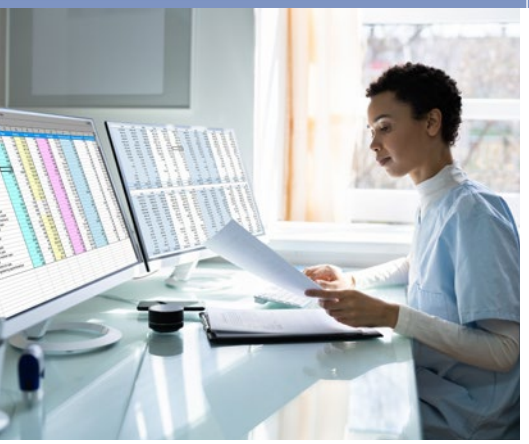
European Commission

Guidance for the safe management of hazardous medicinal products at work

SECOND EDITION






Employment, Social Affairs and Inclusion

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The material contained in this guide is for information and reference purposes only. It is not intended to substitute legal or informed professional advice on health and safety. Use of this guide does not necessarily ensure compliance with statutory requirements in the various EU Member States.

This guide focuses on preventing and controlling risks from occupational exposure to hazardous medicinal products and the information contained therein does not constitute a comprehensive overview of procedures for ensuring worker and/or patient safety. In particular, the information in this guide must be read in conjunction with the applicable legislation and advice/protocols for ensuring patient safety.

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The contents, including any opinions and/or conclusions expressed in this guide, are those of the authors alone and do not necessarily reflect the opinions or policy of the organisations that took part in pilot discussions.

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Introduction

1.1 Why is managing exposure to hazardous medicinal products (HMPs) so important?

1.1.1 What ill health effects may be due to HMPs?

For the purposes of this guide, hazardous medicinal products (HMPs) are defined as medicinal products that contain one or more substances that meet the criteria for classification as:

- Carcinogenic (category 1A or 1B),
- Mutagenic (category 1A or 1B) or
- Toxic for reproduction[1] (category 1A or 1B)

in accordance with Regulation (EC) No 1272/2008 (the CLP Regulation)[2]. This includes medicinal products for both human and veterinary use.

By virtue of the working definition given above, HMPs fall[3] within the scope of Directive 2004/37/EC (the Carcinogens, Mutagens and Reprotoxic Substances Directive, CMRD)[4].

HMPs include some antineoplastics, immunosuppressants, antiviral medicines, and others, see section 2 for a working definition. HMPs are used to treat a wide range of medical conditions including cancer treatment and rheumatology.

HMPs can cause unintended effects in people other than the patients themselves, such as the workers who are exposed to them.

HMPs can have carcinogenic, mutagenic or reprotoxic effects. For example, some HMPs cause cancer or developmental changes such as foetal loss and possible malformations in offspring, infertility, and low birth weight. The upper-end estimates in the COWI study (2021)[5] suggest that an annual burden of 54 cases of breast cancer and 13 cases of haematopoietic cancer in the 2020s, rising to 19 cases per year in the 2070s, can be attributed to occupational exposure to HMPs in European Union (EU) hospitals and clinics. The COWI (2021) study further attributes an estimated 1,287 miscarriages per year in the 2020s, rising to 2,189 miscarriages per year in the 2070s, to occupational exposure to HMPs in EU hospitals and clinics. These represent the 'upper-end' health burden estimate in the COWI (2021) study, which emphasises the uncertainties associated with these estimates. The COWI (2021) study estimates that today almost 1.8 million workers are exposed to HMPs, 88% of which are employed in hospitals, clinics and pharmacies. COWI (2021) further estimates that the percentage of female workers in the relevant occupational groups ranges from 4% (technical staff in waste and wastewater treatment) to 92% (caregivers, animal caretakers and veterinary doctors).

There are also some other potential adverse health effects, including:

- Contact dermatitis, a local toxic reaction or an allergic reaction that may result from direct contact with the skin, eyes or mucous membranes

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1 Under the CLP Regulation (Annex I, Article 3.7.1), the term reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures https://eur-lex.europa.eu/eli/reg/2008/1272.

2 The CLP Regulation defines the hazard categories for mutagens, carcinogens and reproductive toxicants in tables 3.5.1, 3.6.1 and 3.7.1(a) respectively, which can be summarised as: Germ cell mutagens category 1: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans or substances known to induce heritable mutations in the germ cells of humans. Carcinogens category 1: Known or presumed human carcinogens. Reproductive toxicants category 1: Known or Presumed human reproductive toxicant. Source: Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures https://eur-lex.europa.eu/eli/reg/2008/1272

3 Statement of the Commission on Directive (EU) 2022/431 of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (OJ L 88, 16.3.2022, p. 1.) Hazardous medicinal products 2022/C 121/02 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022C0316%2802%29

4 Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405. Following the inclusion of reprotoxic substances to the scope of Directive 2004/37/EC by Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work https://eur-lex.europa.eu/eli/dir/2022/431

5 European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Sand Jespersen, M. et al., (2021), Study supporting the assessment of different options concerning the protection of workers from exposure to hazardous medicinal products, including cytotoxic medicinal products: final report, Publications Office, https://data.europa.eu/doi/10.2767/17127

- Abdominal pain, hair loss, nasal sores, nausea and vomiting, cough, dizziness, headaches
- Hypersensitivity to HMPs
- Alterations to normal blood cell count and platelet function
- Chromosome abnormalities as indicators of exposure to some HMPs
- Damage to organs such as the nervous system, liver, heart, or lungs

There are also additional risks if tobacco consumption is combined with exposure to HMPs.

1.1.2 What is the purpose of this guide?

This guide aims to:

- Increase awareness about the risks of hazardous medicinal products amongst the workers that might come into contact with or handle HMPs and their employers
- Increase good practice by workers handling HMPs across the EU and provide a useful reference point and support for training activities
- Improve the flow of information about HMPs as they pass between the different life cycle stages in their supply chain
- Promote harmonization between Member States and sectors by ensuring comprehensive guidance is available to all stakeholders. There are some existing guides covering the use of HMPs, but they are often written at a regional or local level, or only cover parts of the life cycle or specific roles. This guide should reduce this fragmentation of guidance about HMPs
- Be a flexible up-to-date tool which can be revised in the future, responding and adjusting to pharmaceutical advances
- This guide focuses on preventing and controlling risks from occupational exposure to HMPs and the information contained therein does not constitute a comprehensive overview of procedures for ensuring patient safety. The information in this guide must be read in conjunction with legislation and protocols for ensuring patient safety

1.2 Nature and scope of the guide

1.2.1 How to use this guide?

The guide is divided into sections on general and specific topics, see overleaf. The first seven sections and section 13 on incident management are general and apply to all life cycle stages. Sections 8 to 12 and 14 to 15 cover each stage of the life cycle of HMPs, from manufacturing to waste. There are several annexes providing the glossary, additional information and examples of risk assessment templates and summary sheets.

Throughout the guide, the use of “must” means that the references are covered by EU legislation and there is a footnote linking to the relevant legal provision, or the references relate to the need to follow national legislation. However, it should be noted that only following the statements that use “must” may not be sufficient for ensuring compliance with all applicable legislation, as these statements may not be sufficient to achieve all the results required by EU legislation, nor do they necessarily cover all applicable legislation. Moreover, it should be noted that EU occupational safety and health (OSH) legislation sets minimum requirements, in relation to which Member States are allowed to maintain or adopt more stringent protective measures. Accordingly, even fulfilling all EU OSH legislation requirements, does not guarantee the fulfilment of all relevant national requirements.

It should be noted that this guide:

- is of a general nature only and is not intended to address the specific circumstances of any particular individual or entity;

- is not necessarily comprehensive, complete, accurate or up-to-date;
- is not legal or professional advice and does not provide a comprehensive overview of all the applicable legal requirements; readers are thus advised to familiarise themselves with all the relevant legal requirements in their Member State;
- focuses on preventing and controlling risks from occupational exposure to hazardous medicinal products and does not constitute advice for ensuring patient safety.

The guide structure is as follows:

- Section 1 Introduction
- Section 2 Identification of hazardous medicinal products
- Section 3 Creating a safe working environment
- Section 4 Risk assessment
- Section 5 Exposure assessment
- Section 6 Education and training
- Section 7 Health surveillance
- Section 8 Manufacturing
- Section 9 Transport and storage (except waste)
- Section 10 Preparation
- Section 11 Administration (hospitals, other health-care facilities, care homes and care in homes)
- Section 12 Veterinary practices
- Section 13 Incident management
- Section 14 Cleaning, laundry, and maintenance
- Section 15 Waste and wastewater management
- Annexes
  - Annex 1 Glossary
  - Annex 2 Examples of templates for risk assessments
  - Annex 3 European List of Waste (LoW) codes
  - Annex 4 Personal protective equipment (PPE)
  - Annex 5 Guides reviewed
  - Annex 6 Example of occupational exposure bands and how they relate to control measures
  - Annex 7 Examples of summary sheets

Throughout this guide, whenever there is a reference to a different section of the guide, it contains a clickable cross-reference (the clickable link is underlined).

1.2.2 Are there any other important points about this guide?

This guide aims to provide an overview of the good practices available and give practical ways to reduce workers' exposure to HMPs. It is designed for all types of organisations regardless of size, whether public or private, and at all stages throughout the life cycle of HMPs. It also applies to facilities participating in clinical trials.

It is a non-binding guide designed to be used by Member States, regional and local organisations to underpin their approaches to workers' protection from HMPs. It is based upon existing European legislation.

The advice provided in this guide is without prejudice to any applicable European or national provisions.

In this guide, all references to standards are meant as references to the relevant standards as amended, supplemented, replaced or otherwise modified from time to time.

However, whilst it is important to control workers' exposure to HMPs, and the ideal method of eliminating or reducing workers' exposure under the hierarchy of controls in the CMRD and the EU OSH Framework Directive[6] is to replace HMPs with medicines that are not dangerous or are less dangerous to workers' health, this is rarely an option because the intrinsic properties of the HMPs are usually essential for the patient's treatment and their health should not be compromised.[7] The hierarchy of controls is covered in more detail in section 4.4.1.

[6] Articles 4 & 5 of Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405 and Article 6 of Council Directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (89/391/EEC) https://eur-lex.europa.eu/eli/dir/1989/391

[7] Recital 12 of Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work https://eur-lex.europa.eu/eli/dir/2022/431

The STOP principle[8] is often used in occupational safety and health (OSH):

- S = Substitution
- T = Technical measures
- O = Organisational measures
- P = Personal protection

Throughout the guide, if the text is about one of these four types of measure, the following symbols will appear alongside the text.

S Substitution

T Technical measures

O Organisational measures

P Personal protection

[8] Roadmap on carcinogens, (n.d.), STOP principle, https://roadmaponcarcinogens.eu/solutions/stop-basic-rules/

1.3 Who should read this guide?

The guide provides relevant advice for national authorities, employers and workers.

Any worker that comes into contact with either HMPs or patients using HMPs, or that works in locations or with equipment that comes into contact with HMPs, see section 4.3.1 for more detail about identifying these three categories of risks, should read the relevant sections of this guide, see Table 1-2. The roles typically coming into contact with HMPs are shown in Table 1-1 (which are grouped to make Table 1-2 easier to read).

In addition, the relevant sections of this guide, see section 1.4, should typically be read by any of the following people if they are carrying out any of the above roles:

- Contractors or self-employed staff
- Casual, agency, or temporary workers
- Staff providing short term relief for other workers
- Trainees or apprentices
- Students
- Volunteers

In addition, it is useful for any people with the following responsibilities to read the relevant sections of this guide, see section 1.4:

- Occupational health and safety experts with responsibility for any of the above roles
- Training managers ensuring that any of the above roles are trained in the safe management of HMPs at work
- Nurses and other healthcare workers, such as physiotherapists, radiotherapists, dieticians, or occupational therapists, working in other departments such as intensive care, recovery, and palliative care, that patients may visit after having an HMP administered
- Designers of workplaces for any of the above roles
- Purchasing managers buying HMPs, any equipment used to administer HMPs, or any equipment used to protect workers from HMPs
- Workers' representatives

The guide is designed for workers coming into contact with HMPs. It is not designed for patients, their families, or informal carers (people that are not workers in an employment relationship with a healthcare employer).

1.4 Which parts of this guide should I read?

This guide covers the whole life cycle of HMPs from manufacturing to waste and wastewater management. It is modular in design and the sections that are relevant to each role are shown below. The sections that should be read for each role group in Table 1-1 are shown in Table 1-2, which is coded as follows:

- Green means some or all of this section is relevant to this role
- Yellow means this section is relevant to roles for which they are responsible
- Blue means this section is relevant to the managers and supervisors of this role and all workers should be aware of this section
- Purple means some of this section may be relevant to this role
- Clear/white means this section is not applicable to this role

Table 1-1: Roles typically coming into contact with HMPs

Group	Role
A	• Pharmaceutical production staff
B	• Pharmacists • Pharmacy support staff
C	• Laboratory staff
D	• Nurses, doctors and other medical personnel • Ambulance workers and paramedics • Emergency response workers (such as fire wardens or emergency control officers, who might be called to an incident)
E	• Healthcare assistants, auxiliary nurses, or care home workers
F	• Veterinary surgeons, nurses, and students • Animal attendants
G	• Porters • Non-emergency patient transport workers • Mortuary workers • Funeral home workers • Stores and warehouse workers • Delivery drivers • Couriers
H	• Cleaners • Laundry workers • Maintenance workers
I	• Waste handlers • Waste transporters
J	• Employers, supervisors, and managers of workers with any of the above roles

Table 1-2: Sections relevant to each role group

Group/Section	A	B	C	D	E	F	G	H	I	J
1 Introduction										
2 Identifying HMPs										
3 Safety culture										
4 Risk assessment										
5 Exposure assessment										
6 Education and training										
7 Health surveillance										
8 Manufacturing										
9 Transport and storage										
10 Preparation										
11 Administration in hospitals										
12 Veterinary practices										
13 Incident management										
14 Cleaning, laundry, and maintenance										
15 Waste management										

Green = section relevant to role, Yellow = section relevant to roles for which they are responsible Blue = role should be aware of this section, Purple = some of section may be relevant to role, **Clear/white** = section not applicable to this role

1.5 Which EU legislation underpins this guide?

The EU directives and regulations underpinning this guide include:

- Directive 89/391/EEC: **OSH FD** (Occupational safety and health framework directive[9]) introduces measures to improve the health and safety of workers at work. To that end, it contains general principles concerning the prevention of occupational risks, the protection of safety and health, the elimination of risk and accident factors, providing information, consultation, balanced participation in accordance with national laws and/ or practices, and training of workers and their representatives, as well as general guidelines for the implementation of the said principles. The OSH FD applies to all sectors of activity, both public and private, including to the whole area covered by this guide, without prejudice to more stringent and/or specific provisions contained in the 'specialised' occupational safety and health directives mentioned on the next page.

[9] Council Directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (89/391/EEC) https://eur-lex.europa.eu/eli/dir/1989/391

- Directive 98/24/EC: **CAD** (Chemical agents' directive[10]) sets out minimum requirements for protecting workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents present at the workplace or as a result of any work activity involving those agents.
- Directive 2004/37/EC: **CMRD** (Carcinogens, mutagens and reprotoxic substances directive[11]) has as its aim the protection of workers against risks to their health and safety arising from or likely to arise from exposure to carcinogens, mutagens or reprotoxic substances at work, including the prevention of such risks.
- Regulation (EC) No 1272/2008: **CLP** (Classification, labelling and packaging[12]) lays down uniform requirements for the classification, labelling and packaging (CLP) of chemical substances and mixtures according to the United Nations' Globally Harmonised System (GHS). It requires companies to classify, label and package hazardous chemicals appropriately before placing them on the market.

  Note that the CLP does not apply to finished medicinal products or finished veterinary medicinal products for the final user[13]. Substances and mixtures, such as active pharmaceutical ingredients (APIs) or excipients, that are not yet in the HMP finished state, are subject to CLP regulation.
- Regulation (EC) No 1907/2006: **REACH** (Registration, evaluation, authorisation and restriction of chemicals[14]) establishes, for example, the requirement to provide safety data sheets (SDSs) for hazardous chemicals. Medicinal products for human and veterinary use in the finished state, intended for the final user, are exempted from this requirement.
- Regulation (EU) 2016/425: **PPER** (Personal protective equipment regulation[15]) lays down requirements for the design and manufacture of personal protective equipment (PPE) which is to be made available on the market, in order to ensure protection of the health and safety of users and establish rules on the free movement of PPE in the EU.
- Directive 89/656/EEC: **PPED** (Personal protective equipment directive[16]) lays down the minimum requirements for PPE used by workers at work.
- Directive 92/85/EEC: **PWD** (Pregnant workers' directive[17]) introduces measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding.
- Directive 94/33/EC: **YWD** (Young workers' directive[18]) lays down minimum requirements for the protection of young people at work, including prohibiting work involving harmful exposure to agents which are toxic, carcinogenic, cause heritable genetic damage, or harm to the unborn child or which in any other way chronically affect human health.

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10 Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work https://eur-lex.europa.eu/eli/dir/1998/24/

11 Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

12 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures https://eur-lex.europa.eu/eli/reg/2008/1272

13 Questions & answers section of the ECHA website: Will medicinal products need to be classified and notified to the Classification and Labelling Inventory? Substances and mixtures which are in the finished state and intended for the final user and which are medicinal products within the scope of Directive 2001/83/EC on the Community code for medicinal products for human use, or veterinary medicinal products within the scope of Directive 2001/82/EC on the Community code relating to veterinary medicinal products are on the whole exempted from the provisions of the CLP Regulation, i.e. they do not have to be classified, packaged, labelled and notified to the C&L Inventory. However, in cases where a manufacturer or importer supplies substances and mixtures, e.g. active pharmaceutical ingredients (APIs) or excipients, that are not yet in the finished state, this manufacturer or importer will have to classify, package and label these substances and mixtures in accordance with CLP. In addition, if these substances are placed on the market, they will also have to be notified to the C&L Inventory. The exemption from the provisions of the CLP Regulation does not distinguish between active and non-active pharmaceutical ingredients: it applies to any substance or mixture used in medicinal products, e.g. excipients, which is in the finished state and intended for pharmaceutical use. Source: https://echa.europa.eu/de/support/qas

14 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) https://eur-lex.europa.eu/eli/reg/2006/1907

15 Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 on personal protective equipment https://eur-lex.europa.eu/eli/reg/2016/425

16 Council Directive of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace (third individual directive within the meaning of Article 16 (1) of Directive 89/391/EEC) (89/656/EEC), https://eur-lex.europa.eu/legal-content/EN/AUTO/?uri=CELEX:01989L0656-20191120

17 Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeedinghttps://eur-lex.europa.eu/eli/dir/1992/85

18 Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work https://eur-lex.europa.eu/eli/dir/1994/33

- Directive 2008/68/EC: **Inland TDG** (Inland transport of dangerous goods[19]) lays down common rules for the safe and secure transport of dangerous goods within and between EU countries by road, rail or inland waterway.
- Agreement concerning the international carriage of dangerous goods by road: **ADR**[20] ensures that any dangerous goods transported by road can cross international borders freely if the goods, vehicles and drivers comply with its rules
- Directive 2001/83/EC[21] relating to **medicinal products for human use**, which provides the rules on the sale, production, labelling, classification, distribution and advertising of medicinal products for human use in the EU, including the Summary of product characteristics (SmPC).
- Regulation (EU) 2019/6[22] on **veterinary medicinal products**, which sets out the rules for the sale, manufacture, import, export, supply, distribution, control and use of veterinary medicinal products, including the Summary of product characteristics (SmPC).
- Regulation (EU) No. 1252/2014[23] which supplements Directive 2001/83/EC with regard to principles and guidelines of **good manufacturing practice** for active substances for medicinal products for human use.
- Directive 2003/94/EC[24] which also lays down the principles and guidelines of **good manufacturing practice** in respect of medicinal products for human use and investigational medicinal products for human use.
- Directive 91/412/EEC[25] which lays down the principles and guidelines of **good manufacturing practice** for veterinary medicinal products.

1.6 Why and how was this guide developed?

In the EU strategic framework on health and safety at work 2021-2027[26], published in 2021, the need to protect healthcare staff exposed to HMPs as well as other risks was stressed. The European Commission and European Agency for Safety and Health at Work (EU-OSHA) launched extensive studies and dialogues with experts and stakeholders on how to address these risks. These studies included COWI (2021[27]), which revealed stakeholders' support for further training, instruction, and guidance, as well as the challenges of enacting binding legislation to address this issue.

19 Directive 2008/68/EC of the European Parliament and of the Council of 24 September 2008 on the inland transport of dangerous goods https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008L0068-20221229

20 UNECE: Agreement concerning the International Carriage of Dangerous Goods by Road 2021 https://unece.org/transport/publications/agreement-concerning-international-carriage-dangerous-goods-road-adr-2021

21 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 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0083&qid=1673448360790

22 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128

23 Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R1252&qid=1667415778927

24 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32003L0094

25 Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31991L0412 This directive will be replaced by an implementing act to be adopted under Article 93(2) of Regulation. This is due to be in place by 29 January 2025 at the latest.

26 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the regions EU strategic framework on health and safety at work 2021-2027 Occupational safety and health in a changing world of work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52021DC0323

27 European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Sand Jespersen, M. et al., (2021), Study supporting the assessment of different options concerning the protection of workers from exposure to hazardous medicinal products, including cytotoxic medicinal products: final report, Publications Office, https://data.europa.eu/doi/10.2767/17127

Figure 1-1:

Pilot discussion at the Masaryk Memorial Cancer Institute, Czech Republic, including a project team member, two pharmacists with experience of HMP preparation, the lead nurse of an oncology ward and an exposure scientist with experience of HMP surface sampling

Directive 2004/37/EC[28] (CMRD) states:

No later than 31 December 2022, the Commission shall, after appropriate consultation of relevant stakeholders, prepare Union guidelines for the preparation, administration, and disposal of hazardous medicinal products at the place of work. Those guidelines shall be published on the website of EU-OSHA and shall be disseminated in all Member States by the relevant competent authorities.

This guide was developed with extensive involvement of stakeholders representing the whole life cycle of HMPs. The consultation included for example:

- Ten online workshops (one for each lifecycle stage: production of HMPs, transport & storage, preparation at hospital and community pharmacies, administration to patients in hospitals, care homes and home care, cleaning & laundry, role of healthcare providers/hospital & care home managers, veterinary practices, waste disposal and sewerage)
- A call for comments on the first draft of the guide which resulted in 55 stakeholders providing comments
- 18 pilot discussions with specific organisations throughout the life cycle of HMPs (manufacturers, hospitals, veterinary practices and others)

The process of development of this guide was followed by a tripartite Steering Group set up by Directorate-General for Employment, Social Affairs and Inclusion, with representatives from governments, employers, and workers.

[28] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

1.7 Summary of advice in section 1

Why is it important to manage exposure to hazardous medicinal products (HMPs)?

- HMPs can cause unintended effects in workers that are exposed to them.
- HMPs can cause carcinogenic, mutagenic or reprotoxic (CMR) and other adverse effects.

What is the purpose of the guide?

- The purpose is to increase awareness amongst workers and management.
- The purpose is to increase the uptake of good practice concerning the handling of HMPs.
- The purpose is to improve the flow of information.
- The purpose is to promote harmonisation between Member States.
- And the purpose is for this guide to be a flexible tool.

What is the nature and scope of the guide?

- This guide is non-binding.
- The advice is provided without prejudice to EU or national provisions.
- The hierarchy of controls is covered in more detail in section 4.4.1.

2

Identification of hazardous medicinal products (HMPs)

Hazardous medicinal products (HMPs) should be identifiable throughout their manufacture, transport, storage, use (preparation and administration), and waste disposal. This section provides advice on how HMPs can be identified.

2.1 A working definition and examples of HMPs

2.1.1 A working definition of HMPs

For the purposes of this guide, HMPs are defined as medicinal products that contain one or more substances that meet the criteria for classification as:

- Carcinogenic (category 1A or 1B),
- Mutagenic (category 1A or 1B) or
- Toxic for reproduction[29] (category 1A or 1B)

in accordance with Regulation (EC) No 1272/2008 (the CLP Regulation)[30]. This includes medicinal products for both human and veterinary use.

By virtue of the working definition provided above, HMPs fall[31] within the scope of Directive 2004/37/EC (the Carcinogens, Mutagens and Reprotoxic Substances Directive, CMRD)[32].

However, medicinal products falling under the working definition set out above may also have other adverse effects in addition to carcinogenic, mutagenic or reprotoxic (CMR) hazards.

2.1.2 Examples of HMPs

HMPs belong to the following key therapeutic groups: antineoplastics, antivirals, hormones and hormonal antagonists, and immunosuppressants. There are also some HMPs among antibiotics and other therapeutic groups. The most common areas of HMP use thus include oncology, transplantation, HIV and hepatitis B & hepatitis C treatment and rheumatology. However, many other medical fields are also relevant.

HMPs include cytotoxic, cytostatic and antineoplastic medicinal products and, consequently, many existing guidance documents focus on these types of medicines. Cytotoxic, cytostatic or antineoplastic medicinal products are highly toxic to cells (including healthy cells) and many are CMR. These medicinal products are used in a variety of clinical and laboratory settings for the treatment of cancer and other medical conditions such as rheumatoid arthritis, multiple sclerosis and auto-immune disorders.[33]

There is an ongoing debate about whether monoclonal antibodies (MABs) are HMPs. Monoclonal antibodies are used for the treatment of a wide range of conditions in haematology and oncology, graft rejection, inflammatory or auto-immune diseases.

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29 Under the CLP Regulation (Annex I, Article 3.7.1), the term reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures https://eur-lex.europa.eu/eli/reg/2008/1272

30 The CLP Regulation defines the hazard categories for mutagens, carcinogens and reproductive toxicants in tables 3.5.1, 3.6.1 and 3.7.1(a) respectively, which can be summarised as: Germ cell mutagens category 1: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans or substances known to induce heritable mutations in the germ cells of humans. Carcinogens category 1: Known or presumed human carcinogens. Reproductive toxicants category 1: Known or Presumed human reproductive toxicant. Source: Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures https://eur-lex.europa.eu/eli/reg/2008/1272

31 Statement of the Commission on Directive (EU) 2022/431 of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (OJ L 88, 16.3.2022, p. 1.) Hazardous medicinal products 2022/C 121/02 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022C0316%2802%29

32 Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405. Following the inclusion of reprotoxic substances to the scope of Directive 2004/37/EC by Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work https://eur-lex.europa.eu/eli/dir/2022/431

33 Worksafe Victoria, (2003, with an additional note from 2017), Handling cytotoxic drugs in the workplace: managing health & safety risks associated with handling cytotoxic drugs in the healthcare industry

It is expected that in the future monoclonal antibodies may be used in therapy much more frequently than traditional HMPs, and whilst their toxicity is clear for conjugated MABs, there is still much that is unclear, for example organ toxicity at low doses. It is useful to determine the hazard (and risk) of monoclonal antibodies used in oncology or immunotherapy on a case-by-case basis rather than treat them as a group.

MABs are not cytotoxic (except when conjugated to a cytotoxin) but there is some evidence of an increased risk for patients. In addition, a biological mechanism for teratogenicity has been demonstrated at therapeutic doses (Bauters & Vandenbroucke, 2019).[34] Extrapolation from toxicity data to occupational exposure settings is difficult due to a lack of potential systemic exposure routes for the large molecule MABs (Bauters & Vandenbroucke, 2019). Some conjugated monoclonal antibodies and one monoclonal antibody that is not conjugated to a cytotoxin have been included in the National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.

2.2 Methods of identification

Any medicinal products that are used, stored, transported, or disposed of, should be determined as HMPs or not.[35] Any medicinal products identified as HMPs should be labelled as such and handled in accordance with the recommendations in this document. An up-to-date list of HMPs to which workers are exposed should be maintained by all employers.

It may facilitate the identification of HMPs if these are identified at the earliest opportunity in the supply chain, that is by the manufacturer, and labelled as such using a recognised symbol, with this information also being communicated to downstream actors in the safety data sheet (SDS). An example of good practice is for manufacturers to provide SDSs for all HMPs.[36]

However, to account for the possibility that HMPs may not be identified as such by labels on product packaging or in SDSs, employers should additionally verify whether the medicinal products that are handled are HMPs by means of one or several of the other methods set out in this guide.

The potential methods of identification of HMPs include, for example:

- A: Existing lists and databases
- B: Review of SDSs (where available) and/or summaries of product characteristics (SmPCs/SPCs)
- C: Labelling
- D: Communication within the supply chain

In order to increase the likelihood that HMPs are identified, a combination of these methods can be used. The most effective combination depends on the position of the actor in the supply chain and whether HMPs have already been identified further upstream. A combination of Methods A and B is more likely to be used, for example, when developing a risk assessment, see section 4, whilst a combination of Methods C and D is more likely to be useful in day-to-day practical implementation of the HMP risk management plan, for example, at a ward of a hospital.

[34] Bauters T., Vandenbroucke J., (2019), Development of a flowchart for risk assessment and allocation of preparation of monoclonal antibodies https://journals.sagepub.com/doi/full/10.1177/1078155217743095

[35] According to Article 11(2) of Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405, employers must inform workers of installations and related containers containing carcinogens, mutagens or reprotoxic substances, ensure that all containers, packages and installations containing carcinogens, mutagens or reprotoxic substances are labelled clearly and legibly, and display clearly visible warning and hazard signs

[36] The Regulation establishes the requirement to provide safety data sheets for hazardous chemicals. Medicinal products for human and veterinary use in the finished state, intended for the final user, are exempted from this requirement. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) https://eur-lex.europa.eu/eli/reg/2006/1907

2.2.1 Existing lists and databases

In the first instance, the employer can check whether a list or database of HMPs is available in their Member State, region or organisation. In the absence of a suitable national, regional or institutional list, one or several of the sources in Table 2-1 below could be consulted. It should be borne in mind that the existing lists and databases rely on a range of definitions of HMPs.

The lists of HMPs for human use can also be used to identify which medicinal products used in veterinary medicine are HMPs.

Table 2-1: Existing lists and databases of medicinal products with hazardous properties

Country	List	Brief description	Availability
Europe	ETUI [37]	Definition of HMPs underpinning the development of the ETUI list is consistent with the working definition in sections 1.1.1 and 2.1.1 of this guide, i.e. HMPs within the scope of the CMRD. 121 CMR HMPs used in Europe identified based on this definition.	Available online free of charge: https://www.etui.org/publications/etuis-list-hazardous-medicinal-products-hmps
Australia	eviQ	71 cytotoxic anti-cancer medicinal products with hazardous properties 73 non-cytotoxic anti-cancer medicinal products with hazardous properties 17 medicinal products with hazardous medicinal properties	Available online free of charge: https://www.eviq.org.au/clinical-resources/administration-of-anti-cancer-drugs/909-hazardous-drugs-table#hazardous-drugs-table
France	ANSES [38]	Approximately 130 medicinal products with hazardous properties	Available online free of charge: https://www.anses.fr/fr/system/files/VSR2017SA0237Ra-1.pdf
France	Ordre national des vétérinaires	A list of antineoplastic medicinal products used in veterinary practice	Available online free of charge: https://politiquedesante.fr/wp-content/uploads/2014/12/GUIDE_ANTI_K_cle05f153-1.pdf
Germany	BGW [39]	Almost 500 medicinal products that are carcinogenic, mutagenic or reprotoxic (CMR) or sensitisers identified that belong to a wide range of therapeutic groups	Available online free of charge: https://www.bgw-online.de/resource/blob/18280/ee0680ea57259bad5bab2278b0e10158/bgw09-19-001-arzneistoffliste-inkl-einleitung-data.pdf

[37] The European Trade Union Institute's (ETUI's) list of hazardous medicinal products (HMPs) including cytotoxics and based on the EU CLP classification system of Carcinogenic, Mutagenic and Reprotoxic (CMR) substances https://www.etui.org/publications/etuis-list-hazardous-medicinal-products-hmps

[38] The French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

[39] Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (BGW), Employer's Liability Insurance Association for Health Services and Welfare Care

Country	List	Brief description	Availability
Italy	SIFO [40] and AIIAO [41]	20 antineoplastic drugs classified as IARC Groups 1, 2A and 2B	Available online free of charge: https://www.sifoweb.it/images/pdf/attivita/attivita-scientifica/aree_scientifiche/area_oncologica/CONSENSUS_DOCUMENT_FINALE.pdf
	SIFO	116 non-antineoplastic HMPs	Available online free of charge: http://documentodiconsensofarmacipericolosi.edizioniedra.it/materiali/pdf-farmacipericolosi-eng.pdf
The Netherlands	RiFaS [42]	A large number of medicinal products available in the Netherlands reviewed for evidence of C, M, R and other hazards (such as sensitisers)	Available online for registered users: https://rifas.nl/
Spain	INFOMEP [43]	Around 200 medicinal products with hazardous properties identified	Available online free of charge: https://www.insst.es/documentacion/catalogo-de-publicaciones/base-de-datos-infomep-informacion-para-los-profesionales-sanitarios-sobre-medicamentos-peligrosos-ano-2018
United States	NIOSH [44]	Around 130 Group 1 (antineoplastic) medicinal products with hazardous properties Around 50 Group 2 (non-antineoplastic) medicinal products with hazardous properties Around 50 Group 3 (other medicinal products that pose a reproductive risk)	Available online free of charge: https://www.cdc.gov/niosh/docs/2016-161/default.html

Furthermore, the European Commission will develop an indicative list of HMPs. The CMRD[45] states:

> *Where appropriate and no later than 5 April 2025, taking into account the latest developments in scientific knowledge and after appropriate consultation of relevant stakeholders, the Commission shall develop a definition and establish an indicative list of hazardous medicinal products or the substances contained therein, which meet the criteria for classification as a category 1A or 1B carcinogen set out in Annex I to Regulation (EC) No 1272/2008, a mutagen or a reprotoxic substance.*

[40] Italian Society of Hospital Pharmacists (SIFO)
[41] Italian Association of Oncology Nurses (AIIAO)
[42] Risk Instrument Pharmaceutical Substances (Risico instrument Farmaceutische Stoffen, RiFaS) developed by the Royal Dutch Pharmacists Association (KNMP)
[43] Developed by the National Institute for Safety and Health at Work (INSST) published in 2016 in collaboration with the Spanish Society of Hospital Pharmacists (SEFH)
[44] The NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings
[45] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

2.2.2 SDSs and SmPCs/SPCs

Finished medicinal products for human or veterinary use intended for the final user are exempted from the requirement to provide an SDS under REACH[46]. However, many manufacturers prepare SDSs for finished medicinal products on a voluntary basis. SDSs for finished medicinal products should therefore be requested by downstream actors from manufacturers and/or distributors and the information in 'Section 2: Hazards identification' of the SDS could be used as a method of identifying HMPs.

An overview of the hazard statements that can be used to identify HMPs is provided below.

Box 2-1: Relevant hazard statements for the identification of HMPs

- H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
- H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard), including:
  - H350i May cause cancer by inhalation
- H360: May damage fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard), including:
  - H360F May damage fertility
  - H360D May damage the unborn child
  - H360FD May damage fertility. May damage the unborn child
  - H360Fd May damage fertility. Suspected of damaging the unborn child
  - H360Df May damage the unborn child. Suspected of damaging fertility

Source: Regulation (EC) No 1272/2008 - Classification, labelling and packaging of substances and mixtures (CLP) https://eur-lex.europa.eu/eli/reg/2008/1272

SmPCs/SPCs also provide relevant information (e.g. on authorised use of a medicinal product, mechanism of action and pharmacological properties, special precautions for disposal and other handling) that is useful for the identification of hazard and risk management measures. Medicines agencies and (in some Member States) reimbursement agencies are important sources for information about authorised or reimbursed medicinal products.

2.2.3 Labelling

HMPs can also be identified by inspecting the labels on the packaging. The CLP Regulation does not apply to finished medicinal products or finished veterinary medicinal products for the final user.[47] However, a number of symbols for HMP labelling are in use. For cytotoxic medicines, the symbols are often purple or yellow and include a representation of a cell in telophase or a Yellow Hand. Examples of potentially relevant symbols are provided in Box 2-2.

Inspecting labels on packaging can be a useful method of HMP identification, in particular in day-to-day practice. As an example of good practice, it can be used in conjunction with the other methods set out in this guide rather than as the only method of HMP identification. It should be borne in mind that many labels focus only on cytotoxic medicines and some current labelling practices may thus not fully correspond to the scope of this guide (which includes all HMPs including those that are cytotoxic) and that labels may not be attached to some deliveries. In this regard, it is noted that the Yellow Hand[48] has the advantage of having a broader scope of application than 'cytotoxic' medicines and may thus correspond to the scope of this guide more than labels that focus exclusively on cytotoxicity. It is useful to apply warning labels that identify HMPs across the entire supply chain.

Warning labels should be clearly and easily recognisable. This may include the use of an identifying symbol for HMPs. For external transport of HMPs, contact details alongside hazard warnings can be added to labels to safely report any lost packages.

[46] Article 2(6)(a) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) https://eur-lex.europa.eu/eli/reg/2006/1907

[47] See Regulation (EC) No 1272/2008, Article 1(5); see also footnote 13

[48] https://esop.li/activities-2/yellow-hand/

Box 2-2:
Examples of existing labels

2.2.4 Information flow through the supply chains

It may be beneficial to identify HMPs with a specific HMP label as early on in the supply chain as possible.

As further examples of potential good practice with regard to information sharing within the supply chain:

Manufacturers and distributors of HMPs could indicate that a medicinal product is an HMP at the point of ordering, provide distributors, pharmacies, and compounding centres with SDSs for finished medicinal products and consistently label all deliveries of HMPs in a manner that clearly identifies the HMPs. In some cases, it may be advisable to contact the manufacturer for more information, see section 8.

The **pharmacy service** could make HMPs clearly identifiable as such at the point of storage, handling, ordering by other downstream actors and dispatch, by both electronic means and through labelling. When returning HMPs to the manufacturer, these could be clearly labelled as containing HMPs.

Organisations involved in the administration of HMPs, such as hospitals, care homes, veterinary practices, should ensure that HMPs are identified to all workers involved in their administration and that patients that are receiving, or have received HMPs within the time periods set out in section 11, are identified as such where necessary.[49]

If possible, the electronic systems used in the pharmacy service, as well as for prescribing, ordering, and administering medicinal products could be modified so that a unique electronic descriptor is attached to HMPs, thus making them more easily identifiable for all actors involved.

[49] While ensuring that relevant data protection and other applicable rules are being respected – see, for example, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation - GDPR), in particular Article 9, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02016R0679-20160504&qid=1674485543249

2.3 Summary of advice in section 2

A working definition of HMPs

- The working definition of hazardous medicinal products (HMPs) used in this guide is:
  - Medicinal products that contain one or more substances that meet the criteria for classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B).
  - This includes medicinal products for both human and veterinary use.
  - HMPs fall within the scope of Directive 2004/37/EC (the Carcinogens, Mutagens and Reprotoxic Substances Directive, CMRD[50]).
- Examples of HMPs include:
  - antineoplastics, antivirals, hormones and hormonal antagonists, and immunosuppressants. There are also some HMPs among antibiotics and other therapeutic groups.
- The most common areas of HMP use thus include oncology, transplantation, HIV and Hepatitis B & C treatment and rheumatology. However, many other medical fields are also relevant.

Methods of identification of HMPs

- Methods of determining whether a medicinal product is an HMP include:
  - A. Existing lists and databases
  - B. Review of safety data sheets (SDSs) (where available) and/or summaries of product characteristics (SmPCs/SPCs)
  - C. Labelling
  - D. Communication within the supply chain
- Existing lists and databases include:
  - National lists identified in AU, FR, DE, IT, NL, ES, US
  - ETUI list published in 2022
- As regards SDSs and SmPCs/SPCs, it is noted that
  - finished medicinal products are exempted from the requirement to provide an SDS under REACH but many manufacturers prepare them on a voluntary basis;
  - relevant risk phrases in SDSs are H340, H350, H350i, H360, H360F, H360D, H360FD; and
  - SmPCs/SPCs can also provide some relevant information.
- As regards labelling, it is noted that
  - The CLP Regulation does not apply to finished medicinal products or finished veterinary medicinal products for the final user;[51]
  - Labelling can facilitate communication in the supply chain;
  - HMPs should be identified with a specific HMP label as early on in the supply chain as possible; and
  - A number of labels are in use; many focus on cytotoxic medications; the Yellow Hand has a broader scope than cytotoxic medications.

[50] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

[51] See Regulation (EC) No 1272/2008, Article 1(5); see also footnote 13

3

Creating a safe working environment

3.1 Introduction

It is the employer's duty to ensure the safety and health of workers.[52] This includes taking the necessary measures for the safety and health protection of workers, including the assessment and prevention of occupational risks and provision of information and training, as well as the provision of necessary organisation and means.[53]

The employer is responsible for the safety and health in the company, even where some of the tasks are outsourced to external service providers.[54] The employer must designate one or more workers or enlist competent external services or people to carry out the relevant occupational safety and health (OSH) activities.[55]

Where several undertakings share a place of work, employers must cooperate in implementing OSH in relation to hazardous medicinal products (HMP-OSH), coordinate their actions in matters of the protection and prevention of occupational risks, and inform one another and their respective workers and/or workers' representatives of these risks.[56] Such cooperation may be relevant for healthcare establishments, where certain services, such as cleaning, may be outsourced or where certain tasks are carried out by agency workers, such as care workers, to ensure that all staff potentially exposed at the relevant place of work are protected. In any event, in cases of temporary agency work, the user undertaking and/or establishment is responsible for the OSH of the temporary agency workers.[57]

The remainder of this section provides an example of the division of tasks related to the prevention and reduction of exposure to HMPs among workers in a large organisation where HMPs are administered, such as a hospital. This example is provided for illustrative purposes but takes into account the fact that (subject to risk evaluation and as necessary) the preventive measures and the working and production methods implemented by the employer must be integrated into all the activities of the undertaking and/or establishment and at all hierarchical levels.[58]

3.2 Who is responsible for HMP-OSH?

3.2.1 Introduction

Commitment, involvement, and leadership at all levels of the management are an important prerequisite for attaining a high level of safety culture. An overview of the different safety culture stages is provided on the next page.

It is important for the management to create a high level of safety culture that is not only reactive but looks ahead and proactively anticipates problems, aiming to achieve the generative stage of safety culture. At this level, the safety culture is an integral part of how the organisation operates. There is no competition between safety and business culture.

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52 Directive 89/391/EEC, Article 5(1)

53 Directive 89/391/EEC, Article 6(1); see also Directive 89/391/EEC, Article 6(3)(a); Directive 2004/37/EC, Article 3; Directive 98/24/EC, Article 4

54 Directive 89/391/EEC, Article 5(2)

55 Directive 89/391/EEC, Article 7; according to Directive 89/391/EEC, Article 7(7), Member States may define, in the light of the nature of the activities and size of the undertakings, the categories of undertakings in which the employer, provided he is competent, may himself take responsibility for the relevant measures.

