmonella and E.coli in the product?
	Are cannabinol levels in the finished product controlled and evaluated?
	Are the qualifications and experience of the releasing officer or QP adequate?

T. Preparing Audits for Cell and Gene Therapies (CGT) based Advanced Therapy Medicinal Products (ATMPs)

Background

The European Commission has published a separate regulation for Advanced Therapeutic Medicinal Products (ATMPs) which lays down specific rules concerning the authorisation, supervision and pharmacovigilance of ATMPs (Regulation 1394/2007). The regulation defines three types of ATMPs: gene therapy medicines, somatic cell medicines and tissue engineered medicines.

This article is mainly focused on ATMP based cell and gene therapies (CGT). CGTs can be described as therapies that offer personalised and targeted treatments for a number of rare and chronic diseases. These therapies are classified into two main types: autologous and allogenic.

Autologous CGTs involve using the patient's own cells, which are collected, modified and then reintroduced into the patient. This personalised approach minimizes the risk of immune rejection.

Allogenic CGTs, on the other hand, use cells from a donor. These therapies can be produced in larger quantities and administered to multiple patients, but they carry the risk of immune response and require careful matching of donor and recipient.

1 ATMP-specific Challenges

Due to the specific nature of ATMPs, new challenges need to be addressed. These new challenges and difficulties regarding sterility, out-of-specification handling, batch release and EU import testing are situated throughout the entire manufacturing process.

One of the major challenges is the aseptic risk associated with the ATMP manufacturing. ATMP administration requires injection, infusion or transplantation of the medicinal product. Therefore, the ATMP product needs to be manufactured under aseptic conditions. Unlike traditional small molecule medicinal products, sterile filtration or terminal sterilisation is in most cases impossible, either because these methods impede the product's structure or function, or because cells are simply too large to pass through the pore size of the filter. As stated in Part IV of the EU GMPs (Good Manufacturing Practice), all processes related to aseptic processing need to be validated before entering clinical phase I trials. The combination of gowning requirements, clean room qualification and validation of these aseptic processes by media fill and a validated sterility test method needs to ensure the sterility of the product and, therefore, requires specific attention during an audit according to Annex 1, as applicable.

2 How to audit ATMPs - managing the Complexities of allogenic CGT Manufacturing

2.1. The Challenges of the Supply Chain

The creation of a CGT based ATMP involves the collection or "donation" from an individual. The donated material is then generally modified, engineered or manufactured into a therapy product for delivery to the patient. This complex manufacturing and delivery model is known as the "vein-to-vein supply chain".

CGTs have not yet been adopted on a large scale, due to a combination of clinical, regulatory and cost-related hurdles. At present, supply chains are necessarily bespoke and costly. However, given the potential presented by CGTs and the current focus on developing them, it seems likely that they will form an integral part of future therapies. As they become more prevalent, ensuring the ongoing integrity of their supply chains will be of paramount importance. This also includes the storage and transport of them.

Right from cell collection to the delivery of the therapy product, each step involves several processes which bring their own risks and require controls.

During the collection process (via apheresis, etc.), preparing and monitoring the patient and equipment to yield the appropriate quality raw material is essential.

- The raw material and drug products can get affected by factors such as timing, temperature, microbiological basic load, packaging, etc. and therefore need to be handled, packed and transported with care. Obtaining a sterile starting material can be a challenge.

- Certain complex manipulations and activities are performed during the manufacturing process and are crucial if the end product is to meet specifications. These are often performed manually and require great skill and consistency.
- Understanding the GMP requirements, equipping the team with the necessary skills and rigorous training is critical.

- Lot genealogy, including chain of identity (COI) and chain of custody (COC), are two critical data sets that maintain the record of all the materials, processes, testing and outputs of a batch to ensure that patients are treated using the specific product meant for them.

- It must be ensured that the qualification and performance of vendors meet the required standards, especially since many of them do not operate in a GMP environment.

- Standardised processes and controls ensure that the products are safe and fit for the intended use and comply with regulatory requirements.

- Risks have to be identified, and mitigation measures established using an integrated process for both quality and risk management.

- Continuous improvement has to be set up through monitoring of processes and performance, track and trend investigations, root cause and CAPA analysing of supply chain performance and managing risks.

A robust audit process is critical for ensuring patient safety, mitigating risks, reducing failure and increasing operational efficiency.

