GMP training for contractors and visitors of Boehringer Ingelheim Pharma GmbH & Co KG

This GMP training....

.... is aimed at persons who work in the GMP area.

Please note: Personnel of partner companies (contractors/external companies) as well as BI employees visiting from another site who regularly or frequently work in the GMP areas (e.g., at least 2 to 3 times per month or under an existing framework agreement) are additionally required to complete a GMP examination. The examination must be completed **prior** to any work in the GMP area and must be repeated on a regular basis.

Content

1. **What is GMP and what comprises GFE?**
2. **Entering through the airlock**
3. **Maintaining a particle-free work environment**
4. **GMP-compliant documentation**
5. **Questions? Situations you are unsure about?**

1. What is GMP and what comprises GMP?

What is GMP?

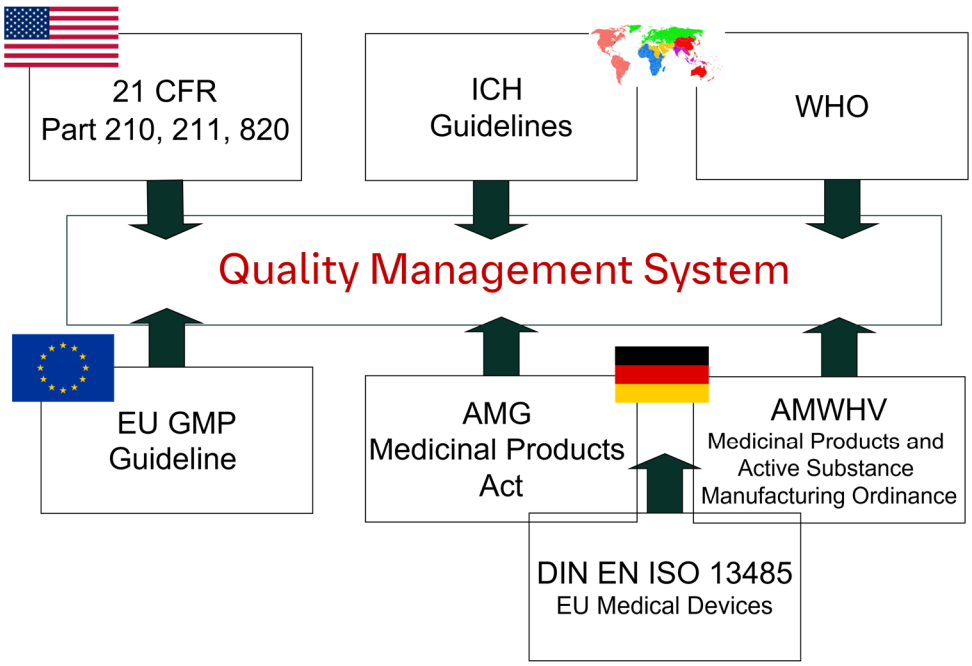
“Good manufacturing practice” / GMP / “Good manners in production”

To protect consumers from dubious products and companies, there are both German and international laws in place that prescribe rules for good manufacturing practice (GMP).

These laws specify who is authorized to manufacture medicinal products and what rules must be followed in their production and all related activities.

Compliance with GMP rules is mandatory and is overseen by the respective health agencies.

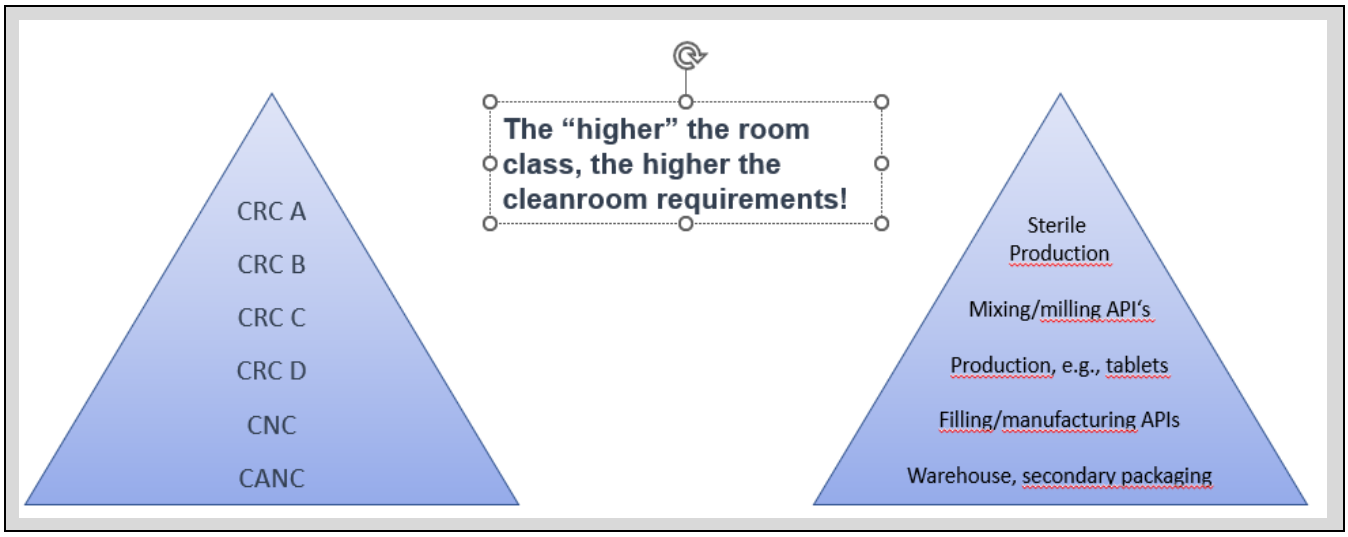
Legal Basics



What comprises GMP?

