GERPAC
European Society of Hospital Pharmaceutical Technologies
V.2023-1

Recommendations on training objectives and staff qualification for the manual preparation of capsules in pharmacy

Frédéric Marçon[1], Frédéric Lagarce[2], Isabelle Roland[3], Denis Brossard[16], Camille Merienne[5], Philip Chennell[6], Elise d'Huart[7], Thomas Briot[8], Laurent Carrez[9], Gregory Podilsky[10], Pascal Rohrbach[11], Damien Lannoy[12], Thomas Storme[13], Marie Noelle Guerraul-Moro[14], Ian Soulairol[15], Sylvie Crauste-Manciet[2]

1 Centre Hospitalier Universitaire d'Amiens–Picardie, Amiens, France.
2 Centre Hospitalier Universitaire d'Angers, Angers, France.
3 Centre Hospitalier Universitaire de Liège, Liege, Belgium.
5 Hôpital Édouard Herriot, Hospices Civils de Lyon, Lyon, France.
6 Centre Hospitalier Universitaire de Clermont Ferrand, Clermont Ferrand, France.
7 Centre Hospitalier Universitaire de Nancy, Nancy, France.
8 Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France.
9 Lausanne University Hospital, Lausanne, Switzerland.
10 Réseau Hospitalier Neuchâtellois, Neuchâtel, France.
11 Hôpital de Verdun, Verdun, France.
12 Centre Hospitalier Universitaire de Lille, Lille, France.
13 Hôpital Universitaire Robert Debré – DMU PRISME – APHP.Nord – Assistance Publique Hôpitaux de Paris, Paris France.
14 Centre Hospitalier Intercommunale de Poissy Saint Germain, Saint-Germain-en-Laye, France.
15 Centre Hospitalier Universitaire de Nice, Nice, France.
16 Scientific committee of GERPAC, France.

1. Introduction and scope

The manual compounding of capsules in pharmacy is a multifaceted process that often requires careful handling of potentially hazardous substances. This procedure generally begins with the exact weighing and volume measurement of various powders to ensure consistent dosage levels. Once accurately measured, these powders are meticulously mixed to create a uniform blend, a crucial step before they are used to fill the capsules. The traceability of the operations carried out is an important aspect of this process, and it is essential to document any non-conformity or problems encountered throughout the procedure so that any difficulties can be reported. These measures should help to strengthen quality assurance, facilitate accountability, and encourage continuous improvement of the process. Therefore, production of capsules in pharmacies requires appropriately trained and authorized personnel to carry out these tasks. This training and authorization of staff are crucial components of a quality system and are essential prerequisites for ensuring optimal quality control. This validation of skills and knowledge is also an essential element when delegating technical tasks.

The aim of this document is to provide comprehensive guidelines describing the essential training objectives and staff authorization requirements for the manual preparation of capsules in pharmacies.

2. Key considerations

As effective training is a critical part of quality assurance in a compounding process, comprehensive capsule compounding training, including the knowledge and skills required to perform the steps of weighing raw materials, measuring apparent volumes, mixing, and distributing powders, should be designed, and delivered to employees. This training program shall be documented and designed to allow validation of all, or part of the achievements related to the target process. The approval of training protocols and the

training and authorization of personnel must be carried out by an authorized pharmacist and approved by the pharmacist in charge of the production.

Learners should also be familiarized with local best practices for compounding and the applicable regulations. These local guidelines, often setting broad quality standards, serve as essential prerequisites and compliance with these standards is crucial for ensuring the quality and safety in capsule compounding.

3. Assessment of Knowledge and Skills

Pharmacists should make the purposes of training explicit, encompassing knowledge, know-how, and attitudes, by formalizing the didactic contract between learners and instructors. Both objective-based and competence-based approaches could be used to build the training program and contribute to comprehensive learning. The former approach ensures a thorough acquisition of domain-specific knowledge, while the latter prioritizes the development of skills pertinent to the practical application (1).

