Adopted in October 2020

EAHP Position Paper on Pharmacy Preparations[1] and Compounding

Making a difference in medication by delivering tailor-made medicines for the benefit of patients

The patient-oriented preparation of medicines is anchored deeply in pharmacy practice. Since the establishment of the profession, hospital pharmacies have manufactured, prepared and compounded medicines to adequately respond to patient needs, especially for those individual patients or patient groups whose medical requirements cannot be met by industrially manufactured medicines.

The term 'compounding'[2] is frequently used in English speaking literature, while in continental Europe the term 'pharmacy preparation'[3] is mainly applied. This position paper regards both the term 'pharmacy preparation' and the term 'compounding' as interchangeable but will mainly refer to 'compounding'. Another process related to preparation is 'reconstitution'.[4] This process is not necessarily confined to a pharmacy. Reconstitution entails, for example, adding a diluent to a powdered medication to prepare a solution or suspension.

Due to the shift towards personalised medicines, including advanced therapy medicinal products (ATMPs), the strain on national healthcare budgets and medicines shortages, compounding has regained significance in Europe. The position paper of the European Association of Hospital Pharmacists (EAHP) aims at providing information about this practice in hospitals and asks for a stronger embedment of compounding and reconstitution practices in European hospital pharmacies, linked to increasing capacity and training.

[1] The term 'pharmacy preparation' is not uniformly used throughout continental Europe when referring to medicines prepared or manufactured by a pharmacist. For this position paper, the term 'pharmacy preparation' shall encompass all wordings referring to pharmacy-made preparations, including but not limited to hospital preparations, individual preparations and large batch preparations, (small) stock preparations, magistral preparation, officinal preparation, extemporaneous preparations, preparations from raw materials and preparations to modify already marketed medicines.

[2] Compounding' is defined as the process of combining, mixing, or modifying ingredients to create a medication tailored to the needs of an individual patient [US Food and Drug Administration, Compounding and the FDA: Questions and Answers. Available at: https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers#what].

[3] Literature divides pharmacy preparations into 'preparation by adapting an existing product' ("reformulating a licensed product into a different dosage form suitable for the intended use") and 'preparation from raw materials' ("formulating active substances and excipients into a dosage form suitable for the intended use") [Yvonne Bowman-Boer, V'lain Fenton-May, Paul Le Brun (eds): Practical Pharmaceutics, Springer International Publishing. 2015, p. 4.].
European law covers compounding/pharmacy preparations and distinguishes between two types, namely the 'magistral formula' ("any medicinal product prepared in a pharmacy following a prescription for an individual patient") and the 'officinal formula' ("any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia that is intended to be supplied directly to the patients served by the pharmacy") [Article 3 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.].

[4] 'Reconstitution' is defined as the "manipulation to enable the use or administration of a medicinal product for products with a marketing authorisation issued by any competent medicines regulatory authority, the reconstitution is carried out in accordance with the instructions given in the summary of product characteristics (SmPC) or the package leaflet." [Council of Europe. Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use], including also pharmacy preparations and investigational medicinal products (IMPs).

To further enhance patient care in Europe, EAHP

- calls on health systems to **create an environment which enables the provision of compounding services by hospital pharmacists** based on the European Statements of Hospital Pharmacy.
- encourages health authorities to facilitate the delivery of pharmacy preparations between hospitals and to **invest in compounding services** since only by building sufficient capacity hospitals will be equipped to better respond to patient needs and extraordinary situations like pandemics and shortages of essential medicines.
- recommends the **revision of pharmacy curricula and the expansion of training opportunities** for the pharmacy workforce to account for the growing demand for pharmacy preparations.
- encourages the **appointment of a hospital pharmacist as a designated person** in every hospital, advocates for the **increased involvement of hospital pharmacies in reconstitution practices**, through setting up procedures and training personnel and promotes the creation of centralised reconstitution in hospitals.
- requires that management of ATMPs, as licensed medications, remains the responsibility of the hospital pharmacist.