56 Directive 89/391/EEC, Article 6(4)

57 Article 8 of Council Directive of 25 June 1991 supplementing the measures to encourage improvements in the safety and health at work of workers with a fixed-duration employment relationship or a temporary employment relationship (91/383/EEC), https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01991L0383-20070628

58 Directive 89/391/EEC, Article 6(3)(a)

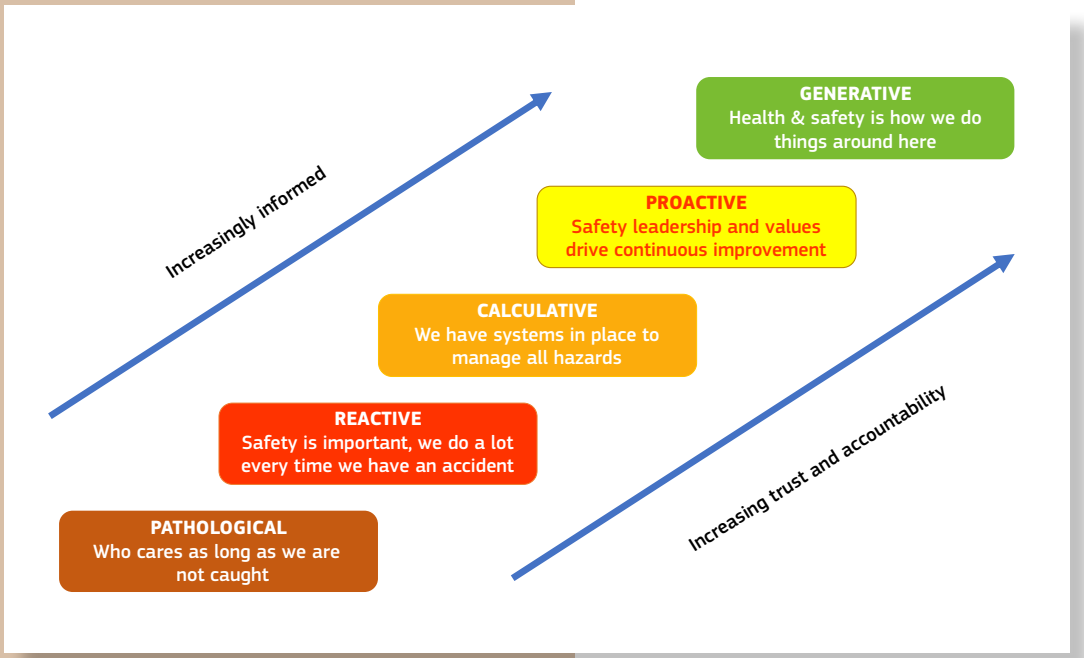


Figure 3-1: Safety culture stages
Source: Hudson (2007)[59]

Pathological, reactive, calculative and proactive stages should only be seen as intermediate steps. A high level of safety culture can also be result rather than means/tool driven.

In order to achieve a high level of safety culture, it is useful for the management to ensure that workers are comfortable raising concerns and reporting incidents without fear of repercussions and that there is a nominated person for receiving such reports who is a member of the HMP-OSH Steering Committee, see section 3.2.2.4.

3.2.2 Examples of HMP-OSH activities by management level

Examples of HMP-OSH that may be undertaken by senior, middle, and operational level management are provided below. In some organisations, there may be more (or fewer) managerial levels and the information in this guide may need to be adapted for a specific organisation. In any case, workers and/or workers' representatives must be informed and consulted, and allowed to take part in discussions on all questions relating to safety and health at work.[60]

This section provides general examples of the possible activities – the specific activities depend on the stage in the lifecycle (manufacturers, pharmacies, etc.). This section is not an exhaustive list of the responsibilities of employers or the different management levels.

3.2.2.1 Examples of possible activities for senior management

It is useful for the top management to define policies, objectives, overall planning and take the most important decisions. The activities undertaken by senior managers could include defining the HMP-OSH policy and the HMP-OSH management plan, deciding (in

[59] Hudson, (2007), Implementing safety culture in a major multinational, Safety science 45:6, https://www.sciencedirect.com/science/article/abs/pii/S0925753507000227 and Directors Safety Alliance (2016) The role of Senior Management within business success, https://www.iosh.co.uk/~/media/Documents/Networks/Branch/East%20Anglia/DSA%20IOSH%20We%20st%20AngliaConstruction%20Leadership.pptx?la=en

[60] Directive 89/391/EEC, Articles 10, 11; see also Directive 2004/37/EC, Article 13, and Directive 98/24/EC, Article 11

consultation with workers/workers' representatives[61]) on important technological/other changes to improve HMP-OSH, deciding on implementing and certifying an HMP-OSH management system, and approving HMP-OSH training structure.

More specifically, the senior management could, for example:

- Make an explicit commitment (e.g. in the policy document) to being the overall guarantor of the OSH-HMP approach within an undertaking or establishment
- Create and maintain an up to date HMP-OSH management plan (standalone or as a section in the general OSH-plan of the organisation)
- Undertake floor visits (with and without middle and operational management)
- Set up an HMP-OSH Steering Committee and ensure that it meets periodically (at least twice a year) or place HMP-OSH on the agenda of the OSH-committee (steering group for OSH issues)
- Organise and discuss the results of audits, workplace monitoring, incident-reports, planning of implementation, training, and instruction and decide if improvement/change is necessary

3.2.2.2 Examples of possible activities for the middle management

The role of the middle management could include, for example, defining departmental (sub)objectives and executing the HMP-OSH management plan with regard to their department, advising, motivating, and supporting lower management and setting key performance indicators based on the objectives of the top management.

More specifically, the middle management could, for example:

- Define HMP-OSH departmental objectives and/or targets, advise and approve HMP-OSH measures and training, collaborate with other departments and senior management
- Highlight to the top management if the resources made available for HMP-OSH are insufficient
- Have an active (walk the talk) attitude to staff
- Undertake floor visits (with and without operational level management)
- Collect and analyse incident reports (including near incidents) and implement improvements
- Submit regular reports to the HMP-OSH Steering Committee
- Guarantee a safe environment for reporting from staff (climate of trust) and be open for suggestions for improvement

3.2.2.3 Examples of possible activities for operational management

The role of lower management could involve, for example, coordinating and supervising workers, providing advice, and reporting to middle management.

More specifically, operational-level management could, for example:

- Train and supervise staff
- Participate in risk assessment, see section 4
- Provide advice on good practice
- Reinforce HMP-OSH rules by having an active (walk the talk) attitude to staff (visible on work floor)
- Report HMP-OSH performance and problems to middle management
- Produce and maintain the required records
- Guarantee a safe environment (climate of trust) for reporting from workers and be open for suggestions for improvement
- Acknowledge positive behaviour. Integrate the highlighting of positive examples into staff meetings (at the operational level)

3.2.2.4 HMP-OSH Steering Committee

It is useful, particularly in large organisations such as hospitals, to establish a Steering Committee for HMP-OSH. This could be a multi-disciplinary Steering Committee that comprises the senior, middle and operational managers, OSH experts (including occupational hygienists, occupational doctors, etc.), as well as representatives of the exposed worker groups, such as a pharmacist, a nurse, a representative of other exposed workers and waste manager. It is also

[61] Directive 89/391/EEC, Article 6(3)(c)

useful to include clinical personnel to ensure that patient safety is not compromised. With regard to the composition of the HMP-OSH Steering Committee, it should be remembered that employers must consult workers and/or their representatives and allow them to take part in discussions on all questions relating to safety and health at work.[62] It could meet periodically (at least twice a year). Alternatively, HMP-OSH could be placed on the agenda of the OSH-committee (steering group for OSH issues).

Amongst other things, the HMP-OSH Steering Committee could discuss:

- The advice provided in this guide
- Risk assessment and HMP risk management plan, see section 4
- Results of exposure assessment and health surveillance, see sections 5 and 7
- Information on learning from mistakes and incidents (managing incidents and near misses, actions after incidents), see section 13
- Exchange of good practice between departments
- Improvement suggestions put forward by the workers
- Coordination with other OSH issues

3.3 Examples of good practice with regard to HMP-OSH

Examples of good practice principles with regard to HMP-OSH include:

- **Specify allocation of sufficient resources for HMP-OSH (time, money, people) as an explicit operating principle:** It is useful to specify the allocation of sufficient resources for HMP as a key operating principle in the organisation's operating procedures
- It is useful for the management to set specific **targets** and define the specific **monitoring indicators** (for example, results of exposure assessments, behavioural change in staff**,** numbers of incidents, results of staff surveys, and results of audits/reviews)
- It is useful to highlight, across all levels of management and amongst workers the **importance of worker involvement** in the establishment, operation, evaluation and improvement of HMP-OSH policy for the creation of a high level of buy-in and awareness of the risks
- It is useful to undertake **audits and reviews** at least once in between risk assessments, see section 4, including **worker surveys and interviews**. The characteristics of the surveys could include, for example:
  - Sufficient numbers to capture a range of views and experiences
  - Preferably anonymous or in a non-threatening manner
  - Include questions on whether management is trusted over safety to test management approaches. Increases accountability
  - Include questions on availability of engineering controls and CE certified PPE
  - Include questions on availability of advice
  - Test accuracy of workers' perception of risk
- It is useful to **nominate a specific contact person** (or people) for HMP related queries. All workers who might come into contact with HMPs should be made aware of the nominated contact person and have their contact details. Their contact details could also be included on spill kits. It may be useful to ensure that the nominated people are available to be consulted at all times
- It is useful to encourage **workers to report concerns** (such as hazards, incidents, non-availability of CE certified PPE) and create a safe, non-punitive, system for reporting ideas and concerns

[62] See footnote 60 above

- It is useful to **remove barriers to participation**, for example, language and/or hold several meetings to ensure participation from different shifts and to ensure that agency workers, contractors and subcontractors can participate

3.4 Communication

The employer must ensure that workers and/or workers' representatives receive the necessary information about HMPs, including on the risks associated with HMPs, the tasks undertaken with HMPs, how and when exposure to HMPs can happen, and what measures are in place to reduce exposure to HMPs[63]. If there are workers from an external organisation that might be exposed to HMPs, the employer should check that they receive the same relevant HMP information from their employer (the external organisation). See also information on co-operation in cases where several undertakings share a place of work in section 3.1. In case of temporary agency work, the user undertaking and/or establishment is responsible for the OSH of the temporary agency workers and thus the user undertaking and/or establishment should provide information to workers and/or workers' representatives.

The employer must ensure that workers with specific functions in protecting the safety and health of workers, or workers' representatives with specific responsibility for the safety and health of workers have access, to carry out their functions and in accordance with national laws and/or practices, among others to the following information[64]:

- Risk assessment and HMP risk management plan, see section 4
- Details about incidents, see section 13, and occupational disease or adverse health effects (but no identification of the injured parties)
- Information on the protective and preventive measures, and information from inspection agencies and bodies responsible for safety and health

The employer must ensure that workers and/or workers' representatives are consulted, allowed to participate in discussions, and make proposals about any issue relating to workers' exposure to HMPs.[65]

During the awareness raising or consultation processes, many different messages relating to HMPs should be clearly communicated to workers covering issues such as:

- Substance specific hazard information including the signs/symptoms of overexposure
- Incident management, see section 13
- Training, see section 6
- Health surveillance, see section 7
- Risk assessment and HMP risk management plans, see section 4
- Exposure assessment, see section 5
- Both male and female workers considering pregnancy, female workers who are pregnant, and female workers who are breastfeeding, see section 4.3.2.4
- Labelling of HMPs, see section 2.2
- Information about storing and transporting HMPs, see section 9
- Information about cleaning in situations where there may be HMPs, see section 14.1
- Information about handling waste that might contain HMPs, see section 15
- One page summaries for different activities, see Annex 7

63 Directive 89/391/EEC, Article 10; Directive 2004/37/EC, Articles 11 and 12
64 Directive 89/391/EEC, Article 10(3)
65 See footnote 60 above

The central element of the communication is the message. The message could be:

- Specific event such as a training course, new HMP risk management plan or a series of workplace monitoring events
- Part of an awareness campaign to ensure that workers know about wider topics such as health surveillance or waste management
- Targeted at specific workers such as workers planning parenthood, or those who are breastfeeding or pregnant

All communication needs to be in a form, manner and language likely to be understood by the workers receiving it. If any workers might not be proficient in the language of the communication or might have low levels of literacy, the communication needs to be carefully constructed to ensure that every targeted worker receives and understands it.

The recipients targeted for a communication depend upon the specific message. The workers with roles listed in section 1.4 might handle HMPs and are the starting point for recipients for any communication relating to HMPs. Most communications are likely to be sent to a small subset of this list.

The communication should be sent through the medium most appropriate to the roles of the workers that need to receive it. Some communications can use more than one medium. Different media include, for example:

- Email
- Notices – printed and placed on noticeboards or walls
- Leaflets or printed documents
- Webpages or other online forums
- Internal newsletters – printed and online
- Letter
- Face to face – one-to-one, meetings or committees

It is useful to follow up face-to-face communication with written summaries.

The timing of the communications varies, for example:

- Initial induction communication for new staff
- Regular communication such as accompanying events such as incident management refresher training, see section 6.3.4, which should be held annually or more often if necessary. Other regular communications could be scheduled monthly or quarterly or at any suitable interval
- Awareness campaigns for example to ensure awareness of HMPs: these could be a series of related communications over a period of a month, quarter, year or other suitable timeframe
- The format and frequency of communication must conform to national legal requirements

3.5 Summary of advice in section 3

Who is responsible?

- It is the employer's duty to ensure the safety and health of workers[66].
- Where several undertakings share a place of work, employers must cooperate in implementing occupational safety and health (OSH) policies and practical measures for the prevention and control of hazardous medicinal product (HMP) risks (HMP-OSH), coordinate their actions in matters of the protection and prevention of occupational risks, and inform one another and their respective workers and/or workers' representatives of these risks[67].
- It is important for the management to create a high level of safety culture that is not only reactive but looks ahead and proactively anticipates problems, aiming to achieve a generative safety culture.
- It is useful, particularly in large organisations such as hospitals, to establish a Steering Committee for HMP-OSH. This could be a multi-disciplinary committee that comprises the senior, middle and operational managers, OSH experts, and representatives of the exposed worker groups, such as pharmacists, nurses, etc. and a waste manager. It is also useful to include clinical personnel to ensure that patient safety is not compromised. Alternatively, HMP-OSH could be placed on the agenda of the OSH-committee (steering group for OSH issues).

Examples of good practice

- It is good practice to specify the need to allocate sufficient resources (time, money, people) to HMP-OSH activities as a key operating principle.
- It is useful for the management to set specific targets and define the specific monitoring indicators.
- It is useful to highlight the importance of worker involvement in the establishment, operation, evaluation and improvement of HMP-OSH policy.
- It is useful to undertake audits and reviews at least once in between risk assessments, including worker surveys and interviews.
- It is useful to nominate a specific contact person (or people) for HMP related queries.
- It is useful to encourage workers to report concerns.
- It is useful to remove barriers to participation, for example, language and/or hold several meetings to ensure participation of workers from different shifts and to ensure that agency workers, contractors and subcontractors can participate.

Communication

- The employer must ensure that workers and/or workers' representatives receive the necessary information about HMPs, including on the risks associated with HMPs, the tasks undertaken with HMPs, how and when exposure to HMPs can happen, and what measures are in place to reduce exposure to HMPs.[68]

66 Directive 89/391/EEC, Article 5(1)
67 Directive 89/391/EEC, Article 6(4)
68 Directive 89/391/EEC, Article 10, Directive 2004/37/EC, Articles 11 and 12

4

Risk assessment

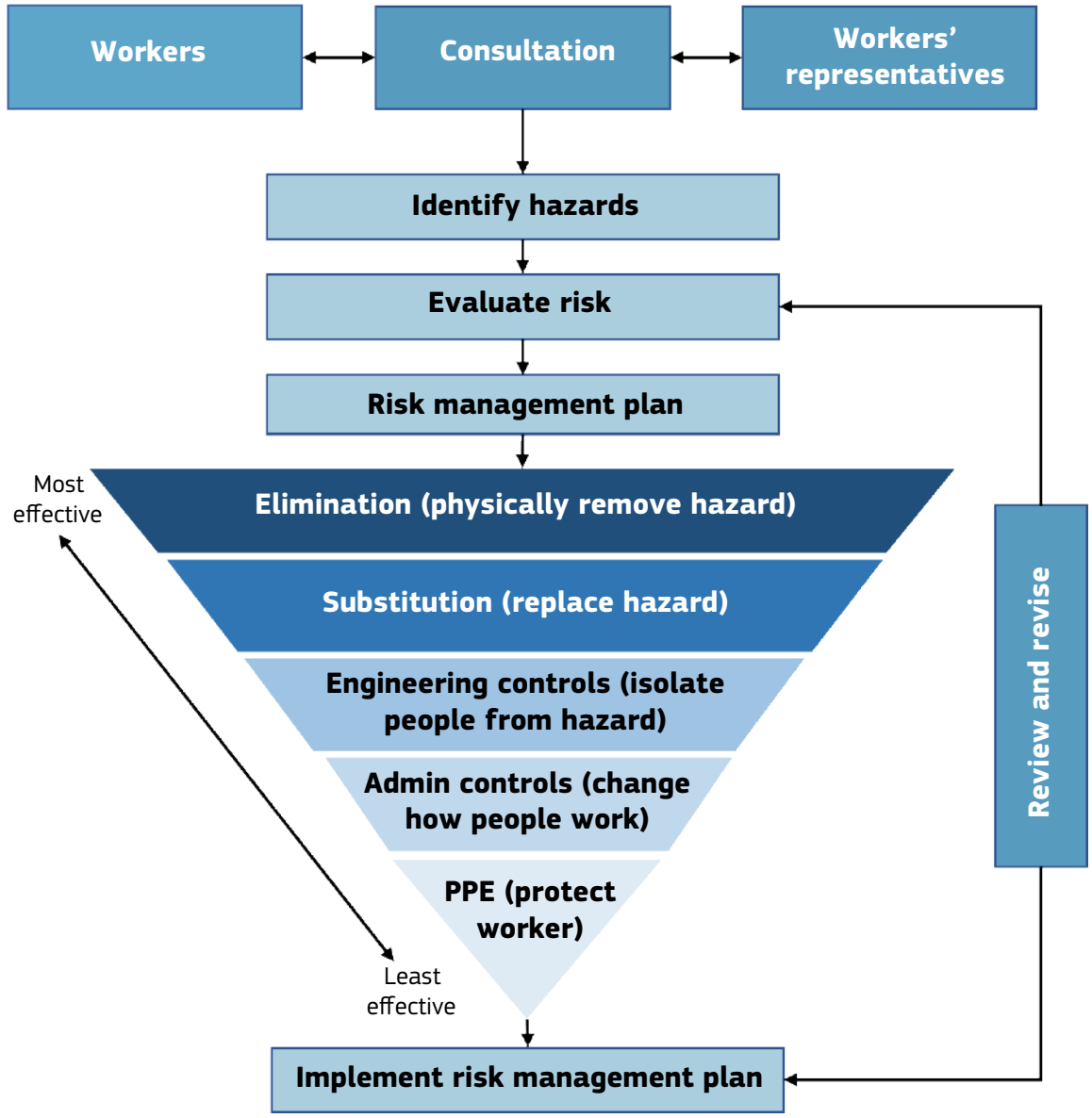
4.1 Introduction

The purpose of a risk assessment is to enable decisions to be made about the appropriate risk management measures, training, exposure assessment and health surveillance required. The two key terms are hazard and risk, which are defined as:

- Hazard - something that could cause harm; in this context the presence of any hazardous medicinal products (HMPs)
- Risk - the likelihood that the hazard will cause harm and how serious that harm might be; in this context, the possible ill-health effects occurring at the exposure levels of the HMPs

The approach to risk management described below is summarised in Figure 4-1.

Figure 4-1: Approach to risk management



4.2 Who is responsible for risk assessment?

The responsibility for the risk assessment of HMPs and for developing and implementing the HMP risk management plan lies with the employer.[69] The employer may enlist the assistance of external services or persons, who should typically have the following competencies (whilst complying with any applicable national legislation or guidance):

- Knowledge, skills and experience to evaluate risks
- Understanding of HMPs, workplace, tasks undertaken, how and when exposure can happen, and health and safety regulations
- Ability to deal with the complexity of the process
- Appropriate authority and seniority level

The employer must ensure that the designated in-house workers or external services or persons include sufficient people to assess the risks, and to develop and implement the HMP risk management plan;[70] the assistance of external services or persons does not discharge the employer from their responsibilities.[71]

Risk assessment is typically performed by an occupational safety and health (OSH) expert or other role with responsibility for OSH, such as a line manager, a higher-level manager, a patient safety coordinator, or a prevention advisor for hazardous waste.

Workers and/or workers' representatives must be informed and consulted at all stages of the risk assessment, i.e. the development, implementation and evaluation of the HMP risk management plan, and any subsequent revisions to the risk assessment and HMP risk management plan, see section 3.4 for information about communications.[72] During the whole process, workers should be able to contact the designated person or their delegate to ask questions.

4.3 Scope

Risk assessments must be undertaken for all activities where workers are likely to be exposed to HMPs as a result of their work.[73] This includes activities where workers handle HMPs or are exposed to them (including temporary, casual and agency workers, trainees and apprentices, see section 1.2.2). In healthcare or veterinary establishments, this also includes all activities undertaken by the persons working in locations where HMPs are used, involved in activities where HMPs are used, and providing care to patients who are being given HMPs.

4.3.1 Identify hazards

When conducting a risk assessment, the first step is to identify the hazards (HMPs), see section 2. For each identified hazard (HMP), the following information should typically be recorded:

- General description of the hazard
- Relevant exposure route(s), see section 5.4
- Official occupational exposure limit (OEL)[74] for the respective HMPs, where appropriate
- OEL set by the manufacturer (following internationally accepted scientific standards), where available

69 Directive 89/391/EEC, Articles 6 and 9; Directive 2004/37/EC, Articles 3-5
70 Directive 89/391/EEC, Articles 7(1) and 7(5)
71 Directive 89/391/EEC, Article 5(2)
72 Directive 89/391/EEC, Articles 10 and 11
73 Directive 2004/37/EC, Article 3
74 The occupational exposure limit (OEL) for an HMP should be taken to be the OEL for the active pharmaceutical ingredient (API). DNELs or DMELs should also be considered, if available, either recommended by the RAC Committee of European Chemical Agency (ECHA) or provided by manufacturers.

- Hazard information such as hazard phrases (H-phrases) related to the HMPs. Such information is typically provided in section 2 of safety data sheets (SDSs)
- Potential adverse health effects and/or toxicity related to HMPs, see section 1.1.1 for a description of ill-health effects resulting from exposure to HMPs and section 7 for health surveillance
- Physico-chemical properties of the HMPs, such as vapour pressure, water solubility at room temperature, lipophilicity (log Po/w), stability, viscosity, particle size and molecular mass
- Other information that might indicate a potential hazard, including:
  - Actions to be taken if a worker is accidentally exposed, such as to their skin (e.g. a sharps accident), eyes (e.g. splashing), inhaled or ingested
  - Precautions for use, and instructions for safe handling of HMPs. Such information is typically provided in safety data sheets (SDSs), summary of product characteristics[75] and on HMPs' labelling

4.3.2 Identify information to assess whether a hazard is a risk

The information required to assess whether the hazard is a risk involves several interrelated activities, typically including identifying:

- Locations and activities where HMPs are used
- Workers exposed to HMPs
- Workers at greater risk – both male and female workers considering pregnancy, female workers who are pregnant, and female workers who are breastfeeding
- Workers at greater risk – young workers
- Patients being treated with HMPs (as a source of exposure of workers)
- Exposure levels, where available
- Control measures, where applicable

4.3.2.1 Identify locations and activities where HMPs are used

The assessment of risks should involve identifying where, when, and how workers might be exposed to HMPs:

- Specific workplace activities with HMPs in the life cycle stage(s) that are relevant to workers in the setting for which the risk assessment is conducted. This may include manufacturing, preparation, transportation and storage, administration, cleaning, handling laundry, maintenance of equipment, waste and sewage disposal
- Locations where HMPs are used in the workplace for which the risk assessment is conducted: the building plan of the setting should be reviewed, for example the administration ward, pharmacy, storage area, and waste disposal area
- Identification and evaluation of any actual incident or near miss (e.g. spills), together with the identification of any potential incident risks
- Identification of exposure paths through the facility
  - For example, for healthcare or veterinary establishments, the course that HMPs take from entering the facility (delivery), through to storage, preparation, internal transport, administration and patient care, to leaving the facility (cleaning, laundry, waste disposal)
  - All potential exposure points along this path
- Which locations are 'contaminated' and 'clean' zones, and are they strictly separated?
- What are the requirements for changing clothes and procedures for personal protective equipment (PPE) and personal hygiene?
- Understanding of how the HMPs are prepared; there are many different formulations and preparations, such as:
  - Solid forms
  - Creams and ointments
  - Liquids and syrups
  - Parenteral bolus injection
  - Intravenous (IV) infusion
  - Parenteral fluids
  - Elastomeric pumps

[75] Union Register of medicinal products, https://ec.europa.eu/health/documents/community-register/html/

- Identification of risks associated with different forms of HMPs, which include:
  - Liquid
  - Solid tablet or capsule
  - Powder (including information about dustiness)
  - Cream, ointment, lotion
- Understanding of how the HMPs are administered and used; there are many different procedures, such as:
  - Oral
  - Intravenous (IV)
  - Subcutaneous (SC)
  - Intramuscular
  - Topical
  - Bladder flushing (intravesical)
  - Pressurised intraperitoneal aerosol chemo-therapy (PIPAC)
  - Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Identification of the type of exposure, which can take place through:
  - Inhalation, such as aerosols, vapours, particulates, and droplets
  - Skin or eye contact, such as touching contaminated surfaces (including situations when workers cannot see contamination), splashes, particularly following an incident (spill or leak)
  - Injection, including injuries from sharps
  - Ingestion, for instance, poor or no handwashing when food or beverages are prepared, stored, or consumed in work areas
- Understanding of the duration and frequency of exposure to the HMPs identified

4.3.2.2 Identification of workers exposed to HMPs

The employer must keep an up-to-date list of all individual workers that the risk assessment indicates are at risk, together with their exposure levels, if known.[76] This can be done by defining groups of similarly exposed workers and determining the exposure for each group (nature, duration, and level); this can be done (semi-)quantitatively. Each worker is assigned to a group; this is the list that is registered and maintained.

4.3.2.3 Combinations of HMPs

If workers are, or might be, exposed to several chemical agents (including several HMPs), the risk of all these chemical agents (including several HMPs) in combination must be assessed.[77] Annex C of EN-689: 2018+C1:2019 about workplace exposure provides an example of how to assess the combined impact of HMPs.[78]

4.3.2.4 Workers at greater risk – workers trying to conceive, pregnant workers, workers who have recently given birth and workers who are breastfeeding

All workers that might be exposed to HMPs must be informed of the potential risks[79], see section 3.4. If relevant, this includes making female workers who are pregnant, or breastfeeding aware of the additional risks that working with HMPs may pose to an unborn or breastfed child. This also includes informing all workers of the reproductive and development hazard, which may affect both male and female workers trying to conceive a child.

Where there is a risk of exposure to HMPs, the employer must undertake a risk assessment[80], see section 4.3, for all female workers who are:

- Pregnant
- Have recently given birth
- Breastfeeding

[76] See Directive 2004/37/EC, Article 12(c-f)
[77] Directive 98/24/EC, Article 4(4)
[78] EN 689:2018, Annex C, Workplace exposure - Measurement of exposure by inhalation to chemical agents - Strategy for testing compliance with occupational exposure limit values (available against payment)
[79] See Directive 2004/37/EC, Articles 11 and 12
[80] Directive 2004/37/EC, Article 3

Employers should take special care to protect all workers that might be exposed to HMPs, because a worker may not be aware that she is pregnant and may be unable or reluctant to inform her employer for the first 30-45 days of pregnancy. The unborn child is most vulnerable to permanent damage during the first trimester (first 91 days), so appropriate measures should be taken to protect the mother and the unborn child as soon as possible. The risk assessment should address different stages during pregnancy and after delivery as pregnancy is a changing process and different risks can affect a woman and her unborn or new-born child to varying extents during the various stages of pregnancy and after delivery.

4.3.2.5 Workers at greater risk - young workers

Young people (under 18 years of age) must not be employed in work involving harmful exposure to HMPs.[81] Young people are vulnerable to risks, amongst others, due to a lack of experience, lack of awareness of existing or potential risks, or due to the fact that they have not yet fully matured.

4.3.2.6 Identification of patients treated with HMPs

In healthcare or veterinary establishments, the risk assessment process should involve the identification of patients treated with HMPs.[82] This enables workers to recognise whether special measures should apply when providing healthcare services to a patient, and when they are dealing with objects in contact with patients, such as changing their bedding. A system for keeping patient records can be used for this purpose, such as an electronic record keeping system or equivalent, accessible to those involved on a need-to-know basis.

4.3.2.7 Monitoring exposure to HMPs

A workplace monitoring system should be put in place at all potential exposure points, see section 5. This helps to assess the degree of potential exposure of workers at all relevant life cycle stages and roles.

4.3.3 Evaluate risks

The risk assessment should evaluate the likelihood of adverse health effects at the assessed exposure levels. It is important to consider the reliability of the evidence throughout the process. If the risk is not well understood and may be severe or irreversible, the risk assessment should take a precautionary approach.[83]

One example of a tool used to evaluate the risks associated with HMPs is the Risico instrument Farmaceutische Stoffen (RiFaS) system in the Netherlands, which is described in Box 4-1.

There are three potential outcomes of the risk evaluation:

- There is *no likelihood* of adverse health effects: work practices are sound, and workers are protected
- The likelihood of adverse health effects is *uncertain*: further assessment and evaluation is required
- There is *a likelihood* of adverse health effects: work practices need improvement

4.3.3.1 Pregnant workers, workers who have recently given birth and workers who are breastfeeding

If the assessment relating to a worker who is pregnant, has recently given birth or is breast feeding reveals there is a risk, the employer must inform the female worker about the risk.[84]

[81] Directive 94/33/EC, Article 7
[82] In the case of human patients, attention must be paid to the need to comply with the applicable data protection rules – see, for example, Regulation (EU) 2016/679.
[83] See recital 14 of Directive 2004/37/EC
[84] Directive 92/85/EEC, Article 4

The employer must take necessary measures to avoid the exposure of the worker to these risks by, for example[85]:

- Adjusting working conditions and/or the working hours of the worker concerned
- If adjustment is not possible, then the employer must move the worker to another job.
- If a move is not possible, then the employer must grant the worker leave to protect her safety or health.

Box 4-1: An example of a risk instrument for pharmaceutical substances

RiFaS (Risk Instrument for Pharmaceutical Substances) is a Dutch risk evaluation instrument for pharmaceutical substances. The aim of this instrument is to provide insight into the risk assessment when handling high-risk medicinal products in pharmacies, and to provide advice on how to reduce the risks.

RiFaS assesses hazard levels based on the intrinsic properties of substances and the level of exposure to this substance during their preparation. It divides hazards into five hazard groups based on human toxicological and pharmacological data:

- OELs
- Carcinogens, mutagens, reprotoxic (CMR) substances list of the Dutch Ministry of Social Affairs and Employment
- Hazard statements
- Therapeutic doses
- Human toxicological information (including side effects)

Cross-examining the hazard group and exposure, creates a **risk matrix** indicating three risk levels to workers (small, moderate, and high).

To evaluate the risks, the instrument asks questions about working conditions in the workplace, such as the presence of isolators, workbenches, intermediate extraction, and ventilation. If specific working conditions are not present in the workplace, the instrument provides advice to pharmacy staff to take additional measures or not to perform the procedure.

The instrument is available on a website [86] and the public pharmacy sector in the Netherlands can access it for free. RiFaS is part of the Health and Safety Catalogue. [87]

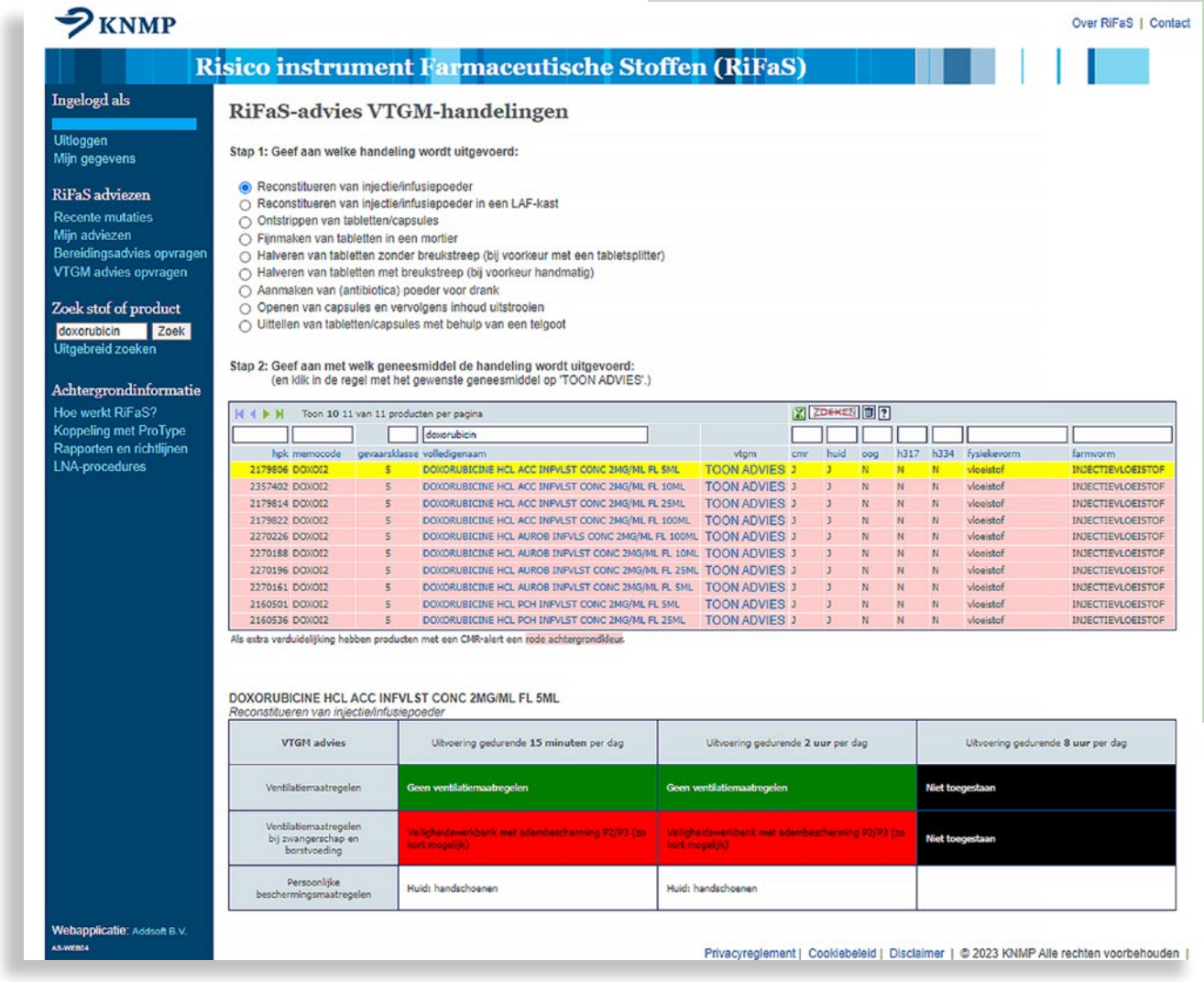
85 Directive 92/85/EEC, Article 5

86 RiFaS - Risk Instrument for Pharmaceutical Substances, https://www.rifas.nl/

87 In an occupational health and safety catalogue, employers and employees take the initiative to describe how they will meet the government's target regulations for healthy and safe working. A list of the tested catalogues is kept in the Health and Safety Catalogue Database, which is updated annually. http://www.arboportaal.nl/externe-bronnen/arbocatalogi

An example of the information available in the RiFaS system is provided below.

Figure 4-2: An example of the information available in RiFaS (Risk Instrument for Pharmaceutical Substances). Reproduced with permission from RiFaS.



4.4 HMP risk management plan

4.4.1 Hierarchy of controls

A HMP risk management plan should be developed. It must be in line with the hierarchy of controls in Directive 2004/37/EC, see Box 4-2, and Directive 89/931/EEC. As patient's health should never be compromised[88], it is not usually possible to replace an HMP with a substance, mixture or process which is not dangerous or is less dangerous to workers' health or safety. An example of a template for a

[88] Recital 12 of Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work https://eur-lex.europa.eu/eli/dir/2022/431

risk assessment in an HMP administration setting is included in Annex 2. Where the risks cannot be avoided or sufficiently limited by technical means of collective protection or by measures, methods or procedures of work organisation, PPE must be used[89]; advice about selecting the PPE is provided in Annex 4. An example approach for the use of Occupation Exposure Bands (OEBs) can be found in Annex 6.

Box 4-2: Hierarchy of controls in the carcinogens, mutagens, and reproductive substances directive (CMRD) (Articles 4 and 5 of the CMRD)

Article 4

Reduction and replacement

1. The employer shall reduce the use of a carcinogen, mutagen or reprotoxic substance at the place of work, in particular by replacing it, in so far as is technically possible, by a substance, mixture or process which, under its conditions of use, is not dangerous or is less dangerous to workers' health or safety, as the case may be.

2. The employer shall, upon request, submit the findings of his investigations to the relevant authorities.

Article 5

Prevention and reduction of exposure

1. Where the results of the assessment referred to in Article 3(2) reveal a risk to workers' health or safety, workers' exposure must be prevented.

2. Where it is not technically possible to replace the carcinogen, mutagen or reprotoxic substance by a substance, mixture or process which, under its conditions of use, is not dangerous or is less dangerous to health or safety, the employer shall ensure that the carcinogen, mutagen or reprotoxic substance is, in so far as is technically possible, manufactured and used in a closed system.

3. Where a closed system is not technically possible, the employer shall ensure that the level of exposure of workers to the carcinogen, mutagen or non-threshold reprotoxic substance[90] is reduced to as low a level as is technically possible.

3a. Where it is not technically possible to use or manufacture a threshold reprotoxic substance[91] in a closed system, the employer shall ensure that the risk related to the exposure of workers to that threshold reprotoxic substance is reduced to a minimum.

3b. The employer shall, with regard to reprotoxic substances other than non-threshold reprotoxic substances and threshold reprotoxic substances, apply paragraph 3a of this Article. In such a case, when carrying out the risk assessment referred to in Article 3, the employer shall duly take into account the possibility that a safe level of exposure for workers' health for such a reprotoxic substance might not exist and shall lay down appropriate measures in that regard.

4. Exposure shall not exceed the limit value of a carcinogen, mutagen or a reprotoxic substance as set out in Annex III.[92]

89 Directive 89/656/EEC, Article 3

90 According to Directive 2004/37/EC, a 'non-threshold reprotoxic substance' is a reprotoxic substance to which there is no safe level of exposure for workers' health and which is identified as such in the notation column of Annex III of Directive 2004/37/EC.

91 According to Directive 2004/37/EC, a 'threshold reprotoxic substance' is a reprotoxic substance for which a safe level of exposure exists below which there is no risk to workers' health and which is identified as such in the notation column of Annex III of Directive 2004/37/EC.

92 This refers to Annex III of Directive 2004/37/EC, not to Annex 3 of this guide.

Box 4-2: Hierarchy of controls in the carcinogens, mutagens, and reproductive substances directive (CMRD) (Articles 4 and 5 of the CMRD)

5. Wherever a carcinogen, mutagen or reprotoxic substance is used, the employer shall apply all the following measures:

(a) limitation of the quantities of a carcinogen, mutagen or reprotoxic substance at the place of work;

(b) keeping as low as possible the number of workers exposed or likely to be exposed;

(c) design of work processes and engineering control measures so as to avoid or minimise the release of carcinogens, mutagens or reprotoxic substances into the place of work;

(d) evacuation of carcinogens, mutagens or reprotoxic substances at source, local extraction system or general ventilation, all such methods to be appropriate and compatible with the need to protect public health and the environment;

(e) use of existing appropriate procedures for the measurement of carcinogens, mutagens or reprotoxic substances, in particular for the early detection of abnormal exposures resulting from an unforeseeable event or an accident;

(f) application of suitable working procedures and methods;

(g) collective protection measures and/or, where exposure cannot be avoided by other means, individual protection measures;

(h) hygiene measures, in particular regular cleaning of floors, walls and other surfaces;

(i) information for workers;

(j) demarcation of risk areas and use of adequate warning and safety signs including 'no smoking' signs in areas where workers are exposed or likely to be exposed to carcinogens, mutagens or reprotoxic substances;

(k) drawing up plans to deal with emergencies likely to result in abnormally high exposure;

(l) means for safe storage, handling and transportation, in particular by using sealed and clearly and visibly labelled containers;

(m) means for safe collection, storage and disposal of waste by workers, including the use of sealed and clearly and visibly labelled containers.

Source: Directive 2004/37/EC (consolidated version published 05/04/2022)[93]

4.4.2 Record risk assessment and plan

The risk assessment process should be recorded, and a HMP risk management plan should be developed. The HMP risk management plan should typically include the following information:

- Names and roles of people involved
- Key dates for action to be taken
- Dates and contents of previous HMP risk management plans, for comparison
- Process of risk assessment
- Workers, locations and activities considered

[93] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

- HMPs considered
- Hazard information about HMPs (in a register)
- Health surveillance to detect early and reversible signs of occupational diseases, see section 7
- Control measures implemented
- Reasoning for the (effectiveness of) control measures
- Hazards and risks identified
- Likelihood of adverse health effects

4.4.3 Review risk assessment frequency

The risk assessment and associated HMP risk management plan must be reviewed regularly.[94] The frequency of the risk assessment review should be agreed, for instance every year or every two years. In addition to the regularly scheduled reviews, a risk assessment review should take place when any change occurs that may affect workers' exposure to HMPs. These typically include:

- Incident or near miss
- New illness or symptoms reported
- New HMPs
- Changes in working practices, processes, and operating procedures relating to HMPs
- New administration techniques relating to HMPs
- Change in duration of workers' exposure to HMPs
- Increased use of HMPs
- New evidence about HMPs and their impact on workers' health

Establishing a causal link between ill-health and occupational exposure, such as attributing new illnesses to HMPs, can be challenging. Nevertheless, an HMP risk assessment plan should encompass recording any new illnesses or symptoms (such as allergic reactions and anaphylactic shocks) that could be related to HMPs. The results of health surveillance, see section 7, should also be used to assess the risks and make amendments to the risk assessment processes accordingly.

4.5 Review and revise

When reviewing risk assessment processes, procedures and strategies, the following aspects typically should be specified:

- Roles and responsibilities of staff members during the review
- Timeframe and frequency of review (date and how often)
- Scope of review, linked to the key performance indicators, focusing on:
  - Effectiveness: Does the risk assessment produce intended results of eliminated or reduced risk?
  - Efficiency: Does the risk assessment produce the results of eliminated or reduced risk in an optimal way?
- Method of review, outlining how to assess and evaluate risks
- Identification and evaluation of incidents and near misses
- Outcomes and effect of the review, including any follow-up actions

Following the review, all risk assessment processes, procedures and strategies should be revised accordingly, if necessary.

[94] Directive 2004/37/EC, Article 3(2)

4.6 Record keeping

The employer should store the key documents in a dedicated place and make them accessible to the extent needed and/or required for health & safety of workers whilst complying with the relevant data protection requirements. These documents typically include:

- Risk assessment documents
- Register of HMPs
- HMP risk management plan
- Register of all incidents, near misses and health surveillance results
- Up-to-date list of all individual workers that the risk assessment indicates are at risk

Record keeping must comply with any applicable national legislation or guidance which can vary considerably.

4.7 Summary of advice in section 4

Introduction

- The purpose of the risk assessment is to enable decisions to be made about appropriate risk management measures, training, exposure assessment and health surveillance, as may be required by legislation.

Who is responsible for risk assessment?

- The responsibility for the risk assessment of hazardous medicinal products (HMPs) and for developing and implementing the HMP risk management plan lies with the employer.[95]

Scope

- Risk assessments must be undertaken for all locations and activities where workers are likely to be exposed to HMPs.[96]
- When conducting a risk assessment, the first step is to identify the hazards of the HMPs.
- The next step includes assessing whether the hazard is a risk. This includes considering, for example, the locations, activities and control measures where HMPs are used, the workers exposed to HMPs, workers at greater risk – both male and female workers considering pregnancy, female workers who are pregnant, female workers who are breastfeeding, and young workers.
- The risk assessment should evaluate the likelihood of adverse health effects at the assessed exposure levels.

HMP risk management plan

- The risk assessment process should be recorded, and a HMP risk management plan should be developed. The HMP risk management plan must be in line with the hierarchy of controls in Directive 2004/37/EC and Directive 89/391/EEC, see section 4.4.1.[97]

Review and revision of risk assessment

- The risk assessment and associated HMP risk management plan must be reviewed regularly.[98] The frequency of the risk assessment review should be agreed, for instance every year or every two years. In addition to the regularly scheduled reviews, a risk assessment review should take place when any change occurs that may affect workers' exposure to HMPs.