It's crucial that the assessments used for certification predominantly evaluate the demonstration of skills within real-world professional contexts, rather than primarily relying on traditional written exams that focus on knowledge acquisition. While knowledge can be evaluated through e-learning methods and a variety of questionnaires, either in-person or online, it's advisable to avoid the use of indexed answers as they may not adequately gauge a student's understanding. Competence can be verified using practical methodologies such as direct observation, simulations, case studies, and problem-solving exercises. The assessments should accurately reflect the skills acquired, those being developed, and those yet to be mastered. This way, subsequent steps can be tailored appropriately, and the evaluations should occur on multiple occasions to track progress effectively.

4. Main topics and training objectives

4.1. Essential principles and procedures in working areas

Within the scope of pharmaceutical production, learners are required to grasp vital principles and methodologies concerning workplace hygiene and the prevention of contamination as it may impact both quality and security (2). This encompasses a thorough understanding and mitigation of cross-contamination risks, ensuring that the production line is empty and adhering to the 'forward motion' principle for the flow of materials. Finally, cleaning is an integral part of this process and plays a major role in ensuring that the environment and the product are free from contamination. Mastery of cleaning and biocleaning procedures is fundamental to preserving product quality and maintaining a safe operating environment (3). In light of these considerations, the following points should be addressed:

- Learners should understand the concept of cross-contamination, its potential sources in the pharmaceutical production process, and its impact on product quality and safety. They should develop skills to identify risks and implement measures to prevent cross-contamination.
- Learners should understand the principle of line clearance and be able to ensure that a production line or area is clear of materials not needed for the next batch, preventing product mix-up and cross-contamination.
- Learners should understand the 'forward march' principle and ensure a unidirectional flow of materials in the production process, from receiving raw materials to dispatching finished products, thereby preventing cross-contamination, and maintaining process integrity.
- Learners should understand and implement standard procedures for equipment cleaning and workspace maintenance. Their skills should cover effective cleaning practices and proper material handling to ensure quality and prevent contamination.

4.2. The Handling of Hazardous Drug Substances

The administration of hazardous medicinal substances is a pivotal component of pharmaceutical operations, necessitating specialized attention and proficiency due to their inherent risks. Management of these substances, especially those categorized as carcinogenic, mutagenic, or toxic to reproduction (CMR), demands the capability to accurately identify potential hazards and implement effective mitigation strategies throughout their lifecycle—from receipt to disposal—following stipulated procedures and existing regulations (4). These substances, their labeling, and their handling align with REACH and CLP regulations (5). Crucial information for handling these substances is encapsulated in Safety Data Sheets (SDS), detailing the use of appropriate personal protective equipment (PPE) for enhanced safety (6). In light of these considerations, the following points should be addressed:

– Learners should be able to proficiently manage the entire lifecycle of hazardous and carcinogenic, mutagenic, or toxic for reproduction (CMR) substances from receipt to disposal. This includes understanding the storage requirements, handling procedures, tracking methods, and safe, environmentally responsible waste disposal practices for CMR substances in line with relevant regulations.

– Learners should be able to accurately identify and interpret hazard labels in compliance with REACH and CLP regulations, including comprehending the significance of pictograms, hazard statements, and precautionary statements.

– Learners should be able to locate, interpret and effectively apply the information contained in Safety Data Sheets (SDS) for various hazardous chemicals, including the application of protective measures and emergency procedures.

– Learners should be able to correctly select and use individual protective equipment (PPE) suitable for handling various hazardous chemicals. This skill includes understanding the different types of PPE, such as gloves, safety glasses, and respiratory protective equipment, and their appropriate use based on the nature of the chemical hazard and the task at hand.

– Learners should be able to effectively use and maintain collective protective equipment (CPE) specific to handling hazardous chemicals. This includes the understanding of different types of CPE such as fume hoods, biosafety cabinets, and ventilation systems, and their appropriate use and operation.

4.3. Weighing powders

Powder weighing is a key element in the quality of capsule preparation. Among the factors influencing the quality of this step, knowledge of the operating principles of precision balances, their characteristics, handling and maintenance is a key element in guaranteeing both measurement accuracy and equipment durability (7). In light of these considerations, the following points should be addressed:

– Learners should understand the operating principle of precision scales and their different characteristics (e.g., range, accuracy, linearity).

– Learners should know the correct handling and maintenance practices for precision scales to ensure their accuracy and durability.