The importance of compounding for addressing patient needs

Compounding, preparing and manufacturing are unique activities of the pharmacy profession. All European countries have established national rules that are tailored to the specificities of pharmacy compounding which guarantee the application of proper procedures as well as the quality and safety of preparations by pharmacists. These are supplemented by detailed guidance documents that have for example been put forward by Dutch[i], German[ii], Irish[iii] and Swiss[iv] hospital pharmacy organisations and Resolution CM/Res(2016)1 of the Council of Europe.[v]

Compounding is essential for patient care since it closes the gap between licensed medicinal products manufactured by industry and the lack of treatment options for certain patient groups and individual patients with extraordinary medical conditions or needs. It is also widely adopted, as shown by EAHP's Statements Surveys, Section 3 on compounding and production.[vi] To foster compounding activities, workforce planning should ensure adequate staffing levels so that this important area of practice can be carried out by all hospital pharmacies across Europe. EAHP also believes in the need for the continuous advancement of the profession.

EAHP strives for the European-wide application of the European Statements of Hospital Pharmacy to improve treatment and to provide all patients with the same level of high quality and safe care. This goes hand in hand with EAHP's support for the universal application of the Council of Europe Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. **To further enhance patient care in Europe, EAHP calls on health systems to create an environment which enables the provision of compounding services by hospital pharmacists based on the European Statements of Hospital Pharmacy.** This includes the provision of adequate facilities and equipment to hospital pharmacies to carry out compounding services.

Engaging hospital pharmacists in the provision of personalised medication

The reasons why hospital pharmacies have to prepare and compound medicines stem directly from the necessity to customise care interventions to address patients' special needs. The area of application for compounding is vast. It is, for example, essential for patients with adherence or ingestion difficulties and those allergic to components present in the industrially manufactured products. Paediatric and elderly

patients particularly benefit from compounding which offers the possibility of age-adapted drug formulation.[vii]

In recent years, compounding has gained more and more importance for addressing medicines shortages. Also, its use has increased to facilitate patient access by for example allowing for the provision of rational proven treatment of products where there is no commercial interest anymore.

Central cytotoxic production has proven to be a mainstay for the prevention of risks and harm to hospital staff onwards.[viii] Cytotoxic treatments depend on the specialised knowledge of pharmacists about anticancer medications that they contribute to as part of the multidisciplinary care team. Other areas of personalised preparation that involve pharmacists include parenteral nutrition therapies. As an integral part of the nutrition support team, hospital pharmacists are responsible for ensuring the appropriateness of the parenteral nutrition supplied, not only in composition but also in quality. The engagement of hospital pharmacies in these types of aseptic preparations is vital since in many cases parenteral medicines with a marketing authorisation cannot be administered directly to patients, which means that they are not presented in a form which is ready to administer, which especially applies for the paediatric and neonatal patients. **EAHP encourages health authorities to facilitate the delivery of pharmacy preparations between hospitals and to invest in compounding services since only by building sufficient capacity hospitals will be equipped to better respond to patient needs and extraordinary situations like pandemics and shortages of essential medicines.**

Adjusting education and training to the increased need for personalised care

The continuous development of the pharmacy profession requires the constant improvement of pharmacy curricula. Compounding remains fundamental to patient care. Today's healthcare delivery has seen a shift towards more personalised care. Consequently, preparation skills have become more and more needed in the daily practice of hospital pharmacists. To meet this demand both an investment into the training of the pharmacy workforce and the education of pharmacy students, in line with Section 3 of the European Statements of Hospital Pharmacy, is needed to ensure that compounding is carried out by well-trained personnel. **EAHP recommends the revision of pharmacy curricula and the expansion of training opportunities for the pharmacy workforce to account for the growing demand for pharmacy preparations.**

The involvement of hospital pharmacies in reconstitution practices

In many hospitals, the reconstitution of intravenous medicines, such as anti-infectives, analgesics and antiemetics prescribed by physicians, is carried out as a collaborative process by hospital pharmacists, nurses and pharmacy technicians. The tasks of the hospital pharmacist in this regard include risk management, the supervision of the quality of the work and the overall work planning.[ix] Depending on the specific setting, reconstitution takes place on the ward or in centralised units.[x] To further enhance patient safety, **EAHP encourages the appointment of a hospital pharmacist as a designated person in every hospital, advocates for the increased involvement of hospital pharmacies in reconstitution practices, through setting up procedures and training personnel and promotes the creation of centralised reconstitution in hospitals.** The procedures should be standardised and include quality control measures that guarantee the sterility of the preparation. A European-wide application of the Council of Europe Resolution on good reconstitution practices in health care establishments for medicinal products for parenteral use should be promoted. Ready-to-administer products prepared under the supervision of hospital pharmacists play an important role in improving patient safety.