GMP areas, cleanroom classes, zones

In areas with particularly strict cleanroom requirements (such as open handling of active pharmaceutical ingredients), special GMP requirements with respect to purity/cleanliness/hygiene apply to both rooms and personnel. These cleanroom requirements for different room uses (production areas, corridor areas, storage areas, etc.) are defined by room classes (zones). The following applies here:



ⓘ **Areas with high cleanroom requirements are labeled as such on site and can only be accessed by way of personnel and material airlocks.**

Examples of room labeling in pharmaceutical production:

00.701 Corridor	00.701 Corridor	00.701 Corridor	00.701 Corridor	00.701 Corridor	00.701 Corridor	00.701 Corridor
Unclassified	CANC	CNC	CRC D	CRC C	CRC B	CRC A

Indicating room and production status

Workroom status	Color	
Released, free	**Green**	
In production / in use	**Yellow**	
Not free (quarantine / cleaning / maintenance)	**Red**	

The status of workrooms is indicated by various colors (traffic light system), whereby the employee responsible hangs a round, colored sign in a clearly visible location near the door.

Alternatively, room and production status can also be indicated visually on an electronic display.

GMP requirements

Specific requirements for rooms include:

- Filtration and climate control of the room air
- There should be no difficult-to clean areas in rooms/equipment/piping.
- Personnel and material airlocks must be used for all transitions from one zone to the next higher or lower zone, and the airlocks must be physically separate from each other.
- Pressure differences between different cleanroom classes

Special requirements for you and for personnel in the cleanroom areas:

- Proper employee/plant hygiene
- Cleanroom class-specific work clothing
- Compliance with rules for entering production areas, including inward and outward airlock transfer of materials and tools
- GMP-compliant behavior
- Particle-free work principles
- It is strictly forbidden for anyone to have unnecessary contact with open product or product-contacting parts.
- Foreign particles and materials must not contact or enter open product.

Personal hygiene

Why is personal hygiene so important?

The human body provides optimal conditions for germs to grow. It is warm, moist, and nutrient-rich.

In addition, a person making sudden, irregular movements or walking quickly can shed up to 30.000.000 particles/min. When seated, that number is “only” 100,000 particles/min. For that reason, it is imperative to prevent contaminants like dirt, dust, dandruff, hair, debris from the soles of shoes, or human germs from being introduced into production areas.

What does that mean for our behavior, clothing, and health?

In general, it is not permitted to bring in or consume the following:

Food and beverages
(this includes candy and chewing gum)

Cigarettes/tobacco and other smoking-related items

Medications
(exception: emergency medications).

ⓘ Use the break areas provided.

– Water is also provided there.

As a rule, any and all unhygienic behaviors are to be avoided.

- Appropriate personal hygiene and regular handwashing and disinfection are required.
- Always follow the clothing requirements posted on site.
- Do not wear any jewelry, including earrings, wedding bands, wristwatches, or visible piercings.
- Fingernails must be kept clean and cut short. Nail polish, nail gel, artificial nails, and artificial eyelashes are prohibited in zones CNC and higher.
- Move calmly and in a controlled manner.
- Wear clean, conductive safety shoes or safety shoe covers and clean socks/clothing that cover the ankle.
- Personal backpacks and bags must not be taken into the production areas.

- Report any contagious illnesses. (Consult with a physician/company physician to make sure there is no risk to the product; also consider the risk of infection from holiday travel.)
- Cover open wounds and any weeping or flaking areas of skin.
- Wearing cosmetics of any kind except hand and face creams is prohibited.

In addition, note the following for cleanroom class D and higher:

- Street clothing is clothing that is worn on the way to the work premises and comes into direct contact with the environment. It is not permitted to wear street clothing directly under GMP clothing. You may wear items of upper body clothing that cover the underarms only if they were worn underneath your street clothes or taken fresh from your personal locker.

Communal areas, toilets, building alarm

- Break rooms, washrooms, and toilets are located outside the production areas. GMP clothing must be discarded when transitioning to those areas and new GMP clothing must be put on before returning to production areas.
- If a building alarm sounds, leave the workstation and the building immediately, without changing out of GMP clothing. When the alarm is over, put on new GMP clothing in the airlock.

Hand washing and disinfection

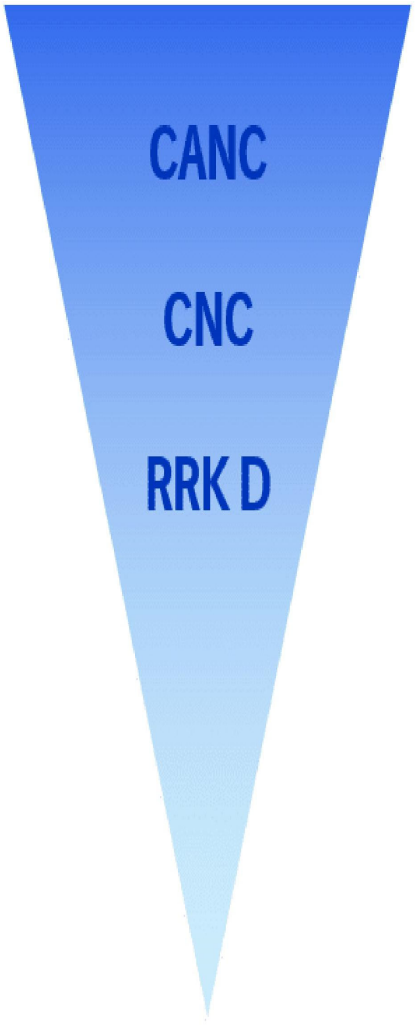
In GMP areas, hands must always be **washed** and **disinfected** at the following times:

- Before starting work
- At the end of work
- Before and after every meal
- After short breaks
- Before and after using the toilet
- After wiping/blowing nose or sneezing
- Whenever they become contaminated
- Whenever hands get in contact with any areas of uncovered skin (e.g., face)

2. Entering through the airlock

General procedure for using the airlock

Depending on the cleanroom class, entering through airlocks may require personnel to go through one or more physically separate areas (gowning area/airlocks). The airlocks serve as a transition from a less clean area to a cleaner area.



Zone CANC is accessed via physical separation and access control (e.g., company ID card). Clothing does not need to be changed if no basic clothing requirements are defined for the building.

Zone CNC is accessed via airlocks/gowning area (in one or two stages). Everyone must follow an area-specific gowning procedure to enter the controlled zones.

Cleanroom class D (CRC D, but “RRK D” in the graphic) is accessed via a second airlock from zone CNC or CANC. Everyone must follow the area-specific gowning procedure to enter cleanroom class D.

ⓘ **Always follow the clothing requirements posted on site.**

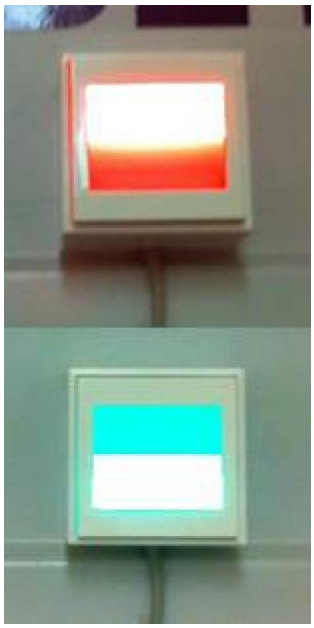
Airlocks and transfer areas

Airlock set-up

The demarcation between a less clean area and a cleaner area can be accomplished in the following ways:

- Through a marked boundary on the floor or a bench that must be stepped over.
- If there are two step-over benches, the space between them is called the transfer area. Transfer shoes or overshoes must be worn in the transfer area.
- In exceptional cases, if the floor of the airlock consists of adhesion mats, shoes do not have to be changed when moving into the next higher cleanroom class.
- Separation by way of two interlocked pass-through doors for cleanroom class D and higher.

Stoplight system in airlocks



In some airlocks, lights signal the airlock's status. Red indicates that the airlock is in use and the airlock doors cannot be opened. A green light means the airlock door can be opened. Always ensure that no two doors are open at the same time.

If there is a stoplight system, learn how to use it.

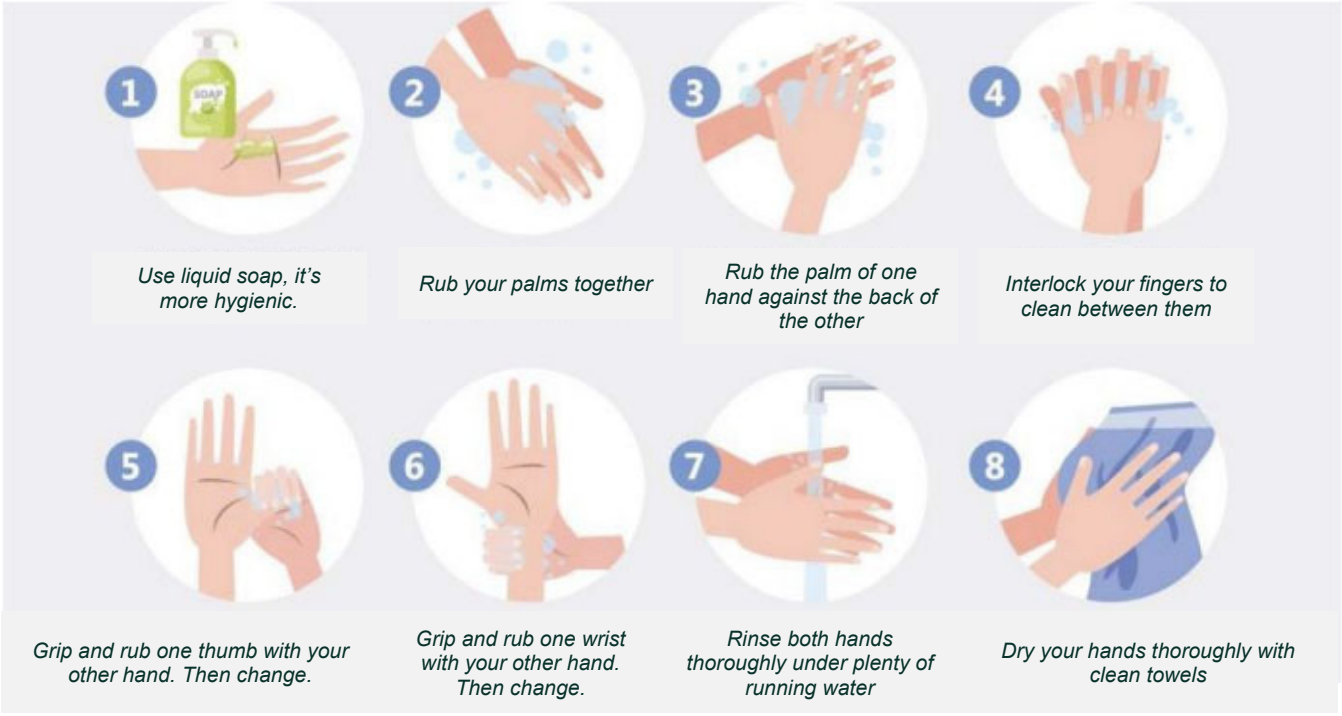
Example: Transfer of personnel via airlock into Zone CNC (E)

As a rule, cleanroom clothing is always put on from the top down in all areas.

When exiting through the airlock, the clothing is removed in reverse order, i.e., the GMP hood is removed last.

1. Wash hands thoroughly with soap:

How to wash hands correctly in 30 seconds



2. Put on GMP hood

Ensure the following:

- Hair is completely covered by the hood
- Ears are completely covered by the hood
- There are no holes in the hood

3. People with beards or stubble must wear a beard cover.

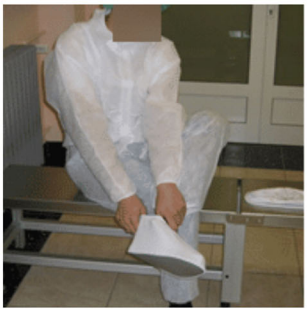
The beard cover must completely cover the beard.

4. Put on GMP clothing / coveralls:

- Choose the correct size coveralls.
- Always wear clean upper body clothing, pants, and socks under the coveralls.
- Take the coveralls and hold the left sleeve/pant leg and right sleeve/pant leg and the waistband in the corresponding hand and then pull it on, beginning with the pant legs.
- Make sure the coveralls do not touch the floor. Do not touch any unclean surfaces with clean clothing.
- Now pull on the upper part of the coveralls and close the zipper completely.
- Make sure that everything is covered and never roll up the sleeves.

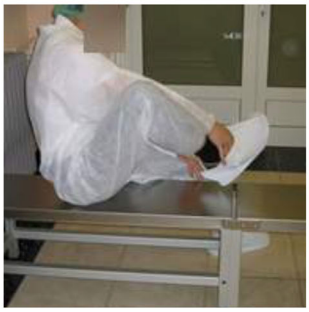
5. Put on GMP overshoes when transitioning to cleaner areas

Choose the correct size overshoes. Sit down on the bench, pull the overshoes on over your shoes, and swing your legs over the bench. Make sure your street shoes do not touch the bench. ***Do not return to the unclean area.***

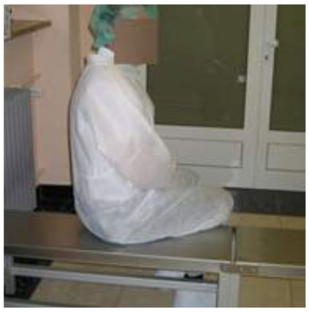


Step 1

Step 2



Step 3



Step 4

6. Disinfect hands

Use your elbow to operate the dispenser and catch the disinfectant in a cupped hand. Make sure your hands are dry first.

- Rub the disinfectant into your skin
- Palms together
- Palm to back of hand
- Fingertips and thumbs
- Areas between the fingers
- Palms and base of thumb
- Don’t forget your wrists.
- Rub hands until they are dry; do not wave your hands.
- Follow the posted signage.

7. Open product/product contacting parts

Gloves and mouth covering (and, if applicable, respiratory protection) must be worn when working with open product or equipment that get in contact with product.

Example of a person in CNC Clothing

Working on ladders in areas with hygiene requirements

If you **work on ladders regularly (> 3 days/week) in areas with hygiene requirements (e.g., GMP areas)**, you must bring your own white GMP safety shoes with you. They must be transported in a sealed plastic bag and not placed on any floor outside the clean area. Disinfect the GMP safety shoes and then put them on in the transitional area (step-over bench) leading to the clean area.

If you **only occasionally work on ladders in areas with hygiene requirements**, you may borrow GMP safety shoes in any size.

Ask your BI contact about this.

Before/after use, the white GMP safety shoes must be disinfected. If cleanroom socks are provided, they must be worn.

Please follow the gowning procedure on site.

Do not wear GMP overshoes when working on ladders.

ⓘ Please note:

In some areas, employees of partner companies (contractors/external companies) must be accompanied and supervised by a production employee or the client during the airlock procedure and the subsequent stay in the production area.

Leave plenty of time to clarify with the client before the start of work (plant/engineering).

Inward transfer via airlock of work equipment and materials

- Work equipment (e.g., tool bag) is to be brought in by way of the designated personnel airlock. The tools must be visibly clean and must additionally be cleaned and disinfected in the airlock.
- Bulky equipment/replacement parts and materials up to the size of pallets are to be transferred via the material airlocks on the building ramps.
- Ladders, pallets, and other materials made of wood are prohibited in Zones E (CNC) and above.

Procedure for inward transfer of materials through the material airlock:

- Bring the material into the less clean area (no GMP clothing) of the airlock (entering the cleaner area without GMP clothing is prohibited).
- Remove any packaging material/film and dispose of outer packaging. If applicable, transfer the material to a pallet that is suitable for the GMP area for Zone CNC and above. Do not transfer boxes.
- Visually inspect the material for cleanliness and clean/disinfect it if necessary
- Transfer the material to the cleaner area of the airlock
- Remove the material from the cleaner area of the airlock (in GMP clothing).

