ECA Foundation
Fostering harmonisation of GMP/GDP regulations

ECA Good Practice Guide – GMP Auditors Reference Handbook

A guidance document by the ECA Foundation
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Contents

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ECA Code of Practice for GMP Auditors	
Authors	
Ingrid Walther (Team Lead) Felix Kern Ágnes Kis Christof Langer Thomas Schmidt Wolfgang Schmitt Ian Holloway Gabriela Schallmeiner David Abraham Afshin Hosseiny	
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Legal Representative	
ECA Foundation c/o VHP Auditing Firm and Legal Trustee Attn. Mr J. Ruland Hebelstr. 7 68161 Mannheim Germany	

Foreword

Over that past decade, the pharmaceutical industry has moved towards outsourcing activities to suitable service providers. A move which necessitates co-operation in a trustworthy manner to ensure that the outsourced activity is performed according to contracts and Good Practice standards. As a general requirement, the outsourcing company must confirm that this is the case. One of the means to achieve this target is auditing.

The ECA Audit Guidance Document (the Handbook) was developed to cover the key elements of an audit.

While establishing the new ECA Working Group and moving towards becoming an Association, it became apparent that the ECA wanted to produce a guiding document, an Auditors Reference Handbook, for its members.

We decided early on that we would focus on the most important subjects first, rather than waiting until an advanced status was achieved before publishing the Handbook. This would enable us to shorten the delivery time for the Handbook and, also, give us an opportunity to collect feedback and improve content in the next version.

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This Handbook is a guiding document and, due to the extremely diverse targets, requirements, types of audits, approaches, practices, check-lists, recommendations and references provided, it may not be exhaustive and may not cover every upcoming need in the context of auditing.

This handbook does not claim to be comprehensive. Instead, it summarises the major aspects of the topic and is intended as a guidance document to support members in their work.

Please note that all examples provided in the handbook and its attachments must be adapted to the respective audit, its purpose, format and result in each case. Relevant sections can be used, or deleted as appropriate for a particular audit.

However, we have done our best to share our experience and expertise!

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1. GMP Auditing – Scope

Having an effective audit system is not only required as a key element within the Pharmaceutical Quality System to ensure regulatory compliance. Moreover, it is mandatory to maintain reliable supply chains and business continuity.

Audits are tools:

- to build trust and confidence
- to identify weak points which serve as the basis for necessary improvements

Audits need to be performed for outsourced activities of all kinds, suppliers of services or materials. In this Handbook, we focus on GMP audits, but we acknowledge that audits are common practice in other areas as well, and the principles outlined in this handbook are mostly applicable for other good practice audits as well.

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2. Identifying the "Need to Audit"

2.1. Occasion for Audits

Audits are required for different reasons and on different occasions.

- Initial supplier qualification
- Requalification Audit (also known as Routine Audits)
- For-cause audits in case of identified deficits of any source; in rare and exceptional cases, these may even be "forensic" audits, where conditions have to be scrutinised due to legal conflicts.
- Internal audits (sometimes referred to as self-inspections in older terminology)
- Inspections is an expression used for the type of audit carried out by official representatives and regulatory authorities. They are a sub-category of audits and basically follow similar rules. However, there are additional and specific conditions and requirements which are not dealt with in this guiding document and are intended for industry representatives.

Table 1 gives an overview of audit occasions, targets and time points

Target and time point / Audit occasion	Target	When to perform the audit (time point)
Qualification audit	Ensure adequacy of envisaged service Identify subjects to be clarified and actions to be completed	Before the co-operation commences
Requalification audit (routine audit)	Confirm reliable supply quality	Pre-scheduled, frequency based on criticality and risk
For-cause audit	Solve problems, avoids negative consequences	In the event of identified deficits, deviations or planned changes communicated by the supplier
Internal audits	Confirm continued compliance	Regularly scheduled, in general annually, for each GMP-related area.

While the time point to perform the audit is fairly clear in the case of qualification audits and for-cause audits, the frequency of routine re-audits is determined by Supplier Management Procedures.

2.1.1. Audit Frequency for Requalification Audits

The audit frequency for requalification audits is determined within Supplier Management Procedures and defined in the respective SOPs. Quality Risk Management processes apply.

As this guiding document primarily focuses on the auditing process itself, only the major criteria used to evaluate suppliers and determine the audit frequency are provided here:

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- Criticality of supply
- Duration of the business relationship
- Reliability and trustworthiness of the co-operation
- Deficits and weak points
- Complaints

Further criteria, such as availability of second suppliers, regulatory impact, service complexity and the need for close process control, may also be relevant parameters.

In any case, the primary goal of supplier auditing is to control the risks associated with supplies.

Typically, audit frequencies ranging from 2 and 5 years result from the supplier evaluation process. Also, the type of audit to be performed may be determined as a result of the supplier evaluation process.

2.1.2. Audit Duration and Auditor Capacity

Evidently, an adequate audit duration is determined by what needs to be seen, checked, verified and clarified. Aspects to be considered include the following:

- Scope of supply
- Complexity of the processes to be audited
- Number of products / services
- Previous experience
- Duration of the business relationship

It should be acknowledged that the interests of auditors, who want to obtain as much information as possible, and auditees, who want to limit the audit duration, may conflict!

Some companies do not allow audits to exceed one day and do not accept more than one auditor. In other cases, fees are charged for allowing any audit activities at all.

When requesting an audit, adequately respect the auditees' capacities, as a balancing of interests should be considered. An audit is more or less a deep spot-check and it is impossible to identify each and every weak-point.

The table below provides some indication for audit duration.

Category	Duration of audit	Auditors
Contract manufacturer	2-3 days	2 auditors
API manufacturer	2-3 days	1-2 auditors
Distributor / Importer	1 day	1-2 auditors
Packaging material manufacturer	1 day	1-2 auditors
Contract lab	1 day	1-2 auditors
External warehouse	0,5 days	1 auditor

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Internal audits (e.g. those performed by the global compliance team) may take longer and may require a larger auditing team. However, this chiefly depends on internal regulations and specific circumstances.

2.2. Types of Audits

Audits may be performed in different manners (i.e. different audit types may apply):

- On-site
- Desktop assessment ("Paper" audit - which is, of course, similar to "electronic")
- Remote
- Hybrid

Adequacy, advantages and disadvantages of the audit types are explained in the following sections.

2.2.1. On-site Audit

On-site audits (i.e. when the auditor or the auditors are physically present at the premises) are the most common way to perform audits and, in general, the audit type for the following:

- Complex processes
- Critical supplies requiring in-depth evaluation
- When personal contact and the need to assess personnel competence is important

This audit type also provides the possibility to involve further expert auditors (SMEs) for specific subjects in a hybrid audit approach (i.e. connecting via video conferencing systems). In such cases, the on-site audit has the characteristics of a hybrid audit!

Advantages	Disadvantages
• Direct contact with auditee contact persons • Possibility to view the facilities • Direct access to procedures and hand-written records • Possibility to involve further SME auditors	• Traveling required (time and cost impact)

2.2.2. Desktop Assessment (Paper Audit)

Desktop assessments are a common and adequate method for the following:

- Initial evaluation of a supplier, often followed by audits of greater depth
- Supplies of low criticality
- Known and qualified suppliers which are selected to supply further products

Desktop assessments are based on supplier evaluation questionnaires or supplier self-disclosures.

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Advantages	Disadvantages
• Quick responses • No scheduling – may be conducted on a short-term basis • No traveling	• No personal contact to auditees • No or limited possibility to evaluate specific processes as standard questionnaires are completed • No or limited possibility to see documents • No possibility to view facilities

2.2.3. Remote Audit (Distant Assessment – Remote Assessment)

Remote audits are performed via video conference platforms (i.e. when no auditor is physically present on site). It is a fairly recent audit type which evolved and matured during the COVID-19 pandemic. It was a useful way to audit suppliers in cases where desktop assessments were not considered sufficient, and to provide adequate, in-depth information.

The assessment is performed through face to face interaction and interviews between the site personnel (auditee) and auditor in real-time, utilising video and screen sharing platforms.

Limitations faced in such audits include the following:

Facilities:

Experience shows that the possibility to see facilities is often limited or impossible. For confidentiality reasons, most auditees do not want to conduct live walking tours (or are not allowed to share such information due to internal regulations) and, consequently, show photos or videos. The information provided by such means may be insufficient for a thorough evaluation of conditions.

Documents:

Documents are shared via technical solutions (document-sharing platforms or email). Documents with handwritten entries frequently cannot be shared, which is the case when technical installations only provide the possibility to screen share scanned documents. Turning pages to go back and forth in a document is only possible with the support of the auditee.

Logbooks are usually inaccessible during remote audits as they are kept at the operational sites and, consequently, are not available in the audit room.

When non-written information (e.g. layouts or diagrams) is shared on a screen, a common difficulty is to indicate a specific location as mouse-sharing, where both parties have cursor access, is often not possible. A common practice has emerged which uses the cardinal points as directional terminology: north, east, south, west.

Considering the aforementioned limitations, remote audits are adequate in the following situations:

- When no traveling is possible, meaning no on-site audits can be conducted (e.g. due to travel restrictions or for safety reasons*)
- For supplies of medium complexity (i.e. for which evaluation is possible without deep insights, and facilities and installations are of secondary importance)

  *Note: If lack of safety during traveling is a permanent or frequent issue, the adequacy of the supplier should be questioned. In urgent cases, it may not be possible to contact the supplier and / or reliable supply delivery may also be questionable.

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Advantages	Disadvantages
• No traveling • Scheduling may be more flexible compared to on-site audits • Possibility to involve a higher number of expert auditors compared to on-site audits • Can be split into several sessions over more than one day • Documents shared via screen are visible for each auditor	• Limited personal contact with auditees (e.g. no possibility to read body language) • Limited possibility to see facilities • Limited possibility to see documents • Stable internet connections required • Long sessions (e.g. over 6 – 8 hours) are difficult to manage (which may bring the advantage of flexibility by splitting into several shorter sessions over more than one day!) • Differences in time zones • No parallel discussions possible (unless there are break-out rooms) • Reliable internet connection required. Test sessions recommended!

PIC/S has published "PIC/S GUIDANCE ON REMOTE ASSESSMENTS, PI 056-1, and an Aide Mémoire on REMOTE ASSESSMENTS, PI 057-1, which contain some useful hints on challenges associated with remote audits.

Tip for auditees subject to remote audits:

As screen shots or video recording may be possible without being noticed, your confidentiality agreement should address and exclude this possibility (unless you want to allow this option!).

2.2.4. Hybrid Audit

Hybrid audits combine elements of both on-site and remote audits, with at least one auditor physically present on-site and further auditors connected via a video conference platform.

The on-site auditor can conduct the facility tour, view what needs to be seen and document reviews both on-site and (or exclusively) remotely.

For the remote part, where the on-site auditor may be present at the auditee's facilities, additional auditors are involved (e.g. experts who need to participate for specific subjects only).

Assuming that any on-site audit in which expert auditors are involved represents the hybrid audit type – it is the preferred choice!

Advantages	Disadvantages
• Traveling for only one person from the auditor team, without the need for experts who only participate part-time (remote) • Possibility to involve a higher number of expert auditors compared to on-site only audits	• Limited number of auditors familiarise themselves with on-site conditions • Stable internet connections required

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2.2.5. Internal Audits

Regulatory requirements for internal audits are defined in Chapter 9 of the EU-GMP Guide "Self-Inspections", which is "legacy" terminology, as "inspections" are in general related to authority activities. The respective Chapter 9 of the EU-GMP Guide is an old regulatory document and, although it does not even have a date, it is still valid!

The document states the following requirements for internal audits. They should be performed:

- in all GxP-related areas
- at scheduled intervals

and

- reports should be prepared and actions defined and performed.

Auditors are normally independent from the audited area.

When compared to supplier audits, a major difference is the fact that internal audits take place among colleagues, even if supported by external auditors! The implications are as follows:

- Any deficit discovered is much more "embarrassing" among colleagues
- The level of openness should be high, as this is beneficial for the company's own organisation.

Both implications may have an impact on the outcome of an internal audit, and their existence should be observed vigilantly.

2.3. Developing the Annual Audit Plan (Audit Programme)

The annual audit plan is prepared to cover the following:

- Requalification audits
- Qualification audits (as far as it is known by the time the annual plan is prepared)
- Internal audits

Typically, these audit types are scheduled in individual audit plans, which may be followed up by different departments. As a matter of fact, not all for cause audits can be covered in the annual audit plans, nor can all upcoming qualification audits be predicted, considered and represented. Therefore, audit plans – although approved - should have room for some flexibility and may require revision over the course of the year.

Furthermore, audit dates may not be confirmed at the time the audit plan is completed. Therefore, in most cases, audit plans indicate quarters or months when the respective audit is scheduled.

The audit plan lists the audits in the envisaged order, providing an overview and allowing the assigning of capacities (auditors), and it avoids any "accumulation" at certain periods of the year.

The annual audit plan is agreed and approved, with final approval being a QA task.

Example (simplified):

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No.	Date	Company	Supply	Criteria	Type of Audit	Auditors	Audit Agenda	Audit Report	Follow-up
1	13 Jan	XY Pharma	Xx tablets	EU GMP Part 1	Requalification audit	Schmitt	Finalised, sent to contractor		
2	12 Feb	CC Lab	HPLC micro	EU GMP Part 1	For-cause audit: Complaint New line	Schmidt/ Schmitt	Finalised, sent to supplier		
3	24 Feb	API for all	Xxx, API	ICH Q7	Qualification audit	Abraham/ Kis	Finalised, to be sent to supplier		
4	16 March	Excipient Kings	Macroxx	ICH Q7 ExciPact	Qualification audit New supplier	Abraham	Draft		
5	Q2	API XY	Dried xxx	ICH Q7 Herbal Products	Requalification audit New supplier	To be determined			
6	Q3	AB Pharma		EU GMP Part 1	Qualification audit Product transferred	To be determined			
7	Q4	E&C Warehouse Ltd		EU-GDP Guidelines	Requalification audit	Abraham			

The audit plan may also indicate the location (country is of high importance!) and contact person.

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3. Planning and preparing an Audit

This section deals with the tasks to be accomplished before the audit takes place and, admittedly, there is no strict order in which the tasks have to be completed.

There are cases where scheduling with the auditees is the first step, while in other cases, nomination of the auditors is realised before scheduling. Collecting information for the audit and preparation of the agenda may be realised parallel to this.

Therefore, although the tasks are described as numbered chapters, this does not mean the order necessarily presents the work order.

3.1. Communication with the Auditee (Supplier)

3.1.1. Scheduling

Responsibility for communication with the auditee should be agreed upon as soon as audit planning starts. Since different departments are usually in contact with the supplier, information regarding the planned audit must be communicated internally. Contact persons within the company should not be surprised to hear from the supplier that an audit is scheduled!