– Learners should know about common weighing errors and the factors that can cause them (e.g. scale instability, air currents, vibrations, static electricity).

– Learners should know the regulations and standards applicable to weighing in pharmacies (e.g. calibration, control, traceability).

– Learners should be able to select a valid and appropriate scale for the quantities to be weighed.

– Learners should be able to properly set up and calibrate a precision balance, taking into account environmental conditions and specific weighing requirements.

– Learners should be able to handle powders appropriately to minimize contamination, material loss, and dust generation, using suitable tools and techniques.

– Learners should be able to identify and troubleshoot weighing issues during the process, adjusting balance parameters, or applying appropriate corrective techniques.

4.4. Measuring a volume of powder

Measuring the apparent volume of a powder is a key step in capsule preparation, as it directly influences the accuracy of the dosage obtained. This apparent volume corresponds to the space occupied by a powder, including the empty spaces between particles, and is strongly influenced by the size, shape, distribution, and arrangement of the particles. Factors such as humidity, static loading and handling methods can further alter the flow characteristics and apparent volume of the powder, which can affect the reproducibility of the specimen filling process (8). A preliminary powder sieving step may be necessary to standardize particle sizes. In light of these considerations, the following points should be addressed:

– Learners should know the factors affecting the apparent volume of powders, such as particle size, particle shape, moisture content, and packing.

– Learners should comprehend the integral role of sieving in ensuring particle size uniformity during capsule compounding, refine techniques for optimal sieve usage, and recognize the criticality of rigorous sieve sanitation to mitigate cross-contamination risks (9).

– Learners should know the difference between bulk and tapped density (7).

– Learners should know the different types of measuring cylinders and their respective characteristics (e.g. accuracy, graduation) that are suitable for powder volume measurements.

– Learners should be able to select a valid and appropriate measuring cylinder for the quantities to be measured.

– Learners should be able to accurately and consistently fill the measuring cylinder with the powder, minimizing air pockets and avoiding compaction or segregation of particles.

– Learners should be able to read the apparent volume of the powder in the measuring cylinder, taking into account the meniscus and potential sources of error or bias.

4.5. Mixing powders

Mixing powders in capsule compounding is essential for achieving uniform active pharmaceutical ingredient (API) distribution, a key determinant of dosage accuracy. The homogeneity of the mixture depends on particle size, distribution, and physical characteristics like density, shape, and surface properties (10). Additionally, factors such as equipment selection, mixing technic, velocity, and duration influence blending efficacy (11). Errors during the mixing process may contribute to inconsistencies in content uniformity during the capsule assay procedure. In light of these considerations, the following points should be addressed:

– Learners should know which factors related to powders may impact the quality of the mixtures.

– Learners should know about the importance of particle size reduction and even distribution of particles when mixing powders for pharmaceutical applications.

– Learners should know about the different types of mortars and pestles (e.g. glass, porcelain, and stainless steel) and their respective characteristics and suitability for various powder types.

– Learners should be able to select the appropriate mortar and pestle for a specific powder type and mixing application, considering factors such as material compatibility, size, and ease of cleaning.

– Learners should be able to use the proper techniques for mixing powders with a mortar and pestle, such as trituration, and geometric dilution, to achieve a uniform and homogenous mixture.

– Learners should be able to monitor the mixing process to ensure that the desired particle size reduction and distribution are achieved, making adjustments to the technique or mixing time as necessary unless otherwise specified in a procedure.

– If using machines, learners should know how to correctly load and unload powders from the mixing machine to minimize material loss and cross-contamination. This includes the correct use of containers, scoops, or other tools.

– If using machines, learners should be able to effectively operate the mixing machine, including adjusting settings for mixing time, speed, and intensity. They should understand the implications of these settings on the quality of the final mix.

4.6. Filling capsules

Manual filling of capsules plays a significant role in compounding, that can directly impact the mass uniformity of capsules. This process, when conducted using manual filler, relies heavily on the operator's skill, accuracy, and consistency. The powder's flow properties, including particle size and distribution, external factors such as humidity and temperature that may affect the powder's characteristics can affect filling uniformity (12, 13). Similarly, variations in applied pressure during the filling process may cause disparities in fill volume and, subsequently, mass uniformity. Hence, meticulous operator technique and understanding of powder characteristics are essential for maintaining mass uniformity in manually filled capsules. In light of these considerations, the following points should be addressed:

– Learners should know about the different types of capsule fillers, such as manual, semi-automatic, and automatic, as well as their respective characteristics and suitability for various production scales and powder types.