95 Directive 89/391/EEC, Articles 6 and 9; Directive 2004/37/EC, Articles 3-5
96 Directive 2004/37/EC, Article 3
97 Directive 2004/37/EC, Articles 4-5; Directive 89/391/EEC, Article 6
98 Directive 2004/37/EC, Article 3(2)

5

Exposure assessment

5.1 Introduction

Workers' exposure to hazardous medicinal products (HMPs) must be assessed at regular intervals or when there are changes to procedures, processes or HMPs used.[99] Worker exposure can be measured by means of workplace monitoring or biomonitoring, or a combination of both approaches. Modelling may also have a role as a complementary approach.

Workplace monitoring should be a part of the risk assessment, see section 4, and should be discussed with workers (e.g. nurses and pharmacists) or workers' representatives involved. This defines future exposure assessment, such as the surfaces to sample, and the workers to engage in any biomonitoring campaigns.

5.2 Who is responsible for exposure assessment?

The responsibility for exposure assessment always lies with the employer.[100] The employer may designate these tasks to in-house workers or enlist the assistance of external services or persons, which should typically have the following competencies (whilst complying with any applicable national legislation or guidance):

- Knowledge, skills and experience in occupational safety and health (OSH) such as occupational hygiene and exposure assessment
- Experience in planning and implementing exposure assessment sampling strategies
- Understanding of HMPs, workplace, tasks undertaken, how and when exposure can happen, and health & safety regulations
- Appropriate authority and seniority level

The employer must ensure that the designated in-house workers or external services or persons include sufficient people to organise adequate exposure assessment.[101]

Workers should be informed, see section 3.4, about the monitoring (workplace and/or bio) including the monitoring plan, the actual monitoring, the results, the personal consequences, the follow-up actions, and revisions to the monitoring plan. The actual monitoring should be unannounced to avoid biassing the results. During the whole process, workers should be able to contact the designated person or their delegate to ask questions.

5.3 Guidance for the exposure assessment

The European standard EN-689: 2018 provides a strategy for an exposure assessment, which was designed to assist with the determination of whether occupational limit values for inhalation of chemical agents are met.[102] But the strategy can also be applied to all HMP exposure routes: the strategy's occupational exposure assessment process is shown in Figure 5-1.

[99] Directive 2004/37/EC, Article 3(2); see also Directive 98/24/EC, Article 6(4), for chemical agents
[100] Directive 2004/37/EC, Article 3
[101] Directive 89/391/EEC, Articles 7(1) and 7(5)
[102] It should be noted that reliance on a standard may not always guarantee the fulfilment of legal requirements. The full text of the standard is not available free of charge.

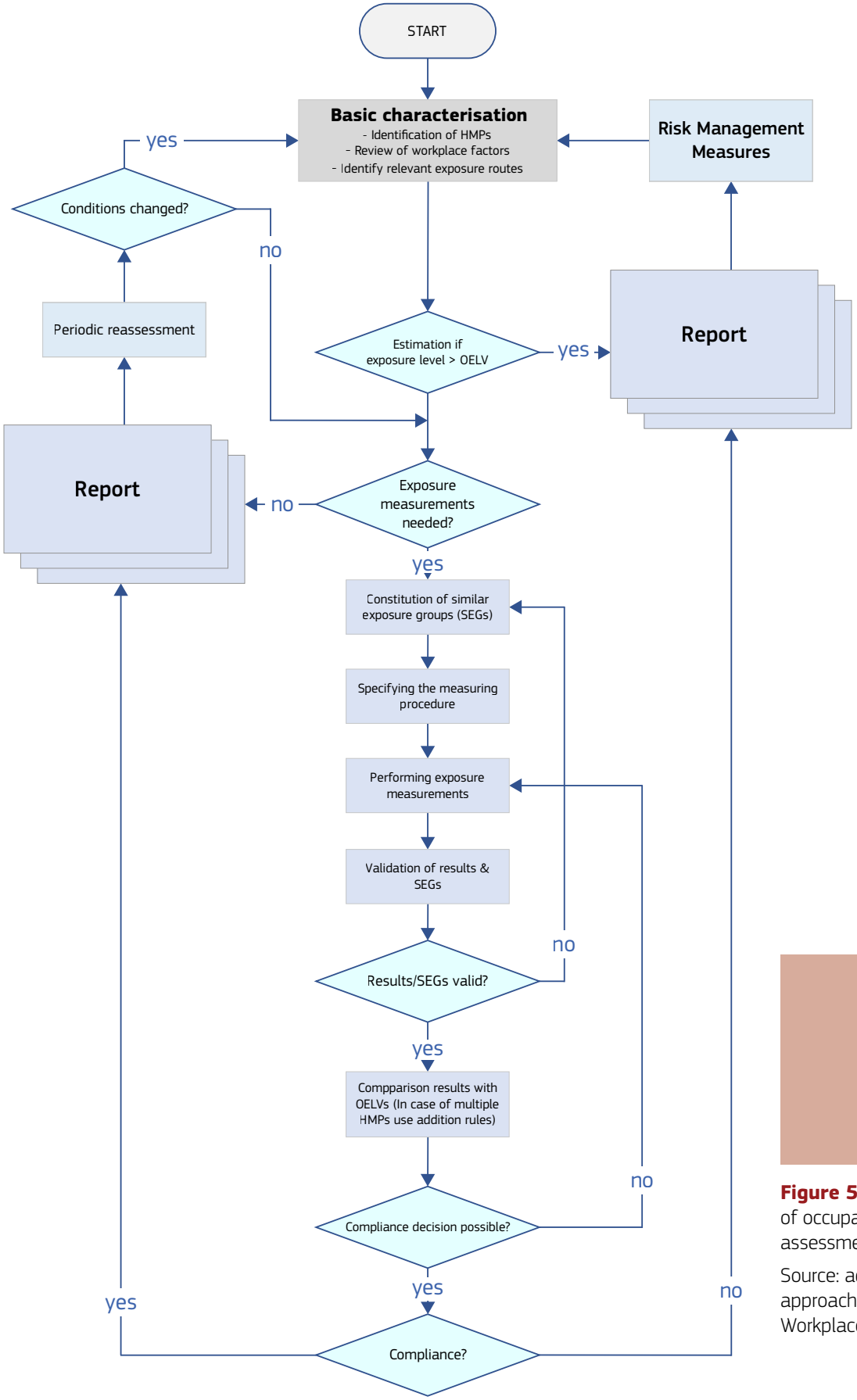


Figure 5-1: Overview of occupational exposure assessment process

Source: adapted from the approach of EN 689:2018 Workplace exposure [103]

[103] EN 689:2018, Annex C, Workplace exposure - Measurement of exposure by inhalation to chemical agents - Strategy for testing compliance with occupational exposure limit values (available against payment). Also summarised in https://www.arbeidshygiene.nl/-uploads/files/insite/sessie-t-fransman.pdf

To assess exposure, Annex A of EN 689: 2018[104] gives guidance when measurements are advisable or if other approaches of assessment may be used:

- Reasonable worst-case measurements
- Measurements of technical parameters (ventilation rate)
- Calculation of exposure (using appropriate models or algorithms)
- Comparison with other workplaces
- Control banding approaches
- Good practice guidance for defined branches or tasks

When simultaneous occupational exposure to several HMPs needs to be assessed, Annex C of EN-689: 2018[105] gives multiple suggestions how to conduct such assessments for chemical agents.

In terms of frequency of monitoring exposure to HMPs, it is recommended to implement a monitoring programme that is based on EN 689:2018.

A monitoring programme for assessment of exposure to HMPs should:

- be conducted at least annually. The frequency of the measurements should be sufficient to capture any potential increase in exposure of all workers potentially exposed to HMPs;
- be based on relevant standard methodologies or protocols;
- ensure a sufficiently low limit of quantification.

The information gathered via the measurements and related contextual information (relevant workplace factors that can influence exposure) should be used to confirm the effectiveness of the control measures and the cleaning programme in place. If needed, introduce additional control measures to further reduce workplace exposure to HMPs to a level as low as technically feasible.

While doing so, the employer should also review and, if needed, update the assessment of the combined exposure for the different groups of workers (called Similar Exposure Groups in EN 689:2018). The monitoring results should be used to further ensure that the application of control measures at the workplace is in accordance with the hierarchy of controls.

The frequency of measurements may be reduced, once it is demonstrated that exposure of workers has been reduced to as low a level as technically possible and that the risk management measures and operational conditions corresponding to the specific exposure scenarios function appropriately. A guidance for decreasing the frequency of measurements can be found in Annex I of the standard EN 689:2018.

Where the frequency of a monitoring programme has been reduced, any subsequent changes to the operational conditions or risk management measures that may affect the exposure of workers to HMPs, should be assessed by monitoring to demonstrate that exposure of workers continues to be reduced to a level as low as technically possible.

Exposure assessments need to be performed by a qualified person who is sufficiently trained and experienced in occupational hygiene principles, working and measurements techniques, see section 5.2.

[104] EN 689:2018, Annex A, Workplace exposure - Measurement of exposure by inhalation to chemical agents - Strategy for testing compliance with occupational exposure limit values (available against payment)

[105] EN 689:2018, Annex C, Workplace exposure - Measurement of exposure by inhalation to chemical agents - Strategy for testing compliance with occupational exposure limit values (available against payment)

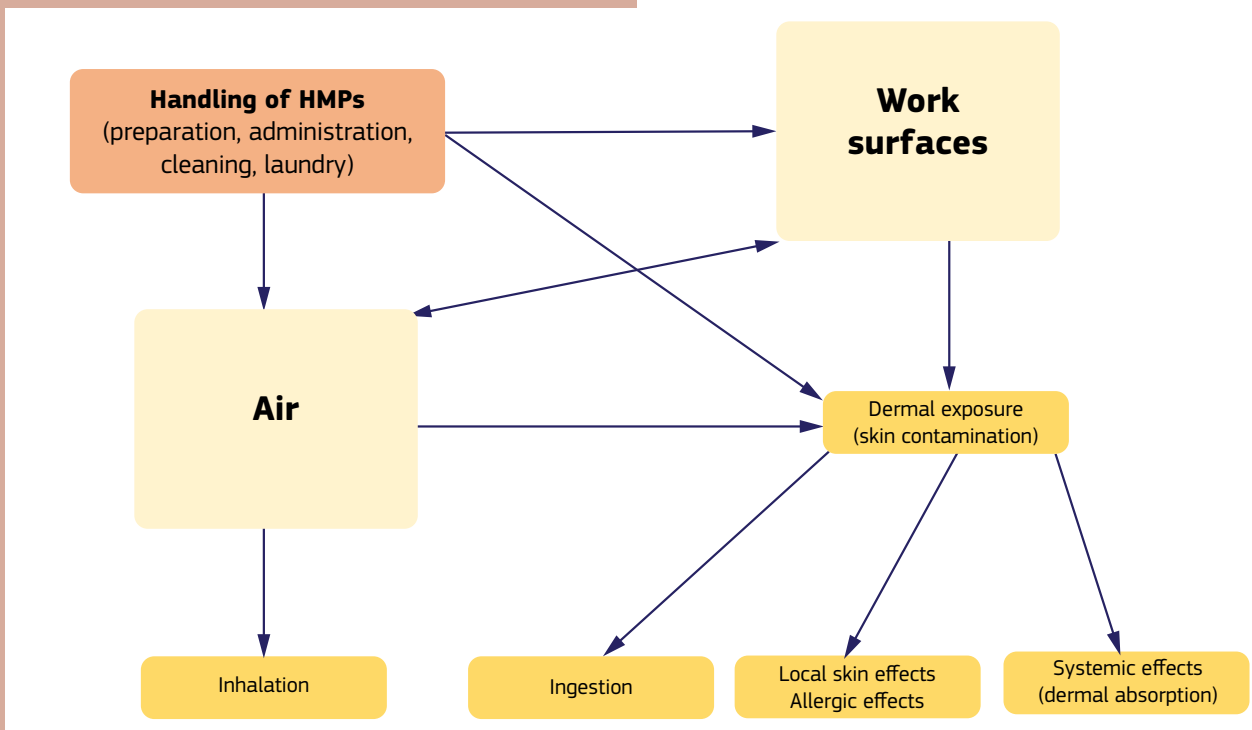
5.4 Information on exposure route(s)

In HMP production, exposure can occur via:

- Inhalation
- Skin
- Ingestion

In downstream sectors, such as hospitals and pharmacies, dermal exposure is the key exposure route. When suitable risk management measures are in place to prevent exposure by inhalation, exposure during HMP preparation and administration will occur mainly by dermal exposure, due to the contact with contaminated workplace surfaces. Exposure by inhalation might still happen in situations where powders are handled such as weighing and dissolving HMPs, production of capsules, crushing tablets, and incidents with spills. Such activities will mainly be performed in the pharmaceutical industry and in hospital pharmacies. Exposure by ingestion will be negligible as drinking and eating must be forbidden[106] during the handling of HMPs. However, hand-to-mouth contact may still result in exposure by ingestion after touching contaminated surfaces, see Figure 5-2.

Figure 5-2: Exposure pathways for HMPs adapted from Jahn et al, 2015[107]



[106] Directive 2004/37/EC, Article 10(1)(a)
[107] Steven D. Jahn, William H. Bullock and Joselito S. Ignaciao, (2015), A strategy for assessing and managing occupational exposures, Fourth edition, AIHA 2015

Dermal exposure can be defined as the amount of a substance that comes into contact with the skin, the outer boundary of the body. Simplified, dermal exposure can be seen as skin contamination. The effects of dermal exposure however are a complex system. Dermal exposure can lead to various reactions in the body:

- The substance can pass through the skin barrier (dermal absorption) and can injure individual organs or groups of organs. These reactions are also called systemic effects. The skin barrier can be affected by skin irritants and skin diseases enhancing dermal adsorption of substances.
- Dermal exposure can lead to local effects, such as skin irritation and dermatitis.
- Dermal exposure can cause allergic skin reactions through complex immune system responses that can then lead to reactions at, near and far from the skin-substance contact site.

Control measures to avoid dermal exposure are put in place for a variety of reasons to prevent spreading of the HMPs (contamination), to avoid the possibility of local or allergic effects and/or to avoid systemic effects by dermal absorption. Since for many HMPs it is relatively unknown if there are risks for local or systemic health effects, it is important to use appropriate protective gloves and clothing when handling HMPs.

5.5 Workplace monitoring

5.5.1 Introduction

Workplace monitoring, also known as occupational hygiene monitoring, is used for measuring substances such as HMPs in the working environment.

For information on the different exposure routes in relation to HMPs, see section 5.4.

Workplace monitoring of HMPs is mostly performed by surface wipe sampling as the skin is the main exposure route. The choice of the surfaces or objects to be sampled can be based on the observed everyday activities and should include surfaces and objects likely to be contaminated and/or touched by workers. The sampling strategy should be defined based on the objectives of the monitoring and the HMP risk management plan, see section 4.4.

Other workplace monitoring options are skin pad tests (Fransman, 2004)[108] and hand rinsing (Crul, 2020)[109] to measure exposure to HMPs. However, both methods are complex to perform in practice, not validated, and therefore not suitable for routine monitoring.

General ISO and CEN standards (ISO/TR 14294:2011, CEN TR 15278, CEN TS 15279)[110] are available for measurement of dermal exposure to chemicals but studies specific for HMPs are lacking.

Air monitoring may be valid in case of nebulising of HMPs in lung treatment, handling laundry and HMP powders.

5.5.2 Surface wipe sampling

Surface wipe sampling is generally performed by applying a liquid on a defined surface or object. With a tissue, the liquid is spread over the entire surface, and finally all liquid is removed via absorption on the tissue. Alternatively, the liquid is applied on the tissue, and the pre-wetted tissue is used to wipe the surface or object. The tissue is collected in a container and sent to a laboratory for analysis to determine the presence (or not) of one or several HMPs. As surface areas may differ between samples, the contamination is reported in ng/cm^2 to enable comparison of the levels of contamination between the surfaces, and to

[108] Fransman W. et al, (2004), Occupational dermal exposure to cyclophosphamide in Dutch hospitals: A pilot study, Ann Occup Hyg 2004; 48(3): 237-244.
[109] Crul M. et al, (2020), Occupational exposure of pharmacy technicians and cleaning staff to cytotoxic drugs in Dutch hospitals, J Occup Environ Hyg 2020; 17: 343-352.
[110] ISO/TR 14294: 2011 Workplace atmospheres- Measurement of Dermal Exposure Principles and Methods and
CEN TR 15278 Workplace Exposure - strategy for the evaluation of dermal exposure and
CEN TS 15279 Workplace exposure - measurement of dermal exposure - principles and methods

Figure 5-3:
A worker collecting surface contamination samples at the Masaryk Memorial Cancer Institute, Czech Republic

compare with other (reference) studies. Hence, it is important to record the area of the surface wiped for each wipe sample.

For some HMPs, quick tests are available, and laboratory analysis is not needed. The results are available in a few minutes, but the test only indicates if the specific HMP is detected or not. No amount or concentration are indicated.

Surface wipe sampling kits including analysis are commercially available.

As surface wipe sampling is used for workplace monitoring, the sampling reflects the period of potential exposure to HMPs. Therefore, the sampling should be performed at the end of the handling of HMPs and not after cleaning (unless the objective of surface wipe sampling is to validate cleaning procedures).

For practical reasons, it is not possible to measure all HMPs. A selection can be made based on the most frequently used HMPs. The selected HMPs can be considered as markers for all HMPs. Surface wipe sampling can generally be used for all handling activities during all stages of the lifecycle as long as the surface is easy to wipe: carpets are not suitable.

Surface wipe sampling can also be applied for other purposes, such as:

- Cleaning validation (sampling before and/or after cleaning) (Crul, 2018)[111]
- Validation of adapted working procedures and techniques (intervention) (Korczowska, 2020)[112]
- After leakages and spills (incidents)

Surfaces for monitoring should be selected based on the risk assessment, see section 4. Potential surfaces for monitoring include:

- Surfaces and objects such as working surfaces, carts, floors, doorknobs, handles, HMP vials, prepared infusion bags, patient chairs, telephones, and packages (primary and secondary)

Examples of frequently contaminated surfaces in a pharmacy/HMP preparation room, hospital oncology ward, staff room, and a hospital toilet are shown on the next two pages.

[111] Crul M, Simons-Sanders K., (2018), Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies, J Oncol Pharm Practice 2018; 24: 483-489.

[112] Korczowska E. et al, (2020), Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries – results of the MASHA project, Eur J Oncol Pharm 2020; 3(2): 1-9.

Figure 5-4:

Examples of frequently contaminated surfaces in a pharmacy/HMP preparation area

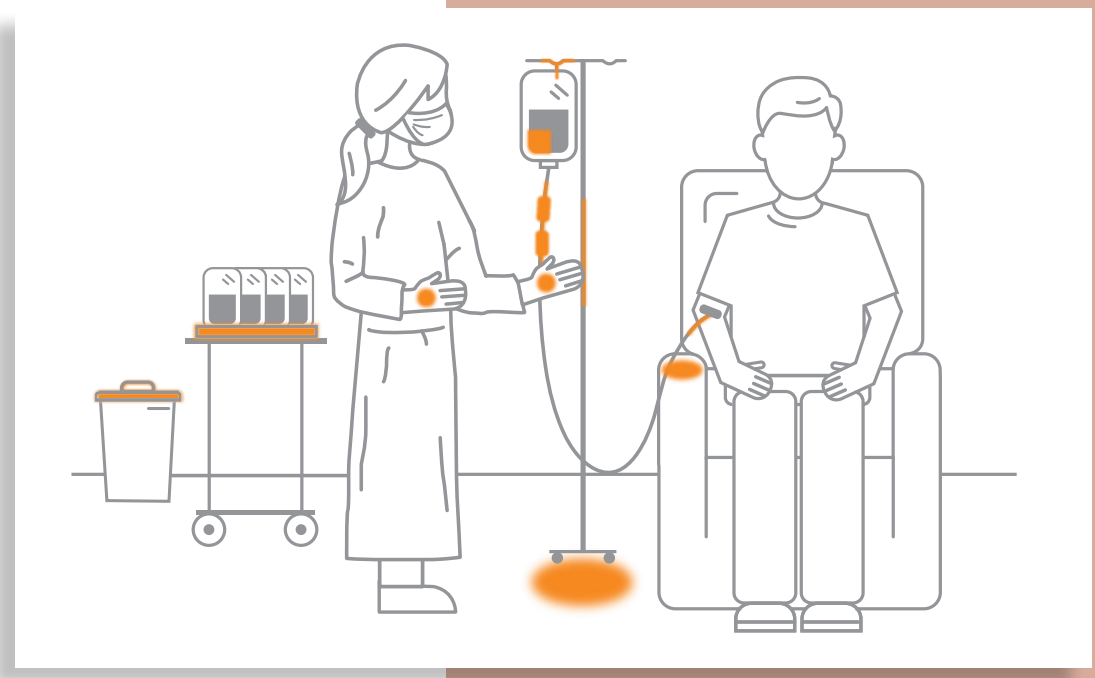


Figure 5-5:

Examples of frequently contaminated surfaces in IV administration

Figure 5-6:

Examples of frequently contaminated surfaces in hospital staff room

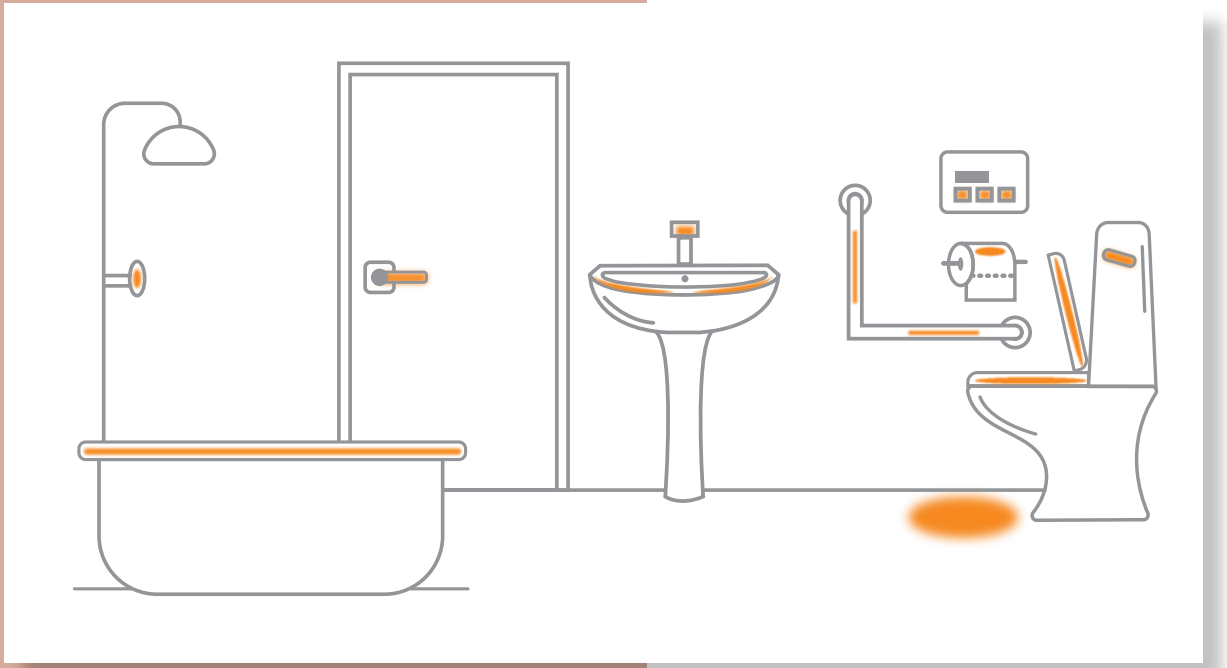


Figure 5-7:

Examples of frequently contaminated surfaces in a hospital toilet

There are no official limit values for surface contamination with HMPs. However, the results can in general be compared with results from other studies (benchmarking) (Schierl, 2009)[113]. They can also be compared with results from previous sampling of the same surfaces (longitudinal studies) (Chauchat, 2019)[114]. Some studies present a guidance value or safe reference value of 0.1 ng/cm^2 (Kiffmeyer, 2013; Sessink, 2011)[115] or alert and action levels (Crul, 2018[111]).[116] The alert and action levels refer to surface wipe sample results after cleaning and are used to validate the cleaning procedure. The monitoring plan defines the reference value that should be used.

In a review of publications on wipe-sampling, a target level is mentioned for cyclophosphamide of 0.1 ng/cm^2 (Connor, 2016)[117]. Based on the target level an action level can be defined of 1.0 ng/cm^2 (10 times the target level). Both levels can be used as a benchmark for all HMPs until more specific or reference values are published.

A wipe sampling monitoring programme based on the approaches in section 5.3 would be:

- Assess the exposure at least once a year using wipe sampling of the relevant HMPs (the ones that are used)
- If the results of the benchmark indicate that you are above the action-level, increase the frequency above once a year: introduce risk management control measures and use the monitoring programme to evaluate their effectiveness
- If the results are between the action level and the target level, determine an adequate interval but at least follow the once a year interval
- If the results are below the target level, consider decreasing the interval to every two or three years. Use other forms of assessment (see Annex A of the EN 689) to assess workers exposure and risks at least every year
- If measurements if changes in the workplace are introduced such as changes in procedures, techniques or HMPs used, increase the frequency of assessment

5.5.3 Air monitoring

Air monitoring is based on the collection of HMP particles or aerosols present in the working environment. Although not used as frequently as surface wipe sampling, air monitoring can be applied during specific processes when particles and aerosols are expected in the air such as weighing and dissolving HMPs, production of capsules, crushing tablets or inhalation administration of HMPs.

Air sampling is performed by the collection of ambient air with a pump at a controlled flow rate defined in the method. The sucked air is passed through a filter, and HMP particles are collected on the filter. After sampling, the filter is extracted and analysed for HMPs at a laboratory. The sampling time is registered, and in combination with the flow, the total volume of air collected can be calculated. Sampling time should reflect the actual handling activities.

Air sampling can be performed as personal air sampling (directly within the breathing zone of the worker) or as stationary air sampling somewhere in the working environment preferably close to potential source(s) of exposure.

The measurements can be compared with official published occupational exposure limits (OELs) or those provided by the manufacturer/supplier in safety data sheets (SDSs) or other documentation.

At the time of writing this guide, there are no EU OELs for HMPs. There appear to be three Member States with OELs for some HMPs: the Netherlands[118], Poland[119] and Bulgaria[120]. The HMPs that appear to have OELs in some or all of these Member States are: arsenic

[113] Schierl R et al, (2009), Guidance values for surface monitoring of antineoplastic drugs in German pharmacies, Ann Occup Hyg 2009; 53: 703–711.
[114] Chauchat L et al, (2019), Surface contamination with ten antineoplastic drugs in 83 Canadian centers, J Oncol Pharm Practice 2019; 25: 1089-1098.
[115] Kiffmeyer TK et al, (2013), Application and assessment of a regular environmental monitoring of the antineoplastic drug contamination level in pharmacies – The MEWIP project, Ann Occup Hyg 2013; 57: 444–455; Sessink PJM, (2011),Environmental contamination with cytostatic drugs, Safety considerations in oncology pharmacy, Special edition Fall 2011: 3-5. PPM Europe.
[116] Crul M, Simons-Sanders K., (2018), Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies, J Oncol Pharm Practice 2018; 24: 483-489.
[117] Connor, T.H. et al, Surface wipe sampling for antineoplastic (chemotherapy) and Other hazardous drug residue in healthcare settings: Methodology and recommendations. Journal of Occupational and Environmental Hygiene, 13:9, 658-667 (2016).
[118] NL Working conditions regulation https://wetten.overheid.nl/BWBR0008587/2020-01-17#BijlageXIII.
[119] Page 81 in COWI (2021): Study supporting the assessment of different options concerning the protection of workers from exposure to hazardous medicinal products, including cytotoxic medicinal products, https://op.europa.eu/en/publication-detail/-/publication/f43015ec-a24f-11eb-b85c-01aa75ed71a1
[120] Ordinance no 13 of 30 December 2003 on the protection of workers from the risks related to exposure to chemical agents at work https://www.lex.bg/laws/ldoc/2135477597

trioxide, azathioprine, cisplatin, cyclophosphamide, cyclophosphamide monohydrate, dacarbazine, fluorouracil, hydroxycarbamide, metronidazole and procarbazine. However, in the case of possible HMP exposure, the inexistence of an OEL does not affect the obligation of implementing risk management measures aiming to prevent and/or minimise exposure.

OELs are necessary to provide a reference to evaluate the results of the personal air monitoring according to EN 689:2018. If the industry does not provide OELs or there are no formal OELs set by the authorities then the organisation is advised to develop its own reference values for inhalation exposure.

5.6 Biomonitoring

In addition to workplace monitoring, biomonitoring can be used to measure the potential exposure of the workers to HMPs. Biomonitoring is a quantitative approach for assessing workers' exposure by analysis of HMPs and/or their metabolites in body fluids such as blood and urine. Biomonitoring integrates HMP exposure from different sources and by different routes of uptake: inhalation, dermal absorption and uptake by indirect routes such as hand-to-mouth contact. Depending on the sampling strategy, it is also possible to distinguish the degree of exposure between the different exposure routes. It provides a different and complementary approach compared to workplace monitoring such as monitoring of surface contamination by wipe sampling. For some HMPs biomonitoring is available (Hon, 2015[121]; Korczowska, 2012[122]; Ndaw, 2010[123]). In a few intervention studies, the combination of surface wipe sampling and biomonitoring was applied (Kibby, 2017[124]; Tanimura 2009[125]; Wick, 2003[126]; Yoshida, 2009[127]). Advances in analytical chemistry may offer increased opportunities to use biomonitoring approaches.

5.7 Record keeping

The employer must keep an up-to-date list of the workers engaged in the activities for which an exposure to HMPs can pose a risk to workers' health or safety, indicating, if the information is available, the exposure to which they have been subjected[128], see section 4.3.2.2. These records must be kept for at least 40 years from the end of exposure for carcinogens and mutagens and five years for reprotoxic substances.[129]

These records are important for the risk assessments, see section 4.

Record keeping must comply with any applicable national legislation or guidance, which can vary considerably.

121 Hon C-Y et al, (2015), Antineoplastic drug contamination in the urine of Canadian healthcare workers, Int Arch Occup Environ Health 2015; 88: 933-941.
122 Korczowska E et al, (2012), Determination of cyclophosphamide in urine of hospital personnel occupationally exposed to antineoplastic drugs, Poster presentation at the European Conference of Oncology Pharmacy, Budapest, Hungary. 27-29 September 2012.
123 Ndaw S et al, (2010), Biological monitoring of occupational exposure to 5-fluorouracil: urinary α-fluoro-α-alanine assay by high performance liquid chromatography tandem mass spectrometry in health care personnel. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(27):2630–2634.
124 Kibby T., (2017), A review of surface wipe sampling compared to biologic monitoring for occupational exposure to antineoplastic drugs, J Occup Environ Hyg 2017; 14: 159-174.
125 Tanimura M, et al, (2009), An environmental and biological study of occupational exposure to cyclophosphamide in the pharmacy of a Japanese community hospital designated for the treatment of cancer, J Health Sci 2009; 55: 750-756.
126 Wick C et al, (2003), Using a closed-system protective device to reduce personnel exposure to antineoplastic agents, Am J Health-Syst Pharm 2003; 60: 2314-2320.
127 Yoshida J et al, (2009), Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment, Ann Occup Hyg 2009; 53: 153-160.
128 See Directive 2004/37/EC, Articles 12, 14 and 15
129 Directive 2004/37/EC, Article 15

5.8 Summary of advice in section 5

Introduction

- Workers' exposure to hazardous medicinal products (HMPs) must be assessed at regular intervals or when there are changes to procedures, processes or HMPs used.[130]
- Worker exposure can be measured by means of workplace monitoring or biomonitoring, or a combination of both approaches. Modelling approaches can also play a role as a complementary approach.

Exposure route(s)

- In HMP production, exposure can occur via inhalation, skin and ingestion.
- In downstream sectors, such as hospitals and pharmacies, dermal exposure is the key exposure route. However, exposure by inhalation might still happen in situations where powders are handled such as weighing and dissolving HMPs, production of capsules, crushing tablets, and incidents with spills. Such activities will mainly be performed in the pharmaceutical industry and in hospital pharmacies.
- Exposure by ingestion is negligible as drinking and eating must be forbidden[131] during handling HMPs. However, hand-to-mouth contact may still result in exposure by ingestion after touching contaminated surfaces.

Surface wipe sampling

- Surface wipe sampling is generally performed by applying a liquid on a defined surface or object. With a tissue, the liquid is spread over the entire surface, and finally all liquid is removed via absorption on the tissue. Alternatively, the liquid is applied on the tissue, and the pre-wetted tissue is used to wipe the surface or object. The tissue is collected in a container and sent to a laboratory for analysis to determine the presence (or not) of one or several HMPs.
- For practical reasons, it is not possible to measure all HMPs. A selection can be made based on the most frequently used HMPs.
- There are no official limit values for surface contamination with HMPs. However, the results can in general be compared with results from other studies (benchmarking) or with results from previous sampling of the same surfaces (longitudinal studies). Some studies present a guidance value or safe reference value of 0.1 ng/cm^2 or alert and action levels.

Air monitoring

- Air monitoring is based on the collection of HMP particles or aerosols present in the working environment. Although not used as frequently as surface wipe sampling, air monitoring can be applied during specific processes when particles and aerosols are expected in the air such as weighing and dissolving HMPs, production of capsules, and crushing tablets.
- The measurements can be compared with occupational exposure limits (OELs) provided by the manufacturer/supplier in the safety data sheet (SDSs) or official published OELs.
- At the time of writing this guide, there are no European OELs for HMPs. There appear to be at least three Member States with some OELs for HMPs.

Biomonitoring

- In addition to workplace monitoring, biomonitoring can be used to measure the potential exposure of the workers to HMPs. Biomonitoring is a quantitative approach for assessing workers exposure by analysis of HMPs and/or their metabolites in body fluids such as blood and urine. Biomonitoring integrates HMP exposure from different sources and by different routes of uptake. It is available for some HMPs.

Record keeping

- The employer must keep an up-to-date list of the workers engaged in the activities for which an exposure to HMPs can pose a risk to workers' health or safety, indicating, if the information is available, the exposure to which they have been subjected.[132] These records must be kept for at least 40 years from the end of exposure for carcinogens and mutagens and five years for reprotoxic substances.[133]

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130 Directive 2004/37/EC, Article 3(2); see also Directive 98/24/EC, Article 6(4), for chemical agents
131 Directive 2004/37/EC, Article 10(1)(a)
132 Directive 2004/37/EC, Articles 12, 14 and 15
133 Directive 2004/37/EC, Article 15

6

Education and training

Education develops a worker's knowledge base to underpin any activities the worker may later undertake. Academic studies for professions with a high risk of exposure to hazardous medicinal products (HMPs) should include education on HMPs.

Training concentrates on building specific skills. Any training which supports developing knowledge and understanding of HMPs is contributing to the worker's education. Training should include practice evaluation.

6.1 Who is responsible for training?

The responsibility for ensuring that workers who handle HMPs or might come into contact with HMPs are adequately trained, always lies with the employer.[134] These workers should be aware of the training available and should have completed it, see section 3.4. Workers' representatives with a specific role in protecting the safety and health of workers should be aware of the training available and must be entitled to complete appropriate training.[135] The employer may designate the training tasks to in-house workers or enlist the assistance of external services or persons, who should typically have the following competencies (whilst complying with any applicable national legislation or guidance):

- Knowledge, skills and experience to assess the training needs for all roles and develop the training programme
- Understanding of HMPs, workplace, tasks undertaken, how and when exposure can happen, and health & safety regulations
- Appropriate authority and seniority level

The employer must ensure that the designated in-house workers or external services or persons include sufficient people to assess the training needs, and to develop and implement the training programme.[136] The assistance of external services or persons does not discharge the employer from these responsibilities.[137]

All training providers should be experienced both in working with HMPs in the workplace and in the specific activities using HMPs to which the training relates.

Where appropriate, external training courses offered by professional organisations should have accreditation from the relevant authority and contribute to the workers continuous professional development.

Workers and/or their representatives must be consulted and allowed to take part in discussions also on questions relating to occupational safety and health training.[138]

[134] Directive 2004/37/EC, Article, 11; Directive 89/391/EEC, Article 12; see also Directive 98/24, Article 8, for chemical agents
[135] Directive 89/391/EEC, Article 12(3)
[136] Directive 89/391/EEC, Articles 7(1) and 7(5)
[137] Directive 89/391/EEC, Article 5(2)
[138] Directive 89/391/EEC, Article 11

6.2 Scope

6.2.1 Scope of the training

The objective of training about HMPs is to prevent and/or reduce[139] workers' exposure to HMPs. The training should cover the risks and safe use of HMPs during normal workplace activities including handling any waste that might contain HMPs, and also cover incidents such as spills. The level of training, instruction and information given to a worker should reflect their work activity and level of exposure to HMPs as is defined in the HMP risk management plan, see section 4.4.

Only workers who have received appropriate training should carry out work involving HMPs and associated waste: this applies to workers with roles listed in section 1.4. Staff working with HMPs should have their competency assessed after the initial training and subsequently at regular intervals such as annually.

HMP training must not be at the workers' expense or at that of the workers' representatives.[140] The training of workers must take place during working hours.[141] The training of workers' representatives must take place during working hours or in accordance with national practice either within or outside the undertaking and/or the establishment.[142]

6.2.2 Which workers need training (roles)

The workers with roles listed in section 1.4 who come into contact with HMPs should be trained in the safe use of HMPs if required by the HMP risk management plan, see section 4.4. This includes workers from external organisations or external persons (including casual, agency, or temporary workers, trainees and apprentices) providing any of the roles in section 1.2.2.

6.2.3 What is required?

Workers' training needs should be assessed by role and should typically consider:

- Level of risks found in the risk assessment, see section 4
- Activities carried out in the workplace
- Workers' roles
- Existing training provided and any evaluation of it
- Workers' level of education and training already received
- Delivery methods likely to be most effective (may differ by size of the organisation)

Based upon the training needs, a structured training programme should be developed to cover all roles, activities, and workplaces involving HMPs. The training needs and, therefore, the training programme relating to HMPs that is required, for example, for pharmacists or laundry workers are quite different.

The summary sheets in Annex 7 may also be a helpful training aid.

Workers should be encouraged to see education as an ongoing process, and attend in-house or external courses, workshops, seminars, and conferences.

139 See Directive 2004/37/EC, Article 5
140 Directive 89/391/EEC, Article 12(4)
141 Ibid
142 Ibid

6.3 Methods

6.3.1 How is it achieved?

The training is achieved through a structured education programme with different modules enabling workers with different roles and levels of risk to receive appropriate training, including practical training. There should be a core set of compulsory training for every worker that handles HMPs, or might come into contact with HMPs, to complete. The remaining HMP training should then also include activities specific to the worker's role and workplace.

Training should be easily understood by workers, in a format, manner and language that is accessible to workers. Written training materials should be provided to workers. If any workers might not be proficient in the language of the training or might have low levels of literacy, the training should be carefully developed to ensure that everyone understands it.

6.3.2 Core training

Core training should include at least (list not exhaustive):

- Identification of HMPs, see section 2
- HMPs labelling and packaging, see section 2
- Health risks of HMPs, including the additional risks due to tobacco consumption
- Rights of workers, including an individual risk assessment to assess exposure levels, see section 4
- Risk awareness, see section 3.4
- Personal protective equipment (PPE), what to use and why, and how to dispose of it, see Annex 4
- Personal hygiene such as hand washing, see section 11.1.7
- Access to first aid resources and location and use of safety stations (eyewash stations and showers)
- Written standard operating procedures (SOPs) including managing personal exposure
- Incident management (what to do in case of emergency (accidents, spills, and leakages) in combination with the use of the spill kit), see section 13.3
- Identification, handling and disposal of patient excreta contaminated with HMPs
- Storage, transport, treatment, and disposal of hazardous waste, including internal transport, see section 9

6.3.3 Additional training

Additional HMP training depends upon the role, activities and workplace of the worker but could typically include (list not exhaustive):

- Health and safety legislation
- Relevant aspects of waste management legislation
- Relevant aspects of the Agreement concerning the International Carriage of Dangerous Goods by Road (ADR)[143]
- Any other legislation such as Member State legislation
- Written SOPs
- Risk assessment process and HMP risk management plan, see section 4
- Responsibilities of different workers' roles in handling HMPs
- Identifying workplace hazards for exposure to HMPs and related waste
- Procedures for handling and transporting HMPs and related waste
- Procedures for internally transporting HMPs and patients being treated with HMPS in healthcare establishments

[143] UNECE: Agreement concerning the International Carriage of Dangerous Goods by Road 2021 https://unece.org/transport/publications/agreement-concerning-international-carriage-dangerous-goods-road-adr-2021

- Correct selection, use (putting on and taking off), cleaning, and disposal of PPE, see Annex 4
- Understanding and correct use of equipment during work activities
- Maintenance of equipment by workers during work activities
- Maintenance of equipment by maintenance workers; equipment such as ventilation filters, clean rooms, and drainage and sewage systems
- Receiving, unpacking, transporting, and storing HMPs
- Cleaning procedures, including how to clean reusable equipment (such as glassware)
- Laundry procedures
- Health surveillance, see section 7
- Workplace monitoring, see section 5.5
- Pregnancy, breastfeeding, and planned parenthood

Additional training related to specific life cycle stages can be found in:

- Preparation of HMPs, see section 10.2.3
- Administration of HMPs, see section 11.1.3
- Maintenance of equipment that may be contaminated by HMPs, see section 14.3.3
- Waste, see section 15.2.2

6.3.4 How often?

Training must take place at the following times[144]:

- New staff or workers returning to work after prolonged absence: immediately upon starting or returning to work, before exposure to HMPs. This should apply to all roles listed in section 1.4 that come into contact with HMPs
- Staff moving to a new role using HMPs: immediately upon changing role
- If new HMPs or equipment are introduced, or amendments made to processes: training should take place before they are introduced. This does not apply to HMPs in clinical trials

Training should also typically take place at the following times:

- All workers returning to work after prolonged absence should discuss whether they require refresher training immediately upon returning to work, before exposure to HMPs
- All workers handling HMPs should have an annual refresher course on incident management (spills)
- All workers handling HMPs should have refresher training on all aspects of HMPs relevant to their role every one to three years to maintain skills and awareness and ensure that all new HMPs and new equipment are included. The frequency depends upon the role and should be identified in the risk assessment, see section 4
- All workers should have regular competency checks, at least annually

All workers using HMPs should receive communications about training appropriate to their role, level of risk, activities, and workplace, see section 3.4.

[144] Directive 89/391/EEC, Article 12; Directive 2004/37/EC, Article 11; see also Directive 98/24/EC, Article 8, for chemical agents

6.4 Evaluate and revise

Several elements of training should typically be evaluated:

- What is the worker's feedback on the training and the trainers?
- What is the trainer's feedback on the worker?
- Is the worker competent at the end of training?
- Does the worker remain competent over time? Competency should be checked at least annually
- Are workers following the training in their work?
- Do the processes given in training actually reduce exposure? This should be checked using workplace monitoring, see section 5.5, before and after the training

Worker assessment could typically include testing their competency to:

- Define basic concepts and specific terms
- Complete tests or practical demonstrations, to show their understanding of processes
- Show how they would transfer their new skills and knowledge into the workplace

The evaluation should also consider any specific reasons to revise the training including:

- The introduction of new HMPs
- New or changed administration processes for HMPs
- Any other changes to working practices relating to HMPs

The evaluation of training should take place annually and be revised as necessary, based upon the information gathered above.

6.5 Record keeping

Records should be kept about the training course and about each worker completing the training. The data kept should typically include:

- Date of the training
- Content of training
- Name of trainer
- Signature of trainer to confirm they provided the training
- Names of the workers attending the session
- Signatures of the workers to confirm that they completed the training
- Feedback from workers on the training
- Training evaluations
- Assessment of competencies

Records about each training course should be held by the education provider. Records of all training completed by a worker should be held in their human resources file until they retire or leave employment.

Record keeping must comply with any applicable national legislation or guidance, which can vary considerably.

6.6 Summary of advice in section 6

Responsibility for delivering training

- The employer is always responsible for ensuring that workers who handle hazardous medicinal products (HMPs) or may come into contact with HMPs are adequately trained.[145] Workers and/or workers representatives must be consulted also on the matters related to training. [146]
- Representatives responsible for the health and safety of workers should be aware of the training available and must be entitled to complete appropriate training.[147]
- Training may be given by in-house trainers or external trainers with certain recommended competencies.
- The employer should ensure that trainers assess the training needs in order to develop and implement the training programme.
- Training providers should be experienced in working with HMPs and the specific activities for which they are providing training.

Scope

- The objective of training about HMPs is to prevent and/or reduce [148] workers' exposure to HMPs.
- The content of the training and level of training should reflect workers' activities and level of exposure according to their HMP risk management plan.
- Only workers who have received appropriate training should carry out work involving HMPs and associated waste.
- Workers or workers' representatives must not pay for HMP training, and training must take place during working hours.[149]
- Section 1.2.2 lists workers that should receive training if required by the HMP risk management plan, see section 4.4.
- Training needs should be assessed by role.
- A structured training programme should be developed to cover all roles, activities and workplaces involving HMPs.
- Education is an ongoing process.

Methods

- Workers should receive training according to their role and levels of risk, including practical training.
- A core set of compulsory training for every worker handling or potentially coming into contact with HMPs is recommended.
- Additional training should also be given on activities specific to the worker's role and workplace.
- Training should be easily understood and in an accessible format.
- There are certain specified times when training must be given to workers before exposure such as for new staff, after a prolonged absence, changing role, or if new HMPs or processes are introduced. [150]
- There are also recommended times when training should take place for example at least annual refresher courses and competency checks.

[145] Directive 89/391/EEC, Article 12
[146] Directive 89/391/EEC, Article 11
[147] Directive 89/391/EEC, Article 12(3)
[148] Directive 2004/37/EC, Article 5
[149] Directive 89/391/EEC, Article 12(4)
[150] Directive 89/391/EEC, Article 12; Directive 98/24/EC, Article 8, for chemical agents

Evaluation and revision of training

- Training should be evaluated annually, and training revised as necessary.
- Several elements of training should be evaluated.
- Worker assessment could typically include testing their competency.
- The evaluation should also assess whether the training should be revised.

Record keeping

- Records should be kept about training courses and each worker completing the training, according to national legislation or guidance.
- The education provider should hold records about each training course.
- A record of all training completed by a worker should be held in their human resources file until they retire or leave employment.

7

Health surveillance

7.1 Who is responsible for health surveillance?

Given that it is the Member States that are responsible for establishing the arrangements for carrying out health surveillance[151], employers should familiarise themselves with national legislation and/or guidance in their Member State to establish the extent of their responsibilities and obligations with regard to health surveillance. Health surveillance must always comply with national legislation and/or practices, including on the protection of personal data.[152]

7.2 Scope

7.2.1 Scope of health surveillance

Health surveillance must be arranged for workers exposed to hazardous medicinal products (HMPs) for whom the results of the risk assessment, see section 4, reveals a risk to health or safety.[153] The objective of health surveillance is to monitor and counsel these workers and identify any changes in their health status which may be attributed to the exposure.

Health surveillance can include detecting early and reversible signs of occupational diseases and contribute to promoting a safe and healthy working environment – to this end, it may be useful to collect as much relevant information as necessary for this purpose, provided that any restrictions on information collection established by legislation, including by the principle of data minimisation[154], are respected. Drawing on the results of the risk assessment, see section 4, the health surveillance programme should be specific to the type of exposure.

7.2.2 Which workers are at risk and may need health surveillance?

Health surveillance should be considered for all roles listed in section 1.4, i.e. those that come into contact with HMPs. The approach to health surveillance should take into account the results of the risk assessment, which identifies individuals with higher risks associated with the tasks that imply (higher) exposure and/or due to personal health conditions that may be exacerbated by exposure, see section 4. These differences imply that the health surveillance programme is adapted to each worker situation.

The risk assessment and HMP risk management plan could, for example, identify the following groups of workers:

- Workers who are suitable to undertake tasks assigned
    - The workers do not indicate a limitation and do not indicate they are unable to fully perform all tasks assigned to their position and comply with individual protection measures

[151] Directive 2004/37/EC, Article 14(1); Directive 89/391/EEC, Article 14; Directive 98/24/EC, Article 10(1), for chemical agents

[152] Directive 2004/37/EC, Article 14; Directive 89/391/EEC, Article 14; Directive 98/24/EC, Article 10, for chemical agents; see also Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation - GDPR), in particular Article 9, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02016R0679-20160504&qid=1674485543249

[153] Directive 2004/37/EC, Article 14 (1)

[154] Regulation (EU) 2016/679, Article 5(1)(c)

- Workers who are suitable but have limitations
  - Adapt their role to avoid tasks that exacerbate the workers' condition
- Workers that are at particular risk of developing adverse health conditions – worker's health condition makes them susceptible to ill health due to a health condition or sensitivity, such as:
  - Allergic to HMPs
  - Severe, extensive dermatological pathology
  - History of fertility issues
  - History of recurrent miscarriages
  - Immunosuppressed

7.2.3 What is involved?

A health surveillance programme should be developed and implemented to consider each type of role, and typically account for:

- Roles with higher potential exposure according to the risk assessment, see section 4
- Workers with previously known health conditions
- Both male and female workers considering pregnancy, female workers who are pregnant, and female workers who are breastfeeding

Where a worker is found to be suffering from an abnormality that is suspected to be the result of exposure to HMPs, it should be considered whether health surveillance should also be arranged for similarly exposed workers.[155] The risk assessment must then be reviewed to take account of this new information.[156]

These workers should be informed about the potential risks associated with exposure to HMPs[157], and, if needed and possible, alternative working solutions and conditions should be provided to accommodate the workers' needs. Those with higher risk should also consult a medical professional regarding the possible implications of exposure to their health.

As part of a health surveillance programme, some organisations may seek to obtain data on worker exposure and effects using biomonitoring (biomarkers of exposure and effect); employers are advised to familiarise themselves with the legislation and conditions in their Member State. There are some limitations in biomonitoring methods and the interpretation of the results may be challenging - they can be inconclusive or difficult to interpret. Biomarkers measuring (geno)toxic risk are under development but are not available for routine monitoring, yet. However, the anticipated future development of biomonitoring may facilitate its use for exposure assessment and health surveillance. Where biomonitoring is used, as good practice, it should be:

- Reproducible under the same conditions
- Sensitive
- Specific
- Cost effective/inexpensive
- Preferably non-invasive, and not cause distress or anxiety for those being tested
- Produce quantitative measurements

Medical practitioners undertaking health surveillance should identify and recognise when it is appropriate to seek additional advice about biomonitoring or other health surveillance issues to guarantee that the most recent knowledge available is used and put in practice.

155 Directive 2004/37/EC, Article 14(3)
156 Ibid
157 Directive 89/391/EEC, Article 10(1)

7.3 Methods

7.3.1 How is it achieved?

To facilitate health surveillance, baseline data and information should be collected by a medical practitioner for all workers undergoing health surveillance, prior to any exposure to HMPs. Health surveillance should subsequently be carried out at regular intervals.

Workers should be consulted to ensure the relevance of health surveillance efforts and encourage workers' active participation, see section 3.4.

7.3.1.1 Baseline health surveillance

Baseline monitoring could typically include collecting the following:

- Collection of demographic data
  - Name and unique Organisation ID
  - Date of birth
  - Gender
  - Address
  - Date commencing employment
  - Descriptive job title
  - Places of previous employments
- Occupational history
  - Work history, including previous work with HMPs, exposure and use of personal protective equipment (PPE)
  - Work history, including previous work with other CMRs, exposure and use of PPE
  - Previous or ongoing exposure to ionising radiation
  - Were or are suitable control measures in place to handle HMPs?
- Medical history (if relevant to the health risks associated with the relevant substances)
  - Any current symptoms
  - General health
  - Personal history of cancer
  - Family history of cancer, liver changes, disabilities related to chromosomal alterations in first relatives
  - History of asthma or other systemic allergic reactions
  - Impaired liver and kidney function
  - History of reproductive and fertility issues
  - Current medication
  - Is worker taking immuno-suppressive therapy
  - Congenital or acquired immunodeficiencies
  - Is worker pregnant or breastfeeding
  - Is worker planning a family or considering pregnancy sometime in the future
- Physical examination
  - Skin, mucous membranes, cardiopulmonary and lymphatic systems, and liver
- Biomonitoring, if appropriate and available[158]
- Any tests could focus on the current risk factors outlined, taking into account the worker's occupational history. Examples of potentially relevant tests include:
  - Full blood count
  - X-ray
  - Liver and kidney function tests

[158] It is recognised that, at the time of completion of this guide, no diagnostic test currently gives a sensitive, specific, and interpretable indication of early or likely health effects.

- Health advice and counselling
  - Cover potential health effects associated with exposure to HMPs and related waste
  - The optimum standard of control measures to expect in the workplace (as covered in the Standard Operating Procedures)
  - Results of the health surveillance, including any abnormal findings
  - Potential risks for male or female workers considering pregnancy, female workers who are pregnant or breastfeeding
- Assess compliance with protective measures (use of protective gloves, face masks/goggles, gowns/coveralls, and cabinets) and encourage their application and use

7.3.1.2 Continued health surveillance

Continued health surveillance should typically be undertaken throughout a worker's career with exposure to HMPs, and could:

- Repeat data collection of the baseline indicators (see above)
- Be undertaken at regular intervals
- Be undertaken if an incident such as a spill or sharps injury occurs
- Be undertaken on worker's request, due to a suspected work-related health issue
- Be undertaken if a health issue in one of the workers is suspected to be caused by work-related exposure to HMPs
- Be undertaken for both male and female workers considering pregnancy, female workers who are pregnant, and female workers who are breastfeeding
  - Immediately when pregnancy or breastfeeding is reported
  - Take into account relevant previous health issues
- Could include the following:
  - Physical examination
  - Laboratory studies, including a complete blood count and liver and kidney function tests
- Provide data for inclusion in health records
  - Health advice and counselling
  - Health surveillance test results
  - Details and outcomes of any investigation related to spills or sharps injuries
- Review of the risk management measures to reduce exposure and risk
- Consider worker privacy rights

7.3.1.3 Health surveillance at end of employment or exposure to HMPs

Health surveillance should be made at the termination of employment or the end of exposure to HMPs, and could typically include:

- Consideration of the information collected to date
  - Nature of the exposure
  - Duration of the exposure
  - Date of termination
  - Reason for termination, such as ill-health, death or other
- Examination
  - Medical history
  - Physical examination
  - Investigation (if appropriate)
  - Health advice and counselling (further testing and frequency)

7.3.2 Cases of abnormality or ill-health effects potentially due to HMPs

A follow-up plan should be created where workers exhibit an abnormality or ill-health effects that may be due to exposure to HMPs, typically covering:

- Health surveillance of similarly exposed workers
- Reassessment of the risk of exposure, see section 4
- Risk management measures for the worker and any other workers that could be similarly exposed
- An action plan with alternative employment options that could be either permanent or temporary
- Communication between the doctor or authority responsible, worker and employer
- Follow-up documentation and confidential notification of any adverse health effects. All cases of cancer, adverse effects on sexual function and fertility in adult male and female workers or developmental toxicity in their offspring identified in accordance with national law or practice as resulting from occupational exposure to a carcinogen, mutagen or reprotoxic substance must be notified to the competent authority. [159]

7.3.3 How often?

Health surveillance should be undertaken at different intervals depending on the different risk levels and roles as indicated by the HMP risk management plan, see sections 4 and 7.3.1.2. The health surveillance must continue after the end of exposure for as long as the doctor or authority responsible for health surveillance consider it to be necessary to safeguard the health of the worker concerned.[160]

Health surveillance should typically be implemented for:

- New workers or those returning after prolonged absence (over six months)
- All workers ending their employment term, prior to their termination.
- All workers developing specific HMP related illnesses, and their colleagues
- All workers potentially contaminated in an incident
- All workers who are of fertile age and considering pregnancy
- Female workers who are pregnant or breastfeeding

Health surveillance should typically be implemented at least:

- Once per year (annually) for all workers considered to be at high risk
- Once every two years (biennially) for all workers considered to be at medium risk
- Once every three years (triennially) for all workers considered to be at low risk

Health surveillance and counselling should be available to workers exposed to HMPs at any point during their employment.

[159] Directive 2004/37/EC, Article 14(8)
[160] Directive 2004/37/EC, Article 14(1)

7.4 Evaluate and revise

Health surveillance should include regular evaluation of workers' health to examine any changes or trends to health that may be relevant to exposure to HMPs.

Evaluation should use workplace monitoring, see section 5.5, to check for exposure and to verify if the health surveillance programme is still suitable and/or needs to be adjusted. Exposure measurements and other information should be used to evaluate whether health surveillance measures and risk management measures are preventing/reducing the occurrence of abnormalities and ill-health effects.

The health surveillance methods should be reviewed annually according to the evaluation findings and the most recent knowledge available.

7.5 Record keeping

Workers must have access to the results of the health surveillance that concerns them, and workers may ask for their personal health surveillance results to be reviewed.[161] The individual medical record, health surveillance data and report should be kept in a manner that assures worker's confidentiality and privacy. Access to medical records (other than by the doctor and the worker) should only be provided by previous explicit written consent of the worker concerned and/or under the terms of applicable legislation.[162]

All health surveillance records should be kept separately from all other human resources (HR) reports and other unrelated hospital medical records.

Upon the termination of employment, employers should provide the worker with a statement of the record which typically includes:

- Substances to which the worker has been exposed
- Period of exposure or potential exposure
- Details about how the worker can gain access to the records
- Any recommendations as to the worker continuing follow-up health assessments after the cessation of employment, together with the types of health examinations and/or biological surveillance that may be related to health risks

Records relating to medical surveillance with regard to carcinogens and mutagens must be kept for at least 40 years from the date of the end of exposure, and records relating to medical surveillance in case of exposure to reprotoxic substances must be kept for at least five years from the end of exposure.[163]

Workers should be advised to keep copies of their own records.

Record keeping must comply with any applicable national legislation or guidance, which can vary considerably.

[161] Directive 2004/37/EC, Article 14(6)
[162] See, for example, Regulation (EU) 2016/679, in particular Article 9
[163] Directive 2004/37/EC, Articles 14(4) and 15

7.6 Summary of advice in section 7

Who is responsible for health surveillance?

- Given that it is the Member States that are responsible for establishing the arrangements for carrying out health surveillance[164], employers should familiarise themselves with national legislation and/or guidance in their Member State, including on the protection of personal data[165], to establish the extent of their responsibilities and obligations with regard to health surveillance.

Scope

- Health surveillance must be arranged for workers exposed to hazardous medicinal products (HMPs) for whom the results of the risk assessment reveals a risk to health or safety.[166]
- Health surveillance should be considered for all roles listed in section 1.4 that come into contact with hazardous medicinal products (HMPs), in line with the risk assessment, which identifies individuals with higher risks associated with the tasks that imply exposure and/or due to personal health conditions that may be exacerbated by exposure, see section 4.
- As part of a health surveillance programme, organisations may seek to obtain data on worker exposure and effects using biomonitoring (biomarkers of exposure and effect); employers are advised to familiarise themselves with the legislation and conditions in their Member State.

Methods

- To facilitate health surveillance, baseline data and information should be collected by a medical practitioner prior to exposure to HMPs.
- Continued health surveillance should typically be undertaken at regular intervals throughout a worker's career with exposure to HMPs and at the termination of employment or the end of exposure to HMPs.
- Health surveillance should be undertaken at different intervals depending on the different risk levels and roles as indicated by the HMP risk management plan, see section 4.4

Evaluation and revision

- Health surveillance should include regular evaluation of workers' health to examine any changes or trends to health that may be relevant to exposure to HMPs.
- A follow-up plan should be created for workers who exhibit abnormalities or ill-health effects that may be due to exposure to HMPs.

Record keeping

- Records relating to medical surveillance with regard to carcinogens and mutagens must be kept for at least 40 years from the date of the end of exposure and records relating to medical surveillance in case of exposure to reprotoxic substances must be kept for at least five years from the end of exposure.[167]

[164] Directive 2004/37/EC, Article 14(1); Directive 89/391/EEC, Article 14; Directive 98/24/EC, Article 10(1), for chemical agents

[165] See, for example, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation - GDPR), in particular Article 9, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02016R0679-20160504&qid=1674485543249

[166] Directive 2004/37/EC, Article 14(1)

[167] Directive 2004/37/EC, Articles 14(4) and 15

8

Manufacturing

8.1 Introduction

8.1.1 European legal framework for Good Manufacturing Practice (GMP)

In the European Union (EU), three legal instruments set out the principles and guidelines of GMP[168]:

- Regulation (EU) No 1252/2014[169] which applies to active substances and medicines for human use
- Directive 2003/94/EC[170] which also applies to active substances and medicines for human use; and
- Directive 91/412/EEC[171] which applies to medicines for veterinary use.

Other related provisions for the codes for marketing authorisation are set out in Directive 2001/83/EC[172] (relating to medicinal products for human use) and Regulation (EU) 2019/6[173] (relating to veterinary medicinal products).

The principles and guidelines in these directives and regulations are explained and interpreted in the EU GMP guidelines. A series of annexes supplement the EU GMP guidelines, providing more detailed guidelines for specific products or on particular topics.

Some answers to Frequently Asked Questions (FAQs) on GMP are provided on the European Medicines Agency (EMA) website[174], with quality assurance provided by the GMP/GDP[175] Inspectors Working Group.

8.1.2 Context for the information provided in this guide

In general, it is expected that manufacturers of HMPs already have in place measures to reduce occupational exposure to hazardous substances. However, these measures vary across companies, for example with regard to the age of the facility, working processes and availability of quantitative exposure data to demonstrate that the working environment is safe. Therefore, there is an identified need to apply standards and good practice more comprehensively across the industry. This section highlights some examples of good practice and signposts the reader to sources of additional information, see additional reading recommended in Box 8-1.

As noted earlier in the guide, to meet the requirements of the CMRD, a risk assessment must be undertaken for all workers who are exposed to HMPs or are likely to be exposed to HMPs[176], see section 4.3. The hierarchy of controls must then be applied to minimise the occupational exposure of workers to HMPs[177], see section 4.4.1. The measures put in place by pharmaceutical companies should ensure both product quality and the protection of workers. It is, however, recognised that pharmaceutical legislation is primarily for patient safety rather than the safety of workers involved in manufacturing or the environment[178], with worker safety aspects being governed by other legislation.

168 EMA, Good manufacturing practice, Legal framework and guidance https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice#legal-framework-and-guidance-section

169 Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use https://eur-lex.europa.eu/eli/reg_del/2014/1252/oj

170 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use https://eur-lex.europa.eu/eli/dir/2003/94/oj

171 Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31991L0412 This directive will be replaced by an implementing act to be adopted under Article 93(2) of Regulation. This is due to be in place by 29 January 2025 at the latest.

172 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 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0083&qid=1673448360790

173 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128

174 EMA, Guidance on good manufacturing practice and good distribution practice: Questions and answers https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers

175 Good Manufacturing Practice (GMP), Good Distribution Practice (GDP)

176 Directive 2004/37/EC, Article 3

177 Directive 2004/37/EC, Articles 4 and 5; Directive 89/391/EEC, Article 6

178 See, for example, the introduction to EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines which excludes safety aspects for the personnel engaged in manufacture https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

Box 8-1: Additional reading for good practice in manufacturing HMPs

ESOP (2018) Quapos 6 Quality standard for the Oncology Pharmacy Service. European Society of Oncology Pharmacy (ESOP)

EC (2015) Eudralex: The Rules Governing Medicinal Products in the European Union. Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.

ISOPP (2022) ISOPP Standards for the Safe Handling of Cytotoxics. J Oncol Pharm Practice 2022, Vol. 28 3(Supplement), p1-126[179]

ISOPP (2010) Cytotoxic Drugs - Manufacturing Practices. Touch Briefings 2010, Standards Committee, International Society of Oncology Pharmacy Practitioners (ISOPP)

ISPE (2017) ISPE D/A/CH Affiliate: Containment Manual (English Translation), March 2017, The International Society for Pharmaceutical Engineering (ISPE)

WHO (2010) Annex 3 - WHO good manufacturing practices for pharmaceutical products containing hazardous substances. WHO Technical Report Series, No 957, 2010

International Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) Leading the international development, implementation and maintenance of harmonised Good Manufacturing Practice standards and quality systems of Inspectorates in the field of medicinal products

General risk management measures (WHO, 2010; EC, 2015) include, for example:

- Use of occupational exposure bands (OEBs)[180], see section 8.3, or health based exposure limits (HBELs)[181] and occupational exposure limits (OELs) to maintain the health and safety of workers
- Reliance on GMP principles to design and operate the relevant facilities
- For production that involves worker exposure to CMR substances, good practice is production in so far as technically possible, in a closed system[182] in line with a risk based approach to prevent worker exposure.
- Internal or third party audits to confirm adherence to GMP principles (for example by the Pharmaceutical Inspection Cooperation Scheme (PIC/S))

[179] This reference is mainly relevant to downstream users, but some information may be relevant to manufacturers, for example about external contamination of packaging.

[180] Occupational exposure banding, also known as hazard banding, involves assigning substances to bands (categories) for the purposes of controlling occupational risks.
Naumann, BD, (2008), Control banding in the pharmaceutical industry, Merck & Co Inc, https://ftp.cdc.gov/pub/Documents/OEL/12.%20Niemeier/References/Naumann%20(ControlBanding)_2008_AIOH.pdf

[181] ISPE, (n.d.), Presentation of a case study setting HBELs throughout a product life cycle, https://www.ema.europa.eu/en/documents/presentation/presentation-case-study-setting-health-based-exposure-limits-throughout-product-life-cycle-bd_en.pdf

[182] Directive 2004/37/EC, Article 5(2)

8.2 Process steps in manufacturing

Manufacturing includes the following overall steps during which workers could be exposed to HMPs:

- Receiving and unpacking raw materials
- Preparation and processing phases
- Primary and secondary packaging
- Storage and loading for distribution

8.3 Control measures in HMP production

Examples of technical measures (also known as engineering controls), organisational measures and personal protective equipment (PPE) which can be used in manufacturing to protect workers from exposure to HMPs are provided below. The choice of control measures should reflect existing legislation and the results of the risk assessment. It may be useful to use OEBs to advise which control measures can be used. Note that OEBs are typically used for less studied substances, set at a precautionary, conservative level, whereas OELs can be calculated where more data are available. OELs are set according to quantified risk, whereas OEBs are for guidance (see Annex 6 for further explanation).

An HBEL[183] can be calculated by deriving a permitted daily exposure (PDE) from toxicological data from a full toxicological assessment, and/or by using the threshold of toxicological concern (TTC) for genotoxic compounds without sufficient evidence for a threshold-related mechanism to derive a conservative HBEL.

OEBs enable substances to be classified into groups based upon health outcomes and potencies in order to advise which control measures are needed. Chemicals can also be grouped according to their OELs (where OELs exist) into OEBs. However, it should be noted that the CMRD requires the employer to minimise workers' exposure to HMPs that contain carcinogenic, mutagenic or non-threshold reprotoxic substances[184] regardless of the existence of an OEL[185]. In the case of threshold reprotoxic substances[186], the employer must ensure that the risk related to the exposure of workers is reduced to a minimum[187].

For example, a classification system with six OEBs ranges from a band starting at 1,000 µg/m³ and going down to a band at <0.1 µg/m³ for substances which are extremely hazardous to workers is provided in Annex 6. This annex includes a table of these OEBs and corresponding control measures which can be used as a look up table to advise which control measures are required based upon the OEB for an HMP.

8.3.1 Technical measures

Examples of relevant technical measures (also known as engineering controls) are provided below[188]. Please also see Annex 6 which provides a look up table for control measures based upon OEBs.

- Manufacturing processes using closed systems or physical barrier technology for the protection of both the operator and the product
- Closed systems whenever technically possible, if not feasible then the best local exhaust ventilation (LEV) system to match the level of risk to workers

183 EMA, (2017), Setting HBEL for highly hazardous products to ensure patient safety – application of the Q&A, https://www.ema.europa.eu/en/documents/presentation/presentation-setting-health-based-exposure-limits-highly-hazardous-products-ensure-patient-safety_en.pdf

184 According to Directive 2004/37/EC, a 'non-threshold reprotoxic substance' is a reprotoxic substance to which there is no safe level of exposure for workers' health and which is identified as such in the notation column of Annex III of Directive 2004/37/EC.

185 Directive 2004/37/EC, Article 5

186 According to Directive 2004/37/EC, a 'threshold reprotoxic substance' is a reprotoxic substance for which a safe level of exposure exists below which there is no risk to workers' health and which is identified as such in the notation column of Annex III of Directive 2004/37/EC.

187 Directive 2004/37/EC, Article 5

188 More detailed guidance on the layout of production facilities and design of air handling systems is provided in: WHO, (2010), WHO good manufacturing practices for pharmaceutical products containing hazardous substances, Annex 3. WHO Technical Report Series, No. 957.

- Use of airlocks, changing rooms, pass boxes, pass-through hatches or decontamination showers
- Suitable facility design and layout to safely contain the materials being handled
- Correctly designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC)
- If a building is shared, then a physical barrier should be used, with separate entrances, separate staff facilities and separate air-handling systems
- Pressure cascades and containment
- Detailed plans for the manufacturing site operations
- Equipment used in manufacturing of HMPs should be specified and designed for easy and effective cleaning
- Validated automatic clean in place systems where possible
- Validated and verified cleaning after each production run
- A well-sealed structure with no air leakage
- A negative air pressure with respect to the environment

8.3.2 Organisational measures

Even the best control measures need to be used correctly to provide effective worker protection. Therefore, the correct operation and limitations of the technical measure (i.e. engineering control) should be communicated to workers so that they understand the importance of procedures and the need for additional measures for protection. Adherence to operating controls should be monitored. Facilities could be graded to encourage and reward adherence.

Organisational measures to control risk of occupational exposure to workers include, for example:

- Well-trained health, safety & environment (HSE) team, with defined roles and responsibilities, including staff trained to undertake industrial hygiene measurements according to national regulations
- Restricting access to the production facilities to authorised personnel only[189]
- Standard operating procedures (SOPs) to be followed at all times, for example for cleaning and decontamination
- Cleaning in compliance with GMP and industry good practice
- Cleaning should be validated by documented methods to prove the efficacy and reproducibility of the cleaning method
- Cleaning protocols should be regularly reviewed and updated
- Established procedures for taking off protective gowns/coveralls and decontamination
- Industrial hygiene (monitoring staff exposure levels)

8.3.3 PPE

For manufacturing facilities, PPE should be selected according to the risk assessment, see section 4 and Annex 4, and can include, for example:

- Protective 'space' suits; the air pressure of the interior of the mask and suit should be greater than the facility's environment
- Breathing air supplied to protective suits should be filtered through a high-efficiency particulate air (HEPA) filter
- Breathing air supply systems should have a 100% back-up system in case of failure of the main system, for example a gas bottle providing at least 5 minutes' air supply
- Where space suits are not suitable, then protective face mask/goggles, gowns/coveralls and gloves
- Boots
- Shoe covers
- Glove ports or glove bags

[189] Directive 2004/37/EC, Article 9

8.4 New product development

It is important to consider the health and safety of workers involved in preparation and administration of HMPs as one of the criteria underpinning decisions about the HMP form and dosage to be brought onto the market. The choice of the container type is fixed during the marketing authorisation process, so it is important to consider the health and safety of all downstream actors before the marketing authorisation application is submitted. It is useful to consult downstream actors in the process of the development of new HMPs and ask them to share their preferences for packaging, for example with regard to the need for unit-dose packaging.

It is important to consider, in new product development and guidance provided by manufacturers to downstream actors, how HMPs are administered in real-life situations, see sections 11 and 12. More specifically, it is important for developers of new medicinal products to take into account the use of systems that reduce occupational exposure during HMP administration, for example (but not limited to) needle-free systems.

8.5 Prevention of external contamination of packaging

Contamination of primary and secondary packaging has been identified as a risk to downstream actors (for example Favier et al., 2003; Crul et al., 2020; COWI, 2021).[190,191,192] To avoid spillage (and therefore contamination of containers), it is important for the filling process to be carefully monitored including dosage control, fill weights, vial positioning during filling and vial stability to ensure the product is accurately filled into vials. Lyophilisation (freeze-drying) cycles could be designed and validated to control pressure effectively and avoid the product overflowing.

An example of good practice is for manufacturers to wash 100% of batches to remove potential contamination on vials and minimise the risk to downstream actors. Some manufacturers rinse vials until the level of contamination is below a certain established threshold. Inactivation can also be used to render any external contamination harmless. However, it is recognised that washing is not practical for all types of packaging, for example it is not possible to wash blister packs. In such instances, production controls should be used to minimise the risk of the outside of the packaging being contaminated. Processes exist for removing the risk of external contamination of blister packs, by ensuring that each tablet is not in physical contact with external packaging (including the product leaflet and secondary packaging).

Technical measures can also be put in place to reduce external contamination of vials by adding shrink foils. However, although plastic shrink wraps can reduce contamination, some contamination often remains on the shrink wrap (see, for example, Cotteret et al, 2022)[193]. Using a plastic shrink foil can also help contain spillage of the drug in case of breakage.

It is good practice to put in place and regularly validate processes for removing contamination, for example washing vials followed by surface testing

190 Favier et al, (2003), External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers, J Oncol Pharm Pract. 9(1)

191 Crul et al., (2020), Occupational exposure of pharmacy technicians and cleaning staff to cytotoxic drugs in Dutch hospitals, Journal of Occupational and Environmental Hygiene, 17:7-8 343-352.

192 European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Sand Jespersen, M. et al., (2021), Study supporting the assessment of different options concerning the protection of workers from exposure to hazardous medicinal products, including cytotoxic medicinal products: final report, Publications Office, https://data.europa.eu/doi/10.2767/17127

193 Cotteret C, et al, (2022), External contamination of antineoplastic drug vials: an occupational risk to consider, Eur J Hosp Pharm 2022, Vol 29 pp284–286.

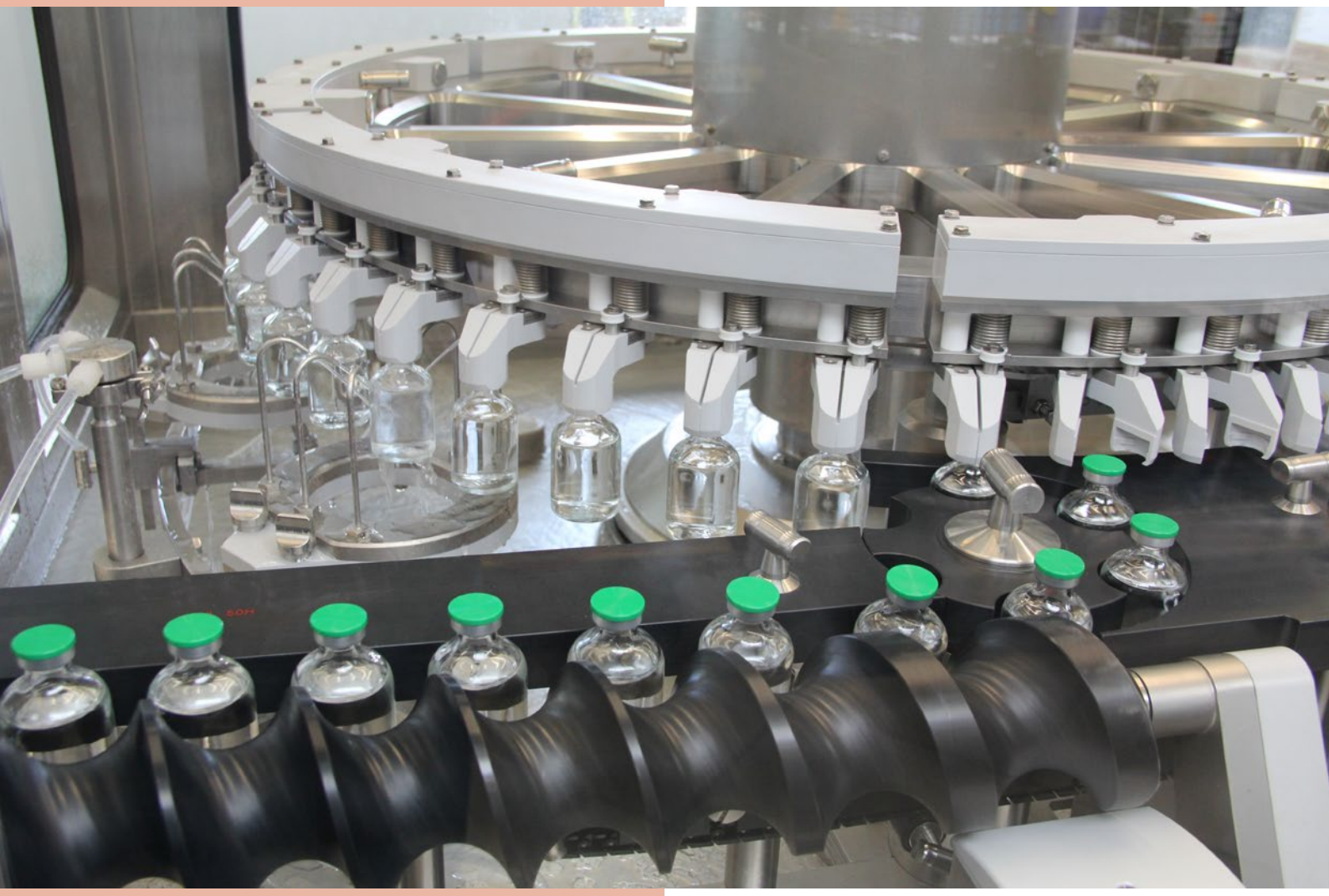

Figure 8-1:

A washing machine for vials containing toxic/potent products.

Source: Image provided by Synthon B.V.

batches of vials via swabbing. Where this is not possible, downstream actors should be made aware of the potential for exposure due to vial external contamination and advised to follow the procedures set out in sections 9 and 10.

Testing is a very useful tool to monitor the levels of surface contamination and the effectiveness of measures to reduce it, as well as to provide downstream actors with relevant information. This can involve:

- Developing a testing strategy
- Carrying out tests
- Using results to improve control and provide certificates to downstream actors

An independent laboratory could be used to validate the level of contamination on vials and other primary packaging.

8.6 Information flow from manufacturers to downstream actors

8.6.1 Labelling

The CLP Regulation does not apply to finished medicinal products or finished veterinary medicinal products for the final user.[194] However, manufacturers should consistently label all HMPs as such in accordance with the recommendations in section 2. Labelling should be attached to all tertiary packaging in a clearly visible manner that allows the identification of the whole consignment as HMPs. If possible, it is also advisable to label secondary and primary packaging as HMPs, although it is recognised that this may not be possible for products with an existing marketing authorisation.

8.6.2 Information provision

The requirement to provide a safety data sheet (SDS) does not apply to finished medicinal products or finished veterinary medicinal products for the final user. However, it is good practice for manufacturers to provide SDSs for all HMPs for downstream workers. This could include summary advice about reducing occupational exposure to HMPs by pharmacists, workers administering HMPs, cleaners and laundry workers. More detailed information can be provided on request.

Manufacturers could provide instructions for handling HMPs that specify the PPE to be used, see Annex 4. Where such information is not provided, it is important for manufacturers to be aware of the possibility that workers involved in the preparation and administration of HMPs may use a range of systems and methods to reduce occupational exposure. When developing new products, it is important for manufacturers to consider the different types of systems commonly in use.

It is helpful for manufacturers to provide sufficient information to assist downstream actors to control occupational exposure. Such information is essential for downstream actors to be able to ensure a high level of worker protection. This includes, for example, the following information:

- Details of the excretion rates for the relevant HMP (duration in days over which the patient or animal patient continues to excrete the HMP; these may be found in the prescriber's digital reference (PDR), www.fachinfo.de, etc.)
- Storage instructions, including data on the physical and chemical stability of their products, and recommended storage conditions as part of the SDS
- Measures to be taken in the event of a spill
- Ideally, manufacturers that have developed intra-company OELs for new HMPs for their own workers could share these with downstream actors, although it is recognised that confidentiality constraints may preclude the sharing of this information. Although it is recognised that the main exposure route is dermal in most downstream situations (and where inhalation is a relevant downstream exposure route, workers are exposed to a number of substances), it is expected that this information may be of relevance to, for example, compounding centres
- Contact details of a person or department that can be contacted by downstream actors for further information (as a part of the SDS)

It is beneficial for manufacturers to establish a communication channel for the provision of additional information to downstream actors upon request. The relevant contact details can be provided on the SDS. Manufacturers may need to set up a system to respond to safety information requests.

Please note that other sections of this guidance provide other sources of information in addition to manufacturers, for example section 2 provides useful sources to assist with the identification of HMPs.

[194] See Regulation (EC) No 1272/2008, Article 1(5); see also footnote 13

8.7 Summary of advice in section 8

Introduction

- In the European Union (EU), the relevant documents that set out the key principles and guidelines of Good Manufacturing Practice (GMP) include Regulation 1252/2014[195]; Directive 2003/94/EC[196] and Directive 91/412/EEC[197], with provisions for marketing authorisation in other legal instruments.
- The EU GMP Guidelines are not intended to cover worker safety aspects for the personnel engaged in manufacture.[198]
- There are some variations in practice across companies and therefore improving awareness of specific good practice approaches to occupational safety is useful.
- All workers exposed or potentially exposed to HMPs must be risk assessed and occupational exposure minimised through the hierarchy of control measures.[199]

Process steps in manufacturing

- Manufacturing includes four key steps during which workers could be exposed to HMPs (receiving and unpacking raw materials, preparation and processing phases, primary and secondary packaging, storage and loading for distribution).

Control measures in HMP production

- The choice of control measures should reflect existing legislation, results of risk assessments, Occupational Exposure Bands (OEBs) and Occupational Exposure Levels (OELs) where these exist.
- OEBs can be used to group substances based upon risk to advise which control measures are needed

New product development

- When new HMPs are developed it is important to consider not only patient safety but also the health and safety of workers involved in preparation and administration of HMPs.
- The choice of container is fixed during marketing authorisation, therefore it is important to consider upfront the implications of the container type and method of administration to the patient on the health and safety of downstream actors.

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195 Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R1252&qid=1667415778927

196 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32003L0094

197 Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31991L0412 This directive will be replaced by an implementing act to be adopted under Article 93(2) of Regulation. This is due to be in place by 29 January 2025 at the latest.

198 See, for example, the introduction to EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

199 Directive 2004/37/EC, Articles 3, 4, 5; Directive 89/391/EEC, Article 6

Prevention of external contamination of packaging

- Contamination of primary and secondary packaging has been identified as a risk to downstream actors.
- Good practice is for manufacturers to wash 100% of batches to remove potential contamination of vials, although there are some cases where this is not practical such as for blister packs.
- Shrink wrapping can reduce contamination but some contamination often remains on the shrink wrap.
- Good practice is to validate the removal of contamination through surface testing and provide certification to downstream actors.

Information flow from manufacturers to downstream actors

- All HMPs should be labelled consistently, see section 2.
- There is no legal requirement for safety data sheets (SDSs) to be provided to the final users of finished medicinal products or finished veterinary medicinal products.
- However, it is good practice for manufacturers to provide SDSs for all HMPs for downstream workers.
- It would be helpful for downstream actors to receive sufficient information to assist them in controlling occupational exposure.
- A communication channel would be useful from manufacturers to downstream users to respond to safety information requests.

9

Transport and storage (except waste)

9.1 Transport

9.1.1 Introduction

Transport and storage of hazardous medicinal products (HMPs) (except waste) takes place throughout the different lifecycle stages of HMPs. The many storage locations and journeys taken by HMPs are illustrated in Figure 9-1. This diagram does not show the return of unused HMPs from pharmacies, compounding centres and vets to the distributor and from the distributor to the manufacturer. This happens occasionally when HMPs are returned for several reasons, such as:

- Quality issues with the HMPs
- HMPs past their expiration date
- HMPs not used in clinical trials

The relevant dangerous goods regulations for all modes of transport include:

- Air (International Air Transport Association (IATA))[200]
- Road (European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR))[201]
- Sea (International Maritime Dangerous Goods (IMDG) Code)[202]

Unused prepared HMPs should be disposed of as HMP waste rather than being returned to the preparation site, see section 15.

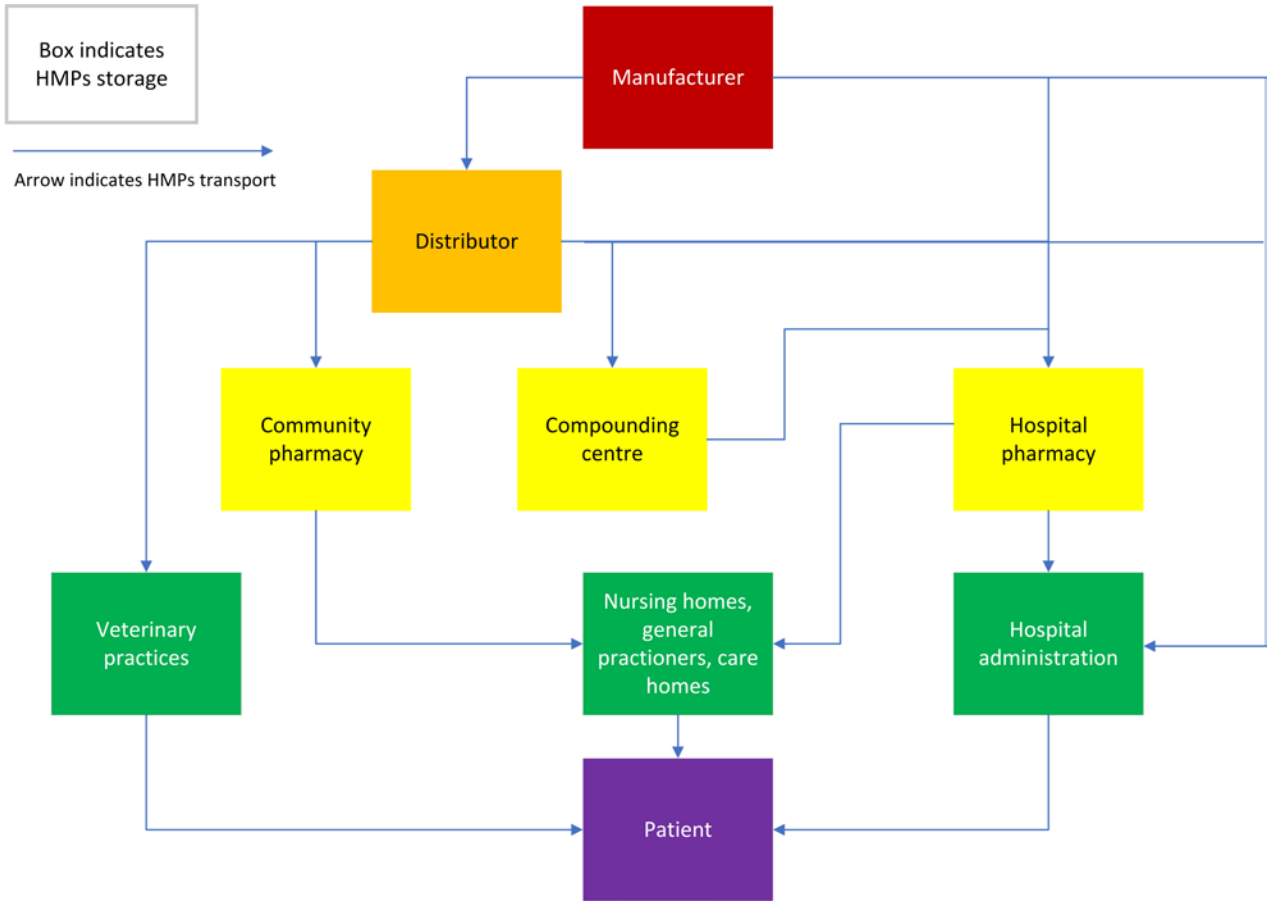


Figure 9-1: Storage and transport of HMPs.

200 IATA Dangerous Goods Regulations, available against payment at https://www.iata.org/en/publications/dgr/

201 UNECE: Agreement concerning the International Carriage of Dangerous Goods by Road 2021 https://unece.org/transport/publications/agreement-concerning-international-carriage-dangerous-goods-road-adr-2021

202 International Maritime Dangerous Goods (IMDG) Code, more information and a list of distributors can be found at https://www.imo.org/en/publications/Pages/IMDG%20Code.aspx

9.1.2 Packaging

Primary packaging containing HMPs should be made of unbreakable material to avoid leakage and spills. Examples include plastic vials, and glass vials packed in unbreakable containers or shrink wrapped in plastic sleeves.

HMPs should be packed separately from non-hazardous goods.

Secondary packaging should always be used for prepared HMPs. Prepared HMPs should be individually packed in a sealed plastic bag or container.

Figure 9-2: Transporting HMPs from a manufacturer/ distributor to a hospital in a sealed plastic bag inside a transport box.
Source: Meander Medical Centre, The Netherlands

9.1.3 Labelling

Packaging for transporting HMPs must be labelled.[203] Labelling must also be in accordance with the Agreement concerning the International Carriage of Dangerous Goods by Road (ADR) and should include an indication that it concerns HMPs.[204] It is useful to ensure that labelling of HMPs is consistent across all lifecycle stages, see section 2.

Prepared HMPs should be individually packed and labelled with an HMP indication. Additionally, the label could provide information about the HMP, dosage, solvent, total volume, date of preparation, expiry date, name and contact information of the preparation unit, and patient data.

A pneumatic tube system should not be used for internal transport of prepared HMPs unless the safety of the system is regularly assessed. Failure of the system could result in broken tubes resulting in substantial contamination of the working environment and exposure of workers to HMPs.

Figure 9-3: A cart with an external barrier used to move external transport boxes with HMPs at Sahlgrenska University Hospital, Sweden.

9.1.4 Transport boxes

Unbreakable, leak-tight, and sealed boxes should be used to ensure that any leakages or spills are contained to avoid the spread of contamination or similar arrangements should be made. The boxes should only be used for HMPs and should be easy to clean.

When transporting large quantities of HMPs, the box(es) should be securely transported on a cart.

[203] Directive 2004/37/EC, Article 5(5) (l); see also Directive 2004/37/EC, Article 11(2)
[204] All 27 EU Member States have ratified the ADR.
UNECE: Agreement concerning the International Carriage of Dangerous Goods by Road 2021 https://unece.org/transport/publications/agreement-concerning-international-carriage-dangerous-goods-road-adr-2021

9.1.4.1 Transport during storage

The outside of the boxes must be labelled.[205] It is useful to include information about each HMP transported on the box.

The boxes should be returned to the pharmacy / warehouse / storage areas when empty and should not be reused for other purposes.

9.1.5 Personal protective equipment (PPE)

When handling HMPs, transport boxes containing HMPs, or prepared HMPs, protective gloves type B should be worn. After use, the protective gloves should be disposed of as hazardous waste, followed by hand washing.

If damaged or contaminated, the protective gloves type B should be replaced immediately, and hands washed before putting them on.

Figure 9-4: A transport box with prepared HMPs being sealed for transport to the administration area (internal transport), being handled by a worker wearing PPE, Sahlgrenska University Hospital, Sweden

9.1.6 Spill kit during transport

A spill kit should be conveniently available during transport in case of emergency, but not kept in the box. The driver of the transport should be trained to use the spill kit, see section 13.3.

9.2 Storage (warehouse, pharmacy, or retail shop)

In reception and storage areas, a list of HMPs and a spill kit should be available.

9.2.1 Reception

9.2.1.1 Inspection

When HMPs are received, a visual inspection of the packaging should be carried out for any signs of breakage or damage to the goods. Processes for handling damaged goods should be established.

PPE used for handling damaged goods should include at a minimum protective gloves type B, see Annex 4. This should be considered as part of the risk assessment for handling damaged goods, see section 4.

9.2.1.2 Contamination (handling of HMPs at pharmacies)

Staff should be aware that primary packaging and vials may be contaminated when they arrive, and that exposure is possible. Studies have shown that the vials can be contaminated on the outside (for example Favier et al., 2003; Crul et al., 2020; and

[205] Directive 2004/37/EC, Article 5(5) (l); see also Directive 2004/37/EC, Article 11(2)

Figure 9-5: Cleaning of vials with 70% ethanol upon reception at the pharmacy at Sahlgrenska University Hospital, Sweden

COWI, 2021).[206,207,208] Care should be taken in handling HMPs during reception at pharmacies. This should include using PPE when receiving HMPs, with the minimum being type B protective gloves, a mask and gown, as defined by the risk assessment, see section 4 and Annex 4 Hands should be washed after handling HMPs.

The cleaning of primary packaging upon their reception should be considered to reduce worker exposure. If this is not possible, then protocols should be established to minimise contact with packaging as determined by the risk assessment, see section 4.

9.2.1.3 Transport during storage

HMPs should be transferred immediately to the storage area once received and treated with caution. HMPs transported internally should be carried in a manner that prevents potential damage to packaging and/or spills, for example by using watertight, protective containers.

9.2.2 Unpacking

Unpacking (bulk and individual card boxes containing HMPs) should be performed by trained staff, preferably in a separate room apart from other medicinal products, see section 6.

206 Favier et al, (2003), External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers, J Oncol Pharm Pract. 9(1)
207 Crul et al., (2020), Occupational exposure of pharmacy technicians and cleaning staff to cytotoxic drugs in Dutch hospitals, Journal of Occupational and Environmental Hygiene, 17:7-8 343-352.
208 European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Sand Jespersen, M. et al., (2021), Study supporting the assessment of different options concerning the protection of workers from exposure to hazardous medicinal products, including cytotoxic medicinal products: final report, Publications Office, https://data.europa.eu/doi/10.2767/17127

9.2.3 Room

If possible, HMPs should be stored centrally in a separate room or area apart from other medicinal products. The room should have ventilation venting to the outside of the building. Some HMPs may need storage in a fridge.

This separate room or area should be subject to only limited movement of individuals and goods and should be indicated with warning and hazard signs.[209]

If a separate room is not available, or cannot be designated due to lack of space, the HMPs should be stored separately from other medicinal products such as in a separate fridge.

Only authorised staff should enter the room where HMPs are stored.[210]

The storage areas should be designed to limit the possibility of breakages. For example, this can include using non-slip surfaces on shelves and ledges, and 'soft' floor coverings such as lino instead of tiles.

Figure 9-6: Storage of HMPs and other medicinal products in separate cupboards and fridges at the Sahlgrenska University Hospital, Sweden

[209] Directive 2004/37/EC, Article 11(2)
[210] Directive 2004/37/EC, Article 9

Figure 9-7: Opening an external transport box with HMPs by a worker wearing gloves at the Sahlgrenska University Hospital, Sweden

9.2.4 Personal protective equipment (PPE)

A risk assessment should be performed to determine the PPE requirements for transport and intermediate storage, see section 4 and Annex 4.

The following minimum PPE should be used for handling HMPs in transport and intermediate storage:

- Type B protective gloves (one-time use)

To ensure that PPE offers adequate protection, see Annex 4.

9.3 Operational procedures and hygiene

General principles for transport and intermediate storage of HMPs include, at a minimum:

- Wash hands before putting on and after taking off protective gloves
- Instruction should be given on how to wash hands properly and how to take off protective gloves correctly
- No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum to be consumed during the handling and transport of HMPs

9.4 Summary of advice in section 9

Transport

- Primary packaging containing HMPs should be made of unbreakable material to avoid leakage and spills.
- HMPs should be packed separately from non-hazardous goods.
- Secondary packaging should always be used for prepared HMPs. Prepared HMPs should be individually packed in a sealed plastic bag or container.
- Unbreakable, leak-tight, and sealed boxes should be used to ensure that any leakages or spills are contained to avoid the spread of contamination.
- Packaging and boxes for transporting HMPs must be labelled.[211] It is useful to ensure that labelling of HMPs is consistent across all lifecycle stages, see section 2.
- When handling HMPs, transport boxes containing HMPs, or prepared HMPs, protective gloves type B should be worn. After use, the gloves should be disposed of as hazardous waste.
- A spill-kit should be conveniently available.

Storage

- When HMPs are received, it is useful to first visually inspect the packaging for any signs of breakage or damage to the goods.
- On reception at the pharmacy, staff should be aware that primary packaging and vials may be contaminated when they arrive, and that exposure is possible. Personal protective equipment (PPE) should be worn.
- Unpacking (bulk and individual card boxes containing HMPs) should be performed by trained staff, preferably in a separate room apart from other medicinal products.
- If possible, HMPs should be stored centrally in a separate room or area apart from other medicinal products. If a separate room is not available, or cannot be designated due to lack of space, the HMPs should be stored separately from other medicinal products such as in a separate fridge.
- The following minimum PPE should be used for handling HMPs in transport and intermediate storage: type B protective gloves (one-time use).

[211] Directive 2004/37/EC, Article 5(5) (l)

10

Preparation (pharmacies and healthcare establishments)

Cover image: Preparation at the Masaryk Memorial Cancer Institute, Czech Republic

10.1 Introduction

This section of the guide focusses on occupational exposure of workers from hazardous medicinal products (HMPs) preparation activities at pharmacies both inside and outside of hospitals. Additionally, preparation at the ward is also covered in this section. Specifically, the following aspects are covered:

- Management and overall organisation (including preparation at the administration area)
- Technical measures
- Organisational measures (procedures)
- Personal protective equipment (PPE)
- Hygiene measures

This guide is for both hospital and community pharmacies. However, it is understood that there may be differences between hospital and community pharmacies in some European Union (EU) Member States and the guidance provided in this document should be tailored to the specificities of the relevant Member State.

It is also important that relevant EU resolutions are followed during preparation activities.[212, 213]

10.1.1 Sterile and non-sterile preparation

Preparation of HMPs can involve both sterile preparation and non-sterile preparation. There are some differences between sterile preparation and non-sterile preparation. Sterile preparation involves protecting the HMP from microbial contamination. The sterile area should meet the requirements of a clean room as set out in ISO 14644-1[214] and also in Annex 1 of Volume 4 of the Good Manufacturing Practice (GMP) guidelines.[215]

This section covers both sterile and non-sterile preparation, and, where there are differences, these are highlighted in the guide.

10.1.2 Compounding centres

There is an increasing trend towards outsourcing preparation from pharmacies to external preparation at compounding centres, especially where standard doses are required in large quantities. There is a potential for increased use of automated robotic systems at such facilities. It should be recognised that not all preparation can be outsourced to such facilities. The extent of further expansion of this trend and the potential for the involvement of the pharmaceutical industry is unknown. This section may not be fully applicable to some compounding centres where activities are more akin to an HMP production environment.

212 Resolution CM/Res (2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients https://statements.eahp.eu/resources/legislation/resolution-cmres20161-quality-and-safety-assurance-requirements-medicinal

213 Resolution CM/Res (2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use https://www.edqm.eu/en/d/162941

214 ISO 14644-1, (2015), Cleanrooms and associated controlled environments- Part 1: Classification of air cleanliness by particle concentration

215 Annex 1 of Volume 4 of the Good Manufacturing Practice (GMP) guidelines, https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf

10.2 Management and organisation

10.2.1 Centralisation

The preparation of HMPs should be centralised within the pharmacies (or, alternatively, compounding centres). This helps reduce the number of workers potentially exposed to HMPs and allows HMP preparation to be performed only by trained staff. However, there may be situations in which centralisation is not possible, such as for the reconstitution of extemporaneous oral suspensions and the adjustment of doses. In these cases, a risk assessment must be performed to ensure the required measures are undertaken for worker safety, see section 4.[216]

The design of the centralised preparation area should take into account the prevention and minimisation of exposure to HMPs (for example, the surfaces should be easy to clean, and separate areas should be used for HMPs and non-HMPs).

10.2.2 Use of dedicated areas

A confined and exclusive area should be used for preparing HMPs, with a warning and hazard sign outside, to alert other workers that HMPs are being prepared in this area. Access to this room should only be available for trained, competent personnel involved in preparation activities and a prohibited entry sign used when activities are being undertaken.[217]

Figure 10-1: Warning signs demarcating a pharmacy area where HMPs are prepared

Sources: Meander Medical Centre, The Netherlands and Sahlgrenska University Hospital, Sweden

[216] Directive 2004/37/EC, Article 3(2)
[217] Directive 2004/37/EC, Articles 5(5)(b) and 9

10.2.3 Workers and organisation

Any activities that are related to the preparation of HMPs should be developed, organised and supervised by a competent/trained, designated person. Workers involved in preparation should be trained and competent for preparing HMPs and their competence should be tested.[218] Clear, written instructions should be prepared and followed.[219] It is useful to report instances where instructions are not/cannot be followed to the management.

The following detailed (non-exhaustive) list of HMP training could be given to workers preparing HMPs, in addition to the core and basic training in handling HMPs, see section 6:

- Basic pharmacology of HMPs
- Routes of exposure to HMPs
- Correct use of PPE, see Annex 4
- Correct use of preparation devices
- Theory of aseptic technique
- Operational standards for aseptic HMP preparation and HMP clean room standards
- Safe handling approaches for HMPs received from the manufacturer such as wiping the outside of vials
- Safe handling aseptic techniques and protective routines
- Safe handling of oral, topical, and pre-packaged hazardous drug dosage forms
- Theory of containment devices and barriers
- Operational standards for containment secondary engineering controls (C-SEC) including airflow, pressures, and safe operating parameters
- Use of a relevant containment primary engineering control (C-PEC): suitable biological safety cabinet (BSC); compounding aseptic containment isolator (CACI); or cytotoxic drug safety cabinets (CDSC), including the parameters for safe operation
- Use of institution-specific specialised equipment
- Use of supplementary engineering controls
- Theory of hierarchy of controls
- Verification of HMP prescriptions and pharmacy medication checks (clinical, computer order entry, and final product release)
- Processes using HMPs (HMP selection, prescription verification, preparation (or purchasing), dispensing, administration, and drug use evaluation)
- Documentation requirements for pharmacy medication checks, HMP clean room standards, and cleaning
- Reducing contamination on the outside of the packaging of the prepared HMPs before transport for administration
- Documentation requirements for pharmacy medication checks and hazardous drug clean room standards

10.2.4 Preparation of HMPs in the administration area

As noted above, preparation activities should be centralised in a pharmacy department (or, alternatively in a compounding centre). However, there are occasions where the preparation of HMPs at the administration area cannot be avoided. This should only occur when there is no possible alternative. For the administration of parenteral HMPs in non-surgical settings, spiking should be performed at the pharmacy. Where an organisation permits preparation outside a pharmacy (or compounding centre), it may be useful to restrict this practice to specific HMPs or HMP groups – this should be determined based on the outcome of the risk assessment. An example of such approach is set out in Box 10-1, based on SESCAM (2022).[220]

[218] See also Directive 2004/37/EC, Article 11; and Directive 89/391/EEC, Article 6(3) (b) and (d)
[219] See also Directive 89/391/EEC, Article 6(2)(i)
[220] SESCAM - Servicio de Salud de Castilla-La Mancha (2022), Guidelines for action on the risk of exposure to hazardous drugs for health service workers in Castile-la Mancha, Rev. 2022

Box 10-1: Example of a group-based approach to permitting HMP preparation in an administration area

Group 1 HMPs and Group 2 parenteral HMPs should always be prepared at the pharmacy.

Non-parenteral Group 2 HMPs, parenteral Group 2 HMPs (in exceptional circumstances) and Group 3 HMPs where preparation at the pharmacy cannot be performed, should be performed under strict working conditions and with the use of PPE.

Note: The HMP groups are from the classifications by the National Institute for Occupational Safety and Health (NIOSH)[221]: (1) Antineoplastic medicinal products; (2) Non-antineoplastic hazardous medicinal products; and (3) Medicinal products with reproductive effects.

Source: SESCAM, 2022[222]

Where preparation needs to be carried out in the administration area, a risk assessment must first be performed to assess the risks and determine the measures to be taken[223], see section 4. At a minimum, the PPE used should include the PPE listed for use during preparation at the pharmacy, see section 10.5. Staff involved in the preparation of HMPs at wards should be trained and competent for this specific activity.[224] Clear, written instructions should be provided to workers, and followed during preparation.[225]

10.3 Technical measures

Engineering and technical measures should be used for the preparation of HMPs to reduce the potential exposure to workers during preparation activities.

Technical measures (whose feasibility should be considered during the risk assessment) should be used and can include the following for the preparation of all forms of HMPs (such as vials, ampoules, tablets, bottles):

- External ventilation of preparation room(s) (C-SEC) to the outside of the building
- A BSC Class II Type 2B[226] in accordance with national/international standards, for example DIN 12980.[227] A BSC Class II Type 2B is particularly important where there is a possibility of activities that may generate airborne particles.
- A laminar air flow cabinet with an upstream main filter stage which is immediately beneath the working surface
- An isolator[228] (preferably negative pressure to protect the worker), certified in accordance with ISO 14644[229]). An isolator is particularly important

[221] NIOSH, (2016), NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, https://www.cdc.gov/niosh/docs/2016-161/default.html
[222] SESCAM, (2022), Guidelines for action on the risk of exposure to hazardous drugs for health service workers in Castile-la Mancha, Rev. 2022
[223] Directive 2004/37/EC, Article 3
[224] See also Directive 2004/37/EC, Article 11; Directive 89/391/EEC, Article 6(3)(b) and (d)
[225] See also Directive 89/391/EEC, Article 6(2)(i)
[226] To maintain the efficiency of the BSC, it should be kept free of all but essential preparation equipment.
[227] DIN 12980. Laboratory installations - Safety cabinets and glove boxes for cytotoxic substances and other CMR drugs. Deutsches Institut Fur Normung E.V. 2017
[228] This should be in accordance with national/international standards. To maintain the efficiency of the isolator, it should be kept free of all but essential preparation equipment.
[229] ISO 14644 (2015). Cleanrooms and associated controlled environments

Figure 10-2: HMP preparation in isolators (externally vented) at the Masaryk Memorial Cancer Institute, Czech Republic

where there is a possibility of activities that may generate airborne particles and also if ampoules are used.

- A CDSC in accordance with national/international standards, for example DIN 12980[230]. A CDSC is particularly important where there is a possibility that activities may generate airborne particles.
- A robotic system for the preparation of HMPs
- A fume hood (when fume hoods are used, they should be used in accordance with EN14175[231])

The technical measures listed above should exhaust 100% out of the building.

In addition, the following measures should be used:

- Needle-free systems should be used, where possible. For example, using syringes with Luer-locks, using needle-free systems with a physical barrier and using syringe-to-syringe connectors for transferring solutions.
- A sterile, impermeable, single-use, waterproof and non-slip absorbent mat with the absorbent side up, should be used. This should be replaced daily, following contamination, or after a spill.
- Fluid bags should be spiked, and tubing should be primed with a compatible fluid before the addition of HMPs.

There is differing information in the literature on the effectiveness of use of closed system transfer devices (CSTDs) for reducing the risks in the preparation of HMPs. It is the decision of the management/staff on whether CSTDs are to be used in accordance with the risk assessment performed and relevant legislation. The technical measures that are used should also be validated with appropriate monitoring techniques.

Examples of technical measures, which can be used for sterile preparation, are shown in Box 10-2.

[230] DIN 12980, Laboratory installations - Safety cabinets and glove boxes for cytotoxic substances and other CMR drugs, Deutsches Institut Fur Normung E.V. 2017

[231] EN 14175, Fume cupboards https://www.en-standard.eu/search/?q=14175

Figure 10-3: Preparation of infusion bags with HMPs in an automated robotic system at the Amsterdam UMC, The Netherlands. Operators are wearing PPE.

Box 10-2 : Measures for reducing exposure during sterile preparation

- Use needle free systems if possible. If this is not possible, take appropriate measures i.e. syringes with Luer-lock connections
- Use wide-bore needles
- Use air-venting devices to equalise pressure and to minimise powder and liquid passage, and use an additional carbon filter along with the hydrophobic filter in the air-venting device to minimise aerosol passage
- Use a biological safety cabinet for preparation
- Purge preparations with dissolvent
- Use a sterile, impermeable, single-use, waterproof and non-slip absorbent mat with the absorbent side up

An antechamber/anteroom should be used for pre-package and storage. This room should also be used to allow access to the clean room and should be at pressure (preferably negative pressure). If it is not feasible to use the anteroom due to the need to doff the PPE in the anterooms, then consider using personal locks.

Note: The use of CSTDs is the decision of the management/staff in accordance with the risk assessment and relevant legislation.

Figure 10-4: A Luer-lock: a commonly used needle-free connection system used for ensuring a firm connection to minimise the possibility of slippage of the needle or tube and leakage

Figure 10-5:
Aerosols escaping during HMP preparation when a vial is spiked by needle

10.4 Organisational measures

10.4.1 Safe working practices

Safe working practices should be used in the preparation of HMPs and it is useful for them to be documented. Workers should also be competent in preparation activities. It is useful to develop standard operating procedures (SOPs) manuals and review and update them as required. At each pharmacy, a list should be developed for the HMPs prepared. This could also include an alert and advice for workers on the prescription system.

Dose fractionation should be avoided where possible and single-dose mixtures used where possible. Where dose fractionation is needed to be performed, then a risk assessment, see section 4, should be carried out to determine the measures required to protect the worker. A spill kit should be available, see section 13.3.

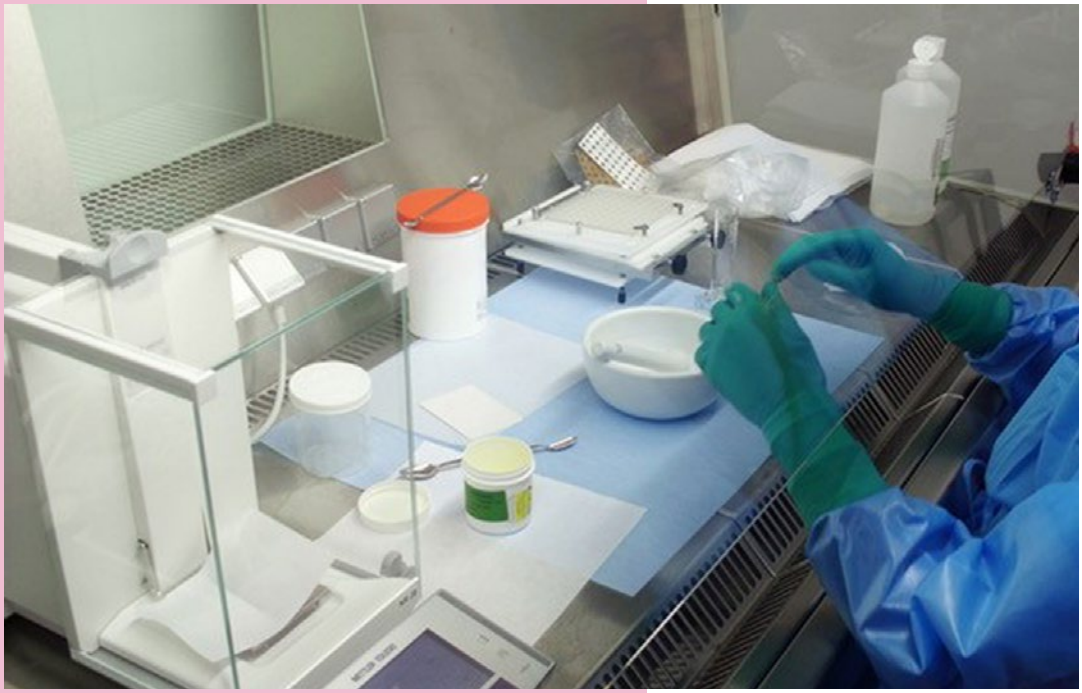
10.4.2 Particle generation

A number of activities should be avoided where possible because of the potential of airborne particle generation, this includes weighing, crushing and/or mixing tablets. If unavoidable, these activities should be performed in a BSC, see section 10.3. Measures should also be taken to minimise the possibility of the high-efficiency particulate air (HEPA) filter becoming clogged, such as using a mortar and pestle inside a plastic bag whilst crushing tablets (not shown in Figure 10-6).

10.4.3 Packaging of HMPs

Prepared HMPs should be sealed in a leakproof plastic bag and labelled. Those that are not used immediately should be stored in appropriate conditions.

Figure 10-6: Capsule production in a BSC at Pharma Assist BV, The Netherlands. Using HMP powders is a high-risk activity that has the potential to generate airborne particles.



10.4.4 Organisational measures by presentation

10.4.4.1 Oral forms (tablets, capsules, powders and liquids)

Oral forms such as tablets and capsules should be packed as individual doses where possible. Unit dose packaging is preferred if possible. Oral forms should be handled in a manner that avoids contact with the skin and protective gloves should be worn.

Figure 10-7: The use of break ampoules should be avoided

Tablets and capsules should not be crushed. For patients who have swallowing difficulties or feeding tubes and for paediatric patients, other forms (such as solutions and suspensions) or dosages should be considered. These should be prepared using special precautions.

A counting machine should not be used for HMP capsules and tablets. Dedicated equipment for HMPs should be used for dispensing HMP oral forms, and this equipment should be correctly labelled and also cleaned after use. To dispose of containers with damaged contents, see section 15.

There may be cases where fractionation or pulverisation is needed. In these cases, alternatives should be considered such as using liquid doses or changing the medication.

10.4.4.2 Ampoules

Where feasible, the use of glass ampoules should be avoided to reduce the risk of contamination and sharps injury. If this is not possible, break ampoules should be avoided.

10.4.4.3 Topical forms preparation (suspensions / solutions / creams / ointments)

Referenced protocols should also be followed for extemporaneous solutions which can be compounds using ampoules and/or vials. If leftover solutions are kept for later use, they should be kept in a dedicated area and should be marked for later use. These solutions should also be kept in a sealed leakproof plastic bag.

10.5 Personal protective equipment (PPE)

To select the PPE, see Annex 4. The PPE used should be determined by the risk assessment, see section 4 and Annex 4.

At a minimum, the following PPE should be used during preparation activities:

- Protective gloves type B, see Annex 4
- Protective face shield/goggles (when using a BSC/isolator this may not be required and should be determined during the risk assessment, see section 4)
- Protective gown/coveralls
- Respiratory protection, see Annex 4

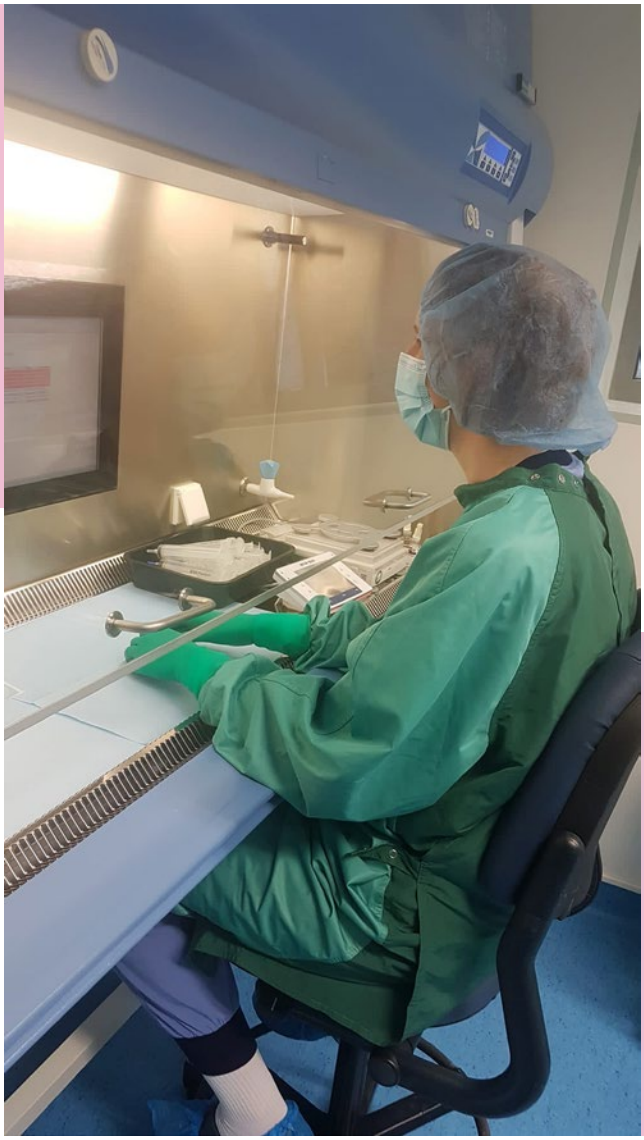


Figure 10-8:
A pharmacist applying the correct protection measures whilst working in BSC Class II
Source: Meander Medical Centre, The Netherlands

Figure 10-9:
A visual reminder of PPE to be worn on the door leading to a restricted area where HMPs are prepared
Source: Meander Medical Centre, The Netherlands

10.6 Hygiene measures

During preparation activities, at least the following hygiene procedures should be followed:

- No hand and wrist jewellery, long necklaces or large earrings
- Keep nails short and clean, do not wear make-up, nail varnish, artificial nails or perfume
- No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum in the preparation area
- No mobile phones, personal devices and headphones in the preparation area
- Tie back long hair
- Wash hands before putting on and after removing protective gloves

Box 10-3: Ensuring proper hygiene

The employer shall take adequate measures to ensure proper hygiene (minimising the risk of contamination with HMPs). Provisions and conditions must be free of charge for the workers, and will include:

- The prohibition of eating/drinking/smoking/vaping in contamination risk areas
- Provision of appropriate protective clothing
- Provision of separate storage places for working/protective clothing and for street clothes
- Access to appropriate and adequate washing and toilet facilities
- Availability of cleaned, checked and maintained protective equipment, stored in a well-defined place
- Repair and replacement of defective equipment

Source: Article 10(1) of Directive 2004/37/EC[232]

10.7 Secondary packaging and labelling

To protect against potential damage, primary packaging and HMPs should be protected with secondary packaging. It is useful to use single-use containers (such as sealed plastic bags) where possible. Mixtures should be individually packaged in a labelled, sealed, leak-proof container, with outer bags heat-sealed where possible. The potential for leakage and breakages during transport should be considered as part of the risk assessment, see section 4, when deciding on secondary packaging.

All secondary packaging should be labelled in accordance with the approaches set out in section 2.

[232] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

10.8 Waste

Single-use PPE as well as used materials that have been in contact with HMPs should be disposed of as hazardous waste in a closable hazardous waste container. Non-disposable equipment and PPE should be cleaned immediately after use.

10.9 Cleaning and laundry

Surfaces, clothing, etc. that have been in contact with HMPs should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable laundry should be treated as HMP-contaminated laundry, see section 14.2.

10.10 Summary of advice in section 10

Management and organisation

- Centralisation: preparation of hazardous medicinal products (HMPs) should be centralised within pharmacies in dedicated, confined areas designed to take into account the exposure prevention and minimisation principle, resulting in fewer exposed workers, a controlled environment, and work carried out by trained workers only.
- Preparation in administration areas should only occur when there is no possible alternative and after a risk assessment has been carried out. For the administration of parenteral HMPs in non-surgical settings, spiking should be performed at the pharmacy.
- Where an organisation permits preparation outside a pharmacy (or compounding centre), it may be useful to restrict this practice to specific HMPs or HMP groups.
- At a minimum, the same personal protective equipment (PPE) as at a pharmacy should be used for preparation in administration areas. Again, requirements such as trained staff only, clear written instruction, etc. apply.
- Activities that are related to the preparation of HMPs should be developed, organised and supervised by a competent/trained, designated person.
- The relevant activities should only be carried out by trained workers.
- Report instances where instructions are not/cannot be followed to the management.

Technical measures

- Technical measures that could be used to prepare of all forms of HMPs such as vials, ampoules, tablets and bottles, include:
  - Preparation room(s) should be externally vented to the outside of the building.
  - Examples of suitable equipment are listed in section 10.3.
  - Closed system transfer devices (CSTDs) are the decision of the country / organisation / management / staff in accordance with the risk assessment and relevant legislation.

Organisational measures

- A list of HMPs should be developed. This can include creating an alert in the prescription system.
- It is useful to document standard operational procedures (SOPs).
- High risk activities that should be avoided include: dose fractionation; activities that can generate airborne particles (weighing, crushing and mixing tablets). If unavoidable, these activities should be performed in a biological safety cabinet (BSC)
- The advice for oral forms includes:
  - Unit dose packaging preferred
  - Use protective gloves
  - Avoid crushing or using counting machines
  - Alternatives to fractionation or pulverisation
  - Ampoules: avoid glass ampoules, if possible. If not possible, break ampoules should be avoided

PPE

- At a minimum, the following PPE should be used during preparation activities:
  - Protective gloves type B
  - Protective face shield/goggles
  - Protective gown/coveralls
  - Respiratory protection

Hygiene measures

- Hygiene measures include no eating, drinking, mobile phones, or jewellery.

Secondary packaging and labelling

- To protect against potential damage, primary packaging and HMPs should be protected with secondary packaging.

Waste

- All materials that have been in contact with HMPs should be disposed of as hazardous waste. Non-disposable equipment and PPE should be cleaned immediately after use.

11

Administration

This section focuses on administration of hazardous medicinal products (HMPs) to patients and other activities related to patient care in the following settings:

Hospitals, hospital satellite clinics (such as outreach centres run by hospitals), **mobile administration units** (such as chemotherapy buses), and **local oncology centres**. The scope of this section includes both inpatient and outpatient administration at hospitals but excludes HMP preparation at hospital pharmacies, see section 10.

Healthcare facilities other than hospitals. The relevant facilities (non-hospital healthcare facilities) may include general practitioners' (GP) practices, local health centres and nursing homes. A pharmacy is generally not physically attached to such patient care facilities. The practices and equipment in place at these facilities may differ from hospitals and, consequently, separate advice is provided for some situations.

Home care, care homes and hospices. This includes administration of HMPs to patients and/or the physical care of these patients after receiving HMPs. The administration of HMPs and patient care in hospices, care homes and home care have similar characteristics which differ from healthcare establishments such as hospitals. A care home is defined as a house or institution providing accommodation and care for people who are unable to look after themselves. A hospice is a medical care facility that gives special care to people who are near the end of life and have stopped treatment to cure or control their disease.

This section has four major subsections:

- General remarks and comments are in section 11.1
- Specific remarks for administration and patient care in hospitals are in sections 11.2 - 11.8
- Focus areas for administration and patient care in other healthcare facilities are mentioned in section 11.9
- Focus areas for administration and patient care in care homes, hospices and homes are in section 11.10

The following administration procedures are considered in this section:

- Oral (tablets, capsules, powders, and liquids)
- Intravenous (IV) infusion
- Injections
- Intravesical (bladder) instillation and transarterial chemoembolisation (TACE) (liver, etc.)
- Inhalation
- Topical
- Surgical procedures

Other relevant activities in which occupational exposure to HMPs may occur in healthcare and care establishments (such as transport, intermediate storage, and cleaning) are covered in separate sections - this section should be read in conjunction with the remainder of this guide.

11.1 Management and organisation

11.1.1 Centralisation

The administration of HMPs should be centralised in a dedicated area to the maximum degree possible to prevent unnecessary contamination and to ensure that HMPs are handled by properly trained workers who have been informed about the relevant risks and protective measures. Centralisation is also helpful in ensuring that facilities for administration are designed to enable safe handling of HMPs and effective and efficient cleaning. If centralisation is not possible, workers should have the necessary tools, equipment and furniture to reduce exposure and workplace contamination to a minimum.

Preparation activities should typically take place in a pharmacy (see section 10).

11.1.2 Risk assessment

A risk assessment must be performed to identify the risks for each particular situation and location[233], see section 4.

The main exposure route for HMPs in administration is dermal. Exposure by ingestion will be negligible as drinking and eating must be forbidden[234] during the handling of HMPs. However, hand-to-mouth contact may still result in exposure by ingestion after touching contaminated surfaces. Unprotected contact (no protective gloves) with contaminated surfaces, tools or equipment should be avoided. Unprotected contact should also be avoided with droplets released from connecting or disconnecting syringes or lines to the infusion container / bag or the patient. Spiking of containers / bags should be done in a pharmacy.

If good practice is used in infusion procedures, aerosols are only released from the infusion system by pressure build-up in the infusion line to the patient. If the infusion procedure is based on gravity, the infusion stops automatically. Modern infusion pumps detect the pressure build-up, stop pumping and give an alarm. An infusion pump is shown in Figure 11-1.

Figure 11-1:
An infusion pump with automatic stop function

Inhalation exposure of HMPs is possible when patients are administered inhalable HMPs. Aerosols may also be released when HMPs are injected into the infusion container / bag or into the patient. Withdrawing the needle from the container / bag or patient can result in a release of aerosols due to a pressure drop or incident when the needle disconnects from the syringe during the procedure. Use of needle-free connections or Luer-lock helps to avoid the pressure change.

The choice of PPE in administration should be based on the risk assessment and the presence of technical and/or organisational measures.[235] In Annex 4, the minimum PPE required to protect the worker during different activities is listed.

[233] Directive 2004/37/EC, Article 3(2)
[234] Directive 2004/37/EC, Article 10(1)(a)
[235] See also Directive 89/656/EEC, Articles 3, 4 and 5

11.1.3 Workers and organisation

Developing and adhering to procedures for e.g. administration, patient care, handling excreta and / or blood, cleaning, waste handling, laundry and incident management is the responsibility of the employer. Only procedures that provide safe administration of the HMPs for workers, patients, and carers should be used.

It is helpful[236] for activities related to HMP administration to be supervised by a dedicated person, such as the head or manager of the centralised administration unit or ward.

Only trained and competent workers should be involved in the administration of HMPs.[237]

The following detailed (non-exhaustive) list of HMP training could be given to workers administering HMPs, in addition to the core and basic training in handling HMPs, see section 6:

- Basic pharmacology of HMPs
- Routes of exposure to HMPs
- Safe administration practices; correct hygiene procedures
- Receipt, unpacking, transport, and storage of HMPs
- Correct use of PPE
- Use of institution-specific specialised equipment for example administration pumps/safe systems for administration
- Theory of hierarchy of controls
- Health and safety legislation
- Waste management legislation
- Risk assessment process and HMP risk management plan, see section 4
- Disposal of HMP waste and patient excreta
- Handling of HMP laundry
- Management of incidents including contamination and spillage
- Health surveillance
- Workplace monitoring
- Pregnancy, breastfeeding, and planned parenthood

11.1.4 Communicate risks associated with patients

Ensuring that patients that have undergone treatment with HMPs are easily identifiable and are identified as such to relevant workers in other wards or departments for therapy or diagnostics over the entire period during which HMPs could be present in excreta (urine, faeces, vomit and sweat) and blood can be very helpful for the protection of the safety and health of such workers. However, any such identification needs to be in conformity with applicable data protection rules.[238]

In case of outpatient treatment, it is important to share information about the entire period during which HMPs could be present in excreta with any employer responsible for care of the patient (for instance nursing homes, care homes or organisations providing home care).[239] Sharing the same information with the patient is good practice that facilitates the awareness of other relevant employers, such as agencies supplying carers or domestic cleaners. Although every patient (and their treatment) is different, and the organisations to which the patients are going vary significantly, a set of information or brochures could be prepared for at least two situations:

- Instructions for the patient
- Instructions for the caring organisation

11.1.5 Technical measures

The choice of products and devices used has an impact on administration practices and should be based on the (type of) HMP, dosage, volume and frequency of administration.

[236] However, supervision of the work with dangerous substances may be mandatory under national legislation – readers are advised to check their national requirements.
[237] See also Directive 2004/37/EC, Article 11; Directive 89/391/EEC, Article 6(2)(i), 6(3)(b) and (d)
[238] Taking also into account that personal data concerning health are a special category of data (sensitive data) – see Regulation (EU) 2016/679
[239] Whilst ensuring that rules on personal data protection are respected – see previous footnote and Regulation (EU) 2016/679

To avoid exposure and for reasons of practicability and ease of use, representatives of all professional groups involved in HMP preparation and administration should be consulted in the process to select the devices used within the hospital.

Techniques and procedures must be used to reduce occupational risks from exposure to HMPs.[240] The use of syringes with needles should be avoided as much as possible in parenteral administration of HMPs.

The use of closed system transfer devices (CSTDs) is the decision of the management/staff in accordance with the risk assessment and relevant national legislation.

All procedures (including personnel, products and devices) used for administration and patient care should be validated with the appropriate measuring and monitoring techniques.

More specific advice is provided in sections 11.2 to 11.8 for each of the administration methods.

11.1.6 Organisational measures

The location where HMPs are administered, or where care for patients whose excreta and/or blood can be contaminated with HMPs is taking place, should have an adequate layout for effective cleaning. It is good practice to have separate toilet facilities for patients.

Protocols for administration, patient care, handling excreta and/or blood, cleaning, waste handling and incident management should be in place and all workers should receive training to ensure that they are familiar with these protocols prior to commencing the relevant activities, see section 6. Activities related to HMP administration should be supervised by a dedicated, trained, person.

11.1.7 Operational procedures and hygiene measures

Care should be taken to avoid the generation of airborne particles (solid or liquid), liquid or powder spills or splashes, and sharps injuries, such as from needles or broken glass.

The general principles for administration of HMPs include, for example:

- Organise work before starting the administration, for example, place all equipment (materials, PPE and waste container) within easy reach
- Put on PPE before starting to handle HMPs or getting in contact with contaminated excreta and blood, see Annex 4
- Wash hands before putting on and after taking off protective gloves. Instruction should be given on how to wash hands properly and how to take off protective gloves correctly
- Use protective gloves to remove protective gown and protective face shield/goggles
- No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum in the administration area

More information on the provisions for hygiene procedures in the carcinogens, mutagens and reprotoxic substances directive (CMRD)[241] is provided in Box 10-3 in section 10.6.

11.1.8 Excreta and blood

Excreta (urine, faeces, vomit and sweat) and blood should be treated as contaminated with HMPs during the time HMPs are being taken by the patient and generally up to 7-14 days after administration. As noted in section 8.6, it would be useful to have information about the presence of HMPs in excreta and blood supplied by the pharmaceutical manufacturer (for instance in a safety data sheet (SDS) and/or the summary of product characteristics (SmPC/SPC)) to enable the pharmacist to inform the workers involved in patient care about the time excreta and blood should

[240] Directive 2004/37/EC, Article 5

[241] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

Figure 11-2:
A closed bedpan washer at Sahlgrenska University Hospital, Sweden

be considered as contaminated. An overview can also be found in pharmaceutical guidelines[242].

Decanting urine manually should only be performed for 24-hour urine collection. Patients should be asked to go to the toilet themselves. Excreta (faeces, vomit and urine) should be handled with care. If possible, excreta should be transported in closed containers (urinals and bedpans). Decanting and washing should preferably be performed automatically inside a closed bedpan washer.

In specific surgical procedures, procedures where cavities / organs are locally treated and topical procedures with HMPs, the systemic uptake of HMPs in the patient is lower than in oral and parenteral procedures. This means that the presence of HMP in excreta differs and that the risk period may be shorter. In the absence of specific information, it should be assumed that the risk period is the same as for the same HMP in other administration forms.

11.1.9 Cleaning and laundry

High concentrations of HMPs can be present in the fluids used in the procedures or body fluids directly after treatment. Any single-use cloths or PPE that have been in contact with excreta from the patient (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMPs and should be disposed of as hazardous waste.

Any clothing, non-disposable bed linen and other laundry or bed linen that have been in contact with excreta from the patient or blood should be treated as HMP-contaminated laundry, see section 14.2.

Any floors, surfaces and administration areas, such as patient rooms, sanitary facilities, operating rooms, radiology rooms, mattresses, and urinals or bedpans, should be cleaned according to cleaning protocols in section 14.

[242] A regularly updated overview of the recommended duration of protective measures is provided, for example, in the full version of Quapos 6 (Quality Standard for the Oncology Pharmacy Service) Commentary Version. See https://esop.li/

11.2 Administration – oral

11.2.1 Management and organisation

Oral formulations of HMPs should not be crushed, dissolved or otherwise altered on the administration ward without the advice of the pharmacy. Tablets and capsules should be packed in individual packages.

If possible, patients should self-administer. When a patient cannot self-administer, another type of administration should be considered, in consultation with the pharmacist.

11.2.2 Technical measures

Dedicated spout cups should be used for administration of liquids whilst keeping a distance during administration, if possible.

11.2.3 Organisational measures

Workers involved in patient care should take into account the potential for exposure during the period that HMPs are present in excreta (urine, faeces, vomit and sweat) and blood. In case of continuous oral administration of HMP, the HMP will be always present in the excreta and blood of the patient.

Administration should be performed by trained workers and supervised.

11.2.4 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required for oral administration of HMPs and patient care (for minimal requirements and procedures for PPE, see Annex 4).

The following minimum PPE should be used for the administration of tablets and capsules (coated and uncoated):

- Type B protective gloves

The following minimum PPE should be used for the oral administration of HMP containing liquids, handling patient excreta or patient care:

- Type B protective gloves
- Protective gown

Figure 11-3:
Giving oral HMPs to patients for self-administration at the Sahlgrenska University Hospital, Sweden

- Protective face shield/goggles (to provide protection from splashes)

PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

11.2.5 Operational procedures and hygiene measures

General operational and hygiene principles for oral administration of HMPs should include:

- Workers should wash their hands before putting on and after taking off protective gloves
- The patient should use a drink container to self-administer tablets and capsules, and a spout cup for liquids

11.2.5.1 Tablets and capsules

- Touching the tablets / capsules should be reduced to a minimum
- Place all equipment (small single-use drink container and tablet pot) within easy reach
- Wash hands and put on protective gloves
- Place a single-use pad over the surface to protect it from contamination in case of a spill
- Let the patient open the primary package with the tablets/capsules or open the package for the patient and add the tablets to the tablet pot
- Use the tablet pot for administration of the HMP and let the patient drink
- Consider used single-use material as hazardous waste
- Remove protective gloves
- Wash hands

11.2.5.2 Liquids

- Place all equipment (small single-use drink container, or a spout cup) within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- Place a single-use pad over the surface that can be contaminated in case of a spill
- Open the container with the HMP liquid and pour it into the drink container
- Use the drink container for administration
- Dispose of the (drink) container as hazardous waste or clean immediately if re-used
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of disposable PPE as hazardous waste
- Wash hands

11.2.6 Waste

Single-use PPE as well as packaging and drink containers (single-use containers used for the application of a liquid medicine) that have been in contact with HMPs should be disposed of as hazardous waste in a closable hazardous waste container, see section 15.

Non-disposable equipment and PPE should be cleaned immediately after use.

11.2.7 Excreta and blood

Excreta (urine, faeces, vomit and sweat) and blood should be treated as contaminated with HMPs during the time HMPs are being taken by the patient and generally up to 7-14 days after administration (see section 11.1.9).

11.2.8 Cleaning and laundry

Surfaces, bed linen, and clothing that have been in contact with HMP containing solution or excreta (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable bed linen and other laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2.

11.3 Administration – IV infusion

This section deals with administration by means of an infusion system (with or without the use of an infusion pump).

11.3.1 Management and organisation

Infusion systems should be filled in the pharmacy with an HMP-free solution before the HMP is added to the infusion bag/bottle or connected to the HMP container.

Figure 11-4:
A nurse wearing protective gloves and a gown administering an IV infusion (with a pump) to a patient at the Sahlgrenska University Hospital, Sweden

Figure 11-5:
Do's and don'ts of HMP administration

LEFT: Do: Administration using gloves, bag is spiked in the pharmacy with side line with clamp (only neutral fluid in side line below the clamp) and using Luer-locks

RIGHT: Don't: No gloves worn AND bag is directly spiked in the administration area

Source: Photos provided by Amsterdam UMC, The Netherlands

11.3.2 Technical measures

Luer-slip connections and needles should not be used.

Preferably, infusion systems with a functional physical barrier between the HMP-containing infusion bag/bottle/container and the connection point for the infusion-port at the patient, should be prepared in the pharmacy. Systems with a physical barrier could be, for example:

- Infusion lines filled with an HMP-free solution
- Systems with a physical barrier for injecting HMP-containing solution into the infusion bag on the ward

Another solution could be to use a system based on filtering the outgoing air.

The effectiveness of all systems used should be validated before being introduced and periodically re-validated when in use.

Figure 11-6: A nurse wearing PPE at Sahlgrenska University Hospital, Sweden

11.3.3 Organisational measures

The connection and disconnection of infusion systems with administration bags should be kept to a minimum and avoided when possible. The risk of HMP-containing liquid dripping can be reduced by not disconnecting the infusion system from the guard infusion after administration.

Disconnection of the infusion system from a patient should be performed after the system has been flushed with at least 100 ml of HMP-free solution.

Administration should be performed by trained workers and supervised.

11.3.4 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required for infusion of HMPs and patient care (for minimal requirements and procedures for PPE, see Annex 4). PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

The following PPE should be used as a minimum for handling infusion bags with a physical barrier:

- Type B protective gloves

The following minimum PPE should be used for handling infusion bags without a physical barrier, and after administration if dripping cannot be avoided in disconnecting the infusion set:

- Type B protective gloves
- Protective gown
- If indicated by a risk assessment: protective face shield/goggles, see section 4

11.3.5 Operational procedures and hygiene measures

General operational and hygiene principles for IV infusion of HMPs are described below for procedures with and without a physical barrier.

11.3.5.1 Procedure for infusion bags with a physical barrier

- Connect guard infusion with neutral IV fluid to the patient
- Place all equipment within easy reach
- Wash hands and put on protective gloves
- Place a single-use pad on the working surface to protect it from contamination
- Connect the infusion line from infusion bag with HMP to the guard infusion
- Close clips and/or clamps from guard infusion
- Open clips and/or clamps for HMP administration
- Remove protective gloves
- Wash hands
- Infusion takes place
- Wash hands and put on new protective gloves
- Close clips and/or clamps and flush with at least 100 ml of neutral IV fluid
- Disconnect the total infusion set from the patient
- Dispose of the materials; consider used single-use material as hazardous waste
- Remove protective gloves and dispose of as hazardous waste
- Wash hands

11.3.5.2 Procedure for infusion bags without a physical barrier

- Connect guard infusion with neutral IV fluid to the patient
- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- Place a single-use pad on the working surface to protect it from contamination
- Connect the infusion line to the infusion bag with HMP
- Fill the line (partially) with the HMP infusion liquid; prevent dripping using a hydrophobic stop filter
- Check if the drip chamber in the guard infusion is sufficiently filled to accommodate the air in the infusion line from the infusion bag with HMP
- Connect the infusion line from the infusion bag with HMP to the guard infusion
- Close clips and/or clamps from the guard infusion
- Open clips and/or clamps for HMP administration
- Remove protective gown and face shield/goggles, then gloves
- Wash hands
- Infusion takes place
- Wash hands and put on new protective gloves, gown, and face shield/goggles
- Close clips and/or clamps and flush with at least 100 ml of neutral IV fluid
- Disconnect the total infusion set from the patient
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of the materials and PPE; consider single-use material and PPE as hazardous waste
- Wash hands

11.3.6 Waste

Administration lines should only be disconnected after they have been flushed with at least 100 ml of a compatible non-HMP solution. Administration sets should not be removed from an IV bag and the

complete set that has been in contact with HMPs should be disposed of as hazardous waste, in a closable hazardous waste container.

Single-use PPE used during infusion should be disposed of as hazardous waste. Non-disposable PPE should be cleaned immediately after use.

For more information on waste disposal, see section 15.

11.3.7 Excreta and blood

Excreta (urine, faeces, vomit and sweat) and blood should be treated as contaminated with HMPs during the time HMPs are being taken by the patient and generally up to 7-14 days after administration (see section 11.1.9).

11.3.8 Cleaning and laundry

Surfaces, bed linen, and clothing that have been in contact with HMP containing solution or excreta (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable bed linen and other laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2.

11.4 Administration – injections

11.4.1 Management and organisation

Intrathecal administration should be performed in designated areas.

Figure 11-7:
DO vs DON'T: use Luer-lock (left), not Luer-slip (right) connections

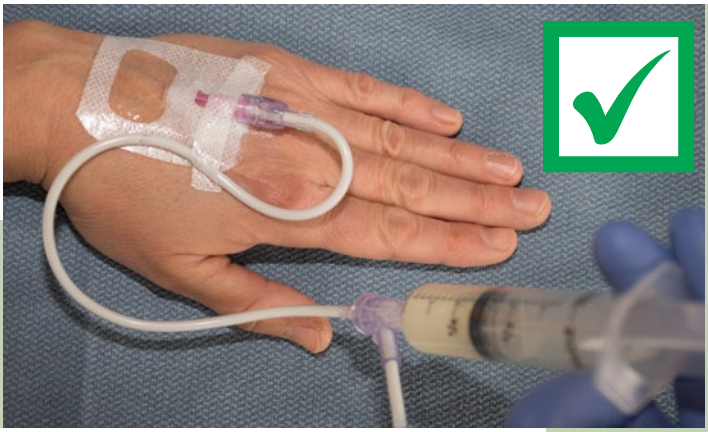


Figure 11-8: Bolus injection administration using a system with a Luer-lock, worker wearing PPE (only protective gloves visible in the picture)

Figure 11-9: Avoid using Luer-slip connections if possible: this photo shows administration by injection using a Luer-slip connection

11.4.2 Technical measures

Needles with a Luer-lock should be used to minimise the possibility of slippage of the needle and leakage. Luer-slip connections and needles should not be used.

For a bolus injection, a peripherical access system for administration should be applied before connecting the syringe.

11.4.3 Organisational measures

Bolus, intramuscular, subcutaneous and intrathecal injections should be performed by trained workers and supervised.

11.4.4 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required for injection of HMPs and patient care (for minimal requirements and procedures for PPE, see Annex 4).

PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

The following PPE should be worn as a minimum for the injection of HMPs:

- Type B protective gloves
- Protective gown
- If indicated by a risk assessment, a protective face shield/goggles (to provide protection in the event of splashing during injection of HMPs with needles without Luer-lock), see section 4

11.4.5 Operational procedures and hygiene measures

General operational and hygiene principles for administration of HMPs by injection are described for respectively bolus injection, subcutaneous injection, and intrathecal injection.

11.4.5.1 Procedure for bolus injection

- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- A peripherical access system for administration should be placed before connecting the syringe (Luer-lock)
- Connect the syringe or CSTD
- After administration, flush with neutral fluid
- Disconnect the total injection set from the patient
- Dispose of the materials; consider used single-use material as hazardous waste
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of PPE; consider used single-use PPE as hazardous waste
- Wash hands

11.4.5.2 Procedure for intramuscular and subcutaneous injection

- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- Place a single-use pad under the parts of the body to be treated
- Perform the injections in accordance with the medical protocol
- After removing the needle, swab the site and apply a dressing when needed to avoid drop spilling
- Dispose of the materials; consider used single-use material as hazardous waste
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of PPE; consider used single-use PPE as hazardous waste
- Wash hands

11.4.5.3 Procedure for intrathecal injection

- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- Lay the patient on the side and place a single-use pad under the parts of the body to be treated
- Localize and disinfect the insertion point
- Put on sterile protective gloves
- Perform lumbar puncture
- Connect the T-connector and allow it to fill with cerebrospinal fluid (CSF), collect CSF
- Connect the locked/secured syringe containing the HMP with a Y-system to the T-connector
- Open the three-way valve to the Y-system and open the clamp on the locked/secured syringe containing the cytostatic
- After administering the cytostatic, close the clamp (of the cytostatic syringe) and open the clamp of the 10 ml locked/secured syringe with neutral liquid and flush with several millilitres
- Close the three-way valve
- Disconnect the Y-system from the T-connector; hold a gauze pad under it to catch any drops and place gauze under T-connector on pad. Place syringes with Y-system on the pad
- Remove lumbar needle with the T-connector and dispose of in a needle container
- After removing the needle, swab the injection site and apply a dressing when needed to avoid drop spilling
- Dispose of the pad with Y-system (syringes) and gauze as hazardous waste
- Dispose of the materials and the outer protective gloves; consider used single-use material as hazardous waste
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of PPE; consider used single-use PPE as hazardous waste
- Wash hands

11.4.6 Waste

Syringes, containers with used needles, peripherical access system and single-use pads should be disposed of as hazardous waste, in a closable hazardous waste container.

Single-use PPE used during infusion administration should be disposed of as hazardous waste. Non-disposable PPE should be cleaned immediately after use.

For more information on waste disposal, see section 15.

11.4.7 Excreta and blood

Excreta (urine, faeces, vomit and sweat) and blood should be treated as contaminated with HMPs during the time HMPs are being taken by the patient and generally up to 7-14 days after administration (see section 11.1.9).

11.4.8 Cleaning and laundry

Surfaces, bed linen, and clothing that have been in contact with HMP containing solution or excreta (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable bed linen and other laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2.

11.5 Administration – intravesical instillation & transarterial chemoembolisation

Intravesical instillations and transarterial chemoembolisation (TACE) are special administration techniques that should only be performed in specialised hospital departments.

11.5.1 Management and organisation

Intravesical (bladder) instillation should be performed in designated units.

TACE microspheres should be prepared in the pharmacy and the procedure should be performed at the radiology department.

11.5.2 Technical measures

Luer-slip connections and needles should not be used.

A peripherical access system for administration with Luer-lock connections should be applied before connecting the syringe.

11.5.3 Organisational measures

Intravesical instillations and TACE administrations should be performed by trained workers and supervised.

11.5.4 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required for intravesical instillation, TACE and patient care (for minimal requirements and procedures for PPE, see Annex 4).

PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

The following PPE should be used as a minimum for intravesical instillation and TACE of HMPs:

- Type B protective gloves
- Protective gown
- If indicated by a risk assessment, see section 4, protective face shield/goggles (to provide protection in the event of splashing during intravesical instillation of HMPs)

11.5.5 Operational procedures and hygiene measures

General operational and hygiene principles for administration of HMPs by intravesical instillations and TACE should include:

- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face shield/goggles
- Place a single-use pad over body parts that can be contaminated in case of spill and underneath the parts of the body to be treated
- Apply the HMP according to medical protocol
- Dispose of the materials; consider used single-use material as hazardous waste
- Remove protective gown and face shield/goggles
- Remove protective gloves
- Dispose of PPE; consider used single-use PPE as hazardous waste
- Wash hands

11.5.6 Waste

Catheters or sondes, access systems and single-use pads should be disposed of as hazardous waste, in a closable hazardous waste container.

Single-use PPE used during infusion administration should be disposed of as hazardous waste. Non-disposable PPE should be cleaned immediately after use.

For more information on waste disposal, see section 15.

11.5.7 Excreta and blood

In specific procedures where cavities/organs are locally treated with HMPs, the systemic uptake of HMPs in patients is lower than from oral and other parenteral procedures. This means that the presence of HMP in excreta (urine, faeces, vomit and sweat) and blood differs and that the risk period may be shorter. In the absence of the appropriate information, the times are applied that are common for the HMP in other administration forms.

11.5.8 Cleaning and laundry

Surfaces, bed linen, and clothing that have been in contact with HMP containing solution or excreta (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable bed linen and other laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2.

11.6 Administration – inhaled medications

Inhaled medication is administered through an inhaler, which the patient usually keeps throughout their treatment for use in hospital and/or at home. In a hospital setting, the inhaler may be supplied and disposed of after each treatment.

Metered-dose inhalers (MDIs), dry powder inhalers, nebulisers and soft mist inhalers are currently available for administration of different medicines. If the device produces mist (dry or aerosols) into the working environment, workers may be exposed to HMPs.

11.6.1 Management and organisation

Inhalation therapy of HMPs for lung treatment should be performed in designated areas.

Patients should self-administer as much as possible.

11.6.2 Technical measures

The release of direct or patient-exhaled mist or aerosols in the room where the administration is performed should be avoided. Devices that produce no mist or aerosols in the room should be preferred. If devices need to be used that produce aerosols, or if during administration the exhaled breath of the patients into the room may contain aerosols, a local exhaust tent should be used around the head of the patient to prevent spreading of the HMP in the room.

11.6.3 Organisational measures

Workers should avoid being present during the treatment. If no local exhaust ventilation is used, the room should be ventilated for at least half an hour for the concentration of HMPs to be reduced before entering without respiratory protection.

Administration should be performed by trained workers and supervised.

11.6.4 Personal protective equipment (PPE)

A risk assessment, see section 4 and Annex 4, should be performed to determine the PPE required for inhalation administration.

PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

The following PPE should be used as a minimum for inhalation treatment with mist/aerosols containing HMPs:

- Type B protective gloves
- Protective gown
- If indicated by a risk assessment, a FFP3 single-use face mask, see section 4

11.6.5 Operational procedures and hygiene measures

General operational and hygiene principles for administration of HMPs by inhaled medications should include:

- Place all equipment within easy reach
- Wash hands and put on protective gloves, gown and face mask
- Apply the HMP according to medical protocol
- Consider used single-use material as hazardous waste and dispose of accordingly
- Remove protective gown and face mask/goggles
- Remove protective gloves
- Dispose of PPE; consider used single-use PPE as hazardous waste
- Wash hands

11.6.6 Waste

Single-use equipment for inhalation treatment and single-use PPE should be disposed of as hazardous waste, in a closable hazardous waste container. Non-disposable equipment and PPE should be cleaned immediately after use.

For more information on waste disposal, see section 15.

11.6.7 Excreta and blood

In inhalation, the systemic uptake of HMPs in the patient is lower than from oral and other parenteral procedures. This means that the presence of HMP in excreta (urine, faeces, vomit and sweat) and blood differs and that the risk period may be shorter. In the absence of the appropriate information, the times are applied that are common for the HMP in other administration forms.

11.6.8 Cleaning and laundry

Surfaces, bed linen and clothing that have been in contact with aerosols or dust during the administration should be considered as contaminated with HMP. Surfaces and administration areas, such as patient rooms, sanitary facilities, and mattresses should be cleaned according to cleaning protocols, see section 14.1, or treated as HMP-contaminated laundry, see section 14.2.

11.7 Administration – topical

11.7.1 Management and organisation

Patients should self-administer HMPs as much as possible.

11.7.2 Technical measures

Single-use spatulas should be used, if possible.

11.7.3 Organisational measures

Administration should be performed by trained workers and supervised.

11.7.4 Personal protective equipment (PPE)

A risk assessment, see section 4 and Annex 4, should be performed to determine the PPE required for topical administration.

PPE should be worn during administration of HMPs and disposed of or cleaned immediately afterwards to avoid transfer of potential contamination.

The following PPE should be used as a minimum for topical treatment of HMPs:

- Type B protective gloves
- Protective gown

11.7.5 Operational procedures and hygiene measures

General operational and hygiene principles for topical administration of HMPs should include:

- Place all equipment within easy reach
- Wash hands and put on protective gloves and gown
- Put the patient in a suitable position and ask the patient to bare the skin to be treated
- Place a single-use pad under the parts of the body to be treated
- Apply the ointment thinly using a single-use spatula
- Cover the affected parts of the client's skin with a bandage
- Consider used single-use material as hazardous waste and dispose of accordingly
- Remove protective gown
- Remove protective gloves
- Dispose of PPE; consider single-use PPE as hazardous waste
- Wash hands

11.7.6 Waste

Packaging, spatula and PPE should be disposed of as hazardous waste, in a closable hazardous waste container.

For more information on waste disposal, see section 15.

11.7.7 Excreta and blood

In topical procedures with HMPs, the systemic uptake of HMPs in the patient is lower than from the oral and infusion and injection procedures. This means that the presence of HMP in excreta (urine, faeces, vomit and sweat) and blood differs and that the risk period may be shorter. In the absence of specific information, it should be assumed that the risk period is the same as for the same HMP in other administration forms.

11.7.8 Cleaning and laundry

Any surfaces, bed linen or clothing that have been in contact with HMP creams or lotions should be considered as contaminated with HMPs.

These surfaces should be cleaned according to cleaning protocols, see section 14.1. Non-disposable bed linen and other laundry should be treated as HMP-contaminated laundry, see section 14.2.

11.8 Administration – surgical procedures

This section applies to the following surgical procedures that involve HMPs:

- Intra-peritoneal administration (HIPEC (Hyperthermic IntraPEritoneal Chemotherapy) and PIPAC (Pressurized Intra-Peritoneal Aerosol Chemotherapy))
- Intra-pleural administration
- Regional perfusions

11.8.1 Management and organisation

A sign should be placed outside the operating room indicating that HMPs are used. In case of HIPEC or PIPAC, the sign should be placed before the start of the administration of the HMPs until the operating room is cleaned.

11.8.2 Technical measures

The following technical measures should be used:

- Floor protective sheets
- Buffalo filter system

- Patient's body covered with a sheet (for example for open HIPEC), similar to those used for a Caesarean section
- For PIPAC: A laminar airflow, controlled aerosol waste and protection curtain. A three way stopcock connected to the syringe and cap applied to balloon of the trocars. A protective sheet placed under the injector and next to the patient (Solaß, W. 2013, Willaert, W. 2017)[243].

11.8.3 Organisational measures

The number of workers in the surgery team should be as limited as possible. It is important to consider whether male or female workers who are trying to conceive or female workers that are pregnant or breastfeeding should participate in the operating procedure. This is particularly relevant to surgical procedures where there may be personnel present in the operating room that does not handle HMPs but can be exposed to them.

In the case of the PIPAC procedure, the patient is guarded from the outside of the operating room during the actual administration (no staff present during the administration procedure). When the surgeon has ended the administration and the pressure in the abdomen is deflated, the surgical team can enter the operating room to finish the procedure.

Administration should be performed by trained workers and supervised.

11.8.4 Personal protective equipment (PPE)

A risk assessment, see section 4 and Annex 4, should be performed to determine the PPE required for surgical procedures that involve HMPs.

The following PPE should be used as a minimum for surgical procedures that involve HMPs:

- Double long-sleeve surgical gloves
- Protective surgical masks with face shield/goggles
- Reinforced gowns/plastic gowns
- Shoe covers

11.8.5 Operational procedures and hygiene measures

The normal routine for surgical procedures should be followed but special attention should be given to prevent spillage and splashing of HMP containing fluid.

11.8.6 Waste

An HMP-waste bin should be present in the operating room. The HMP-containing perfusion liquids that are used in the procedure should be disposed of as hazardous liquid waste. Single-use sheets, covering material, PPE and surgical material should be disposed of as hazardous waste, in a closable hazardous waste container.

Non-disposable equipment and PPE should be cleaned immediately after use.

Surgical equipment should be cleaned according to protocol or disposed of as hazardous waste, in a closable hazardous waste container.

For more information on waste disposal, see section 15.

[243] Solaß, W, et al, (2013), Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Occupational Health and Safety Aspects, Annals of surgical Oncology 20, 3504-3511. Willaert, W. et al, (2017), Occupational safety of pressurized intraperitoneal aerosol chemothearpy (PIPAC), Pleura and Peritoneum (2017) 1-7.

11.8.7 Excreta and blood

In surgical procedures, the systemic uptake of HMPs in the patient is lower than from oral and injection administration. This means that the presence of HMP in excreta (urine, faeces, vomit and sweat) and blood lower and that the risk period may be shorter. In the absence of specific information, it should be assumed that the risk period is the same as for the same HMP in other administration forms. A high concentration of HMPs can be present in the fluids used in the procedures or in body fluids that have been in contact with the treatment fluid.

11.8.8 Cleaning and laundry

Surfaces, bed linen, and clothing that have been in contact with HMP containing solution or excreta (urine, faeces, vomit and sweat) or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable bed linen and other laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2. A separate washing protocol for surgical laundry may apply based on the specific needs for this type of laundry.

11.9 Administration at other healthcare facilities

This section focuses on administration of HMPs at healthcare and care facilities other than hospitals. A pharmacy is generally not physically attached to such patient care facilities.

Examples of the relevant facilities (non-hospital healthcare facilities) include:

- GP practices or local health centres
- Nursing homes

The practices and equipment at these facilities may differ to those at hospitals and, consequently, separate advice is provided for these facilities in this section of the guide.

11.9.1 Management and organisation

Developing and adhering to procedures for patient care, handling excreta, waste, cleaning, and laundry is the responsibility of the employer.

A risk assessment should be performed[244], see section 4. For further guidance on risk and exposure assessment for HMP administration, see section 11.1.2.

In healthcare and care settings outside of a hospital, effective coordination and cooperation between the different employers involved in HMP preparation, transport, administration, and patient care should be established. One organisation should be nominated as being responsible for overall coordination, for example the organisation responsible for the treatment of the patient.

For example, a pharmacy could be responsible for preparing, packaging, delivering (transport) of HMPs and the provision of information about the HMPs to the employer/department involved in the administration. This could include information about the risk period during which the HMP remains present in the excreta (urine, faeces, vomit and sweat) and blood (ideally obtained from the manufacturer), how to use the provided equipment in administration procedures, and how to handle patient-related incidents with HMPs (for instance extravasation).

Administration of HMPs and the associated patient care should only be performed by trained workers. The training is determined by the risk assessment, see section 4.

11.9.1.1 Centralisation

The administration of HMPs should be centralised in a dedicated area to the maximum degree possible to prevent unnecessary contamination and ensure that HMPs are handled by properly trained workers

[244] Directive 2004/37/EC, Article 3(2)

that have been informed about the relevant risks and protective measures. The facilities for administration should also be designed to enable safe handling of HMPs and effective and efficient cleaning. If centralisation is not possible, workers should have the necessary tools, equipment and furniture to ensure that the risk from occupational exposure to HMPs is eliminated or reduced to a minimum in a decentralised environment.

11.9.2 Organisational measures

Activities related to HMP administration should be supervised by a dedicated, trained, person, such as the head or manager of the non-hospital facility.

Only trained and competent workers should be involved in the administration of HMPs. Pharmacists' instructions should be followed, see section 10.

11.9.2.1 Communicate risks associated with patients

In case of outpatient treatment, it is important to share information about the entire period during which HMPs could be present in excreta with any employer responsible for care of the patient.[245] Sharing the same information with the patient can facilitate the awareness of other relevant employers, such as agencies supplying carers or domestic cleaners.

11.9.3 Excreta and blood

Excreta (urine, faeces, vomit and sweat) and blood should be treated as contaminated with HMPs during the time HMPs are being taken by the patient and generally up to 7-14 days after administration. As noted in section 8.6, it would be useful if information about the presence of HMPs in excreta and blood is supplied by the pharmaceutical company in the safety data sheet. An overview can also be found in peer-reviewed and published pharmaceutical guidelines[246].

For handling excreta with care, see section 11.1.8.

11.9.4 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required in the administration areas of HMPs and sanitary facilities. See also Annex 4 for advice on the appropriate PPE.

Surfaces and administration areas (bedroom), sanitary facilities, and mattresses should be cleaned using at least:

- Type B protective gloves
- Protective gown
- Protective face shield/goggles (in case of splashing)

11.9.5 Waste

Packages, drink containers (single-use containers used for the application of liquid HMPs), administration spatula/bags/syringes/infusion systems, single-use PPE and protective sheets that have been used during administration of HMPs or HMP contaminated excreta (urine, faeces, vomit and sweat) should be disposed of as hazardous waste, in a closable hazardous waste container.

For more information on waste disposal, see other parts of section 15.

11.9.6 Cleaning and laundry

Surfaces, bed linen and clothing that has been in contact with excreta (urine, faeces, vomit and sweat) and blood from the patient should be treated by workers as HMP contaminated. HMP laundry should be washed twice separately from other laundry; first cold pre-wash programme followed by normal warm programme, see section 14.2. Surfaces and equipment should be cleaned directly after administration using regular cleaning detergents. It is useful for cleaning to be recorded (for example, in an activity control log).

Cleaning agents should be selected based on compatibility, effectiveness and possible residues. Water and

[245] Whilst ensuring that rules on personal data protection are respected – see footnote 238 and Regulation (EU) 2016/679

[246] A regularly updated overview of the recommended duration of protective measures is provided, for example, in the full version of Quapos 6 (Quality Standard for the Oncology Pharmacy Service) Commentary Version. See https://esop.li/

cleaning agent should be used in combination with dedicated cloths.

For example, the following items may need regular cleaning in administration areas:

- Equipment, floor and surfaces
- Chair / bed / bedside table
- Carpet
- Door handles
- Phones, TV remote and keyboards
- Toilet / shower
- Equipment for handling excreta

11.10 Administration and care in care homes, hospices, and in homes

This section focuses on administration in two types of location:

- Care homes or hospices
- In patient's home

Patients who were receiving treatment in hospital or other medical facility prior to moving to a care home or hospice or returning to their home, may need to continue such treatment in the new care setting. HMPs could still be present in the excreta (urine, faeces, vomit and sweat) and blood and may need attention during patient care.

The responsibility for preparation, transport, administration of HMPs and patient care can be divided across several employers.

For administration, the same preventive measures should be taken as for healthcare facilities other than hospitals, see section 11.9.

11.10.1 Management and organisation

See section 11.9.1.

11.10.2 Communicate risks associated with patients

In case of outpatient treatment, it is important to share information about the entire period during which HMPs could be present in excreta (urine, faeces, vomit and sweat) and blood with any employer responsible for care of the patient.[247] Sharing the same information with the patient can facilitate the awareness of other relevant employers, such as agencies supplying carers or domestic cleaners.

11.10.3 Organisational measures

Developing and adhering to procedures for patient care, handling excreta, waste, cleaning, and laundry is the responsibility of the employer. Only procedures that provide safe administration of the HMPs for workers, patients, and carers should be used. A risk assessment, see section 4, should be performed to determine the PPE required. For guidance to perform a risk assessment and exposure assessment, see section 11.1.2.

The choice of products and devices used has an impact on reconstitution and administration practices. All professional groups involved in HMP preparation and familiar with home care administration should be consulted in the selection of devices used within the home care situation.

Preparation activities should typically take place in a pharmacy, except for HMPs that need to be prepared in the home of the patient. In such a case, it is useful that the pharmacy provides specific instructions for preparation, administration, and handling of waste.

Only trained workers should be involved in the preparation, administration, and waste handling of

[247] Whilst ensuring that rules on personal data protection are respected – see footnote 238 and Regulation (EU) 2016/679

HMPs, see section 6. Pharmacists' instructions should be followed, see section 10.

Workers should have sufficient and adequate training, necessary tools, PPE, and equipment.

Special attention should be paid to the transport and intermediate storage of HMPs. Where possible, HMPs should be stored in a designated, sealable cabinet at the patients' home, care home or hospice. It is important for workers, patients, and carers to be informed / instructed about the risks the HMPs might pose to workers.

11.10.4 Procedures and technical measures

The same preventive measures apply as those taken at healthcare facilities other than hospitals, see section 11.9.

Protect surfaces, carpets and furniture with protective sheets when required by the risk assessment, see section 4.

11.10.5 Personal protective equipment (PPE)

A risk assessment, see section 4, should be performed to determine the PPE required in the administration areas of HMPs and sanitary facilities. See also Annex 4 for advice on the appropriate PPE to use for cleaning.

Surfaces and administration areas (bedroom), sanitary facilities, and mattresses should be cleaned using at least:

- Type B protective gloves
- Protective gown
- Protective face shield/goggles (in case of splashing)

11.10.6 Waste

Packages, drink containers (single-use containers used for the application of liquid HMPs), administration spatula/bags/syringes/infusion systems, single-use PPE and protective sheets that have been used during administration of HMPs or HMP contaminated excreta (urine, faeces, vomit and sweat) should be disposed of as hazardous waste, in a closable hazardous waste container.

For administration at home, waste take-back schemes should be established to ensure a safe disposal of HMP-contaminated waste, see section 15.4.4. For more information on waste disposal, see other parts of section 15.

11.10.7 Cleaning and laundry

Surfaces, bed linen and clothing that have been in contact with excreta (urine, faeces, vomit and sweat) and blood from the patient should be treated by (home)care workers as HMP contaminated. HMP laundry should be washed twice separately from other laundry; first cold pre-wash programme followed by normal warm programme, see section 14.2. Cleaning protocols should be available for all care workers that enter the home, see section 14.1, for example, nurses, rehabilitation workers, cleaners. Surfaces and equipment should be cleaned directly after administration using regular cleaning detergents. It is useful for cleaning to be recorded (for example, in an activity control log).

Cleaning agents should be selected based on compatibility, effectiveness and possible residues. Water and cleaning agent should be used in combination with dedicated cloths.

For example, the following items may need regular cleaning in administration areas:

- Equipment, floor and surfaces
- Chair / bed / bedside table
- Carpet
- Door handles
- Phones, TV remote and keyboards
- Toilet / shower
- Equipment for handling excreta

11.11 Summary of advice in section 11

Management and organisation

- Administration should be centralised in a dedicated area to the maximum degree possible.
- Preparation activities should typically take place in a pharmacy.
- Only trained and competent workers should be involved in the administration of hazardous medicinal products (HMPs).
- The relevant activities should be supervised by a competent/trained dedicated person, such as the head or manager of the centralised administration unit or ward.
- The use of syringes with needles should be avoided as much as possible.
- If possible, patients should self-administer (oral, topical or inhalation).

Risk assessment for HMP administration

- The main exposure route for HMP in administration is dermal exposure.
- If good practice is used in infusion procedures, aerosols are only released by pressure build-up in the infusion line to the patient. If the infusion procedure is based on gravity, the infusion stops automatically.
- Withdrawing the needle from the container/bag or patient can result in a release of aerosols due to a pressure drop or incident when the needle disconnects from the syringe during the procedure. The use of needle-free connections or Luer-lock helps avoid the pressure change.
- The previous bullet points focus on the infusion procedure, which is a common method of HMP administration. For information on other administration procedures (oral, topical, etc.) please refer to 11.2 and 11.4 to 11.8.

Technical measures

- Choice of technical measures should be based on the HMP, dosage, volume and frequency of the HMP administered.
- The use of closed system transfer devices (CSTDs) is the decision of the management/staff in accordance with the risk assessment and the relevant national legislation.
- The use of all technical measures should be validated and periodically re-evaluated.

Organisational measures

- Work should be organised in advance.
- Facility layout should allow for effective cleaning.
- Standard Operating Procedures (SOPs) should be in place for e.g. for patient care, handling excreta, waste, cleaning, and laundry.

Personal protective equipment (PPE)

- PPE should be used for administration based on risk assessment and in line with the advice in sections 11.2 to 11.10.
- Protective gloves should be used for removing other personal protective equipment (PPE).

Hygiene measures

- Examples of hygiene measures include no food, drink, cigarettes/vaporisers, jewellery, medication for personal use, or chewing gum in the administration area.

Excreta and blood

- Due to risk of HMPs being present in excreta and blood, ensuring that patients that have undergone treatment with HMPs are easily identifiable can be very helpful. However, any such identification needs to be in conformity with applicable data protection rules. Excreta and blood is contaminated generally up to 7-14 days after administration.
- In case of outpatient treatment, information about the entire period during which HMPs could be present in excreta and blood should be shared with any employer responsible for care of the patient, whilst ensuring that rules on personal data protection are respected.

Waste

- All materials that have been in contact with HMPs should be disposed of as hazardous waste. Non-disposable equipment and PPE should be cleaned immediately after use.

For an example of a summary of advice on controlling exposure to HMPs for oral and intravenous (IV) administration of HMPs, see Annex 7.

12

Veterinary practices

12.1 Introduction

The use of hazardous medicinal products (HMPs) in veterinary practices is less frequent than in human medical practices, however, the European College of Veterinary Internal Medicine of Companion Animals reports that the use is increasing (ECVIM-CA, 2007[248]). Occupational exposure to HMPs can occur during preparation and administration of HMPs, during the handling of animal waste, cleaning, and maintenance. An additional risk is that animal patients may behave with less predictability and be less co-operative than human patients. Workplace sampling of veterinary oncology centres has detected platinum containing antineoplastic HMP contamination on multiple surfaces and equipment (Janssens et al., 2015)[249] demonstrating the potential risk of occupational exposure to HMPs during animal patient care. Veterinarians, veterinary nurses and students, animal attendants, cleaners and maintenance workers may be exposed to HMPs and related waste during the treatment and care of animals. This section provides guidelines for the treatment of pet animals within veterinary facilities only and does not include guidelines on home-based activities.

12.2 Preparation of veterinary HMPs

12.2.1 Management and organisation

12.2.1.1 Centralisation

As good practice, HMPs should not be prepared at veterinary practices. It is good practice for them to be prepared at pharmacies and ready-to-administer HMPs to be supplied to veterinary practices.

12.2.1.2 Risk assessment

It is acknowledged that preparation in pharmacies is not always feasible and, in such instances, HMPs need to be prepared in the veterinary practices. A risk assessment must be carried out[250], see section 4 and should cover the entire preparation process from the reception of HMPs from the manufacturers, the storage of HMPs, the preparation stages of HMPs, through to the cleaning and maintenance of equipment and preparation area. Veterinary practices that use external companies to conduct risk assessments must[251] advise assessors if HMPs are prepared on site, even if done infrequently.

Workers who may be exposed during the preparation of HMPs include veterinarians, veterinary nurses, cleaners, and maintenance workers. Common routes of exposure include direct dermal contact with HMPs, contact with contaminated surfaces, inhalation of aerosols or HMP particles, ingestion, and needle stick injuries.

12.2.1.3 Use of dedicated areas

Veterinary practices which prepare HMPs on-site should have a designated, secure preparation area, identified with warning signs. Access must be restricted to authorised personnel.[252] It is recommended that veterinary practices that are unable to follow the outlined preparation guide source HMPs already prepared by a pharmacy or a wholesaler. Veterinary practices that obtain HMPs from external suppliers should store them in accordance with the advice in section 9.2.

12.2.1.4 Workers and organisation

Please refer to the measures for the preparation of HMPs for human use in section 10.2.3.

[248] ECVIM-CA, (2007), Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine, Document of the European College of Veterinary Internal Medicine of Companion Animals
[249] Janssens, T. et al, (2015), Determination of platinum surface contamination in veterinary and human oncology centres using inductively coupled plasma mass spectrometry, Vet Comp Oncol, 13, 305-13.
[250] Directive 2004/37/EC, Article 3(2)
[251] Directive 89/391/EEC, Article 5(2)
[252] Directive 2004/37/EC, Article 9

12.2.2 Organisational measures

Any activities that are related to the handling of HMPs should be developed, organised and supervised by a competent, designated person such as a veterinary surgeon, or a suitably trained veterinary technician. All workers who could be potentially exposed to HMPs that have been identified in the risk assessment, see section 4, need be taken into consideration. It is important to consider female or male workers who are trying to conceive or female workers that are pregnant or breastfeeding should be advised not to be present in areas where exposure may occur. In smaller veterinary practices, it may not be possible to completely eliminate risks for workers most at risk, and so the risks of working with HMPs must be identified through a risk assessment, and clearly communicated to these workers, see section 3.4. Workers who are involved in handling of HMPs should be trained and competent[253], see section 6.

12.2.3 Technical measures

The technical measures that should be used during the preparation of HMPs are the same as for the preparation of human HMPs, see section 10.3.

In addition to technical measures reported in section 10.3, HMPs should also be sealed into a bag or container before removal from the biological safety cabinet (BSC) / isolator, if this is recommended in the risk assessment. If the preparation and administration areas are in close proximity to each other, then the risk assessment may conclude that this step is not necessary.

12.2.4 Personal protective equipment (PPE)

For how to select personal protective equipment (PPE), see Annex 4. This should be determined by a risk assessment, see section 4.

At a minimum, the following PPE should be used during preparation activities:

- Protective gloves type B
- Face shield/goggles
- Protective gown/coveralls

If there is a risk of exposure due to ineffective exhaust ventilation, appropriate respiratory protection equipment should be considered. The respiratory protection for workers working with HMPs should be at least FFP2 filtering face pieces depending on the task.

For instruction on putting on and taking off protective gloves, see Annex 4.

12.2.5 Operational procedures and hygiene measures

Safe working practices should be used when handling HMPs and these should be documented. Standard operating procedure (SOP) manuals should be developed and also reviewed and updated as required. A list should be developed for the HMPs prepared at the practice.

SOPs should be clear and readily available. Where possible, preparation and administration tasks could be coordinated to limit potential HMP exposure to workers. A spill kit should be readily available in these areas, see section 13.3. SOPs should also cover the safe disposal of waste, see section 15.

12.2.5.1 Particle generation

To prevent the generation of airborne particles, the manipulation of medicines containing HMPs should be avoided; such as tablet splitting, breaking, and crushing. Mixing and weighing powders should also be avoided. If unavoidable, these activities should be performed in a BSC, see section 12.2.3. If the veterinary practice does not have a BSC, it should consider if it is possible to avoid tablet splitting by adjusting dosage, sourcing smaller tablets, adjusting the dose and timing (for example, taking several tablets over several days), looking for alternatives or having the relevant activities undertaken at a pharmacy with a BSC.

[253] See also Directive 2004/37/EC, Article 11; Directive 89/391/EEC, Article 6(2)(i), 6(3)(b) and (d)

12.2.5.2 Packaging of HMPs

All HMPs (including prepared HMPs) should be labelled clearly and consistently, see section 2.

Those that are not used immediately, stored in appropriate conditions, see section 10.4.3.

12.2.5.3 Hygiene procedures

During preparation activities, the following hygiene procedures at least should be followed:

- No hand and wrist jewellery, long necklaces or large earrings
- Keep nails short and clean, do not wear make-up, nail varnish, artificial nails or perfume
- No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum in the preparation area
- No mobile phones, personal devices and headphones in the preparation area
- Tie back long hair
- Wash hands before putting on and after removing protective gloves
- Hands should be washed before leaving the preparation area

More information on the provisions for hygiene procedures in the carcinogens, mutagens and reprotoxic substances directive (CMRD)[254] is provided in Box 10-3 in section 10.6.

12.2.6 Waste

Single-use PPE as well as used materials that have been in contact with HMPs should be disposed of as hazardous waste in a closable hazardous waste container. Non-disposable equipment and PPE should be cleaned immediately after use.

12.2.7 Cleaning and laundry

Surfaces, clothing, etc. that have been in contact with HMPs should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable laundry should be treated as HMP-contaminated laundry, see section 14.2.

12.3 Administration of veterinary HMPs

12.3.1 Management and organisation

12.3.1.1 Centralisation

The administration of HMPs should be centralised to the maximum degree possible to prevent unnecessary contamination and ensure that HMPs are handled by properly trained workers that have been informed about the relevant risks and protective measures. Centralisation is also helpful for ensuring that facilities for administration are designed to enable safe handling of HMPs and effective and efficient cleaning. If centralisation is not possible, workers should have the necessary tools, equipment and furniture that ensures exposure and workplace contamination is reduced to a minimum.

12.3.1.2 Risk assessment

See section 4 for guidance on performing the risk assessment. In addition to the previously mentioned risks; direct dermal contact with HMPs, contact with contaminated surfaces, inhalation of aerosols or HMP particles, ingestion, and needle stick injuries, there are additional risks associated with working with animals, who may behave unpredictably. In addition, there are increased potential routes of exposure from animal patients who are hospitalised in practice, which arises

[254] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

from HMPs excreted in animal patient urine, faeces, saliva and sebum. Workers who may be exposed during this stage include veterinarians, veterinary nurses and students, animal attendants, maintenance workers and cleaners.

12.3.1.3 Use of dedicated areas

Administration should ideally be carried out in clearly designated (isolated) areas that are secure with restricted access. Where a designated area is not possible, the room should not be used for other purposes during administration activities or until it has been cleaned according to protocol. During the administration activities and until it has been cleaned, the room should also be clearly labelled. There should be dedicated HMP administration equipment that is not utilised for non-HMP administration. The dedicated area should have hazardous waste disposal containers that can be opened with a foot pedal or another mechanism to prevent direct contact with hands/gloves.

12.3.1.4 Workers and organisation

See section 11.1.3.

12.3.1.5 Animal patient identification and housing areas

The containment of animal waste can be challenging, for this reason there should be a designated area within the veterinary practice to house animal patients that have been treated with HMPs. The space should be in a low traffic area, have sufficient room to allow workers to move around freely and safely store any hazardous waste prior to removal, see section 15. This area must be restricted to essential workers, with clear signs indicating this.[255]

Animal patients who have received HMP treatments should be clearly identifiable by the placement of signs on cages which report the treatment, possible excretion routes and the duration that PPE use is recommended. Additional identifying information may include, but is not limited to, the name and breed of the animal patient as well as owner details to aid differentiation of animal patients treated with HMPs. To limit additional sites of contamination, cages that contain and remove animal waste directly into the sewerage system should be considered where possible. Cages should be kept clean during the housing of animal patients, and should also be cleaned following patient discharge, see section 14.1.

Figure 12-1: Example of sign on cage of animal patient receiving HMP treatment

Due to the potential for animal patients to excrete HMPs, all materials used in housing areas should be considered contaminated and treated as hazardous waste. Where possible, single-use absorbent bedding and towels should be used. Bowls for food and water should be single-use, or made from non-porous material, such as metal. For the handling of non-disposable bedding, see section 14.2.

[255] Directive 2004/37/EC, Articles 9, 5(5)(j), 11(5)

12.3.2 Technical measures

Protective measures must be used for the administration of HMPs to reduce the potential exposure to workers.[256] Technical measures that should be considered include:

- The use of infusion systems with a physical barrier, if this is not available to the veterinary practices then it is recommended that, at a minimum, infusion sets and syringes with Luer-lock fittings should be used to administer HMPs.
- Other protective techniques include the priming[257] of intravenous (IV) tubing with a non-HMP solution during HMP preparation, which should be done inside a ventilated cabinet.

Work should be done below eye level to minimise the potential for personal contamination. The animal patient should be positioned on a floor or table to maximise animal patient comfort and co-operation to facilitate the safe administration of HMPs.

12.3.3 Organisational measures

The number of people in the designated administration area must be as limited as possible.[258] It is important to consider whether female or male workers that are trying to conceive or female workers that are pregnant or breastfeeding should be present in areas where exposure may occur.

12.3.4 Personal protective equipment (PPE)

Annex 4 explains how to select the appropriate PPE. The PPE required should be determined by a risk assessment, see section 4.

At a minimum, the following PPE should be used during administration activities:

- Protective gloves type B
- Protective gown/coveralls
- If indicated by a risk assessment: protective face shield/goggles, see section 4

If animals are placed on a table for the administration of HMPs, PPE should be worn by HMP administrators before the animal patient is placed on the table to reduce the risk of contamination.

Double protective gloves offer greater protection, however, to ensure animal patient cooperation through rapid HMP administration, the use of single protective gloves may be considered.

For instructions on putting on and taking off protective gloves, see Annex 4.

12.3.5 Operational procedures and hygiene measures

12.3.5.1 Working practices

Safe working practices should be used in the administration of HMPs, and these should be documented. Workers should also be competent in administration activities. SOP manuals should be developed and also reviewed and maintained on a regular basis. These should also be updated when required. At each centre, a list should be developed for the HMPs administered.

SOPs should be clear and readily available. Where possible, it is recommended that preparation and administration tasks are coordinated to limit potential HMP exposure to workers. A spill kit should be readily available in the area, see section 13.3. SOPs should also cover the safe disposal of waste, see section 15.

12.3.5.2 Pre-administration

For veterinary practices that receive HMPs from an external source (for example, from a pharmacy), the HMP should be examined for leakage while it is contained in the transport bag. If intact it can be removed from the transport bag. Damaged packaging

[256] Directive 2004/37/EC, Article 5(5)(c)
[257] Priming refers to placing fluid in the tubing in order to eliminate air prior to administration. Source: adapted from Anderson et al (2018): Clinical Procedures for Safer Patient Care, Thompson Rivers University. Available at https://pressbooks.bccampus.ca/clinicalproceduresforsaferpatientcaretrubscn/
[258] Directive 2004/37/EC, Article 5(5)(b)

should be disposed of as hazardous waste, see section 15. The HMP should be placed on an absorbent pad prior to administration. If applicable, the transport bag should be used as a containment bag for materials contaminated during administration.

12.3.5.3 Animal patient handling

Measures should be taken to ensure the comfort and cooperation of the animal patient to minimise risk and disruption during the administration of HMPs. The presence of owners may aid animal patient relaxation, however this should be determined by the individual practice and be covered in the risk assessment, see section 4, as is dependent on the size of the facility and the level of risk from the HMP being administered. Animal patients should be adequately restrained by trained personnel during the administration of HMPs.

If the animal's temperament does not guarantee the safe administration of HMPs, then treatment should be postponed until it is safe to do so and/or the use of a chemical restraint, for example a sedative or anaesthetic, should be considered.

Figure 12-2:
The administration of HMPs to an animal patient, with all workers present wearing PPE at Oncovet - Veterinary Cancer Centre, Villeneuve-d'Ascq, France

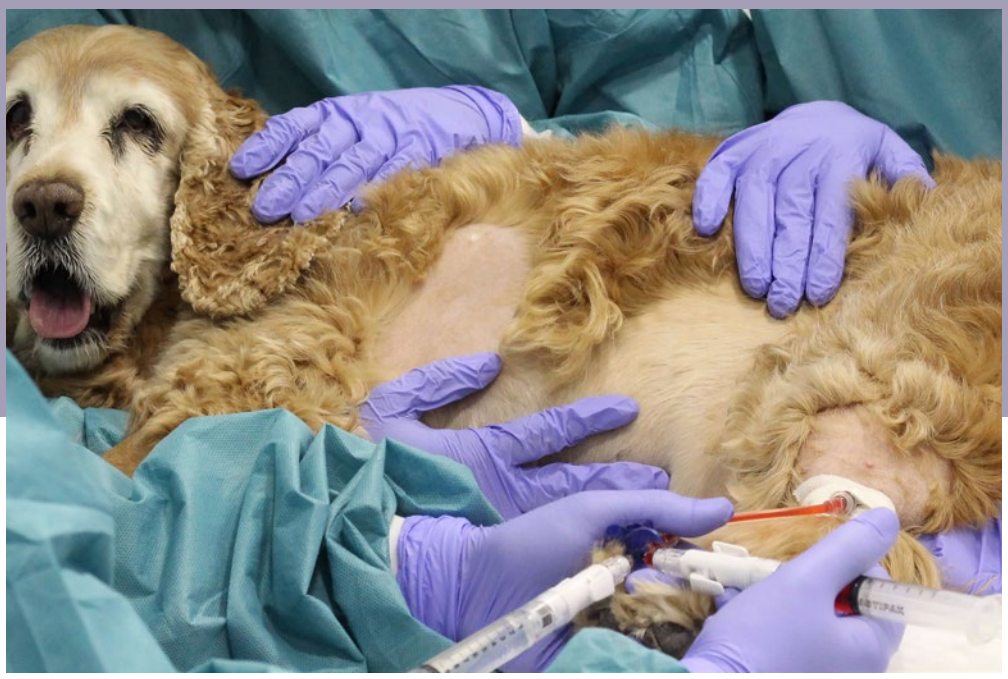


Figure 12-3:
The administration of HMPs to an animal patient, with all workers present wearing PPE at the Hospital Auna Especialidades Veterinarias-IVC Evidensia, Spain

12.3.5.4 Oral administration

The oral administration of HMPs carries a greater risk of contamination when compared to parenteral administration, and injection should be considered as an alternative form of delivery. When oral administration of HMPs takes place at a veterinary practice, it should only occur under the supervision of a registered veterinary practitioner; this advice does not extend to administration of oral HMPs in the home. HMPs should be given intact. Tablets should not be crushed or split, and capsules should not be opened.

12.3.5.5 Intralesional and subcutaneous administration

The intralesional and subcutaneous administration of HMPs should only occur under the supervision of a registered veterinary practitioner. As this is a high-risk activity for worker exposure, it is recommended that additional precautions are taken, such as placing a larger single-use sheet under the animal patient and cleaning the area the animal patient was treated on afterwards. All workers involved in the intralesional administration should wear the appropriate PPE, not just the veterinary surgeon administering the HMPs, as there is a high risk of splashes. For this reason, all workers present should wear a protective face shield instead of goggles.

12.3.5.6 Intravenous (IV) administration

Intravenous (IV) administration should only occur under the supervision of a registered veterinary practitioner and the IV catheter should be placed in the vein by experienced personnel. The most appropriately sized catheter for the size of the animal to best accommodate HMP administration should be chosen. During treatment the administration site should be monitored to check the catheter connection for potential leakages and ensure that the animal patient's veins are not blocked or obstructed. The animal patient should not be left unattended during IV administration. For this reason, IV pumps should be

Figure 12-4: The administration of HMPs to an animal patient, with the workers present wearing PPE at the Hospital Auna Especialidades Veterinarias- IVC Evidensia, Spain

Figure 12-5: Example of bad practice for HMP administration: no PPE worn by workers during the administration of HMPs and jewellery worn during animal patient restraint

avoided if possible[259]; however, if these are required, there should be regular checks as determined in the risk assessment.

A bolus injection can be administered through a catheter system, which can then be flushed with 0.9% sodium chloride solution before being removed from the animal patient (except for carboplatin, which is administered and flushed in a 5% glucose solution).

IV tubing should never be removed from the IV bag that contains HMPs and tubing at other points in the system should not be disconnected until it has been thoroughly flushed (as above). Where possible, it is recommended that the IV catheter, tubing and bag remain intact during removal.

12.3.5.7 Animal patient care when hospitalised in practice

This section relates to animals that remain in the veterinary practice post treatment, as the guide only covers occupational exposure.

HMPs have been detected in excreta (urine, faeces, saliva and sebum) of HMP treated animal patients[260,261,262] and therefore, pose a risk to workers who care for animal patients, or work around animal patient housing areas and the procedures required to protect these workers should be defined in the risk assessment, see section 4.

[259] Whilst human patients can be expected to sit/lie still during their infusions, animal patients cannot. Therefore, the use of IV pumps should be avoided.

[260] Hamscher, G. et al, (2010), Determination of Drug Residues in Urine of Dogs Receiving Anti-Cancer Chemotherapy by Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry: Is There An Environmental or Occupational Risk?, Journal of Analytical Toxicology, Volume 34, Issue 3, April 2010, Pages 142–148, https://doi.org/10.1093/jat/34.3.142

[261] Knobloch, A., et al, (2010), Cytotoxic Drug Residues in Urine of Dogs Receiving Anticancer Chemotherapy, Journal of Veterinary Internal Medicine, 24(2), pp. 384–390, https://doi.org/10.1111/j.1939-1676.2009.0453.x

[262] Knobloch, A., et al, (2010), Drug Residues in Serum of Dogs Receiving Anticancer Chemotherapy, Journal of Veterinary Internal Medicine, 24(2), pp. 379–383, https://doi.org/10.1111/j.1939-1676.2009.0469.x

12.3.5.8 Handling animal patients

Animal patients should be confined to their caged areas during periods when HMPs may be excreted. If possible, the hospitalised animal patient should be allowed to urinate and defecate outside in a separate, designated, low-traffic area that can be cleaned easily. Interactions with treated animal patients should be limited and restricted to only trained individuals. PPE should be worn during the handling of animal patients, see section 12.3.4.

12.3.5.9 Hygiene measures

Hygiene measures in section 12.2.5.3 should be followed.

12.3.6 Waste

12.3.6.1 Post administration

All potentially contaminated material used in the administration of HMPs, including sharps, should be disposed of in hazardous waste disposal containers that can be opened with a foot pedal or another mechanism to prevent direct contact with hands/ gloves. Protective gloves should be used for the removal of the gown/ and face shield/goggles if used, and PPE should be disposed of as hazardous waste, see section 15. For decontamination and cleaning procedures, see section 14.1.

12.3.6.2 Animal patient waste

Advice for handling of animal patient waste is provided in section 15.

12.3.7 Cleaning and laundry

Surfaces, clothing, etc. that have been in contact with HMP containing solution or excreta or blood should be considered as contaminated with HMP. These surfaces should be cleaned according to cleaning protocols, see section 14.1.

Non-disposable laundry that is used during the procedure should be treated as HMP-contaminated laundry, see section 14.2.

12.4 Summary of advice in section 12

Introduction

- Workers exposed include, for example, veterinarians, veterinary nurses and students, animal attendants, cleaners, maintenance workers, etc.
- A risk assessment must be prepared and cover the entire process (preparation, administration, and post-administration). [263]
- Special consideration should be given to male and female workers considering conceiving, female workers who are pregnant, and female workers who are breastfeeding. [264]
- Activities with exposure to HMPs should be supervised by a competent, designated person.

Preparation

- Management and organisation:
  - Centralisation: as good practice, HMPs should be prepared at pharmacies. Where not centralised, use of a designated, secure preparation area is recommended.
- Technical measures for preparation:
  - For example, biological safety cabinet (BSC) Class II Type 2B, cytotoxic drug safety cabinet (CDSC), isolator, etc.
- Personal protective equipment (PPE) for preparation:
  - At a minimum, type B protective gloves, face shield/goggles, protective gown/coveralls
  - If there is a risk of exposure due to ineffective exhaust ventilation, appropriate respiratory protection equipment should be considered.
- Operational procedures and hygiene measures for preparation:
  - Working practices for preparation: develop standard operating procedures (SOPs), spill kits available, etc.
  - Avoid activities that generate particles: tablet splitting, breaking, crushing, mixing powders, etc.
  - Examples of hygiene procedures for preparation: hand washing, no eating/drinking, etc.

Waste:

- All materials that have been in contact with HMPs should be disposed of as hazardous waste. Non-disposable equipment and PPE should be cleaned immediately after use.

Administration

- Management and organisation:
  - Administration should be centralised to the maximum degree possible in dedicated areas using dedicated equipment.
  - Designated area for housing animal patients that have been treated with HMPs in a low traffic area are recommended, with ample space and restricted access.
  - Animal patients who have received HMP treatments should be clearly identifiable.
  - Cages that remove waste directly to the sewerage system should be considered.
- Examples of technical measures include:
  - Infusion systems with a physical barrier or infusion sets and syringes with Luer-lock fittings, priming of intravenous (IV) tubing during preparation in a ventilated cabinet or priming with a non-HMP solution

263 Directive 2004/37/EC, Article 3(2)
264 See also Directive 2004/37/EC, Article 3(4)

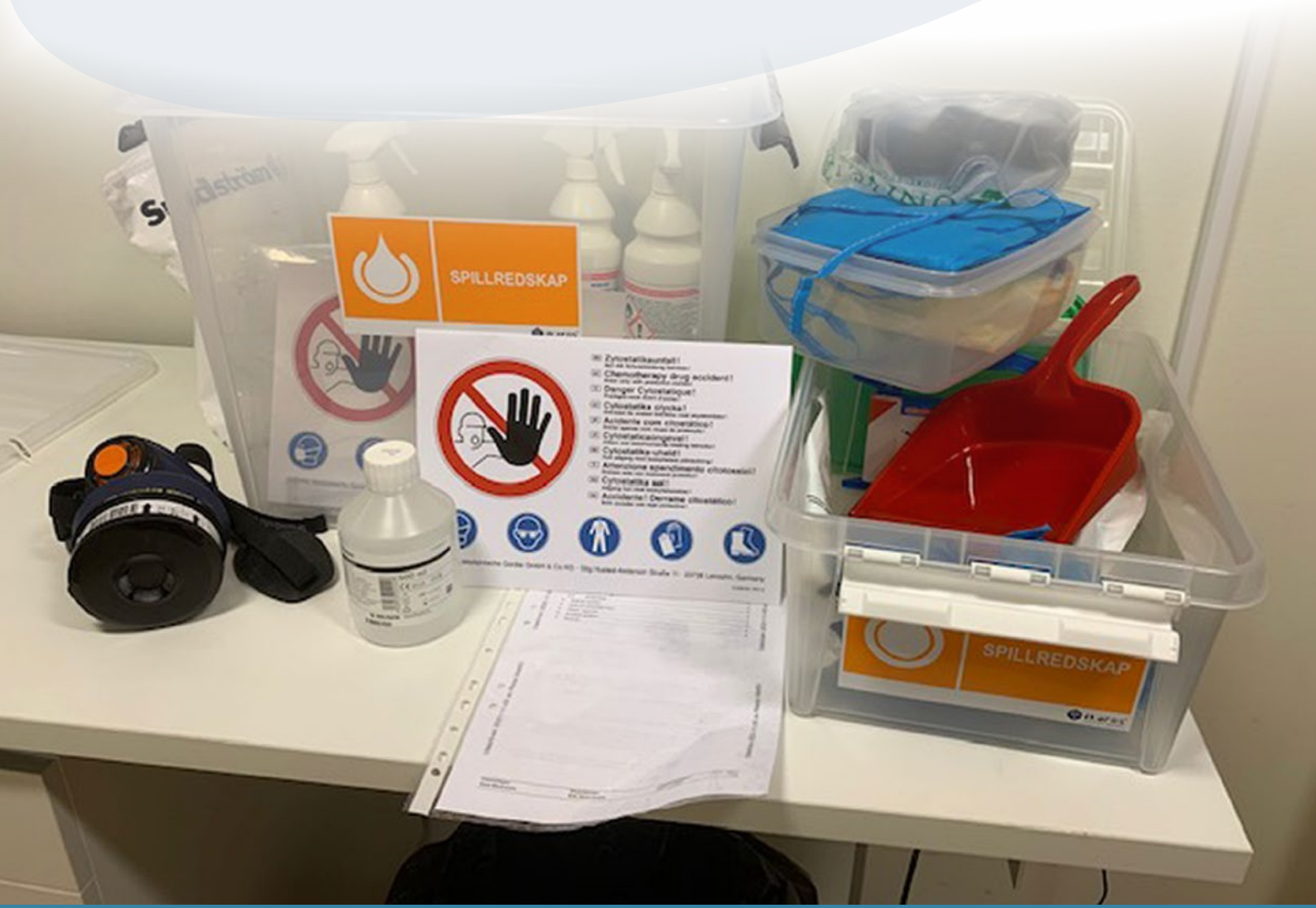
- Organisational measures:
  - The number of people in the designated administration area should be as limited as possible.
- PPE for administration:
  - At a minimum, type B protective gloves, face shield/goggles protective gown/ coveralls should be used.
- Operational and hygiene measures for administration include:
  - Comfort and co-operation of the animal patient should be ensured; if administration not safe, it should be postponed, or a chemical restraint considered.
  - Oral administration: an injection should be considered as a less risky alternative. Capsules should not be crushed/split/ opened.
  - Intralesional administration is high risk activity additional precautions such as a larger disposable sheet should be considered.
  - IV administration: there should be monitoring to check for leaks, the animal patient should not be left unattended or and IV pumps should be avoided if possible, a bolus injection can be administered through a catheter system which can then be flushed before removing from the animal patient, tubing should not be disconnected before it has been flushed, etc.
  - Animal patient care: If hospitalised, animal patients should be confined to their cages during periods of excretion, interaction with them should be limited and PPE should be worn.
  - Hygiene measures: the same hygiene measures as for preparation should be followed.

Waste

- Post administration: Contaminated materials should be disposed of as hazardous waste. Protective gloves should be used to remove other PPE.
- All materials in housing areas should be considered contaminated, disposable absorbent bedding, towels, bowls, etc. should be considered.

13

Incident management



13.1 Who is responsible for incident management?

The responsibility for prevention of incidents and development and updating of incident management procedures and plans relating to hazardous medicinal products (HMPs) always lies with the employer.[265] The employer may designate these tasks to in-house workers or enlist the assistance of external services or persons, who should typically have the following competencies (whilst according with any applicable national provisions):

- Occupational safety and health (OSH) knowledge, skills, and experience to develop and update the incident management protocols for all roles required based on the risk assessment
- Understanding of HMPs, workplaces, tasks undertaken, how and when exposure and incidents can happen, health & safety regulations
- Appropriate authority and seniority level

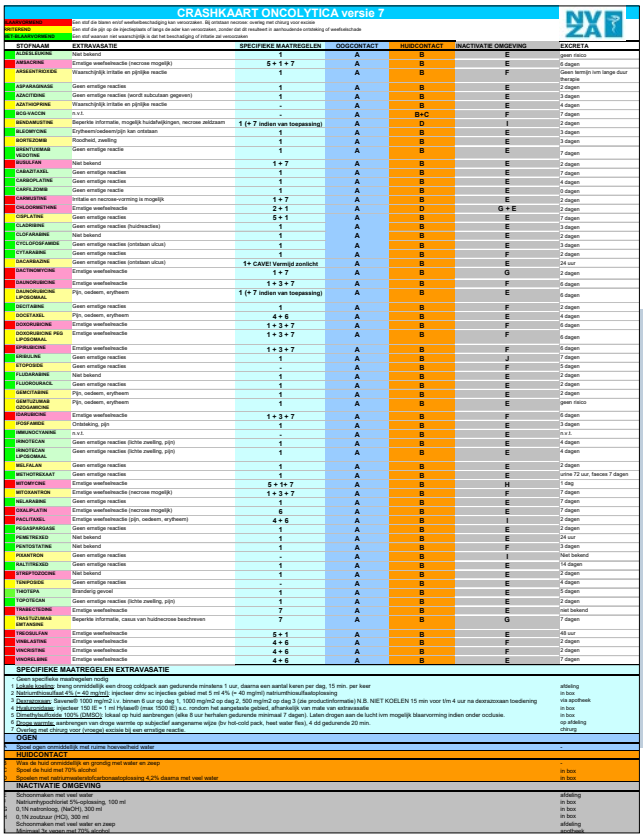
The requirements for the protocols are driven by the risk assessment, see section 4. The employer is also responsible for ensuring that all workers that handle HMPs or might come into contact with HMPs, are trained in incident management, see section 6, and are provided with all the necessary tools and equipment. The training should be practical and typically include relevant scenarios or simulations and explanations on how to:

- Prevent exposure of other individuals handling the incident
- Prevent spreading contamination
- Prevent personal contamination

13.2 Scope

A risk assessment, see section 4, and the HMP risk management plan should typically identify:

- Likely incident scenarios
- How to prevent exposure of workers handling the incident
- Content of the spill kit required for potential incidents
- How to prevent further spreading of HMPs in the environment
- Whether specially trained workers should handle the incident



CRASHKAART ONCOLYTICA versie 7

STOFNAAM	EXTRAVASATIE	SPECIFIEKE MAATREGELEN	OOGCONTACT	HUIDCONTACT	INACTIVATIE OMGEVING	EXCRETA
ALDESLEUKINE	Niet bekend	1	A	B	E	geen risico
AMSACRINE	Ernstige weefselnecrose (necrose mogelijk)	5 + 1 + 7	A	B	E	5 dagen
ARSEENTRIOXIDE	Waarschijnlijk irritatie en pijnlijke reactie	1	A	B	F	Geen termijn ivm lange duur therapie
ASPARAGINASE	Geen ernstige reacties	1	A	B	E	2 dagen
AZACITIDINE	Geen ernstige reacties (wordt subcutaan gegeven)	1	A	B	E	3 dagen
AZATHIOPRINE	Waarschijnlijk irritatie en pijnlijke reactie	-	A	B	E	4 dagen
BCG-VACCIN	n.v.t.	-	A	B+C	F	7 dagen
BENDAMUSTINE	Beperkte informatie, mogelijk huidafwijkingen, necrose zeldzaam	1 (+ 7 indien van toepassing)	A	D	I	2 dagen
BLEOMYCINE	Erytheem/oedeem/jeuk kan ontstaan	1	A	B	E	3 dagen
BORTEZOMIB	Roodheid, zwelling	1	A	B	E	3 dagen
BRENTUXIMAB VEDOTINE	Geen ernstige reactie	1	A	B	E	7 dagen
BUSULFAN	Niet bekend	1 + 7	A	B	E	2 dagen
CABAZITAXEL	Geen ernstige reacties	1	A	B	E	7 dagen
CARBOPLATINE	Geen ernstige reacties	1	A	B	E	4 dagen
CARFILZOMIB	Geen ernstige reacties	1	A	B	E	3 dagen
CARMUSTINE	Irritatie en necrose-vorming is mogelijk	1 + 7	A	B	E	2 dagen
CHLORMETHINE	Ernstige weefselnecrose	2 + 1	A	D	G + E	2 dagen
CISPLATINE	Geen ernstige reacties	5 + 1	A	B	E	7 dagen
CLADRIBINE	Geen ernstige reacties (huidreacties)	1	A	B	E	3 dagen
CLOFARABINE	Niet bekend	1	A	B	E	3 dagen
CYCLOFOSFAMIDE	Geen ernstige reacties (ontstaan ulcus)	1	A	B	E	3 dagen
CYTARABINE	Geen ernstige reacties	1	A	B	F	2 dagen
DACARBAZINE	Geen ernstige reacties (ontstaan ulcus)	1+ CAVE! Vermijd zonlicht	A	B	E	24 uur
DACTINOMYCINE	Ernstige weefselnecrose	1 + 7	A	B	G	2 dagen
DAUNORUBICINE	Ernstige weefselnecrose	1 + 3 + 7	A	B	F	6 dagen
DAUNORUBICINE LIPOSOMAAL	Pijn, oedeem, erytheem	1 (+ 7 indien van toepassing)	A	B	E	6 dagen
DEGITABINE	Geen ernstige reacties	1	A	B	F	2 dagen
DOCETAXEL	Pijn, oedeem, erytheem	4 + 6	A	B	E	4 dagen
DOXORUBICINE	Ernstige weefselnecrose	1 + 3 + 7	A	B	F	6 dagen
DOXORUBICINE PEG LIPOSOMAAL	Ernstige weefselnecrose	1 + 3 + 7	A	B	F	6 dagen
EPIRUBICINE	Ernstige weefselnecrose	1 + 3 + 7	A	B	F	6 dagen
ERIBULINE	Geen ernstige reacties	1	A	B	J	7 dagen
ETOPOSIDE	Geen ernstige reacties	-	A	B	F	5 dagen
FLUDARABINE	Niet bekend	1	A	B	E	2 dagen
FLUOROURACIL	Geen ernstige reacties	1	A	B	E	2 dagen
GEMCITABINE	Pijn, oedeem, erytheem	1	A	B	E	2 dagen
GEMTUZUMAB OZOGAMICINE	Pijn, oedeem, erytheem	1	A	B	E	geen risico
IDARUBICINE	Ernstige weefselnecrose	1 + 3 + 7	A	B	F	6 dagen
IFOSFAMIDE	Ontsteking, pijn	1	A	B	E	5 dagen
IMMUNOCYTANINE	n.v.t.	-	A	B	E	n.v.t.
IRINOTECAN	Geen ernstige reacties (lichte zwelling, pijn)	1	A	B	E	4 dagen
IRINOTECAN LIPOSOMAAL	Geen ernstige reacties (lichte zwelling, pijn)	1	A	B	E	4 dagen
MELFALAN	Geen ernstige reacties	1	A	B	E	2 dagen
METHOTREXAAT	Geen ernstige reacties	1	A	B	E	urine 72 uur, faeces 7 dagen
MITOMYCINE	Ernstige weefselnecrose	5 + 1 + 7	A	B	H	1 dag
MITOXANTRON	Ernstige weefselnecrose (necrose mogelijk)	1 + 3 + 7	A	B	F	7 dagen
NELARABINE	Geen ernstige reacties	1	A	B	E	7 dagen
OXALIPLATIN	Ernstige weefselnecrose (necrose mogelijk)	6	A	B	E	7 dagen
PACLITAXEL	Ernstige weefselnecrose (pijn, oedeem, erytheem)	4 + 6	A	B	I	2 dagen
PEGASPARGASE	Geen ernstige reacties	1	A	B	E	2 dagen
PEMETREXED	Niet bekend	1	A	B	E	24 uur
PENTOSTATINE	Niet bekend	1	A	B	F	3 dagen
PIXANTRON	Geen ernstige reacties	-	A	B	I	Niet bekend
RALTITREXED	Geen ernstige reacties	1	A	B	E	14 dagen
STREPTOZOCINE	Niet bekend	1	A	B	E	2 dagen
TEMOZOLOMIDE	Geen ernstige reacties	-	A	B	E	4 dagen
THIOTEPA	Branderig gevoel	1	A	B	E	5 dagen
TOPOTECAN	Geen ernstige reacties (lichte zwelling, pijn)	1	A	B	E	2 dagen
TRABECTEDINE	Ernstige weefselnecrose	7	A	B	E	niet bekend
TRASTUZUMAB EMTANSINE	Beperkte informatie, casus van huidnecrose beschreven	7	A	B	G	7 dagen
TRIOXIDIJZAN	Ernstige weefselnecrose	5 + 1	A	B	E	48 uur
VINBLASTINE	Ernstige weefselnecrose	4 + 6	A	B	F	2 dagen
VINCRISTINE	Ernstige weefselnecrose	4 + 6	A	B	F	2 dagen
VINORELBINE	Ernstige weefselnecrose	4 + 6	A	B	E	7 dagen

SPECIFIEKE MAATREGELEN EXTRAVASATIE

1. Geen specifieke maatregelen nodig
2. Lokale koeling: breng onmiddellijk een droog coldpack aan gedurende minstens 1 uur, daarna een aantal keren per dag, 15 min. per keer — afdeling
3. Natriumthiosulfaat 4% (= 40 mg/ml): injecteer drnv sc-injecties gelaagd met 5 ml 4% (= 40 mg/ml) natriumthiosulfaatoplossing — in box
4. Dexrazoxaan: Savene® 1000 mg/m2 i.v. binnen 6 uur op dag 1, 1000 mg/m2 op dag 2, 500 mg/m2 op dag 3 (zie productinformatie) N.B. NIET KOELEN 15 min voor t/m 4 uur na dexrazoxaan toediening — via apotheek
5. Hyaluronidase: injecteer 150 IE + 1 ml Hylase® (max 1500 IE) s.c. condom het aangetaste gebied, afhankelijk van mate van extravasatie — in box
6. Dimethylsulfoxide 100% (DMSO): lokaal op huid aanbrengen (elke 8 uur herhalen gedurende minimaal 7 dagen). Laten drogen aan de lucht ivm mogelijk blaasvorming indien onder occlusie. — in box
7. Droge warmte: aanbrengen van droge warmte op subjectief aangename wijze (bv hot-cold pack, heet water fles), 4 dd gedurende 20 min. — op afdeling
8. Overleg met chirurg voor (vroege) excisie bij een ernstige reactie. — chirurg

OGEN

1. Spoel open onmiddellijk met ruime hoeveelheid water —

HUIDCONTACT

1. Was de huid onmiddellijk en grondig met water en zeep —
2. Spoel de huid met 70% alcohol — in box
3. Spoelen met natriumwaterstofcarbonaatoplossing 4,2% daarna met veel water — in box

INACTIVATIE OMGEVING

1. Schoonmaken met veel water — afdeling
2. Natriumhypochloriet 5%-oplossing, 100 ml — in box
3. 0,1N natronloog, (NaOH), 300 ml — in box
4. 0,1N zoutzuur (HCl), 300 ml — in box
5. Schoonmaken met veel water en zeep — afdeling
6. Minimaal 1x wassen met 70% alcohol — apotheek

Figure 13-1: HMP crib sheet - summary information about individual HMPs is useful in many situations, including a spill

Source: https://nvza.nl/wp-content/uploads/Crashkaart-Oncolytica-versie-7-v1.xls

[265] Directive 2004/37/EC, Article 5(5)(e) and (k); see also Directive 98/24/EC, Article 7(1), for chemical agents

The incident management protocols should provide technical instructions and means for cleaning contaminated surfaces, equipment, and decontamination of persons.

Incident management varies with the life cycle stage and the potential incidents that can happen. In the case of large incidents, specially trained first responders may be necessary: this should be considered in the risk assessment, see section 4.

Near misses, spills and/or exposure should be recorded and frequently evaluated. Discussions about incidents and near misses allows workers to raise any questions or feedback information about procedures used and the overall safety culture. For example, is there sufficient awareness of the presence and hazards of HMPs, and do workers have a proactive attitude towards potential problems such as sources of exposures, and spills that might occur.

13.3 Spill kit and protocols

A spill kit should be available in all locations where there is a risk of an incident. All locations where HMPs are prepared, administered, stored or HMP-contaminated waste is handled should be equipped with a spill kit. For HMP administration in the patient's home, it is advised that homecare nurses carry a spill kit with them or in their vehicle.

13.3.1 Incident protocols for administration to humans

Protocols should be in place for all types of HMP incidents that could be expected, such as:

- Leak from primary package/ampoule/vial in transport container
- Leak from a transport container
- Spillage in safety cabinet/isolator
- Leak from secondary package/ampoule/vial outside transport container
- Spill of liquids with HMPs
- Spill of powder with HMPs
- Personal contamination with HMPs
- Incidents handling HMPs
- Incidents handling HMP contaminated laundry or waste
- Incidents with excreta or blood containing HMPs (use appropriate protocol for liquid spills)

13.3.2 Spill kit

The spill kit could typically include:

- Worksheet with protocol
- Personal protective equipment (PPE) (such as overall, shoe covers, filtering facepiece, protective gloves, protective goggles, protective coveralls, hair and beard covers, protective footwear), see Annex 4
- Eye bath
- Detergent
- Cleaning equipment
- Cleaning materials
- Brush and dustpan
- Forceps
- Scoop
- Tweezers (to remove glass fragments)
- Marker pen
- Hazard signs
- Cable clips
- Absorbent cloth
- (Pre-labelled) waste bags and labels
- Incident reporting form

The spill kit should contain enough material for a minimum of two people.

Figure 13-2:
A spill kit at the Sahlgrenska University Hospital, Sweden

Spill kits can be compiled by the organisation based on the risk assessment and their preferences for materials or tools. Commercial spill kits are also available.

13.3.3 Personal contamination

The protocols set out in Table 13-1 describe typically how to manage different types of personal HMP contamination.

Figure 13-3:
Contents of a spill kit available from the European Society of Oncology Pharmacy (ESOP)
Source:
https://esop.li/spill-kits/

Table 13-1: Protocols for managing different types of personal contamination

Personal contamination	Protocol
Eyes	Rinse eyes with an appropriate solution such as hand-warm water for 15 minutes or use eye bath/shower if this is available Check with physician if medical treatment is needed
Skin	First, rinse exposed skin with hand-warm water. Then wash exposed skin thoroughly with neutral detergent. Rinse detergent with water. Dry the skin carefully by dabbing, no rubbing Check with physician if medical treatment is needed
Clothes	Handle clothes as contaminated laundry, see section 14.2
Injury with sharp items (such as needle, glass)	Handle as a needle stick injury. Follow the procedures for extravasation for the specific HMP

Figure 13-4: A shower and an eye shower in a pharmacy of a hospital (for emergency purposes in case of an incident) at the Meander Medical Centre, The Netherlands

13.3.4 Incident protocol for spillage of HMP liquids

The general procedure for an incident involving spillage of HMP liquids is typically to:

- Ask for assistance and for the spill kit
- If someone is exposed, prioritise their decontamination
- Inform the persons in the immediate surroundings
- Stop people entering the spill area: mark the area and put out signs
- Prevent spill spreading to a larger area
- Put on PPE
- Prevent splashing
- Cover liquids with drying material like paper towels
- Work from outside (clean area) to inside and from top to bottom
- Remove all of the visible spillage
- Clean the contaminated area with the recommended detergent
- Rinse with water
- Repeat the last two action points at least three to five times
- Inform colleagues when the area is free from contamination
- Complete an incident report

The following PPE could be used for a spillage of HMP liquids:

- Type A (and puncture class 3 where necessary) protective gloves
- Protective gown/coverall
- Shoe covers
- Eye protection
- If no aerosols, face shield/ goggles (splashes)
- If aerosol formation, respiratory protective equipment (FFP3)

A summary sheet for handling an incident is in Annex 7.

13.3.5 Incident protocol for spillage of HMP powders

The general procedure for an incident involving spillage of HMP powders typically is to:

- Ask for assistance and for the spill kit
- If someone is exposed, prioritise their decontamination
- Inform the persons in the immediate surroundings
- Stop people entering the spill area: mark the area and put out signs
- Avoid air disturbance by closing windows and doors
- Prevent spill spreading to a larger area
- Put on PPE
- Do not use a brush
- Cover powder by spraying water mist over the spill
- Do not spray water into the spill, which would disturb it
- Cover the spill gently with wet cloths or wet paper towels
- Remove the powder with the wet cloths or wet paper towels
- Work from outside (clean area) to inside and from top to bottom
- Remove all of the visible spillage
- Clean the contaminated area with the recommended detergent
- Rinse with water
- Repeat the last two action points at least three to five times
- Inform colleagues when the area is free from contamination
- Complete an incident report

The following PPE could be used for a spillage of HMP powder:

- Type A and puncture class 3 protective gloves
- Protective gown/coverall
- Shoe covers
- Eye protection
- Respiratory protective equipment (FFP3)

A summary sheet for handling an incident is in Annex 7.

13.3.6 Handling waste from an HMP incident

Used paper towels/cloths, absorption material, protective gloves, non-permeable gowns/coveralls, respiratory protective equipment (FFP3), and broken fragments should be disposed of as hazardous waste.

Place in a waste bag, seal and place in a closable hazardous waste container. Disposal should also comply with the relevant regulations and trained workers should supervise this stage, see section 15.

Non-disposable equipment and PPE should be cleaned immediately after use.

13.4 Incidents involving HMP waste

Incidents involving HMP waste should be handled in the same manner as HMP liquid spills.

- Follow procedure for spillage of HMP liquids, see section 13.3.4
- Use PPE, see section 13.3.4 and Annex 4
- Complete an incident registration form, see section 13.6

13.5 Incidents involving HMP contaminated laundry

Incidents involving HMP contaminated laundry should be handled in the same manner as HMP contaminated laundry.

- For handling HMP-contaminated laundry, see section 14.2.3
- Use PPE such as type B protective gloves
- Complete an incident registration form, see section 13.6

13.6 Record keeping

The incident registration form should typically include:

- Context of the incident (date, time, location, amount)
- Exposed area
- Exposed persons
- Exposure concentrations, if known
- Medical treatment/HMPs involved
- Control measures
- Learning points for adjusting protocols, equipment, training and instructing workers
- Safety alert for communication

The incident registration form should be kept with the risk assessment and a trend analysis should be undertaken in the risk assessment, see section 4. If a worker is contaminated, a copy should be kept with the individual's medical file, see sections 5.7 and 7.5.

Record keeping must comply with any applicable national legislation or guidance which can vary considerably. Some Member States require incidents to be reported to the relevant authority.[266]

[266] See also Directive 89/391/EEC, Article 9(1)(c) and (d); Directive 2004/37, Article 12(b)

13.7 Summary of advice in section 13

- Incident protocols should be in place for all types of incidents with hazardous medicinal products (HMPs).
- A spill kit should be available in all locations where there is a risk of an incident. All locations where HMPs are prepared, administered, stored or HMP-contaminated waste is handled should be equipped with a spill kit. For HMP administration in the patient's home, it is advised that homecare nurses carry a spill kit with them.
- Incident protocols for personal contamination are provided in section 13.3.3.
- Incident protocols for handling an incident involving HMP liquids and powder are provided in sections 13.3.4 and 13.3.5 respectively.
- Used paper towels/cloths, absorption material, protective gloves, non-permeable gowns/coveralls, respiratory protective equipment (FFP3), and broken fragments should be disposed of as hazardous waste in closable containers. Non-disposable PPE and equipment should be cleaned immediately after use.
- All incidents should be recorded in an incident registration form.

14

Cleaning, laundry, and maintenance

14.1 Cleaning

Surfaces in the workplace can be contaminated with HMPs and workers (such as cleaners) can thus be exposed to HMPs during cleaning activities. This section provides advice on reducing exposure to HMPs during regular cleaning. Incident management is dealt with in section 13.

14.1.1 Cleaning protocols (general)

14.1.1.1 Cleaning regime

A cleaning regime should be implemented to prevent spreading and/or build-up of contamination of hazardous medicinal products (HMPs). The cleaning regime should define the frequency of the cleaning operations and the cleaning tasks for each situation, and both should be determined in the risk assessment, see section 4. The use of specific detergents depends on the requirements of the facility.

The relevant areas/surfaces and the recommended cleaning frequency typically could be:

- Incident/spillage areas (immediately), see section 13
- Surfaces in preparation areas (directly after preparation)
- Surfaces and floor in administration areas (daily)
- Surfaces and floor in patient rooms, toilets and showers (daily)
- Storage areas (daily)
- Biological safety cabinets (BSCs) and isolators (daily)
- Transport container boxes (inside: daily)

For specific information on the cleaning of preparation and administration areas for human HMPs, see sections 14.1.4 and 14.1.5. For specific information on the cleaning of veterinary practices, see section 14.1.6. Specific information for the cleaning of storage and transport premises and equipment is provided in section 14.1.7.

14.1.1.2 Cleaning protocols

Written cleaning protocols and cleaning supplies should be provided by the employer and be readily available and accessible for workers.

There should be different practical cleaning protocols for floors, equipment, and surfaces. Different situations and the person responsible typically could be:

- Equipment in preparation areas of pharmacies (pharmacy technicians)
- Preparation areas in pharmacies (cleaning personnel)
- Administration areas in hospitals or care homes (cleaning personnel)
- Patient rooms (cleaning personnel)
- Toilets/showers (cleaning personnel)
- Incident/spillage (person responding to incident), see section 13

All cleaning, disinfection and decontamination should be recorded (for example using a quality control log).

14.1.1.3 General cleaning procedures (not spillage)

The general procedures when cleaning administration areas/ patient rooms/toilets typically include:

- Personal protective equipment (PPE) should be worn before entering the potentially contaminated area before cleaning, as a minimum type B protective gloves and a protective gown/coverall should be worn, see Annex 4
- Clean tap water and cleaning detergents should be used for cleaning
- Floors should be cleaned by working from a clean area onwards to the (potentially) contaminated area (for example, from the entrance door to the back of the room or by starting the cleaning in a patient's room and at the end cleaning the patient's bathroom and toilet)

- Vertical surfaces should be cleaned from top to bottom
- Single-use cloths and PPE should be disposed of as hazardous waste when leaving the area
- Non-disposable PPE and equipment should be cleaned immediately after use
- Cleaning should be documented / registered, so it can be verified that it has been done

14.1.1.4 Design considerations for cleaning

Facilities and the equipment within them should be designed to allow adequate access to and ease of cleaning. Surfaces should be designed to minimise particle shedding and prevent the build-up of particulate matter. Where possible, walls should be fixed in place and have a smooth and durable surface; floors should be poured and seamless.

14.1.1.5 Cleaning of frequently touched areas

Workbenches in pharmacies, administration areas, and surfaces that are frequently touched with bare hands (for example, door handles) should be cleaned with a regular detergent (Simon, 2019[267,268]; Simon, 2020[269]).

In general, deactivating agents are not recommended. Cleaning by spraying of surfaces with detergents or decontamination agents should be prohibited due to the risk of inhaling aerosols.

14.1.1.6 Spillage

A spill kit, see section 13.3, and hazardous waste containers, see section 15.4.2, should be readily accessible in areas where there is a risk of exposure to HMPs.

If a spill or breakage of a vial occurs, repeated decontamination and cleaning procedures should be in place, adapted for different surfaces and HMPs, see section 13 (Petit, 2020[270]).

14.1.1.7 Risk management and effectiveness of cleaning

The cleaning protocol should be specified in the HMP risk management plan / occupational safety and health (OSH) management system (or handbook) for cleaning. The procedures should be checked at least annually for necessary adjustments based on the risk assessment, see section 4.

The cleaning procedures and personnel performing it, should be periodically validated for all workplaces where HMPs are handled (including sterile environments).

The quality of the cleaning should be checked regularly, and the effectiveness of the cleaning regime should be periodically assessed (for example, using wipe sampling to determine the residual contamination of the areas cleaned, see section 5.5). A protocol should define the frequency and methods for the cleaning assessment. The protocol should take into account the sampling frequency based on the volume and frequency with which HMPs are handled and the results of the performed assessments.

14.1.2 Cleaning equipment and procedures

Only approved cleaning equipment should be used to clean HMP designated areas.

HMP dedicated cleaning equipment should only be used and stored in HMP designated areas and should be clearly labelled for ease of identification.

14.1.2.1 Personal protective equipment (PPE)

Workers undertaking cleaning should wear PPE appropriate to the exposure risks of the tasks as defined by the risk assessment, see section 4 and Annex 4.