The role of hospital pharmacists in the preparation and use of ATPMs

The term advanced therapy medicinal products (ATMPs) includes biological medicinal products that can be classified as either gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue-engineered medicinal products (TEPs) or any combination of the three.[xi] ATMPs are medicines and so by definition, they fall under the responsibility of the hospital pharmacist. The hospital pharmacist should therefore be involved in procurement, production in the hospital, reconstitution, quality control and logistics. **EAHP requires that management of ATMPs, as licensed medications, remains the responsibility of the hospital pharmacist.**

[i] Nederlandse Vereniging van Ziekenhuisapothekers, GMP-Z Richtlijn. Available at: https://nvza.nl/voor-professionals/gmp/.
[ii] Expertengremium, Guidelines by the German Hospital Pharmacy Organisation (ADKA) on the preparation and assessment of medicines in the hospital pharmacy. Krankenhauspharmazie 2017; 38:26-41.
[iii] Working group of the HPAI Aseptic Services Special Interest Group (ASSIG), National Guidelines for Aseptic Compounding in Irish Hospital Pharmacy Practice (H-PIC\S). Version 1.0. November 2013. Available at: https://hpai.ie/resources/Documents/HPICS-complete.pdf.
[iv] AG Fabrikation der GSASA, Positionspapier Eigenherstellung in Spitalapotheken. May 2017. Available at: https://www.gsasa.ch/deliver.cfm?f=0CD89DA59212A7CBAEDB92D04866B8AB822D41B39CAE138ABE7A989FD2CF90692D92AE5C8DFCB0FA7898DBB0AB459C8FFFA9DED7A19789A39B8346BCE66088954602C510848DAABEA11AD3FDFF5FCA09CD50A9B79FA250534F8E9F87FE5E0BFC0C8D125E400859F48B8EA991A9F6A31C7B2C9AC14FDBF1DA0B2F9C0F7D939E5F5A8B498A9EDAB65251E22D5E60DB552F4A83&type=.pdf.
[v] Council of Europe. Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.
[vi] Keele University Centre for Medicines Optimisation and EAHP, European Statements of Hospital Pharmacy – Survey Results 2018: Statements Sections 1, 3, 4. Available at: https://www.eahp.eu/sites/default/files/eahp_survey_report_2018-19_1.pdf.
[vii] Breitkreutz, Jörg & Boos, Joachim. (2007). Pediatric and geriatric drug delivery. Expert opinion on drug delivery. 4. 37-45. 10.1517/17425247.4.1.37.
[viii] Bourika K, Koutras A, Kalofonos H, et al. Improvement of Chemotherapy Solutions Production Procedure in a Hospital Central Chemotherapy Preparation Unit: A Systematic Risk Assessment to Prevent Avoidable Harm in Cancer Patients. Clin Med Insights Oncol. 2019;13:1179554919852933. Published 2019 Jun 10.
[ix] Yvonne Bowman-Boer, V'lain Fenton-May, Paul Le Brun (eds): Practical Pharmaceutics, Springer International Publishing. 2015.
[x] Nydert P, El-Edelbi R, Obaya S, et al5PSQ-140 Reconstitution practice by a paediatric and neonatal ward-based pharmacist, European Journal of Hospital Pharmacy 2018;25:A228-A229. Yvonne Bowman-Boer, V'lain Fenton-May, Paul Le Brun (eds): Practical Pharmaceutics, Springer International Publishing. 2015.
[xi] European Medicines Agency, Reflection paper on classification of advanced therapy medicinal products, 21 May 2015, available at: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf.