CLASSIFICATION OF HAZARDOUS MEDICINAL PRODUCTS – IMPROVING HANDLING REQUIREMENTS ACROSS EUROPE

A GUIDE FOR HOSPITAL PHARMACY ASSOCIATIONS

INTRODUCTION

Why should you read this guide? Why is it important for you as a professional association representing hospital pharmacists of today and for hospital pharmacy of tomorrow?

The purpose of this guide created by the European Association of Hospital Pharmacists (EAHP) is to make you aware of and to provide you with some useful tools. These tools will help you position yourself and the profession to stakeholders in both the hospital and wider healthcare environment when discussing the classification of hazardous medicinal products (HMPs). In other words, the guide aims to empower you to convey the true value and measurable benefits of this profession linked to the handling of HMPs. It also aims to inspire you to advocate for yourself, your knowledge, your skills, and your capabilities in the eyes of decision-makers, other healthcare professionals, the patients, and the society.

The guide is divided into two parts outlining why national hospital pharmacy association should regularly engage with national competent authorities and what kind of topics should be discussed with them in relation to HMPs. The annexe of this guide contains the recommendations of EAHP's Special Interest Group (SIG) on Hazardous Medicinal Products.

WHY SHOULD NATIONAL HOSPITAL PHARMACY ASSOCIATIONS ENGAGE REGULARLY WITH NATIONAL COMPETENT AUTHORITIES?

For national associations representing hospital pharmacists, it is important to regularly engage with national competent authorities, such as Chambers of Pharmacy, Authorities for Occupational Safety and Health, Medicines Agencies, Ministries of Health and Labour.

What should be prepared before engaging with competent authorities?

Meetings are a good way to discuss the needs of the hospital pharmacy profession in relation to HMPs with authorities. In this context, don't forget to also outline what hospital pharmacists are doing for the patient. To set up the meeting with the authority, prepare a formal letter outlining the points that you would like to discuss.

Having a detailed agenda is key when organising a meeting with national competent authorities (e.g. what are you going to discuss, what documents are you going to share). To underpin your arguments and to better showcase what your association, as well as European hospital pharmacists, want to achieve, you could bring the following to the meeting:

- ☑ **Recommendations developed by EAHP's Special Interest Group on Hazardous Medicinal Products**
- ☑ **Information about the activities of your association**

☑ **Other supporting documents** (e.g. the results from surveys you conducted linked to the handling of HMPs or projects that you were involved in)

After the meeting, it's important to follow up with authorities and to keep them regularly updated.

Inviting national authorities to national events

By inviting national competent authorities to specific events focusing on HMPs, you might be able to get your message across easier when authorities are seeing what you are doing. Regional meetings with national competent authorities and other stakeholders (e.g. doctors, hospital managers, nurses, etc.), as well as patient groups, are also a great way to showcase the needs of hospital pharmacists in a particular hospital or region.

WHAT SHOULD YOU DISCUSS WITH NATIONAL COMPETENT AUTHORITIES CONCERNING HAZARDOUS MEDICINAL PRODUCTS?

Between February 2021 and February 2022 EAHP's SIG on Hazardous Medicinal Products looked at the different classification models for hazardous medicinal products that are used throughout Europe and examined whether these approaches are fit for their purpose. The SIGs research showed

☑ a high awareness of and significant effort into the management of HMPs at the institutional level;
☑ a good identification of safety precautions for handling HMPs in the oncology and haematology setting, but a less clear understanding of the safe handling of HMPs for other conditions;
☑ the absence of a European definition for and clear guidance on the management of HMPs;
☑ exposure risk to healthcare workers and caregivers as well as a rapid response system to appropriately identify the inherent hazard level of new technologies and potential for modification;

Based on the recommendations of the SIG on Hazardous Medicinal Products, the national hospital pharmacy association should encourage their national competent authorities to push for **a structured approach in Europe to the topic of HMPs**.

On the one hand, this should involve the creation of a European definition for the term 'HMPs' that should build on the definition developed by EAHP's SIG. The definition of the SIG encompasses the intrinsic hazardous nature of a substance while recognising modifications that alter the risk profile of a medicine during use. The SIG recommends that this definition should be used as a basis for a discussion with European authorities and other healthcare professionals working with HMPs for the development of a European definition.

On the other hand, national governments and health system managers should be encouraged to immediately engage with the European Statements of Hospital Pharmacy and implement best practices relating to HMPs.

In relation to the handling of HMPs, the SIG recommends further presentation of the Dutch model for consideration at a European and national level. This model provides practical support to users, is flexible for the introduction of new products, recognises and assesses new evidence in a timely manner, promotes a standard approach to risk management of HMPs and enables efficiency in the health system by reducing duplication at the institutional level. The SIG considers that national systems should be developed with a linkage at the European level to inform shared practice and

standardisation. One example of such an approach is seen in the European approach to medicine shortages,[1] adaption of this model may enhance handing of HMPs across Europe.

Due to the findings that there is a significant interest of hospital pharmacists in further education on HMPs, national competent authorities should be encouraged to include this topic in the education for both undergraduate and post-graduate students.

[1] European Medicines Agency. Shortages catalogue, available at: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue (last visited 18 January 2022).

ANNEX I – RECOMMENDATIONS: EAHP SPECIAL INTEREST GROUP ON HAZARDOUS MEDICINAL PRODUCTS

The Special Interest Group (SIG) considers that while there is evidence of much ongoing work and activity on the topic of hazardous medicinal products (HMPs) there is an absence of a coherent approach to the management of HMPs in Europe. Much of the risk assessment activity takes place at the institutional level with guidance from the national levels but little further oversight of implementation. The exposure of healthcare workers to hazardous medicinal products is a serious issue that in the view of the European Association of Hospital Pharmacists (EAHP) needs to be addressed uniformly across the European Union and its Member States to ensure the protection of patients and healthcare personnel.

The complex nature of handling HMPs requires training that is tailored to the conditions of the working environment which differ depending on the settings in the hospital or community as well as from country to country.

To ensure the safety of patients and staff in the handling of HMPs hospital pharmacists contribute and promote their safe handling in institutions in Europe. To improve the current position and to support the work of hospital pharmacists proactive steps need to be taken to minimise the risks of HMPs for everyone. The SIG believes that additional guidance at the European level to promote healthcare workers wellbeing is desirable. This guidance should

- Promote the implementation of best practice;
- Recognise and support training and education of the workforce;
- Permit all available processes to reduce exposure to hazardous medicinal products in the workplace; and
- Allow for adaptability as new products or new evidence become available.

This guidance should also factor in efficiency and cost-effectiveness for the healthcare sector.
Therefore, EAHP's SIG on Hazardous Medicinal Products makes the following recommendations.

EAHP calls on the EU Commission and national governments across Europe to actively engage with hospital pharmacist representatives in the review of relevant Directives for the management of hazardous medicinal products (HMPs) in the healthcare environment.

EAHP asks national governments and health system managers to immediately engage with the European Statements of Hospital Pharmacy and implement best practices relating to HMPs.

EAHP recommends an EU wide standard approach to the classification and management of HMPs.

EAHP advises the European Commission and national governments across Europe to initiate best practice sharing on the classification and handling of HMPs between Member States.

EAHP advocates for the revision of pharmacy curricula and the expansion of training opportunities for the pharmacy workforce to account for the growing demand for management of HMPs and related Health and Safety issues.

ANNEX II – DEFINITION OF HAZARDOUS MEDICINAL PRODUCTS (HMPs)

The EAHP Special Interest Group on Hazardous Medicinal Products has agreed the following definition of hazardous medicinal products (HMPs).

A medicinal product is defined as hazardous when the intrinsic characteristics of the substance potentially jeopardise the well-being of healthcare workers and exposure presents a significant risk to users after consideration of measures that may eliminate or substantively reduce such risks during product preparation and administration by healthcare workers and subsequent patient care. The risks associated with the intrinsic characteristics of a medicinal product may be further modified by good handling/manufacturing practices in the healthcare setting leading to an altered classification of the medicinal product at the point of handling (including activities such as proper storage, preparation, dispensing, administration, cleaning, transportation, etc.) and patient care.

A medicinal product is defined by the European Medicines Agency (EMA) as:

A substance or combination of substances that are intended to treat, prevent, or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action. Once a marketing authorisation application (MAA) has been assessed by the European Medicines Agency (EMA), a scientific body with the expertise required to assess the benefits and risks of medicines, the European Commission takes a final legally binding decision on whether the medicine may be marketed in the EU. These decisions encompass the review and approval of medicinal products for paediatric use, orphan medicines, traditional herbal medicines, vaccines, and clinical trials for a candidate or authorised medicinal products approved under special rules by EMA.

Intrinsic Hazardous Qualities

Consistent with the US National Institute for Occupational Safety and Health (NIOSH) definition of a "hazardous drug", a substance approved for use as a medicinal product may be classified as hazardous when it possesses any one of the following five characteristics:

- Genotoxicity, or the ability to cause a change or mutation in genetic material;
- Carcinogenicity, or the ability to cause cancer in humans, animal models, or both;
- Teratogenicity, or developmental toxicity, the ability to interfere with normal development, either before or after birth.
- Fertility impairment.
- Serious organ toxicity at low doses in humans or animal models.

Subsequent modification of risk

The risks associated with the classification of a substance as hazardous may be modified by the formulation of the final medicinal product as well as exposure opportunities for either healthcare workers or other individuals (for example family members or care givers exposed to the hazardous medicinal product). Modification factors include:

- Concentration
- Formulation
- Route of administration
- Molecule size
- Manipulation/compounding steps required
- Adherence to good handling/manufacturing practices
- Exposure – frequency, duration and intensity
- Daily dose

Risk Assessment

The potential risks to healthcare workers handling hazardous medicinal products are a combination of the intrinsic hazardous qualities of the product and the specific handling requirements (including activities such as proper storage, preparation, dispensing, administration, cleaning, transportation, etc.) and patient care. Guidance on the requirements for risk assessments should be provided at EU level and implemented together with the practices in force at the local, regional and/or national level.

A risk assessment is informed by the available evidence. Consideration of the reliability of the evidence should be a feature of the assessment. Studies undertaken for a MAA process will have been conducted according to, or consistent with established methods to identify hazards. Other studies without prior external review will require expert analysis and the use of tools to evaluate study reliability,[2] and the direction, magnitude, and importance of individual biases identified prior to inclusion in the risk assessment[3][4] including pre-clinical data provided by independent research groups or agencies. This evidence is more difficult to evaluate and may give rise to the application of the precautionary principle[5] in instances where the types and degrees of risk are not well understood and may be serious or irreversible. The precautionary principle shall be informed by three specific principles:

- the fullest possible scientific evaluation, the determination, as far as possible, of the degree of scientific uncertainty;
- a risk evaluation and an evaluation of the potential consequences of inaction;
- the participation of all interested parties in the study of precautionary measures, once the results of the scientific evaluation and/or the risk evaluation are available.

The precautionary principle may be invoked when a phenomenon, product or process may have a dangerous effect, identified by a scientific and objective evaluation, if this evaluation does not allow the risk to be determined with sufficient certainty.

[2] Arroyave, W. D., Mehta, S. S., Guha et al. (2021). Challenges and recommendations on the conduct of systematic reviews of observational epidemiologic studies in environmental and occupational health. J Expo Sci Environ Epidemiol, 31(1), 21-30. doi:10.1038/s41370-020-0228-0. NTP. (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Available at: http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf (last visited on 1 February 2022). Savitz, D. A., Wellenius, G. A., & Trikalinos, T. A. (2019). The Problem with Mechanistic Risk of Bias Assessments in Evidence Synthesis of Observational Studies and a Practical Alternative: Assessing the Impact of Specific Sources of Potential Bias. Am J Epidemiol, 188(9), 1581-1585. doi:10.1093/aje/kwz131.

[3] Joint Research Center. (2017). ToxRTool - Toxicological data Reliability Assessment Tool European Commission. available at:https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/toxrtool(last visited on 19 January 2022).

[4] Schneider, K., Schwarz, M., Burkholder, I., Kopp-Schneider, A., Edler, L., Kinsner-Ovaskainen, A., . . . Hoffmann, S. (2009). "ToxRTool", a new tool to assess the reliability of toxicological data. *Toxicol Lett, 189*(2), 138-144. doi:10.1016/j.toxlet.2009.05.013.

[5] Summary of Communication (COM(2000) 1final) on the precautionary principle, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM%3Al32042 (last visited on 17 January 2022).

ANNEX III – MANAGEMENT OF HMPs IN THE NETHERLANDS

The Risk Instrument for Pharmaceutical Substances (RiFaS) is the national approach to the management of HMPs in the Netherlands[6]. Developed and managed under the auspices of the Professional Association of Pharmacists in the Netherlands (KNMP)[7] and in particular its Special Interest Group on Product Care and Preparation. This group consists of pharmacists who are interested in all facets of the medicinal product as a product (product care): from the receipt of a product or its preparation in the pharmacy to its administration to the patient and for whom handling hazardous substances is an important topic.

RiFaS adopts the approach that actual risk = intrinsic hazard x exposure opportunities[8]. RiFaS provides individual advice on request on the safe handling of products via Rifas.nl. The advice is tailored to the equipment available in the requesting pharmacy, such as a dust extractor or a safety bench. It also takes into account how long the healthcare worker will be working with the substance. The theoretical underpinning for the risk classification of pharmaceutical substances consists of a number of reports from TNO (Netherlands Organisation for Applied Scientific Research)[9] and KNMP. RiFaS is suitable for queries arising from compounding and non-compounding pharmacies in institutions (universities and hospitals) as well as community pharmacies.

This standardised national approach to each hazardous substance while enabling consideration of local factors such as equipment and workload ensures appropriate safeguards regardless of the workplace and individual knowledge level. It enhances efficiency by minimising unnecessary reproduction of the same work in each location. The system is funded on a subscription basis.

EAHP's SIG on Hazardous Medicinal Products considers the Dutch model to be an exemplar and that this model should be used as a reference for future development.

[6] Information about the Risk Instrument for Pharmaceutical Substances (RiFaS), available at: https://www.knmp.nl/producten/producten-diversen/risico-instrument-farmaceutische-stoffen-rifas (last visited on 19 January 2022).
[7] Information about the Professional Association of Pharmacists in the Netherlands, available at: https://www.knmp.nl/knmp (last visited on 19 January 2022).
[8] Presentation on file. Please contact EAHP (info@eahp.eu) for further information.
[9] Information about the Netherlands Organisation for Applied Scientific Research, available at: http://www.tno.nl/en/(last visited on 19 January 2022).