ⓘ **When transferring work equipment and materials into and out of the cleanroom through the airlock, follow the plant-specific requirements on site.**

3. Maintaining a particle-free work environment...

...in the production areas

- Maintaining a particle-free work environment begins with conscientious preparation in the workshop and ends with leaving a clean, orderly workstation.
- In general, only clean/cleaned work equipment/tools are to be brought into the area.
- Rooms and equipment must be cleaned after each activity.
- Waste must be removed from the production area immediately or temporarily stored in labeled containers while the work being carried out and then removed immediately upon completion of the work. Do not leave any unlabeled containers in the production area.
- This helps ensure the purity of all products we manufacture and minimizes the risk of contamination.
- Foreign particles in active pharmaceutical ingredients/pharmaceutical products can result in costly rework, supply delays and even inability to deliver and, in the worst case, product recalls.

... in the workshop and in temporary storage facilities

- Tools and spare parts must always be clean and free of paints and particles
- Spare parts from third-party suppliers/Technical Magazin/storage areas must be examined for cleanliness and cleaned if needed
- Keep the workbench/tool cart tidy and equipped in a systematic way
  - Dispose of parts that will not be used.
  - Clean and then pack away in an orderly manner all parts that are not currently needed
  - Label parts legibly, with name and date
  - In Chemical Production Group B, follow the process described in “Handling mobile equipment and small parts for cleaning at the workshop.”

Maintaining a particle-free work environment on site

Before starting work	• Release certificate and work permit present and signed. • Observer safety measures on the release certificate and use required PPE. • Check installation area for cleanliness beforehand and sweep or wipe it down if necessary. • Hang any chain hoists *before* opening a piece of equipment. • Do not leave equipment/system openings open. If they cannot be closed, seal them appropriately; a poly bag is not sufficient. • All required work materials are present. Use clean tools
While working	• If you notice deviations/errors or irregularities compared with the normal state of a room or piece of equipment, or if an accident occurs, notify your BI contact person.
After completing work	• Sweep work platforms before dismantling. • Leave the workspace clean and orderly. • Check in release certificate properly according to procedure

Examples of maintaining a particle-free work environment in chemical production

Flanges/sealing surfaces/seals/bolts must always be clean and free of paints and particles

Green = like this

Red = not like this

- Wipe flanges/seals with a white, lint-free cloth before assembly
- Remove loose paint/particles by hand
- Stored sealing materials must be clean
- Nuts and bolts with paint residue must be replaced.
- Use the correct length bolts
- Grease bolts with the specified grease prior to assembly

4. GMP-compliant documentation

Some type of record is needed to record all the work we do:

- An inspection and maintenance record,
- Records of air volume flow measurements,
- Calibration, etc.

Give the original copy of these documents to your contact person at BI.

ⓘ **"Good documentation constitutes an essential part of the quality assurance system... Records should be free of errors and available in writing. Legibility of the documents is very important."**

EU GMP Guidelines

What does correct documentation look like?

- unambiguous and complete, easily legible
- Timely. Always write times in four-digit format, on the 24-hour clock (e.g., 08:50)
- Always use the complete, two-digit date format (DD.MM.YY or DD.MM.YYYY)
  (e.g., 13.09.12)
- Traceable (also for those not directly involved)
- Do not use repetition symbols (ditto, ", "as above," etc.)
- All entries must be made with permanent blue or black ink, e.g., with an uniball or ball point pen.

- Documentation must always be signed by **two** people, the person carrying out the work and a reviewer from BI, and always with both printed name and signature.

Data integrity

The integrity of our data is extremely important. To ensure data integrity, the following principles must be followed. Data should be:

- **Attributable:** It must be possible to attribute every action, creation, or change of data to a specific employee.
- **Legible:** Data must be recorded so that it is permanently legible in a stable storage medium.
- **Contemporaneous:** Data/actions must be recorded at the same time as they are generated/carried out.
- **Original:** Data must be stored as an original record or as a verified, true copy.
- **Accurate:** The data/actions must be recorded/described precisely and without errors.
- **Complete:** Records must contain all necessary information that is required for traceability, interpretation, or further processing.
- **Consistent:** If a process comprises several steps, the data must be recorded in the same sequence as these steps.
- **Enduring:** Data must last for lifetime of the document.
- **Available:** readily available for review or inspection and can be restored from an electronic backup

No blank fields

- Clearly mark (N/A) or strike through
- Fields marked as “not applicable” or with strikethrough must be signed and dated. (The signatures of contractors/personnel from external companies must be accompanied by the full printed name).

What if I make a mistake?

- Clearly cross out errors with a single line.
- The original content of a record must remain legible: Never completely obscure the incorrect entry with heavy marking or taping over.
- Never use white-out or other correction fluid/tape.
- Corrections must be signed and dated. (In the case of partner companies (contractors/external companies), the signature must be accompanied by the full printed name).
- You must record the reason for the correction. Either provide a comment or use one of the following permissible abbreviations:

Type of error	Abbreviation ING	Abbreviation for GFE in BC	Example
Error in handwriting / typographical error [Schreibfehler]	SF		Illegible entry
Calculation error [Rechenfehler]	RF		Error in the calculation of factors, weights, yields, or mean values
Transfer error (including reading error) [Übertragungsfehler]	UF		Error in transferring a value from a device display onto paper
Entry error [Fehleintrag]	FE		Entry in the wrong line of a batch record
Subsequent entry [Nachtrag]	NT		Entry added after original data was recorded
Supplement/addendum [Ergänzung]	ERGP		If a device prints too few columns due to system limitations, columns may be added.

Logbooks

A logbook is the chronological listing of all events that are subject to documentation requirements, such as calibration / maintenance work / cleaning / changes to technical equipment, etc.

Logbook entries must be made by the person carrying out the task or by a supervisor. They must be made at the start of work and upon completion of the work and should be written in such a way that they are clear, easily readable, and self-explanatory.

All necessary entries, such as time / description of the action / date of entry / required signatures, etc., must be clear in the logbook (all times must be read and recorded from BI clocks).

If necessary, entries can extend over multiple lines. The important point here is to ensure that the activity can be clearly attributed to a date (and time, if applicable).

Examples of GMP-compliant documentation

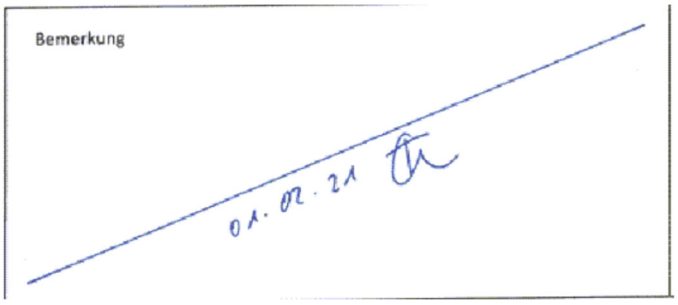
All names and signatures are for demonstration purposes only and do not represent actual employee data.

Date and signature

Signature clearly readable

(Name in capitals can be omitted, if a signature list is available)

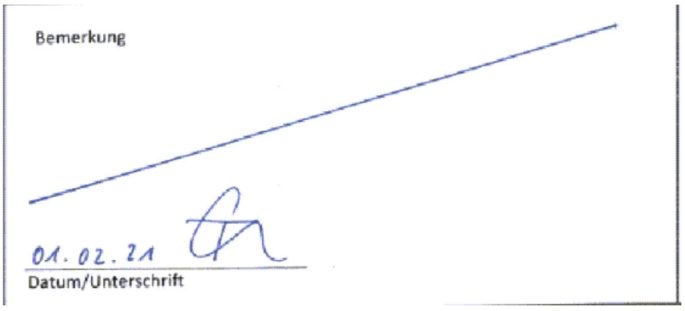
Examples of empty fields (no tick box present)



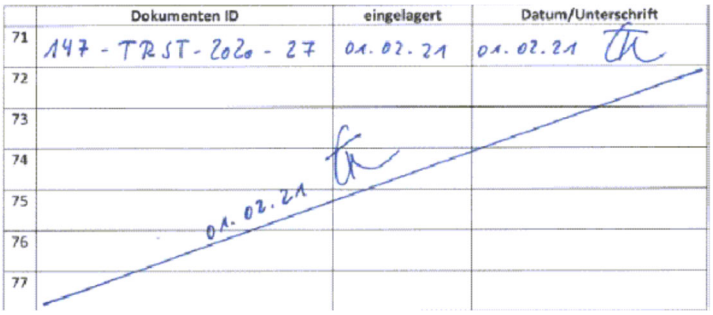
Example 1-4

Example 1

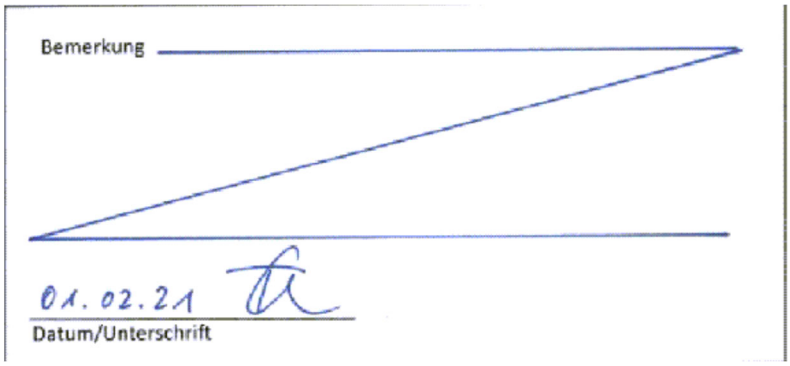
Crossing line plus date and signature



Example 2



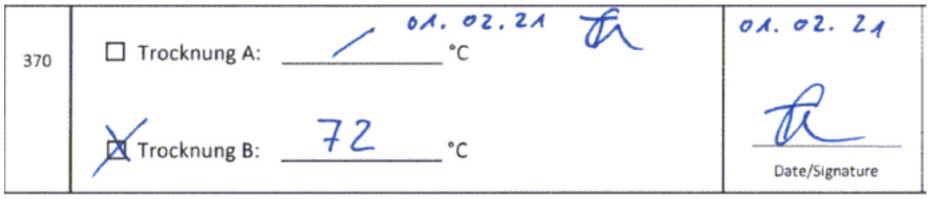
Example 3



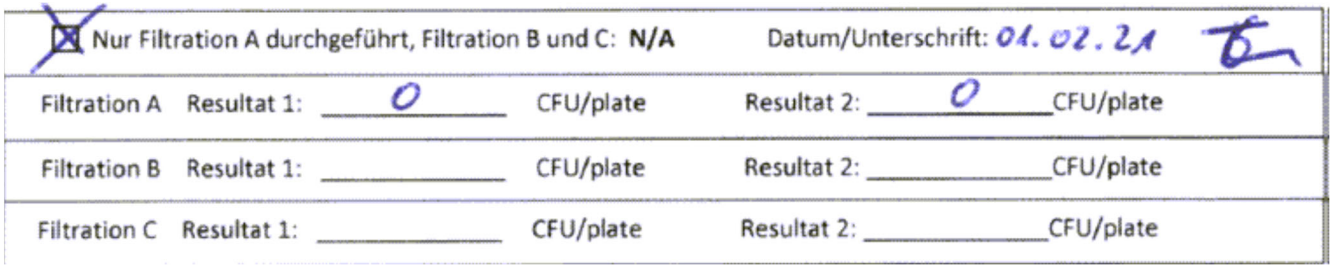
Example 4

"Z" mark, plus date and signature

Examples with tick boxes

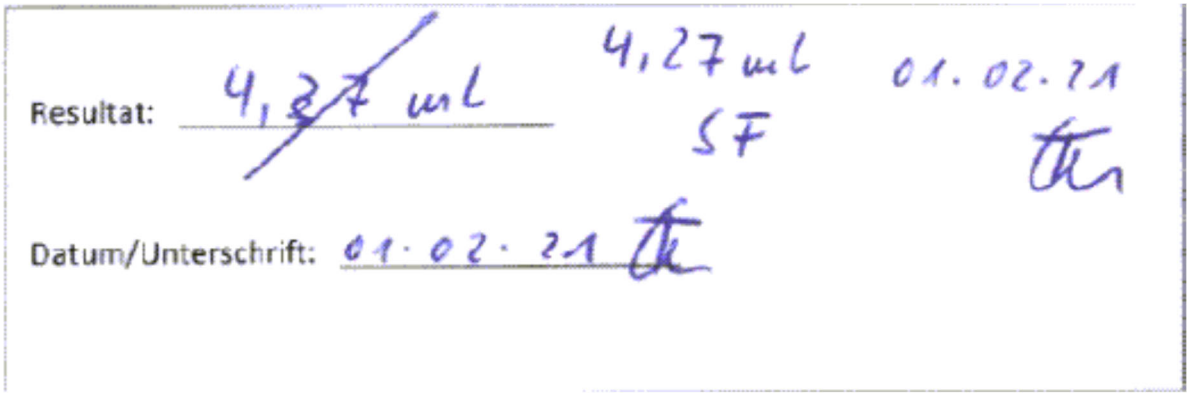


Tick box "drying A" not marked, but field invalidated to avoid mistaken entries.

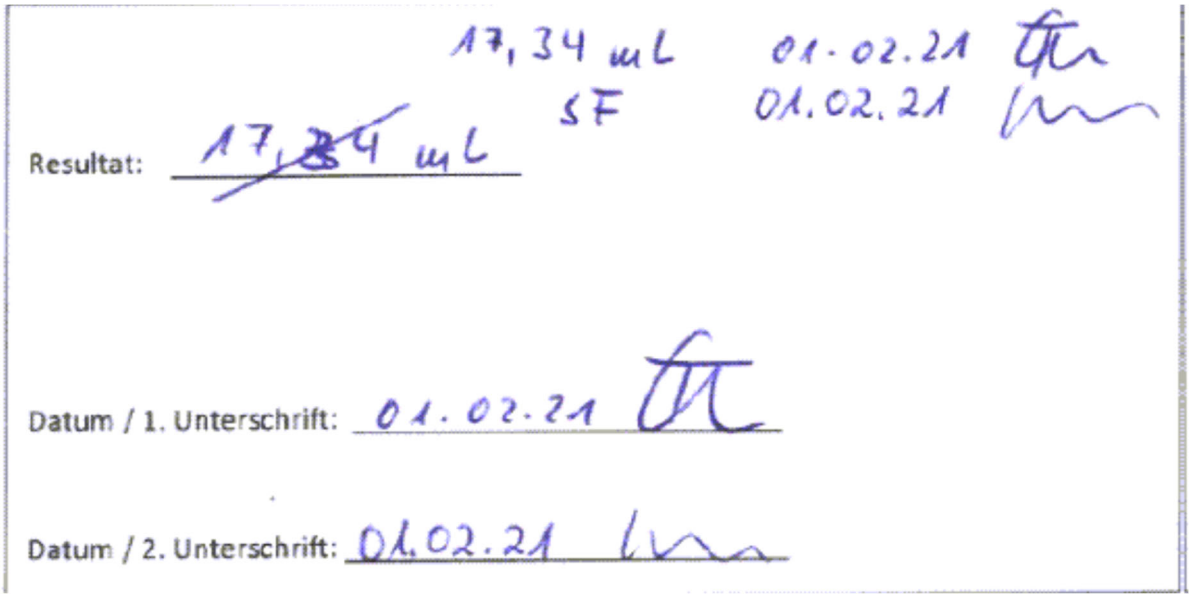


Invalidation of lines "filtration B" and "filtration C" by ticking the box up left meaning, that further filtrations are not necessary.