2.2. Where to start at the Manufacturer

When manufacturing an ATMP, it is important to pay attention to the choice of raw materials used. These materials influence the entire process, from clinical development to market authorisation. GMP guidelines contain important considerations.

This requires specialist expertise, with careful consideration and impact assessment undertaken, which is not routinely available for the dense supplier management needed. Agreements with suitable suppliers such as blood centres are required to facilitate delivery of these specialist materials to be of suitable specified quality. Audits and continuing oversight arrangements should confirm the technical quality and suitability of the services documented in a quality and technical agreement.

Therefore, when auditing manufacturers, an essential focus should be on raw material supplier management.

2.3. ATMP OOS Batches being used

Due to a higher variability and the quality of raw materials, a higher level of deviations and OOS results is more likely. In case of an OOS result, there is the possibility to release the batch and administrate it to the patient. This contrasts with traditional medicinal products, where a product which does not comply with the specifications cannot be certified and released.

During an audit the following should be checked with regard to OOS documentation:

- A description of the OOS with a risk analysis by the manufacturer on the impact on the following:

- The quality of the product, including the percentage of batches that is OOS on the total of commenced productions and a reflection on the production process (root cause analysis and CAPAs (Corrective Action and Preventive Action)),
- Role of the QP
- The safety and efficacy of the product in relation to the patient;
- There should also be a feedback loop in place to the critical quality attributes (CQAs), which have been identified during the quality target product profile (QTTP) process to define the quality, safety and efficacy attributes of the desired final product during the risk-based process development (e.g. quality by design)

- A confirmation of the physician to the manufacturer to accept the product;
- A declaration from the MAH (marketing authorisation holder) as to whether or not the product has been administered.

A Q&A document on how to handle an OOS for authorised batches was first published by the EMA in April 2019.

2.4. QP Certification of ATMP and Import

According to EU directive 2001/83/EC, a registered qualified person (QP) is responsible for the certification of medicinal products prior to their release. This and the applicable responsibilities of a QP do not differ for ATMPs. However, the difficulties which might be faced by a QP are different throughout the entire manufacturing process.

- A QP cannot certify an OOS ATMP batch, the release of these batches is based on a documented request by a treating physician.
  The QP needs to assure that verification according to GMP Part IV – 11.27 has been performed. Prerequisites to release the OOS batch are mentioned in GMP Part IV – 11.5.
  As a reminder, QP certification is a written signed statement that the manufacture and testing of a batch has been conducted in accordance with GMP and the relevant approved marketing authorisation or clinical trial application before the batch can be released.

- The obligation to perform import testing in case a medicinal product is manufactured in a third country, does not always apply to ATMPs (e.g. for ATIMPs, import waiver). There are exemptions from EU batch retesting laid down in paragraph 11.17 of GMP Part IV. In case of exemptions, the manufacturing of the ATMP needs to be performed according to EU GMP. This implies that an audit prior to first importation is required. As the QP takes on the responsibility of certifying this batch from a third country, the audit is preferably performed by the QP. A Q&A document on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country was published first by the EMA in July 2019

2.5. Transport and Storage of ATMPs

Much of the discussion in the ATMP industry today focuses on the complexity of manufacturing. However, the ultimate success of an ATMP rests on the ability to deliver a viable, potent product to the patient.

In order to ensure that this "living" drug is delivered to the right patient at the right time, location and temperature is essential to patient safety and product effectiveness and therefore should not be forgotten when auditing.

The logistics of these types of medicines are complex, due to specific requirements regarding temperature, reliability and traceability. For example:

- Frozen storage requirements: Cryogenic storage and distribution capabilities are established for many ATMPs. Distribution in deep-frozen or cryogenic conditions needs specialist shippers, to keep the temperature stable and track the location and conditions during the shipment.

- Short shelf lives —ATMP or their starting materials may have an extremely short shelf life. This could even mean that not all test results are available at the time points of release or even administration. A risk assessment, risk mitigation and processes (e.g. what happens if a specification is not met) need to be in place.

Any deviation from storage, distribution or traceability requirements has the potential to impact the quality of the ATMP and, therefore, the safety of patients. Storage and distribution under GMP and good distribution practice (GDP) guidelines are applicable for CGTs, too.

The challenges of CGT for pharma logistics are as followed:

- Delays due to inspection and compliance checks
- Complexity calls for experienced logistics partners
- Limited visibility in logistics because of low quantity
- Scalability of transport methods
- Unforeseen disruptions in supply chains