Normally, it is advantageous to involve the colleagues from the purchasing department, as they can provide support in finding the right contacts and speed up scheduling.

When scheduling an audit, the following aspects may be relevant – especially if the audit takes place in a foreign country:

- Seasons – weather conditions
- Bank holidays
- Festival seasons

The supplier to be audited will provide you with more details regarding relevant considerations when determining the right period and date.

3.1.2. Clarification of relevant Conditions

Normally, auditees ask for the auditors' dietary restrictions. If not, auditors should proactively inform the auditees of these.

Shoe and gown sizes are often requested by auditees. If not, auditors should make auditees aware of specific requirements (e.g. certain sizes such as 4XL overalls may not be available as a standard size).

Keep in mind that there are countries where shoe sizes are measured in cm.
Size 42 is a standard size in Europe but appears as an unusual outsize in, for example, Japan, where it is read as "42 cm".

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3.2. Audit Scope and Criteria

The type of products or services supplied trigger the relevant scope and audit criteria. The table below lists some typical supplies and related criteria. Please note that these criteria are not exhaustive.

Supply	**Criteria**
Medicinal Products	EU-GMP Part 1, plus related Annexes (e.g. Annex 1, Annex 15)
API	EU-GMP Part 2 / ICH Q7
Laboratory Services – Product Release / Stability Testing	ICH Q2 (Validation of Analytical Methods) ICH Q1A (Stability Testing) Ph.Eur. compendial requirements
Excipients	Exipact Guideline of 19 March 2015 on formalised risk assessment for ascertaining the appropriate GMP for excipients of medicinal products for human use
Herbal Substances	GACP, Annex 7, EU GMP Part 2 / ICH Q7
Medical Devices	ISO 13485
Sterile Medical Devices	EN ISO 13408
Primary Packaging Material	DIN EN ISO 15378 ISO 9000 ff, compendial requirements (Ph. Eur.)
Investigational Medicinal	EU-GMP Part 1, Annex 13
GMP-related IT-Services	Annex 11, GAMP 5
Storage and Distribution	GDP
Sterile Medical Devices	EN ISO 13408

Additional local requirements may be applicable. The supplier self-assessment normally reveals which codes and standards are followed by the supplier. Familiarisation with these guiding documents is recommended!

Keep in mind that, although the products or services supplied may be applied or used in the GMP environment and processes, the level of Good Manufacturing Practice to achieve adequate quality does not necessarily have to be the same as the standard set forth in the "EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use". Although different, the supplier's standard may still be adequate.

3.3. Auditors and Audit Team

3.3.1. General Requirements and Considerations regarding Auditors

3.3.1.1. Skills and Competence

It goes without saying that auditors should have the skills and knowledge to achieve the required audit results.

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Requirements regarding auditor competences and achieving and evaluating them is comprehensively described (in around 10 pages!) in:

DIN EN ISO 19011 Guidelines for auditing management systems

This guiding document briefly summarises the qualification criteria for auditors:

- Personal integrity
- Ability to respectfully communicate
- Trustworthiness
- Technical expertise related to the audit subject
- Objectivity – unbiased
- Accuracy, diligence
- Vigilance regarding potential influencing attempts
- Ability to perform evidence-based evaluations
- Upright character, refraining from using information obtained for any other purpose than the audit
- Ability to keep information confidential
- Be capable of understanding and accepting adequate alternative approaches
- Focused and adequately persistent to obtain the required information
- Acceptance and understanding of own limitations when it comes to expert knowledge on the auditees' side
- Ability to set priorities and focus on relevant aspects
- Awareness that audit conclusions are drawn from spot checks which may not provide a comprehensive overview
- Comprehensive and meaningful note taking

Further relevant competences depending on the situation and role:

- Audit experience
- Specific regulatory knowledge
- Familiarity with the legal situation
- Knowledge about the business relationship
- Language skills
- Familiarity with local habits and conditions
- Respect towards other cultures
- Willingness to travel – no health restrictions

Moreover, it is essential that the auditor should have time to prepare the audit report!

When the audit team is nominated, the responsible person must ensure that the chosen team possesses all relevant competences. A typical team consists of two auditors and, in some cases, is supported by a technical expert or an audit trainee.

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One aspect that must not be underestimated or neglected is the potential closeness of auditors to auditees, which may develop over years of working together. On the one hand, close relationships may prevent objectivity while, on the other, they may support an open and efficient atmosphere enhancing a positive business relationship. Both are possible, and the prevailing aspects depend on the individual situation.

3.3.1.2. Attitude and Conduct

Here, we should have a short look into the origin of the word "audit". The root is the Latin word "audire", which means "to listen". Thus, "auditors" are persons who listen to understand the auditees' processes.

Auditors should be aware that the primary objective of audits is generally to build mutual trust for the reliable supply of adequate quality. This should be supported by both auditors and auditees. Aiming for numerous audit observations as an indicator for effective auditing may lead to suspicion and mistrust, potentially destroying fruitful co-operation in the future.

Although these principles should be respected, it is unquestionable that an audit should identify conditions that are disadvantageous for product and subsequent patient safety.

3.3.2. Lead Auditor's Role

The lead auditor should possess the aforementioned attributes. However, lead auditors should also have the following additional capabilities and competences:

- Audit experience
- Ability to lead the audit team
- Management of difficult and critical situations

The lead auditor's main function is to ask questions and focus on the audit target.

Lead auditors should be willing to share knowledge and experience with co-auditors and auditor trainees.

3.3.3. Co-Auditor's Role

The co-auditor is often less experienced than the lead auditor. However, the co-auditor may have higher technical competence (i.e. may be the SME).

In cases where the co-auditor is the technical expert (SME), refer to Section 2.7.4.

In other cases, typical roles of a co-auditor may include the following:

- Taking notes
- Review of selected documents
- Keeping an eye on timing and the agenda
- Being vigilant and aware when things start to go in the wrong direction
- Being available for consultation with the lead auditor (may be important when different opinions have to be considered)

3.3.4. Technical Expert's (SME) Role

As the title indicates, this audit participant has the task of auditing their area of expertise and sharing and communicating the results with the other audit team members.

The related part of the audit report is prepared by the technical expert.

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3.3.5. Audit Trainee's Role

The audit trainee is clearly the "learner" in the team! Therefore, although the subjects may be of the utmost interest, the audit trainee should concentrate on audit practices and stay in the background. Asking questions is certainly fine, but asking too many questions may slow down the audit process and may even lead to inefficient and unreliable audit results.

3.3.6. External Auditor's Role and Considerations

External auditors are involved to:

- bring in additional experience
- provide additional capacity
- broaden technical experience

The external auditor may therefore adopt a role as a:

- lead auditor
- co-auditor
- technical expert

Contracts with external auditors should be in place, and evidence regarding their competence is required. A CV may be sufficient.

Confidentiality agreements are mandatory, either with the auditee or the employing company. In some cases, both are required.

Ensure that the external auditor has all the necessary information to support the audit according to your needs.

Note: Ensure that the confidentiality agreement between the auditee and the external auditor does not prevent the external auditor from sharing any information with a third party – meaning your company. Otherwise you may not be able to use of the information obtained by the external auditor!

3.3.7. Interpreters

This chapter will be added in a future version

3.4. Collecting Audit Information

Information must be collected to prepare for the audit. The enumeration below indicates areas and subjects where information may be obtained.

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Internal information:

- Product / Type of service
- Do other sites purchase the same supply?
- Standards and specifications
- Contracts
- Quality history (including audits, complaints, deviations, reliability of deliveries and services, etc.)
- Have products / processes been introduced / transferred
- Are there new legal requirements or expectations from regulatory authorities
- Previous audits
- Information from the marketing authorisation
- Anything that should be clarified during the audit – do colleagues have questions?
- Understand the "political" situation – any recent conflicts in the business relationship? Any areas that should not be touched?
- Familiarisation with the importance your company has for the auditee! Are they considered a premium client, or do they have low business volume?

External information:

- Consult the internet, press releases and website (new owners, products, extensions, renovations, reorganisations, relocations, etc.)
- Indication for recalls?
- FDA Warning Letters and Import Alerts
- EudraGMDP database

Documentation that may be requested / reviewed before the audit (if possible):

- Open parts of the DMF (US) / ASMF (EU) (internal document)
- Site Master File (SMF) incl. site layout
- Quality manual, incl. necessary key SOPs
- GMP and other certificates

3.5. Travel Planning and Traveling

3.5.1. General Considerations

Although nowadays, thanks to the internet, travel planning may appear to be "a piece of cake", there are important aspects to be considered:

- Visa requirements – invitation letters may be necessary!
- Passport validity
- Time difference
- Local weather conditions
- Cultural norms and expectations
- Hotel recommendations from the auditee may be helpful

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- Means of travel – car, train, plane?
- Local transportation
  - Pick-up by auditee
  - Taxi
  - Rental car
  - Public transportation

When packing your suitcase, do not forget all those things that cannot be provided electronically:

- Adapters
- The right outfit (sorry, but dress codes may be of specific importance for female auditors!)
- Business cards

And, although it should not happen, suitcases can get lost. Have **spare clothing in your hand luggage** in case your suitcase does not arrive. You are traveling for an audit – extra time for shopping is unlikely, and there may not even be a place to shop!

3.5.2. Country-specific Considerations

No doubt there are many aspects to consider, such as cultural, geographic, language differences, and it is impossible to reliably summarise ALL important aspects in this Reference Handbook. However, we can provide some hints and point out that these are just a subjective selection of information we want to share.

Consult your country's Ministry of Foreign Affairs website for travel information.

Germany

The German Ministry of Foreign Affairs provides an app that supports safe travel. You may enter the country of your current position and, for example, allow push notifications related to this country.

https://www.auswaertiges-amt.de/de/ReiseUndSicherheit/app-sicher-reisen

There may be similar possibilities in other countries!

Europe

Traveling in Europe for business purposes requires an A1 certificate. Surprisingly, this certificate is also required even when you do not receive any payment in the country into which you are traveling.

Access can be found here:

> https://europa.eu/youreurope/citizens/work/unemployment-and-benefits/social-security-forms/index_de.htm

China

China is mentioned in this Reference Handbook because there is a new legal regulation, as China recently passed the revised Counter-Espionage Law ("CEL"), effective from July 1, 2023. A translation may be found (without adopting any responsibility related to correctness or preciseness of this translation!) here:

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https://www.twobirds.com/en/insights/2023/china/what-you-need-to-know-about-chinas-counter-espionage-law

*iii. Any activity carried out, instigated, or funded by a foreign institution, organisation, or individual other than espionage organisations and their agents, or carried out in collusion therewith by any domestic institution, organisation, or individuals, to steal, spry for, purchase, or illegally provide any state secrets or intelligence, or other documents, **data, materials**, or items of concern to national security, or to incite, entice, coerce, or bribe a state employee to defect.*

Admittedly, not much information about the practice of Chinese authorities is available. It is known that inspectorates are currently reluctant to travel to China for inspections. There is, therefore, reason to believe that the risk is not evaluated as "zero". Conclusively, as a matter of precaution, the following measures could be taken:

- Travel with "empty computers" – do not have data / photos on your systems, except those which are absolutely necessary. It cannot be excluded that a system may be seized and searched. Consequently, information not related to the reason of travel may no longer be "in your custody".
- Travel with "empty mobile phones" for the same reason.
- Have a letter / confirmation from the Chinese company to be visited, in which this company confirms that you are entitled to possess / obtain certain information.

3.6. Audit Agenda

An audit agenda should be provided to the auditee. It helps to structure the audit. Auditees ask for agendas, although frequently, there is a tendency to more or less ignore them.

Auditors may not know local business hours, break times and lunch times. Therefore, request this information before preparing the agenda. Scheduling may need to be done around some fixed time points.

The agenda should include the following information:

- Company to be audited
- Audit host
- Audit date
- Type of audit
- Audit scope
- Auditors
- Regulatory basis

The schedule, indicating suggested duration and subject, should be provided. Suggested participants may also be part of the agenda.

An agenda may look like this:

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Time	Subject	Suggested participants
Tuesday, December 12		
09.00 – 10.00 am	Kick-off-meeting (mutual introduction, company presentation)	all responsible persons
10.00 am– 11.00 am	Plant tour for overview	someone who can give an overview
11.00 am – 01.00 pm	QA-System (Quality Manual, Site Master File, SOP-system, training of personnel, self-inspections, Change-control, handling of deviations, etc.)	QA Manager
1.00 – 2.00 pm	*Break*	
2.00 – 5.00 pm	Production Equipment (technical issues, qualification, maintenance) Production Process (process parameters, cleaning, validation, operational safety) Documentation	Head of Production Responsible for Qualification and Validation
5.00 – 5.30 pm	time for wrap-up, questions, etc.	all participants
Thursday, December 13		
9.00 – 10.00 am	Computerized Systems (Validation status)	QA Manager
10.00 – 12.00 am	Utilities: HVAC-System, Water treatment (technical issues, qualification, calibration, monitoring)	Technical manager
12.00 am – 1.00 pm	Storage Areas / Warehouse	Head of Logistics
1.00 – 2.00 pm	*Break*	
2.00 – 5.00 pm	QC laboratories, QC documentation, (equipment and instruments, qualification thereof, test procedures, method validation, handling of OOS-results, etc.)	QC-Manager
5.00 – 5.30 pm	time for wrap-up, questions, etc.	all participants

A template for an agenda can be found in Attachment 1.

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4. Performing the Audit

This section describes how audits are typically conducted, gives some hints regarding behaviour and, most relevantly, describes how to identify relevant criteria and define an adequate scope of examples (sampling!) that needs to be audited. As potential criteria are vast, these are added as attachments.

4.1. Introductory Meeting

What happens during this meeting:

- Mutual introduction of the participants
- Exchange of business cards
- Warm welcome
- Final agreement on scope and agenda

and

- the auditee's company presentation

Experience shows that the company presentation (often too promotional and not with an adequate technical and audit-relevant focus!) tends to be longer than scheduled, which unnecessarily consumes audit time. Auditors should be vigilant and intervene early if they perceive that there is the risk that time is being wasted.

After the introductory meeting, the team starts the tour.

4.2. Tour

Typically, the tour follows the product flow:

- Warehouse, incoming material
- Sampling
- Production
- Utilities
- Laboratory

Note:
Auditees are typically perfectly prepared to present the handling of incoming goods (they know that all auditors want to see this and the questions can easily be anticipated!). Therefore, auditors can see examples, SOPs, etc. and it is likely that the team will spend too much time in this area, even though it may not be very relevant.

Ensure that you allocate sufficient time to audit production, utilities and the laboratory with the same intensity!

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4.3. Focusing on Relevance – "risk-based approach"

4.3.1. Selecting Areas of Focus

This major section of the guiding document lists important criteria that could and should be audited.

However, it is impossible to audit all criteria. Thus, an audit has to focus on:

- the QM system, which is always part of the audit
- critical / relevant areas
- questionable areas (e.g. related to complaints)

Further supporting areas are audited for general understanding and overview.