– Learners should know about the factors affecting capsule filling accuracy, such as powder flow properties, capsule shell quality, and equipment settings.

– Learners should be able to select the appropriate capsule size, color and type (e.g. gelatin or vegetable-based) based on the intended dosage and patient population.

– Learners should be able to select the appropriate capsule filler for a specific powder formulation and production scale, considering factors such as material compatibility, dosage accuracy, and production efficiency.

– Learners should be able to set up the capsule filler according to the manufacturer’s instructions.

– Learners should be able to operate the capsule filler to fill capsules accurately and consistently with the powder formulation, monitoring the process for any issues or inconsistencies, and adjusting as necessary.

4.7. Documentation and traceability

In capsule compounding, documentation serves as a crucial element for consistency, traceability, adherence to local best practices for compounding, and facilitates continuous process improvement. It encompasses recording of each compounding step, materials utilized, and any encountered deviations. Through this, any batch of compounded capsules can be traced back through its production and distribution, improving accountability and enabling rapid response if quality issues arise. Insufficient or inaccurate documentation, however, can compromise these aspects and potentially affect the overall quality, safety and efficiency of the finished product and future productions. In light of these considerations, the following points should be addressed:

– Learners should know how to properly document each step of the compounding process, including the recording of raw materials (source, lot number, expiration date), equipment used, environmental conditions, and the specifics of each procedure performed.

– Learners should be able to prepare and maintain comprehensive and up-to-date batch production records that document each step of the compounding process, including the specific raw materials, equipment, and personnel involved.

– Learners should ensure to record any deviations from the established procedure and the corrective actions taken in response to these deviations.

– Learners should understand the importance of transparent error reporting. They should be trained to document any errors promptly and thoroughly, including details of the incident, the root cause, the corrective actions taken, and the steps planned to prevent recurrence.

5. Suggested Test Formulations

In order to evaluate the learner's skills, the following formulations are suggested. The selection of the appropriate capsule size is among the skills to be tested. The number of capsules (e. g., 100, 200 or 300) to be prepared is left to the examiner's discretion, depending on the skills to be evaluated, particularly regarding the use of small or large capsule filler.

5.1. Microcrystalline Cellulose Capsules

Without an active ingredient present, these capsules (Table 1) serve as a safe method for testing the standard operating procedures in capsule preparation, and for assessing the learner's proficiency during the capsule filling stage. The accuracy of measuring the apparent volume may significantly impact the success of this stage. The preparation could be easily controlled by conducting only a mass uniformity test (see supplementary material).

Table 1. Microcrystalline cellulose capsules formula (the quantity should be adapted to produce 100, 200, 300 size 3 or 4 capsules)

Components	Quantity (for 1 caps)
Mycrocristalline Cellulose	QS

5.2. Crystallized Sodium Chloride (10 mmol) Capsules

These capsules (Table 2) encompass a crystallized active principle, designed to assess the learner's proficiency in the particle size reduction and powder blending stages. As the powder density varies with the granulometric reduction of the active ingredient, any lack of homogeneity may be perceived in terms of mass. The preparation could be controlled by conducting a mass uniformity test (see supplementary material). A uniformity of content test can also be carried out.

Table 2. Crystallized sodium chloride capsules formula.

Components	Quantity (for 1 caps)
Sodium chloride	584 mg
Lactose	QS

5.3. Micronized Spironolactone (1 mg) Capsules

The challenge in the preparation of these capsules (Table 3) lies in the dilution of a micronized active ingredient present in a very small quantity. This will serve to assess the learner's ability to homogenize the powder blend. Spironolactone is classified as a hazardous substance, with CMR (Carcinogenic, Mutagenic, or toxic to Reproduction) therefore the proper application of procedures for handling dangerous substances is essential. This preparation must be tested for both mass and content uniformity to reveal any preparation flaws. It is recommended to calculate the corrected contents to attribute the source of error to either the blending or the capsule filling process (see supplementary material).

Table 3. Micronized spironolactone capsules formula.

Components	Quantity (for 1 caps)
Spironolactone	1 mg
Lactose	QS

5.4. Amiodarone Hydrochloride (60 mg) Capsules

Amiodarone hydrochloride is a powder that tends to be very sticky due to its hygroscopic nature (i.e., it absorbs moisture from the air). This property can make it difficult to mix amiodarone hydrochloride with excipients when preparing capsules (Table 4), as it can clump together and not disperse uniformly. Amiodarone is also classified as a hazardous substance, with CMR (Carcinogenic, Mutagenic, or toxic to Reproduction) therefore the proper application of procedures for handling dangerous substances is essential. This preparation must be tested for both mass and content uniformity to reveal any preparation flaws. It is recommended to calculate the corrected contents to attribute the source of error to either the blending or the capsule filling process (see supplementary material).

Table 4. Amiodarone hydrochloride capsules formula.

Components	Quantity (for 1 caps)
Amiodarone hydrochloride	60 mg
Lactose	QS

6. Conclusion and perspective

From the perspective of a pharmacy manager this document underscores the criticality of structured training and qualification for pharmacy staff involved in manual capsule preparation. It highlights the multi-faceted nature of the process and the potential risks if not done correctly, making it clear that staff training cannot be overlooked. Effective training can reduce content and mass uniformity errors in capsule compounding. This results from enhanced understanding and execution of powder handling, equipment operation, and capsule filling procedures. While recognizing the importance of knowledge acquisition, it underscores the significance of practical skills applicable in real-world scenarios, thereby indicating the necessity for competence-based certification.

References

1. Nguyen D-Q, Blais J-G. Approche par objectifs ou approche par compétences ? Repères conceptuels et implications pour les activités d'enseignement, d'apprentissage et d'évaluation au cours de la formation clinique. Pédagogie Médicale. 2007;8:232-251.
2. Sargent EV, Flueckiger A, Barle EL et al. The regulatory framework for preventing cross-contamination of pharmaceutical products: History and considerations for the future. Regulatory Toxicology and Pharmacology. 2016;79:S3-S10.
3. Tanyous JN. Cleaning Validation: Complete Guide for Health - Based Approach in Chemical Cross - Contamination Risk Assessment. PDA J Pharm Sci Technol. 2019;73:204-210.
4. McDiarmid MA. Chemical hazards in health care: high hazard, high risk, but low protection. Ann N Y Acad Sci. 2006;1076:601-606.
5. European chemical agency. Guidance on labelling and packaging in accordance with Regulation (EC) No 1272/2008. Helsinki: European Chemicals Agency; 2021:200.
6. European chemical agency. Guidance on the compilation of safety data sheets. Helsinki: European chemical agency; 2020:137.
7. European Directorate for the Quality of Medicines & HealthCare (EDQM). Balances for analytical purposes (01/2022:20107). European pharmacopoeia. Strasbourg: Council of Europe; 2023.
8. Shah UV, Karde V, Ghoroi C, Heng JYY. Influence of particle properties on powder bulk behaviour and processability. Int J Pharm. 2017;518:138-154.
9. European Directorate for the Quality of Medicines & HealthCare (EDQM). Sieves (01/2008:20104). European pharmacopoeia. Strasbourg: Councils of Europe; 2023.
10. Venables HJ, Wells JI. Powder mixing. Drug Dev Ind Pharm. 2001;27:599-612.
11. D'Hondt M, Wynendaele E, Vandercruyssen K et al. Investigation of active pharmaceutical ingredient loss in pharmaceutical compounding of capsules. J Pharm Biomed Anal. 2014;96:68-76.
12. Sandler N, Reiche K, Heinämäki J, Yliruusi J. Effect of Moisture on Powder Flow Properties of Theophylline. Pharmaceutics. 2010;2:275-290.
13. Osorio JG, Muzzio FJ. Effects of powder flow properties on capsule filling weight uniformity. Drug Dev Ind Pharm. 2013;39:1464-1475.