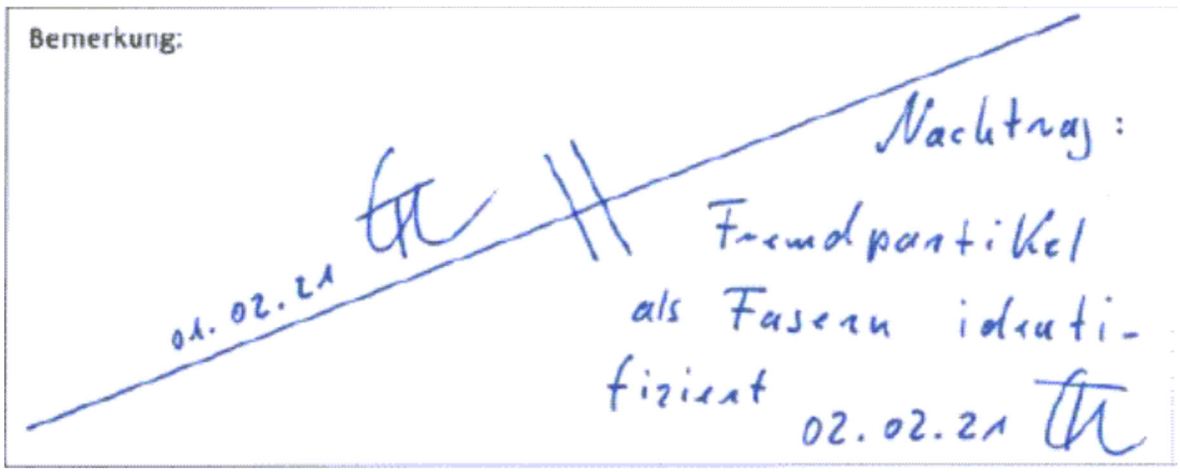
Usage of correction with shortcut for error.



In case of four-eyes check two persons need to sign the correction:

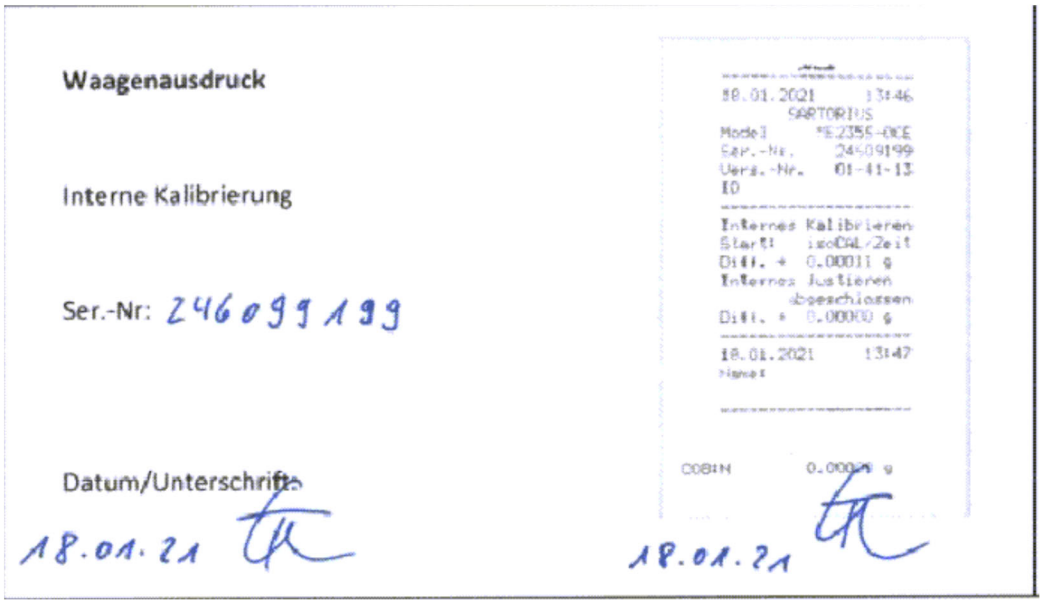


Invalidation of formerly invalidated fields:



Use the short double line for invalidation together with date and signature.

Documentation of printouts on templates



Example 1

Sign both the pasted printout and the carrier paper.

Kontrollblatt DVY305-2 Version 05	**Packungsmaterial**	Seite: 1 von: 1
Gültig seit: 11.11.2016	Produkt: Duovent HFA 10 µg Auftrag: 238755 Charge: 702229	
Label:		

Example 2

Examples of incorrect documentation

Incorrect

	Analyse Nr. 1		Analyse Nr. 2
1.	9,34 µg	1.	9,36 µg
2.	"	2.	
3.	"	3.	
4.	"	4.	
5.	"	5.	
6.	"	6.	↓

Erste Analyse: Datum/Unterschrift: _____ 01.02.24

Zweite Analyse: Datum/Unterschrift: _____

Inverted commas or arrows for same values are forbidden, each field must be filled.

Bracketing is forbidden, each signature field must be filled.

Correct:

	Analyse Nr. 1		Analyse Nr. 2
1.	9,34 mL	1.	9,36 mL
2.	9,34 mL	2.	9,36 mL
3.	9,34 mL	3.	9,36 mL
4.	9,34 mL	4.	9,36 mL
5.	9,34 mL	5.	9,36 mL
6.	9,34 mL	6.	9,36 mL

Erste Analyse: Datum/Unterschrift: 01.02.21

Zweite Analyse: Datum/Unterschrift: 01.02.21

ⓘ **In pharmaceutical manufacturing:**
If it's not documented, it's not done.

5. Questions? Situations you are unsure?

If you have questions or need help clarifying a situation on site, your contact at BI will be happy to help you. Please ask!