4.3.2. Defining the Spot Check Scope

Auditing, which may sound surprising, is based on "sampling". Thus, "sampling area" and "sample size" should be defined to get a representative result.

Thus, define the "sampling area" and the "sample size" in the course of audit planning and keeping in mind that results of the sample checks should be adequate to lead to an overall picture. Therefore, they should be defined and "collected" with care.

Nevertheless, allow for flexibility, as there may always be unexpected "discoveries" on which you need to focus during the audit.

Some examples:

Auditing the QM-System

Defining the "sampling areas" could result in reviewing the following SOPs:

- Deviation management
- Change control
- Training

As a next step, define the "sample size" - how many samples you want to see (possibilities!):

- 1, 2, 3 – all deviations (related to your product)?
- How many change procedures? Focus on major impact changes?
- How many training documents? Employees of which area? Employees who have participated in the production of one of your batches?

Auditing "Qualification":

Defining the "sampling areas" could result in a document review:

- Validation master plan
- SOP for risk assessments
- SOP qualification
- Requalification schedule

As a next step, define the "sample size" - how many samples you want to see (possibilities!):

- Full documentation of one major piece of equipment (from URS to PQ)
- URS – PQ – all documents, but from different pieces of equipment

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- More than one example of equipment / room qualification
- Proven adherence to the requalification schedule – 1, 2, 3 examples?

4.4. Using Checklists in an Audit

A pre-prepared checklist (questionnaire) may be used allowing the auditors to ask appropriate questions relevant to the operations. The advantage of using checklists is that they enforce a standard format, thus ensuring that follow-up audits carried out by other audit teams are comparable.

Checklists also provide a good tool to avoid omitting important points when there are many aspects to be checked. They help the audit team to determine relevant topics and details in advance and to track the agenda, preventing them from forgetting topics of interest.

However, the use of checklists in audits can have several disadvantages:

- Checklists can be restrictive if they are the auditor's only support or source of information
- Checklists should not be a substitute for thorough audit planning
- Generic checklists, which do not reflect the specific organisation and its quality system, may not add much value and may interfere with the actual objective of the audit
- Poorly prepared checklists can slow down an audit due to duplication and repetition
- The focus of the checklist may be too narrow or superficial in scope and, therefore, may not allow the identification of areas with specific problems

It is important to note that, while checklists can be helpful, they should be used as a guide rather than as the only tool.

4.5. Specific Audit Areas and Criteria

A selection of audit areas and related criteria can be found in Attachment 3**.**

4.6. Closing Meeting

4.6.1. Preparation of the Closing Meeting

After the audit, some time should be reserved for the auditors

- to exchange views on the observations and their preliminary classification
- to consolidate what shall be communicated during the closing meeting
- to agree on who will present the results, which is usually done by the Lead Auditor, although the task may also be shared and the Co-Auditor may present his/her results
- to identify potential subjects that may require further clarification

The time available for preparation is normally not more than 30 minutes. Experience shows that very often even less time is available, since preparation time is consumed by the audit process itself.

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As the time for preparing the closing meeting is short, it is generally recommended to highlight subjects that should be addressed in the closing meeting already when taking the audit notes.

The preparation of the closing meeting should also consider the required depth of information and level of detail. This does not only depend on the available time, but also on the participants. If senior management attends the meeting, i.e. persons who have not been involved in the details of the audit, additional background information may be required and the level of detail should not be too high.

4.6.2. Communication of Audit Results during the Closing Meeting

The Closing Meeting, which typically does not exceed 30 minutes, should provide comprehensive feedback to the auditees.

The Lead Auditor, who may be supported by the Co-Auditor, should summarise the audit results, including:

- Thanking the auditees for
  - hosting the audit
  - sharing valuable information
  - answering all questions
- Expressing appreciation for the atmosphere during the audit (which was hopefully positive and supportive of fruitful future cooperation)
- Enumerating and explaining the observations — also mentioning areas where no observations were identified. For the observations, a preliminary classification may be provided.
- Highlighting subjects that require further clarification

It is not recommended to communicate a final classification of the audit observations, since the evaluation may still need to be adjusted during the preparation of the audit report after deeper consideration of the findings.

Furthermore, it is not recommended to state that all observations have been mentioned, as auditors should be aware that not all relevant subjects may have been extracted from their notes during the limited preparation time.

The Closing Meeting should conclude with agreements regarding:

- How and when the audit results will be shared (e.g. audit report or report excerpt)
- The timeline for the auditees to respond (e.g. CAPA list)
- Agreement on open actions:
  - Is further information required?
  - Who is responsible?
  - What is the timeline?

… and hopefully in a pleasant and constructive atmosphere.

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5. Audit Report and Evaluation of the Audit Result

5.1. Preparation of the Audit Report

5.1.1. General

The audit report should be prepared as soon as possible after the audit has taken place. No matter how good your notes are, humans tend to forget details in the course of time. Preparing the report within two weeks after the audit is advantageous compared to reports that are written after months!

The audit report should be a comprehensive, easy-to-read, and easy-to-understand document. It should objectively describe the audited areas and state observations.

State all areas that have been audited and indicate:

- when there were no observations (this is also helpful for future audits as it shows that the area was covered and it may indicate that the area does not need further attention)
- if and which observations have been made:
  - Describe in which way the observation is not in line with the requirements
  - Make reference to the standard / guideline / internal agreement
  - Classify the observation (refer to Section 4.2)
- if more than one person has conducted the audit, different sections may be prepared by the individual auditors and this may be indicated in the report.
- should there be a time delay between the audit and the finalisation of the report, it may be advisable to state the date of the draft version of the report.

5.1.2. Structure and major Sections

Audit reports should have sections for documentation of the following:

- Auditee: company, location, audited site, contact data
- Scope of the audit / Reason for the audit / Audit subject
- Date / duration
- Audit participants (auditors and auditees)
- Executive summary, stating relevant observations and the overall conclusion
- In detail: audited area, conditions, and observations
- Evaluation of the audit observations
- Attachments

A list of documents that have been reviewed may be prepared. Alternatively (if not better!), the reviewed documents may be quoted in the text, related to the respective context.

Further information, for example a reference to an internal audit plan, an audit number or a distribution list may be relevant.

Normally, companies have templates for audit reports and, of course, these templates have to be used. However, experience shows that many such templates:

- require writing in prose, which can make it difficult to distinguish general information from observations

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- have pre-defined sections like "Production" and no pre-defined sub-sections. If the auditor does not introduce sub-sections, but writes prose texts for everything that was audited in "Production", it is difficult for the reader to identify which areas have been covered and if there are areas which have not been audited.
- want the repetition of observations in several sections (what makes it tedious for the author, and difficult for the reader as the reader has to go back and forth between the table of observations and the text, where details are described)

Audit reports, which have pre-defined sections and tables (the criteria of which may be adapted due to specific conditions!), provide an easy overview – as shown in an example below:

3.2 QM-System / Document Review

3.2.1 QM-System / General QA-Subjects

No.	Subject / Question	Answer / Situation	Result / Observation	Rating
3.2.1.1	Quality Manual			
3.2.1.2	Site Master File			
3.2.1.3	Document Management			
3.2.1.4	SOP Index			
3.2.1.5	PQR / APR			
3.2.1.6	Handling of Deviations			
3.2.1.7	Deviation Investigation Report			
3.2.1.8	CAPAs			
3.2.1.9	CAPA-Form			
3.2.1.10	Change Control			
3.2.1.11	Change Control Form			
3.2.1.12	Root Cause Analysis			
3.2.1.13	Internal audits			
3.2.1.14	Quality Risk Management			

Having individual numbers for each audited criterion provides an additional advantage. For example, you have made observations regarding "inadequate record keeping practice" in, for example, production and quality control. The observations are stated in production and the QC section, but the audit observation is actually related to a deficit in QA under the criterion "good record-keeping / GMP-compliant documentation". The individual numbers (per line) allow cross-referencing of observations in production and quality control to the respective section "QA" in the document (and back).

During an audit, there are always conditions that

a) you have seen, read, observed by yourself

and other subjects, where

b) auditees have explained the conditions.

The audit report should be prepared in a way that a) can be distinguished from b).

Make clear that the statements in the audit report refer to the conditions found and, as a matter of fact, cannot be conclusive for the entire facility. For example, do not positively confirm conditions like "personnel were trained adequately" (normally, you cannot say this for each and every employee!), but rather state more carefully that, for example, "personnel appeared adequately trained" or "during the audit, examples of training records were reviewed and these confirmed an adequate training status".

5.1.3. The Language

As the observed conditions may have been a singular event, and may not be the same by the time the report is being prepared, such observations should be written in the past tense (e.g. "An

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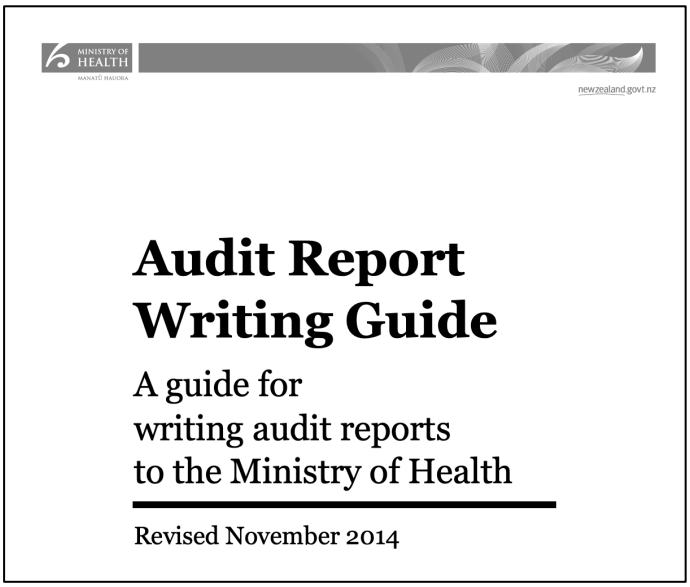
operator was seen handling xxxxxx"). If referring to SOPs / procedures, the report may be written in the present tense (e.g. "Material is received in the warehouse according to SOP xxxx").

A publicly available document that provides good support and hints has been issued by the New Zealand Ministry of Health.



https://www.health.govt.nz/system/files/documents/publications/audit-report-writing-guide-v3.pdf:

An example template for an audit report can be found in Attachment 2

5.2. Classification of Audit Observations – final Evaluation

There are numerous different ways for classifying audit observations, and what we present here is only an example.

Typically, a distinction is made between observations that are classified as:

- critical
- major
- minor

and observations that are worthy of a:

- remark

or

- recommendation

Furthermore, room for post-audit clarification should be provided.

Rating	Description	Number of Observations
Critical	The observed condition: - Does or may seriously affect product quality / patient safety.	

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Rating	Description	Number of Observations
	and / or - Essentially violates GMP requirements. and / or - Fundamentally affects regulatory compliance. The observations require immediate actions.	
Major	The observed condition: - Does or may affect the product quality / patient safety. and / or - Violates GMP requirements. and / or - Affects regulatory compliance. The observations require high priority actions.	
Minor	The observed condition: - Does not comply with good practice. and - There is no indication that it affects product quality / patient safety. The observations require action within a reasonable timeframe.	
Remark	Condition appears questionable, although there is no documented evidence for an out-of-compliance situation. Improvement action may be taken.	
Recommendation	Improvement action recommended; observation not related to GMP or compliance.	
Open issue	Issue could not be conclusively clarified during the audit. Post-audit clarification will take place.	

How to count the number of observations in the individual rating-criteria? Would 3 times seen inadequate "good record keeping practice" result in 3 observations? Or should this be summarised in one observation? Or even be related to "inadequate training", which could be the cause?

Final conclusions regarding the adequacy of a supplier, although often drawn in audit summaries, should be drawn with care. There may be further aspects that need to be taken into account for a conclusive and overarching supplier evaluation. However, and in any case, the outcome of an audit is an important factor in supplier evaluation.

A disclaimer may be of importance for external auditors. Depending on the situation, wording may be as follows:

> "The audit has been performed based on best knowledge, independently, using the available competence and experience of an *external auditor*.
>
> The rating in this report was agreed with the *client*.

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All information provided in this report is based on information given, received and seen during the 2-day audit. To give the reader an overview, all audit results are presented, regardless of whether there were observations or not."

5.3. Communicating Audit Results to the Auditee

There is no general rule or best practice for communicating the audit results to the auditee. In any case, the auditee must receive the information about the observations and the auditing company's expectations.

5.3.1. Sharing the entire Report

If the entire audit report is shared, auditees will review the report and (most likely) send remarks. This communication between the parties lead to a long process until the report can be concluded and actions can be initiated.

5.3.2. Sharing the audit observations

The most common practice is to share the audit observations. However, the information sent with the observations should be sufficient for the auditee to understand the observations and to have the possibility to react adequately.

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6. Follow-up – Action Plan/ CAPA Plan – Closing of the Audit

6.1. Action Plan/ CAPA Plan

The common name for the action plan is "CAPA plan". Naming the action plan "CAPA plan", the definitions for CAs and PAs should not be forgotten (ICH Q10 Pharmaceutical Quality System, quoted from the glossary):

> **Corrective Action:**
> Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)
>
> **Preventive Action:**
> Action to eliminate the cause of a potential non-conformity or another undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence, whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Therefore, when considering these definitions, "corrective actions" are actions to prevent something, the recurrence of a situation / non-conformity, whereas the preventive action (PA) is taken to prevent occurrence. And, in fact, once non-conformity has occurred (i.e. an audit observation), it is no longer possible to prevent its occurrence, which means that for this specific observation, no preventive action (PA) can be taken!

Furthermore, some of the actions to be taken do not address the cause of non-conformity, as they are not "CAs", but corrections aimed simply at eliminating non-conformity.

However, accepting the denomination "CAPA plan" as the overarching term for actions to be taken, auditees should prepare a CAPA plan promptly.

Normally, four weeks are acceptable though, depending on the severity of the observations, four weeks may be too long. This is especially so when we consider that the four weeks are only for sending the action plan and, presumably, none of the actions will be performed within the four weeks.

6.2. Responding to the Action Plan/ CAPA Plan

The auditors' organisation should check the suggested actions and confirm or, in cases where they do not agree, ask for clarification or discuss and update. Experience shows that sending comments back and forth is not really helpful. It neither improves the relationship and seldom leads to an enhanced willingness for modification of the CAPA plan.

A conversation with the auditees is strongly recommended!

Once the CAPA plan is agreed upon and confirmed, auditors / the auditing company should keep track of the status. Most commonly, the actions are transferred into the auditing company's CAPA system (action management system).

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6.3. Performing the Actions

Auditees should perform the actions within the agreed timeframe and communicate completion to the auditing company.

6.4. Closing the Audit

The audit can be closed when all actions have been completed. It is recommended that this be confirmed with the auditee.

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7. Potential Difficulties and Challenges – and Possibilities to avoid or overcome these

Whoever has been audited or inspected knows that the role of an auditee is neither comfortable, nor would we call it desirable. It is clear that auditors and auditees have different objectives (in most cases).

Auditors want to find out as much as possible – auditees, even if they do not want to hide anything, are reluctant to share all information. It is in an auditee's well-justified interest not to share confidential information and not to reveal potential weaknesses.

It is not necessarily a conflict of interest, but a situation that can lead to difficulties and challenges. To adequately act or react in such situations, or even to avoid difficulties, the authors' team has compiled some ideas and tools.

7.1. Ways to avoid Difficulties

At the beginning of the audit, the auditor may point out that:

- It is the auditor's role to ask questions, and that they are aware of and understand the auditee's situation.
- The audit is performed to build mutual trust, although questions may be probing and sometimes "nasty" and have nothing to do with the final evaluation of the audit outcome.

Auditors should "listen" (remember "audit" has the Latin root "audire", which means "to listen") and understand the auditee's systems and approaches and not impose their own expectations concerning "the right way" to do something.

Adopt the attitude that auditees are competent and know what they are doing, even if they may do it differently from what the auditor expects!

Avoid putting unnecessary pressure on the auditee by asking closed questions that can only be answered with "yes" or "no". Closed questions are a good way to communicate when a clear answer should be forced. In other cases, open questions are preferable. Provide the possibility for auditees to explain their system. Examples include:

- "How do you (ensure) …."
- "What is your way to …"
- "We have seen xxxx, can you explain it to us …."

Value the auditee as a peer with different knowledge – neither inferior, nor superior!

And:

- Do not touch anything in the audit areas (without asking)
- Respect privacy (reading internal publications displayed for employees may be inadequate)
- Do not open doors, cabinets. If looking into closed rooms, cabinets appears necessary, ask auditees to open them.

However, sometimes difficulties arise. In the next chapters, examples and potential solutions for such challenges are provided.

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7.2. Responding/ Reacting/ Behaving in difficult and challenging Situations

Please keep in mind that we share possible approaches to react to difficulties. Specific situations require individual responses, and there are many adequate ways to handle challenges!

Also keep in mind that it may not necessarily be the auditees who are causing the difficulties!

Speaking of the "meta-level". This is the level to speak about communication as such. In some cases, this may be very helpful to solve difficulties.

As a general note, when it gets tricky, the auditor can step back and open the situation for further discussion, e.g.:

- "I'm afraid I'm (a little) annoying now, but I would like to return to ...."
- "Sometimes an audit like this is difficult for the auditor too. I hate to make myself unpopular, but could we review ..."
- "Now I have to put on the Miss Marple / Sherlock Holmes costume again and keep asking ...."

What can happen	**Potential ways to solve the situation**
You realise that you are not really well prepared (e.g. did not read the contract / prepared for a technology that does not apply /....). ... A mistake can always happen, even if it is unpleasant for us.	• Admit that you have made a mistake. • Ask for a little time out and catch up on what you've missed. → The audited company might be against a short interruption. The success of the audit could be jeopardised if you do not catch up on the preparation.
The audited company makes a sales pitch at the audit or is in the middle of an endless company presentation with subjects totally unrelated to the audit.	• Avoid the situation from the beginning by providing an agenda (admittedly, and very often, this does not avoid such a situation!). • Point out the tight schedule and limited time. "We would like to start the audit in xxxx minutes". → The audited company will likely not easily stop selling, if you do not intervene.

During the tour, you see something, but because you are not yet familiar with the process, you are not sure if it is a deficit / worthy of a remark.	Depending on the situation:
	• If the observation refers to something that is going on at that very moment: ask immediately.
	• Ask about the background: "I see ...., could you explain what the background is?"
	• If the tour takes place at the beginning:
	  • Take a note and add the point later.
	  • Check with the co-auditor.

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What can happen	Potential ways to solve the situation
Someone from the group of auditees feels attacked and speaks up loudly.	Try de-escalation: • Consider that you have said something provocative; address the possibility - it is better to apologise once more than once too little. • "Please let us try to clarify the facts. There may have been a misunderstanding" – ask to re-discuss the situation. • "I understand you don't agree with ..... I would like to clarify this with you. May I please speak to you alone / with my co-auditor?" • Hope that a supervisor - if present - will address the employee and influence them! (should not be the auditor!) • Stay calm, don't say anything - don't smile! - wait a while. • If the situation is really severe - consider interrupting / ceasing / cancelling the audit!
There is a procedure that is incomprehensible and against good practice, but the auditees have the argument: "We are US-FDA approved" / "We are GMP-certified".	Of course, authority approval does not mean that inspectors have read and seen everything. • Explain calmly why you do not agree with the procedure and what the impact could be. • Confirm that – of course – you are happy that the auditee is GMP-certified, but it may still be that there is a deficit since the inspector has certainly not seen each and every detail.
You have the impression that the company wants to hide something - information only comes hesitantly or late.	• Enquire - explain that you are waiting. • Intervene carefully: "May I raise something? I have the impression that it takes a very long time for me to receive the requested information. Could you make sure that I get the answers a little more quickly. Otherwise we might run out of time (and I may have to come back!)." • Emphasise that: • Long waiting times may result in a finding. • Information not received is considered "not available". • Ask another participant the same question – and see what their answer is. • Ask for a time-out and consult with the co-auditor: Do they have the same impression?

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What can happen	Potential ways to solve the situation
The contact persons do not understand the question or pretend not to understand the question.	Try to find out whether auditees do not understand or do not want to understand. • Reformulate and repeat the question using simpler language. • Does the company perhaps use a different term for the matter you are referring to? • Give an example of what you want to know. • Describe a situation that explains the question. ("We do this and that in this situation, what would your approach be like?") • Meta level: "If I understand correctly, then my question is not entirely clear. Let me explain why the point is important and I'll ask the question again." → If the question could be clarified, that's great there will be an answer! But – if not? Move to the next set of potential ways out….
The contact persons do not understand a question or pretend not to understand a question.	All attempts to clarify the issue have failed. Too bad. • Meta-level: "I have now made some effort to clarify my question and explain why the answer is important. Is there no way at all that you could describe what your approach is?" • Ask for time-out and consult with the co-auditor. Do they have the same impression? Agree on the next steps. • They have the same impression. Make it (carefully) clear that you do not accept the auditees attitude. Are there reasons for refusing to answer? • They don't have the same impression. There must be a reason for this, perhaps they know why the question was not understood? → Clarify on the basis of the results of your consultation. • If you feel uncomfortable having to / wanting to insist on an answer: "I know I've asked before, but the point is very important. Please understand why I am asking again....."

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What can happen	Potential ways to solve the situation
One of the auditors "gets stuck on a topic" and, on closer inspection, the topic is not really relevant.	Unfortunately, "biting down" happens quite often... • Ask a question that gets back to the actual / an important topic. • Refer to the timetable. • Take up a point in the discussion that offers the opportunity to enter into a new topic. • Ask auditees for a time-out. • Agree on a signal before the audit between auditor and co-auditor – and hope the other one remembers at the right time: • "Do you have a handkerchief for me?" - "It's hot / cold here". • Send a text message or write a message on the PC and show it to the "stuck auditor".
The auditor makes an observation, and the auditees reply: "Why do you think we are not acting correctly here? We are acting exactly according to guideline xxx!" - and unfortunately, you don't know this guideline!	• Don't try to hide your lack of knowledge → It is quite likely that auditees will discover this weakness, and it is better to frankly admit it than trying to conceal the lack of knowledge. After all, you can't know everything! • Simply admit that you are not aware of this special regulation and ask for more information about it → Audits serve to build trust and hopefully, auditees will support you! • Ask for the guideline, familiarise yourself with the regulation in question. • You can also say: "Oh, thanks for the tip." • Consultation with the co-auditor. • What you may have done before the audit. Familiarise yourself with the relevant guidelines.
The auditor wants to take a photo of a certain situation; the auditee points out that this is not permitted.	Of course, avoid unauthorised action and confrontation! Is the photo intended to document an "advantageous" situation in order to demonstrate to the responsible persons not participating in the audit a positive impression? Possibilities: • Ask the auditees to take the photo for their records and explain that you will refer to the situation in the report – the auditees will have the photo and know exactly what you are referring to! • Forego taking the photo (if it is not very important). • Ask for clarification of authority with the responsible QA contact person, including during the audit. • If it is crucial for product quality and patient safety → ensure that the photo may be taken or is taken by the auditees and later provided to you.

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What can happen	Potential ways to solve the situation
The auditor does not agree with a certain procedure, but the procedure is described in an SOP.	• Listen to the arguments of the auditee. • Be prepared to change your mind - maybe you misunderstood something or didn't know the background? • Check whether there are perhaps regulations elsewhere in the company that make the procedure appear plausible / justify it? • If the differences of opinion cannot be clarified, record the point and agree with the auditee that the matter will be addressed elsewhere (e.g. your QA).
Someone is sitting in the audit room who doesn't seem involved, just leafing through documents and giving you an "angry look" every time you ask a question. You start asking yourself whether you should not ask any more questions....	• Address what you are observing. • Ask if you have done something wrong. • Carefully say that you have the impression that the auditees do not seem happy with your questions. • Highlight the importance of the audit in terms of good cooperation. • Request that auditees help to create a more pleasant atmosphere and, of course, emphasise that you will contribute to this on your part.

You are denied access to a room on site, access to a document or information in response to a question in order to "protect company secrets".
However, you need this information or access in order to be able to evaluate a situation.
	• Explain why the matter is important and the consequences of not receiving the information.
	• Would it be possible for the auditees to take a photo of the situation (hide everything "secret") and make this photo available? - here and now, not weeks later.
	• Alternative:
	  • Have the situation explained verbally.
	  • Jointly agree on how to present the facts in the audit report
	  • Write a report with the note "For confidentiality reasons, it was not possible to visit the xxx area. Auditees confirm that the situation is xxxx."
	Remember: The starting point for an audit is that you can / should / want to trust the audited company.

You identify a serious non-compliance that is either very expensive or very time-consuming to rectify. There is a risk that management will refuse to rectify the problem because you are only a small customer for the company.	Admittedly – a difficult situation! • Does non-compliance have a clear impact on the safety or quality of the goods / services you purchase? - or • Can it be proven that non-compliance has no impact? • During the audit: No announcements of consequences - only recordings of the situation. Follow-up actions (the CAPAs) will be decided after the audit. • Could tests be carried out on the goods to prove that non-compliance does not have an impact on your product?

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What can happen	Potential ways to solve the situation
You have doubts about the truthfulness or completeness of information you have been given.	• Ask another contact person the same / a similar question. • Explain why the information is considered incomplete / implausible → Ask for clarification. • Meta level: Explain that the audit serves to strengthen the basis of trust and that you do not actually intend to proceed like an inspector, but ask for appropriate openness.
You were given false information. You wanted to verify it, but the fraud was discovered. Your counterpart has now lost face and prefers to remain silent.	The false information has become evident - What can you do to help the other person save face? • Make it appear as a "misunderstanding" (on your part) → Opportunity to present the actual facts (whether finding or not!) • Take the offensive: "I understood what is going on. I'm here to support mutual trust and understanding and what I just experienced does not align with this. Please, do me a favour and support creating a more open environment." • Take a very relaxed approach and let auditees act: "This is a really uncomfortable situation for me now ....." / "What can we do now to save the situation?"
Shortly before the end of the audit, you come across an issue that represents a possible observation, but due to time constraints no clarification is possible.	• Agree to a post-audit clarification with the auditee. Further information should be provided following the on-site audit depending on what information is required. • Consider prolonging / extending the audit. • Include in the audit report as: "Issue could not be conclusively clarified." This category is important, in addition to minor, major, critical.
A "know-it-all" person tries to point out your weaknesses.	Counteract, e.g. by: • "I understand that this is your core competence, but please help me to understand …." • "This audit is to build mutual trust and understanding and I am certain there is no reason to highlight that I know less than you."
Auditees share "too much information" without giving any explanation (You ask a question and the answer is: "The document is on the shared drive" – and you find a 50 page document and there is nobody to talk you through the document.) –	Not a clear point to complain, because you have received the information, but there is reason to act: • Ask for a person to explain the document / give the specific answer • Point out that it will take too long if you have to read the entire document and that this may lead to an "incomplete audit" • Providing documents is not "supporting the audit" and when auditees do not communicate, this may be regarded as an indication that they are not interested in co-operation. Depending on the target of the audit, consider abandoning the audit.

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8. Glossary

Term	Abbreviation	Definition
Annual audit schedule/ programme	-	List of audits to be carried out for the current and, if applicable, subsequent year.
Active Pharmaceutical Ingredient	API	A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound.
Audit agenda	-	Prepared in advance for the implementation and procedure of an individual audit. Defines the objectives and scope of the audit.
Co-auditor	-	Qualified individual supporting internal or external audits.
Distant Assessment	-	An assessment of the GxP compliance of a site where the auditor is not physically present on site. Face to face interactions between the site and auditor in real-time utilizing video and screen sharing platforms = Remote Audit / Remote Assessment
Hybrid Audit	-	An audit that combines the remote audit aspects or distant assessment and on-site presence by at least one auditor.
Lead Auditor	-	Responsible for leading the audit team in preparing and conducting the audit.
Marketing Authorisation	MA	A legal document issued by the competent drug regulatory authority that established the detailed composition and formulation of the product and the pharmacopeial or other recognised specifications of its ingredients and of the final product itself, and includes details of packaging, labelling, and shelf-life.
Observation		Condition not in compliance with the general Good Practice Requirements, contractual obligations or with specific conditions, which need to be fulfilled in order to supply adequate quality of the audit subject. Observations are also called "findings", "deficits".
Pharmaceutical Quality System	PQS	Describes the procedures and controls in place to ensure constancy and traceability of operations across the organisation. Ensures all operations follow the current GMP requirements, as well as the local regulatory expectations and compliance with the licensing requirements.
Product (Audit subject)	-	In this document, "Product" stands for the "audit subject", which may be any kind of substance ("material") or service ("immaterial") that needs to be supplied in a defined quality.

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Term	Abbreviation	Definition
Quality Risk Management	QRM	A systematic approach for the assessment, control, communication and review of risks to the quality of the product across the product lifecycle.
Remote Audit Remote Assessment	-	Refer to "distant assessment"
Site Master File	SMF	Document prepared by a pharmaceutical manufacturer which contains specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations and any closely integrated operations at adjacent and nearby buildings.
Subject Matter Expert	SME	Expert in a particular process, procedure or method.
Supply		Supplied good, which may be any kind of product or service.
Supplier		Any company or individual supplying a product - in context with this document "the auditee".

Attachments:

Attachment 1	Audit Agenda Template
Attachment 2	Audit Report Template
Attachment 3	Audit areas and audit criteria

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