267 Simon, N, et al, (2019), Chemical decontamination of hazardous drugs: a comparison of solution performances, Annals of Work Exposures and Health, 2019, 1-11.
268 Simon, N. et al, (2019), Efficiency of degradation or desorption methods in antineoplastic drug contamination: A critical review. J Oncol Parm Practice 2019, vol 25(4) 929-946.
269 Simon, N. et al, (2020), Efficiency of four solutions in removing 23 conventional antineoplastic drugs from contaminated surfaces. PloS ONE (2020), 15(6) 1-14.
270 Petit, O. et al., (2020), Fastidious chemical decontamination after cyclophosphamide vial breakage in a compounding unit, J Oncol Parm Practice 2020, vol 0(0) 1-4.

Unless specified otherwise in the remainder of this section, the following PPE should be worn as a minimum for general cleaning (not spillage):

- Type B protective gloves
- Protective gown/coverall

Hands should be washed after removal of PPE.

For specific areas or surfaces where protocols prescribe the use of decontamination agents, additional respiratory protection and protective face shield/goggles should be used.

For wet cleaning (using wet cloths) of surfaces, equipment and floors, protective footwear, protective gloves, and protective gowns/coveralls should be used.

For intense cleaning of toilet rooms and showers use protective gloves, a protective coverall and protective footwear

14.1.2.2 Cleaning materials

Detergent should be used for cleaning. Water should be used for rinsing. Dedicated equipment, such as a dedicated broom, should be used and stored in the area where the HMPs are prepared, administered, or patient care takes place.

A wide range of cleaning agents and decontaminants are available: their selection should be based on a number of factors, such as compatibility (with disinfectants), effectiveness, and possible residues. Cleaning products should be applied by wiping, not by spraying.

In sterile environments, alternative cleaning procedures may be used.

14.1.3 Training

Only trained workers should clean areas where HMPs are handled: they should understand the risks involved, and undergo competency checks, see section 6. The training should be practical, cover different scenarios, and include instructions on how to prevent exposure and the spread of contamination.

14.1.4 Cleaning of preparation areas

14.1.4.1 Clean room cleaning

Work surfaces should be cleaned and disinfected daily, at the end of the day, after a spill, and at any other time considered necessary by the risk assessment, see section 4. Carts, tables, stools, and other hard surfaces in the clean room should be cleaned weekly. Shelving units should be cleaned weekly. Floors should be cleaned daily by mopping; the ceilings and walls at least monthly. The exterior surfaces of ventilation equipment should be cleaned at least weekly.

14.1.4.2 Anteroom cleaning

Anterooms should be cleaned at least once a week. The passage/doorway connecting the anteroom to the clean room should be cleaned daily; storage shelving should be cleaned at least monthly.

14.1.4.3 BSC/isolator cleaning

The BSC/isolator should be cleaned daily, and after any spill, with the external areas and lower part cleaned at least weekly. If the BSC/isolator runs for 24 hours a day, it should be cleaned at the beginning of the day and at several additional time points through the day, as defined by the risk assessment, see section 4. Decontamination should occur at least weekly. If the ceiling grill needs to be wiped, high-efficiency particulate air (HEPA) filter should not be dampened.

14.1.5 Cleaning of administration areas

14.1.5.1 Additional and repeated cleaning

Additional cleaning should be considered between a change of patients to prevent build up and cross contamination of HMPs.

In case of a spillage repeated cleaning is necessary to remove HMP-contamination of surfaces before the area can be used again, see section 13.

14.1.5.2 Personal protective equipment (PPE)

A risk assessment, see section 4 and Annex 4, should be performed to determine the PPE required for cleaning administration areas of HMPs and sanitary facilities.

The following PPE should typically be used for cleaning:

- Type B protective gloves
- Protective gown/coverall
- Protective face shield/goggles (if splashes are likely, for example whilst cleaning sanitary equipment)
- Class P3 face mask (if the risk assessment, see section 4, in case of intense cleaning of toilets and showers and/or the cleaning requires decontamination agents and aerosols are likely)

To remove PPE: start with gown, then face shield/mask/goggles and finally gloves.

14.1.6 Cleaning of veterinary practices

14.1.6.1 Surfaces

Areas that are at risk of HMP contamination should be designed for the ease of cleaning, surfaces should be made from non-porous materials and have seamless fittings.

All equipment, counters, and work surfaces should be cleaned with a cleaning agent or detergent. Surfaces should be cleaned before and after each activity (preparation/administration), and after a spill. Practices that handle high volumes of HMPs should also clean surfaces at the beginning and end of each day.

Furniture in preparation/administration areas, such as carts, tables, stools, and other hard surfaces should be cleaned weekly, or at the end of each activity (depending on the frequency of HMP administration). Storage and shelving should be cleaned weekly, and floors should be mopped daily. Ceilings and walls should be cleaned on at least a monthly basis.

It is not recommended to directly spray surfaces or use pressure washers for the initial stages of cleaning. Cleaning products should be applied to paper towels which are then used to wipe the surfaces. Spilled HMP solutions should be absorbed with single-use material, with powders and residues absorbed onto moistened single-use material, prior to cleaning.

14.1.6.2 BSC/isolator cleaning

For veterinary practices that have a BSC/isolator this should be cleaned daily, or at the start and end of a session; and after the event of a spill. The external areas and lower part should be cleaned at least weekly. If the BSC/isolator is required to run for 24 hours a day, it should be cleaned at the beginning of the day and at several additional time points throughout the day, based on the risk assessment, see section 4.

Decontamination should occur weekly. Should the ceiling grill be wiped down with detergent, care should be taken to not dampen the HEPA filter.

14.1.6.3 PPE for cleaning

The PPE for cleaning should include:

- Type B protective gloves
- Protective gown/coverall
- Protective face shield/goggles
- Shoe covers
- Class P3 face mask (if the risk assessment, see section 4, requires decontamination agents and thus aerosols are likely)

To remove PPE: start with gown, then face shield/mask/goggles and finally gloves.

14.1.7 Cleaning of storage/ transport premises and equipment

14.1.7.1 Cleaning of transport boxes

Cleaning of transport boxes should be performed daily (inside) and at regular intervals but at least once a month (outside). Frequency of cleaning should be based on the risk assessment, see section 4, and should be recorded, for example in a quality control log.

14.1.7.2 Cleaning of transport equipment

Cleaning of transport equipment should be performed at regular intervals based on the risk assessment, see section 4, and should be recorded, for example in a quality control log.

14.1.7.3 Cleaning of storage premises

Cleaning storage premises including fridges should be performed at regular intervals based on the risk assessment, see section 4, and should be recorded, for example in a quality control log.

14.1.8 Waste arising from cleaning

14.1.8.1 Single-use cleaning material

Single-use cleaning materials that are used for cleaning of HMP-contaminated areas and surfaces should be treated as hazardous waste and disposed of in a closable hazardous waste container, see section 15.

14.1.8.2 Non-disposable cleaning equipment

Non-disposable HMP cleaning equipment and PPE should be immediately cleaned.

Leave used cleaning materials at the designated area in a specific storage closet.

14.1.8.3 Contaminated wastewater

Wastewater used for regular cleaning of HMP-contaminated areas or surfaces does not need special treatment. It can be disposed of as regular wastewater, or in accordance with the practices of the relevant facility.

14.2 Laundry

Workers can be exposed to HMPs during the washing of clothes contaminated with HMPs, including when contaminated clothes are collected, transported and washed at professional laundrettes. This chapter describes the protection measures established for people involved with the washing of contaminated laundry.

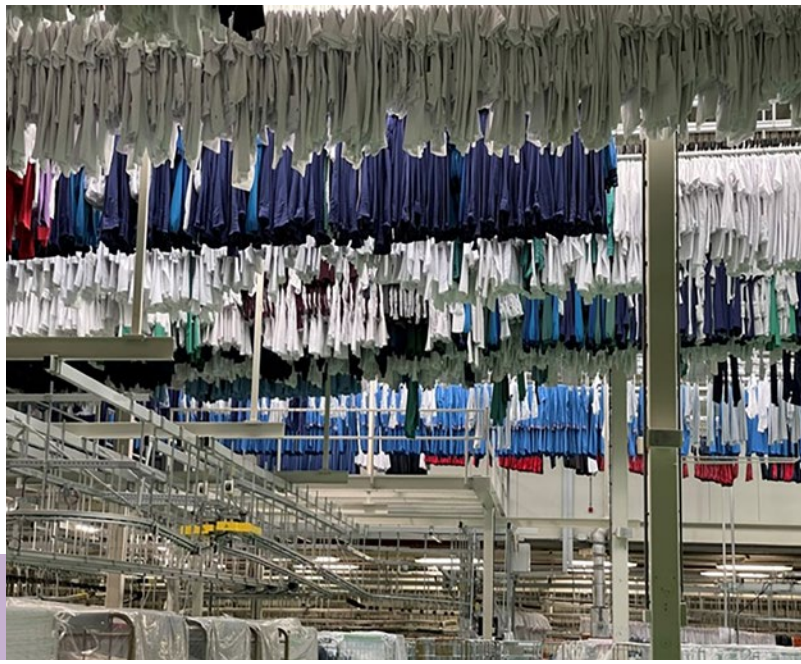


Figure 14-1:
Hospital staff uniforms at a laundrette
Source: Rentex, The Netherlands

14.2.1 Identification of HMP-contaminated laundry

Potentially HMP-contaminated laundry by urine, faeces, vomit, sweat and blood may typically include:

- Bed linen (such as sheets and pillowcases)
- Clothes (hospital clothes and/or patient's personal clothes)
- Towels used for washing patients
- For veterinary practices: animal patient bedding

HMP-contaminated non-disposable items should be treated as HMP-contaminated laundry, the laundering of these items should be considered in the risk assessment, see section 4, so that the appropriate protocols on how to handle HMP-contaminated laundry are in place.

HMP-contaminated single-use items should be treated as HMP-contaminated waste, see section 15.

Figure 14-2: HMP-contaminated laundry transported inside a laundrette using a separate cart
Source: Rentex, The Netherlands

14.2.2 Training

Workers handling contaminated laundry in hospitals, care homes or home care should be trained to identify and handle HMP-contaminated laundry; this may include a worksheet about handling laundry to prevent exposure (to self and others), see section 6.

Workers in a laundrette should be instructed and trained how to handle HMP laundry in sealed bags.

14.2.3 Transport and handling of HMP-contaminated laundry

HMP-contaminated laundry should be handled at the site of contamination and should be sealed into dedicated bags. The bags could be identified using a specific designated colour and/or label to recognise the content as HMP-contaminated. Special bags, which dissolve during the washing process, could be used. HMP-contaminated laundry should be handled separately from other laundry, for example, transported in separate carts or chutes.

Bags with HMP laundry should be handled with protective gloves and when opened in the washing machine respiratory protection (FFP3) should be worn.

Figure 14-3: Collecting HMP laundry in a plastic bag (water soluble) placed inside a standard laundry bag, protective gloves being worn by the worker
Source: Sahlgrenska University Hospital, Sweden

Dispose of single-use PPE as hazardous waste, in a closable hazardous waste container.

Washed plastic laundry bags can be discarded as normal plastic waste.

14.2.4 Washing procedures

HMP-contaminated laundry should be washed separately from other laundry, at least during the first wash. HMP-contaminated laundry should preferably be washed twice (cold and warm), following a two-step washing procedure.

Figure 14-4: A separate first wash of HMP-contaminated laundry. Single-use laundry bags are washed together with the laundry prior to disposal.
Source: Rentex, The Netherlands

14.3 Maintenance

Maintenance of equipment and facilities that might be contaminated by HMPs can result in occupational exposure of maintenance workers. This includes instances where maintenance is carried out by external workers. Advice on reducing exposure of maintenance workers to HMPs is provided in this section.

14.3.1 Protocols and procedures

An inventory list of potentially HMP-contaminated equipment and/or areas that need to be maintained should be created as part of the risk assessment, see section 4, to define the appropriate protocols and PPE, see Annex 4.[271] Protocols and/or procedures should be in place to handle potentially contaminated equipment and work in potentially contaminated areas.

14.3.2 Personal protective equipment (PPE)

The following PPE could typically be used as required by the risk assessment, see Annex 4:

- Type A protective gloves
- Protective gown/coverall
- Hair/beard cover
- Protective goggles
- Shoe covers

FFP3 respiratory protection should be worn if the risk assessment, see section 4, indicates HMP fine dust or aerosols may be present[272].

For general procedures about cleaning, see section 14.1. If HEPA filters from a BSC/isolator are being changed, the BSC/isolator should remain off until the filter is replaced. Where possible, use safe change filter methods (bag in/bag out). Used filters, and those affected by a spill, should be disposed of as HMP-contaminated waste, see section 15. If pre-filters are used to protect HEPA filters they should be changed weekly, or if there is visible contamination, and following maintenance. HEPA filters are normally checked for integrity annually.

If possible, the organisation should provide its own maintenance tools to the contractor: if this is not possible, externally supplied maintenance tools should be decontaminated of HMPs after use.

All maintenance should be documented and recorded (for example using an equipment control log).

14.3.3 Maintenance workers

Maintenance of equipment that might be contaminated by HMPs should only be carried out by qualified personnel. If possible, specialist workers should be considered for any maintenance relating to clean rooms.

Maintenance workers could be at risk of exposure to HMPs and should be made aware of the associated hazards and clean room protocols, if appropriate.[273] This should be supported by mandatory safety procedures with training courses as required in the risk assessment, see section 4. In addition to core and basic training in handling HMPs, see section 6, training specific to maintenance work should typically include:

- Cleaning of the equipment before maintenance
- Protection during maintenance tasks
- Detailed instruction on the use of PPE during maintenance, as required by the risk assessment
- Detailed instruction on the cleaning and disposal of PPE, if required by the risk assessment

External maintenance workers should be accompanied at all times and monitored to ensure that they wear the correct PPE and follow the right procedure.

[271] Directive 98/24/EC, Article 4(3)
[272] Directive 2004/37/EC, Article 8
[273] See also Directive 2004/37/EC, Articles 8, 11, 12

14.4 Summary of advice in section 14

Cleaning

- A cleaning regime and protocols should be in place.
- Written cleaning protocols and cleaning supplies should be readily available and accessible for workers.
- For specific information on the cleaning of preparation and administration areas for human hazardous medicinal products (HMPs), see sections 14.1.4 and 14.1.5. For specific information on the cleaning of veterinary practices, see section 14.1.6. Specific information for the cleaning of storage and transport premises and equipment is provided in section 14.1.7.
- Personal protective equipment (PPE) should be worn before entering the potentially contaminated area to be cleaned.
- PPE for general cleaning includes Type B protective gloves and a protective gown/coverall.
- Clean tap water and cleaning detergents should be used for cleaning.
- Floors should be cleaned by working from a clean area onwards to the (potentially) contaminated area (for example, from the entrance door to the back of the room).
- Vertical surfaces should be cleaned from top to bottom.
- Cleaning should be documented/registered and validated (for example, by wipe sampling).

Laundry

- HMP-contaminated laundry should be separated and sealed into dedicated bags.
- HMP-contaminated laundry could be handled separately from other laundry, for example, transported in separate carts or chutes.
- PPE should be worn, protective gloves and when opened in the washing machine respiratory protection (FFP3).
- HMP-contaminated laundry should preferably be washed twice (cold and warm) in a two-step washing procedure. HMP-contaminated laundry should be washed separately from other laundry, at least during the first wash.

Maintenance

- An inventory list of potentially HMP-contaminated equipment and/or areas that need to be maintained should be in place.
- Maintenance of equipment that might be contaminated by HMPs should only be carried out by qualified and trained personnel.
- PPE should be worn, see section 14.3.2.
- External maintenance workers should be accompanied at all times and monitored to ensure that they wear the correct PPE and follow the procedure.

Waste

- Single-use cloths and PPE should be disposed of as hazardous waste in a closable hazardous waste container.

15

Waste and wastewater management

Waste management is covered by the carcinogens, mutagens and reprotoxic substances directive (CMRD)[274] since workers handling hazardous medicinal product (HMP) waste are potentially exposed to carcinogenic, mutagenic or reprotoxic (CMR) substances. Consequently, employers must undertake a risk assessment,[275] see section 4, and ensure that the level of exposure of workers is minimised by following the hierarchy of control measures. For example, under the CMRD, the employer must provide[276]:

"*means for safe collection, storage and disposal of waste by workers, including the use of sealed and clearly and visibly labelled containers".*

Since hazardous waste poses a greater risk to the environment and human health than non-hazardous waste, there is a stricter regime for hazardous waste, as set out in the Waste Framework Directive (WFD) (2008/98/EC).[277] The WFD sets out obligations from hazardous waste generation to final disposal or recovery, including additional labelling, record keeping, monitoring and control. Article19(1) of the Waste Framework Directive (2008/98/EC) states that:

"*Member States shall take the necessary measures to ensure that, in the course of collection, transport and temporary storage, hazardous waste is packaged and labelled in accordance with the international and Community standards in force*."

The WFD prohibits the mixing of hazardous waste with other categories of hazardous waste, and with non-hazardous waste; section 15.3 of this guide summarises how hazardous waste should be separated from non-hazardous waste and labelled.

This section of the guide focuses on occupational exposure to HMP contaminated waste and wastewater at pharmacies, healthcare and care establishments and veterinary practices, but also covers the internal and external transport of waste. Final disposal of solid waste and municipal wastewater treatment are outside the scope of this guide. The final disposal of HMP contaminated waste should follow the requirements for the disposal of the relevant hazardous waste.

Many manufacturers and a few hospitals have wastewater treatment operations on site to remove active pharmaceutical ingredients (APIs) before discharging the effluent to municipal sewer, in which case worker protection on site is covered by this guide. Once wastewater or effluent has left the site, it is outside the scope of this guide, and is covered by national, regional or municipal legislation on discharges to municipal sewers.

274 Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405

275 Directive 2004/37/EC, Article 3(2)

276 Directive 2004/37/EC, Article 5(5)(m)

277 Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008L0098-20180705

Box 15-1: Further reading on HMP waste management (healthcare waste)

This chapter provides a summary of advice for reducing occupational exposure to HMPs during the handling of HMP waste. For further information about handling HMP waste, see, for example, the following references:

ISOPP Standards (2022) ISOPP Standards for the Safe Handling of Cytotoxics, Section 15–Waste handling and patient excreta, Journal of Oncology Pharmacy Practice, Vol. 28 3 (Supplement) p. 60-64: Available from: *https://journals.sagepub.com/doi/10.1177/10781552211070933*

ICRC (2011) Medical Waste Management, International Committee of the Red Cross, Geneva, Switzerland, November, 2011. Available from: *https://www.icrc.org/en/publication/4032-medical-waste-management*

WHO (2014) Safe management of wastes from health-care activities, 2nd Edition, Edited by Chartier, Y et al. World Health Organisation, Geneva, Switzerland. Available from: *https://www.who.int/publications/i/item/9789241548564*

WHO (2019) Overview of technologies for the treatment of infectious and sharp waste from health care facilities, World Health Organisation, Geneva, Switzerland. Available from: *https://apps.who.int/iris/handle/10665/328146*

15.1 Definition of waste within the scope of this guide

Both waste HMPs and contaminated materials should be disposed of as hazardous waste as soon as possible after the waste has been generated. These include for example:

- Out of date or damaged medicines (including damaged packaging and broken vials[278])
- Out of production specification medicines (from manufacturing)
- Concentrated and diluted solution residues such as injectable products, infusions and instillations
- Contaminated materials from HMP preparation and administration, such as syringes, needles, gauzes, vials, ampoules, medicine cups, mats, and swabs

- Personal protective equipment (PPE) used during HMP preparation and administration, including type B protective gloves, gowns, shoe covers and P3 breathing protection
- HMP packaging
- Single-use cleaning materials such as cloths and mops
- HMP spillages (liquids/solids), including the materials that have been used to clean spills
- Nappies, urine bags, stoma bags, catheters, and catheter bags
- Patient and animal patient excreta, including urine, faeces and vomit from patients
- Contaminated laboratory samples
- Linen and patient clothing that is unsuitable for cleaning[279]
- Air filters from safety cabinets or isolators

[278] Damaged HMPs that are received at the pharmacy should be quarantined and disposed of as hazardous waste and the supplier contacted.
[279] Linen rented from a laundry company by a hospital is typically returned to the hire company in a protective alginate bag, and the laundry company decides if the linen can be laundered, or not. Where unsuitable for washing, the laundry becomes waste.

As regards veterinary care, the following materials should also be disposed of as hazardous waste:

- Any materials that have been in contact with the animal patient during the period of risk
- Single-use bowls for food and water
- Single-use bedding
- Products used for cleaning and decontamination (such as preparation and treatment areas, and kennels)
- Products used in the handling of animal excreta such as single-use shovels and towels

For practical reasons and to avoid costly analyses, all waste potentially contaminated with HMPs can be disposed of as hazardous waste (please note that reusable items such as lightly soiled bed linen can be washed and reused, see section 14.2). For example, irrespective of the activity performed during HMP preparation, all single-use clothing used can be disposed of as hazardous waste as it is likely to be contaminated.

15.2 Management and organisation

15.2.1 Waste manager and waste management plan

Each facility involved in the handling, preparation and administration of HMPs, or care for patients receiving or who have recently received HMPs, could have a fully trained waste manager. Every such facility could also have a waste management plan, which can be reviewed and updated regularly. The plan could detail how to manage all waste as identified by a waste audit.

It is useful for the waste manager to take part in the HMP occupational safety and health (HMP-OSH) Steering Committee, see section 3.2.2.4.

15.2.2 Training specific to the worker's role

Workers handling hazardous waste are often working in inherently precarious conditions, with a high turnover of workers, and although training and protection is legally required, in practice it may be inadequate. This section suggests ways that this situation could be improved, ultimately to improve the occupational safety and health of workers.

The following detailed (non-exhaustive) list of HMP training could be given to workers generating or handling hazardous waste, in addition to the core and basic training in handling HMPs, see section 6:

- Basic pharmacology of HMPs
- Training on the risks of exposure from handling hazardous waste
- How to define and classify hazardous waste
- Training on all the HMPs in use on site that could be present in waste
- Theory of hierarchy of controls
- Safe handling of hazardous waste – which PPE to use
- Training on how to deal with spills and incidents
- Explanation of the waste management plan, roles, and organisation in place
- How to segregate (separate) waste
- How to contain waste, including regional/national colour-coded systems in place
- What secondary packaging to use?
- How to label hazardous waste, use of consignment notes
- How to store hazardous waste
- How hazardous waste is transported on-site (and off-site where relevant)

15.3 Separation of HMP-contaminated waste

HMP-contaminated waste should be segregated at source and treated as hazardous waste. All potentially contaminated waste should be separated and contained regardless of the level of contamination.[280] Contaminated sharps, however, should always be disposed of in a sharps container that is puncture-proof and sealable. Sharps can include needles, spikes and broken glass.

Segregation of hazardous waste at source prevents unintended contamination, pollution and worker exposure downstream.

To protect workers handling hazardous waste, it is useful to treat all waste from HMPs, see section 15.1, the same as cytotoxic and cytostatic waste as classified in the European List of Waste (LoW), previously known as the European Waste Catalogue (EWC), see Annex 3, as long as this practice is in accordance with national or regional legislation.

Across Europe, waste from "cytotoxic and cytostatic human medicines" is classified[281] as LoW code 18 01 08* (asterisk denotes hazardous waste). For waste from cytotoxic and cytostatic medicines for animals the LoW classification code is 18 02 07*. For relevant non-healthcare waste, the code is 20 01 31* cytotoxic and cytostatic medicines. Depending on national or regional regulations, HMPs other than cytotoxic or cytostatic medicines can also be classified under other LoW codes or (some HMPs) can be included under LoW 18 01 08*, the hazardous waste codes mentioned above or other relevant codes for hazardous waste.

15.4 Containment of hazardous waste

Separated hazardous waste should be stored in suitable containers after being bagged or double-bagged.

Waste generated in HMP preparation areas should be placed into a waste bag, sealed, and placed in the relevant waste container, see section 15.4.2, with minimal disturbance. All waste containers should be sealed and clearly and visibly labelled. It is useful to clean (wipe) small containers and sharps containers used in a biological safety cabinet (BSC) or isolator, prior to removal. Large containers (of 30 litres capacity or greater) cannot be placed inside a BSC or isolator.

15.4.1 Containment through double-bagging

In order to prevent any spillages or contamination on the bag handled by the waste operative, it is useful to seal the items in a small bag prior to placing in the larger bag which is the one that will be handled by the waste operative. It should be considered whether a box is needed for soft waste.

Double bagging should not be relied upon as an alternative to using waste containers.

15.4.2 Waste containers

HMP-contaminated waste should be contained in a robust, closable, leak-proof container located close to where the waste is being generated. Waste containers should be opened with a foot pedal or have another mechanism to prevent direct contact with hands/gloves to avoid contamination.

Currently, containers are colour-coded depending upon national or regional requirements. For example, containers for HMPs are:

[280] There should be no distinction between a low level of contamination and a high level of contamination. This distinction would have to be scientifically justified based upon worker exposure. As a practical solution, it is recommended that a precautionary approach is taken to protect workers handling waste both on site and downstream, by separating, containing and labelling all contaminated items as Hazardous so that it is treated as such.

[281] Waste, including hazardous waste must be classified using the European List of Waste (previously known as the European Waste Catalogue) as established by EC Decision (2000/532/EC), as required by the WFD (2008/98/EC) and also for the purposes of the Waste Shipments Regulation (EC) No 1013/2006

- Yellow or grey container in Belgium
- Grey (soon to be black) container in Germany
- Red container in Greece
- Yellow container with a purple lid in Ireland
- Yellow container with purple lid or a purple bag for soft waste in the UK

Healthcare and waste workers, including agency workers[282], may be working across different regions or countries which use differently coloured containers, which creates a potential for mistakes. This should be taken into account in cases where workers move between regions and countries.

As noted above, sharps should be disposed of in a sharps container.

Facilities workers should seal HMP-contaminated waste containers to prevent leaks during transport. Waste containers should not be overfilled. Once sealed, HMP waste containers should never be opened to move the waste between containers (for example to decant from a smaller to larger container, or sharps containers) as this represents a risk of occupational exposure to HMPs and risk of needle stick injury to workers, potentially resulting in exposure to HMPs.

Figure 15-1: Labelled container with HMP contaminated waste
Source: Sahlgrenska University Hospital, Sweden

15.4.3 Secondary packaging (healthcare facility)

If good-quality primary packaging has been used to contain hazardous waste, secondary packaging may not be needed to prevent leakage during storage and transport to the waste disposal facility. However, if secondary packaging is used, it should consist of a leak-proof and rigid waste container.

Non-rigid containers, for example bin bags, should always be placed in a rigid-walled container, for example, a wheelie bin.

15.4.4 Packaging (home care)

It is important for patients that are undergoing HMP treatment at home to be educated by their healthcare provider on what constitutes hazardous waste and how it is contained and disposed of safely, to prevent exposure of carers and hazardous waste from entering municipal waste streams with the associated risk of exposure of municipal waste workers and contamination of other waste streams.

Article 20 of the WFD (2008/98/EC) requires Member States to set up separate collection of hazardous waste from households by 1 January 2025. The Commission has drawn up guidelines on how this could be done, stating that Member States could require pharmacies, civic amenity sites, nursing homes or retirement communities to accept waste pharmaceutical products. However, the definition of 'domestic healthcare waste' in the Commission guidelines is narrower than the definition of 'HMP waste' used in this guide, referring only to medicinal products that are unused or have expired[283] including cytotoxic and cytostatic medicines under LoW code

[282] Workers employed through an external agency, often on a temporary basis.

[283] Domestic healthcare waste section 2.2.1: Pharmaceutical products, Commission Notice: Separate Collection of Household Hazardous Waste. 2020/C 375/01, *Official Journal of the European Union,* 6 November 2020. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020XC1106(01)

20 01 31*. Therefore, recommended good practices for handling other types of household HMP waste are provided below.

A leak-proof plastic bag or container should be used as primary or secondary packaging, this should be correctly labelled and ideally returned to the healthcare provider for final disposal. A sharps container should be provided to patients where needed for homecare. Good practice is for hospitals to run take-back schemes. Good practice is also for pharmacies to run take-back schemes for hazardous waste. In some cases, take-back schemes are not yet available or possible, in which case the existing hazardous waste practices as advised by the healthcare provider should be followed, for example, arranging collection of hazardous waste by the local authority.

However, if households do not follow instructions on handling hazardous waste, take-back schemes can introduce an occupational exposure risk to hospital/pharmacy workers taking back the hazardous waste from patients. This underlines the need for clear instructions to be given by the hospital/pharmacy to the patients and their families, and provision of the correct hazardous waste containers.

In instances where hazardous waste has to be disposed of through municipal waste, disposal should only occur after containment in a bag or container. Nappies and incontinence pads should be treated as hazardous waste. Home care workers handling nappies and incontinence pads should be made aware of the potential contamination and use PPE, see section 15.4.5. Education materials could be developed, for example a manual for educating patients.

15.4.5 Patient excreta in healthcare facilities

Excreta and excreta-contaminated waste can be a significant source of HMP exposure. After consumption of cytostatic medicine, degradation of the medicines by human metabolism varies widely from 10-97% (Zhang et al, 2013 in HCWH, 2021[284]). In other words, 3-90% of cytotoxics that are administered will be excreted by patients.

HMP contamination in excreta can occur during the time HMPs are being taken by the patient and generally up to 7-14 days after administration. Information about the presence of HMPs in excreta could be supplied by the pharmaceutical company in the safety data sheet (SDS), see section 8.6.2. An overview of the duration of HMP excretion for selected HMPs can also be found in peer reviewed and published HMP handling guidelines.[285]

HMPs are mainly eliminated from the patient in urine and faeces. However, all body substances (including sweat) should be considered to be contaminated with the original HMP or its active metabolites.

Practical instructions for healthcare workers handling patient's excreta include, at a minimum:

- Any surfaces, bed linen and clothing that have been in contact with excreta from the patient (including sweat) should be considered as contaminated with HMP
- Appropriate PPE (type A protective gloves, face shield/goggles and if necessary, a protective gown) should be used to prevent exposure of skin in contact with excreta, contaminated surfaces, bed linen or clothing

- Single-use PPE should be worn to protect caregivers handling excreta for 7-14 days after treatment with HMP has been completed
- For incontinent patients, single-use incontinence pads should be used and disposed of as hazardous waste

[284] Lockwood, S et al (2016) Options for a strategic approach to pharmaceuticals in the environment. In: Health Care Without Harm (2021) Pharmaceutical residues in hospital wastewater: five case studies from European hospitals. Brussels, July 2021. Available at: https://noharm-europe.org/sites/default/files/documents-files/6831/14-07-2021_Pharmaceutical-residues-in-hospital-wastewater-FINAL.pdf

[285] A regularly updated overview of the recommended duration of protective measures is provided, for example, in the full version of Quapos 6 (Quality Standard for the Oncology Pharmacy Service) Commentary Version. Developed by https://esop.li/

15.4.6 Animal patient waste

HMPs have been detected in excreta (urine, faeces, saliva and sebum) of treated animal patients. Excretion rates are dependent on medicines and the animal. It is important to use animal data when available; for most HMPs there are animal excretion rates available (mainly for dogs). In the absence of available animal data, human excretion rate data can be used.

All materials that have been in contact with the animal patient or its bodily fluids during the period of risk should be considered as potentially contaminated.

If possible, the hospitalised animal patient should be allowed to urinate and defecate outside in a separate, designated, low-traffic area that can be cleaned easily. Urine can be diluted with water from a low-flow hose or watering can. Faeces can be cleaned up by scooping with a single-use shovel and put into a plastic bag to be placed in a hazardous container, see section 15.4.2. When cleaning animal patient cages, care should be taken to minimise aerosol generation. Single-use towels should be used to clean excreta if possible, and cleaning materials should be double-bagged for disposal, see section 15.4.1. All hazardous waste should be placed into compliant bags and containers that are appropriately identified.

Appropriate PPE such as type A protective gloves, face shield/goggles and, if necessary, a protective gown to prevent skin exposure in contact with excreta should be used.

Where possible, systems of collecting body fluids should be used. Containers of body fluids should be disposed of sealed, as hazardous waste.

15.5 Categorisation and labelling of HMP-contaminated waste

Hazardous waste should be categorised[286] under the relevant LoW code, for example, LoW code 18 01 08*, and LoW code 18 02 07*, see Annex 3. There may also be a hazard of infectious material in the waste or sharps which would classify it as 18 01 03*/18 01 09 in certain countries.

Hazardous waste should be clearly labelled, identifiable by colour and ideally the date waste was produced. The same label as for HMPs, see section 2, could be used to clearly indicate that HMPs are present. Waste codes may not be 100% indicative of HMPs present. Good practice is to provide a description of what is in the container, possibly on the basis of the HMPs that are typically prepared or administered at the relevant facility.

[286] Waste, including hazardous waste, must be classified using the European List of Waste (previously known as the European Waste Catalogue) as established by EC Decision (2000/532/EC), as required by the WFD (2008/98/EC) and also for the purposes of the Waste Shipments Regulation (EC) No 1013/2006.

15.6 Storage of hazardous waste

Waste should not be allowed to accumulate or be stored inside preparation or administration areas.

15.6.1 Internal movement of hazardous waste on site

Appropriate safety measures should be taken, PPE (type A protective gloves) should be worn and waste collection should occur at off-peak times, if possible.

Sealed containers should be transported on wheel-driven carts. These carts should be cleaned all over regularly to remove any potential external contamination.

15.6.2 Storage of hazardous waste

Hazardous waste should be stored at a suitable location on site with suitable lighting and ventilation but away from drains. The hazardous waste storage facility should be clearly labelled, with warning and hazard labels indicating the presence of HMPs.[287] Sealed containers should be locked and should not be reopened, and hazardous waste should not be reprocessed on site. Bins should be secured with mobile or fixed stands. Cages should not be used as these are not appropriate for hazardous waste.

HMP spill kits should be located near to storage and loading areas and should be easily accessible by workers.

15.7 Transport of hazardous waste

All applicable national and international regulations regarding transport of HMP waste must be followed.

15.8 Wastewater treatment on site

15.8.1 Prevention of contamination

Use of technologies that can prevent HMPs from entering municipal wastewater should be considered.

15.8.2 Treatment technology

Good practice is for API treatment technology to be used at source, on site, if possible, to remove APIs before discharge of wastewater effluent to municipal sewers under authority permits. Many HMP manufacturers already undertake wastewater treatment on site before discharge of effluent. Some European hospitals have trialled or are trialling wastewater treatment technologies to remove APIs. However, some technologies are in early stages of development and can carry their own risks. The removal rate of HMPs varies from one compound to another for different treatment technologies. If treatment is used, it is important to verify its effectiveness and the potential danger of resulting chemical residues.

At on-site wastewater treatment works, PPE should be worn to control worker exposure. 5- or 6-point[288] PPE (often including protective gloves, face masks and goggles) is

[287] See also Directive 2004/37, Article 11(2)

[288] Five or six of the following: gloves, hard hat, goggles, ear defenders, hi-vis, coveralls, and steel-toe capped boots.

likely to be worn as standard practice to prevent exposure to biohazards which also provides some protection from HMP effluent. HMP effluent is diluted by other wastewater, but this does not negate the presence of HMPs and the need for worker protection. Stakeholders in this study identified the need to raise awareness of the risk of exposure to HMP amongst wastewater treatment workers.

15.8.3 Permit to discharge to sewer

If discharges are regulated for the site, the permit conditions must be met as these are legally enforceable.

15.9 Summary of advice in section 15

The guidance in this section relates to occupational exposure to hazardous medicinal product (HMP) waste generated in health care settings but excludes final disposal of solid waste and municipal wastewater treatment.

Waste – roles, organisation, management plan

- It is useful for each facility handling HMPs to have a fully trained waste manager and waste management plan.

Separation of HMP-contaminated waste

- HMP contaminated waste (or potentially contaminated waste) should be separated and contained and treated as hazardous waste.
- Contaminated sharps should be placed in a puncture proof, sealable, sharps container.
- Segregation at source prevents unintended contamination, pollution and worker exposure downstream.
- It is useful to treat all HMP waste in the same manner as cytotoxic and cytostatic waste.

Containment of hazardous waste

- Hazardous waste should be contained in suitable containers, sealed and clearly labelled.
- Double bagging may be used to prevent spillages or contamination on the bag handled by the waste operative, but should not be relied upon as an alternative to using waste containers.
- HMP waste containers should be robust, leak proof and ideally opened using a foot pedal to prevent direct contact with hands/gloves.
- If needed, secondary packaging (in a healthcare facility) should consist of a leak-proof, rigid waste container.

Excreta

- As cytotoxic medicine will be largely excreted by patients, patient excreta and excreta-contaminated waste can be a significant source of HMP exposure.
- Excretion rates vary depending upon the medicine and the patient.
- Patient excreta will be contaminated by HMP (and their metabolites) during treatment, generally up to 7-14 days after administration.
- HMPs are mainly eliminated from the patient in urine and faeces, but all body substances should be considered to be contaminated.
- Animal patient's excreta will similarly be contaminated with HMPs and their metabolites, and should be treated as such.

Wastewater treatment on site

- To prevent downstream contamination, technologies to prevent HMPs from entering municipal wastewater can be considered.

16

Annexes

Annex 1. Glossary

Term	Definition (for the purposes of this guide)
Administration (of HMPs)	The act of giving a treatment, such as HMPs, to a patient, which may use many different methods including parenteral, oral, and topical administration
ADR	Agreement concerning the International Carriage of Dangerous Goods by Road (ADR 2021)
Aerosol	Very fine droplets or particles that are dispersed in air
Alginate bag	Bag made of artificial fibres spun from a constituent of kelp. The fibres become gelatinous when moist and so are biodegradable
Allergic	Unduly sensitive to some substances
Ampoule	Small, sealed bulb, usually of glass, typically designed to contain a single dose of a HMP for injection
Anteroom	Clean area for donning personal protective equipment that precedes the buffer zone
API	Active pharmaceutical ingredient
Aseptic	Free from contamination caused by harmful bacteria, viruses, or other microorganisms
Authorised personnel	A worker who has been authorised by the employer to carry out certain tasks on the basis of his or her ability to do them correctly, in accordance with the procedures set out in this guide
Auto-immune disease	Alteration of the function of the immune system, causing it to attack the body's own cells
BGW	Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (Employer's Liability Insurance Association for Health Services and Welfare Care in Germany)
Biological safety cabinet (BSC)	An enclosed, ventilated workspace used to protect personnel against biohazardous or infections agents and maintain quality control of the material being worked with. BSCs are classified into classes I, II, and III depending on the level of protection provided
Biomonitoring	Measurement and evaluation of a substance or its metabolites in the body tissue, fluids or exhaled air of an exposed person
Breakthrough time	The time it takes a chemical to permeate completely through the material
BSC	Biological safety cabinet
CACI	Compounding aseptic containment isolator
CAD	Chemical Agents Directive (89/391/EEC) Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC)
Carcinogen	Defined in the CMRD (Directive 2004/37/EC) as "a substance or mixture which meets the criteria for classification as a category 1A or 1B carcinogen set out in Annex I to Regulation (EC) No 1272/2008 of the European Parliament and of the Council" or "a substance, mixture or process referred to in Annex I to this Directive as well as a substance or mixture released by a process referred to in that Annex"[289]

[289] Directive 2004/37/EC, Article 2(a)

Term	Definition (for the purposes of this guide)
Carers	Patient's family members/friends/volunteers providing care and support for the patient
Catheter bag	A urine-collecting bag connected to a tube inserted into the bladder
CDSC	Cytotoxic drug safety cabinet
CE marking	A marking by which the manufacturer indicates that the product is in conformity with the applicable requirements set out in EU harmonisation legislation (according to Decision No 768/2008/EC).[290]
Clean room	Area designated for preparing sterile products; a room in which the concentration of airborne particles is controlled by minimising the introduction, generation, and retention of particles
Closed system	A device that does not exchange unfiltered air or contaminants with the adjacent environment.
Closed system transfer device (CSTD)	A medicine transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the HMP or vapour concentrations outside the system
CLP	Classification, packaging and labelling Regulation (1272/2008/EC) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
CMR	Carcinogenic, mutagenic or reprotoxic
CMRD	Carcinogens, mutagens or reprotoxic substances Directive (CMRD) (2004/37/EC) Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC)
Compounding	The process of combining, mixing, or modifying ingredients to create a medication tailored to the needs of an individual patient
Compounding centre	An external provider of HMP preparation services other than a pharmacy, for example, a large scale centre for automated reconstitution of HMPs for infusions
Control measure	A measure implemented to prevent or minimise the risk of injury from a particular hazard
C-PEC	Containment primary engineering controls
C-SEC	Containment secondary engineering controls
CSF	Cerebrospinal fluid
CSTD	Closed System Transfer Device (see above)
Cytostatic	The property of inhibiting cell multiplication or development
Cytotoxic	Ability to interact directly with DNA or DNA-associated macromolecules resulting in cell death in an indiscriminate manner, affecting healthy cells in addition to tumour cells, and causing serious systemic toxicity and in most cases genotoxicity
Damage to health	Any disease or damage to a person's physical or mental condition, or any possible effect on the pregnancy or the unborn or new-born infant, or to female workers who have recently given birth
Dermal exposure	A route of exposure – the amount of a substance that comes into contact with the skin, the outer boundary of the body

[290] Article R1 of Decision No 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products, and repealing Council Decision 93/465/EEC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32008D0768

Term	Definition (for the purposes of this guide)
Dermal absorption	Transport of chemicals from the outer surface of the skin both into the skin and into circulation
Dermatitis	Inflammation of the skin
Dose fractionation	The division of the total dose into smaller fractions separated by time
DP	Drug product
EC	European Commission
ECS	Environmental Control System
ECVIM-CA	European College of Veterinary Internal Medicine of Companion Animals
EMA	European Medicines Agency
Employer	Any natural or legal person who has an employment relationship with the worker and has responsibility for the undertaking and/or establishment[291]
Engineering control	A type of control measure which uses technological means to isolate or remove hazards
ESOP	European Society of Oncology Pharmacy
EU	European Union
EU-OSHA	European Agency for Safety and Health at Work
EWC	European Waste Catalogue
Excreta	Body substances including e.g. sweat, urine, bile, vomit, faeces, sebum and fluid drained from body cavities
Excretion rates	The speed relative to time that an exogenous compound is removed from a body system
Exposed	A person is exposed to a hazardous chemical if they are in a situation where they absorb or are likely to absorb the substance by ingestion, inhalation or through the skin or mucous membrane – exposure may also occur as a result of percutaneous injuries
Exposure (to an HMP)	Exposure to an HMP in the workplace that involves contact between the HMP and the worker, usually by inhalation or through the skin
Extemporaneous	The preparation of a therapeutic product for an individual patient in response to an identified need
Extravasation	Unplanned escape of a liquid from a vessel or tube into surrounding body tissues
Faeces	Waste from the intestines
FAQ	Frequently asked questions
Fertile age	According to WHO, the average fertile age for women is 15 to 44 years of age, and for men it is 14 to 60 years of age
FFP2	Filtering face pieces (FFP) for protection against particles. Medium filter performance (94% efficiency)
FFP3	Filtering face pieces (FFP) for protection against particles. High filter performance (99.97% efficiency)

[291] Directive 89/391/EEC, Article 3

Term	Definition (for the purposes of this guide)
Finished medicinal product	Substances and mixtures which are in the finished state and intended for the final user and which are medicinal products within the scope of Directive 2001/83/EC on the Community code for medicinal products for human use, or veterinary medicinal products within the scope of Directive 2001/82/EC[292]
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GMP	Good Manufacturing Principles (WHO, 2010)[293]
GP	General Practitioner
Handling HMPs	The set of operations performed when preparing a dose from a commercial presentation, its administration to the patient, the collection of waste derived from professional action, the removal of the excreta and biological fluids of patients in treatment with HMPs, and any other action that involves potential contact with the medication
Hazard	The intrinsic property that has the potential to cause harm
Hazard statement	A statement assigned to a hazard class or hazard category describing the nature of the hazards of a hazardous chemical including, if appropriate, the degree of hazard
HBEL	Health based exposure limit
Healthcare facility	Includes hospitals, clinics, ambulatory care facilities and medical practices
Health surveillance	The assessment of an individual worker to determine the state of health of that individual, as related to exposure to specific carcinogens, mutagens or reprotoxic substances at work[294]
HEPA filter	High-efficiency particulate air filter that removes at least 99.97% of dust, pollen, mould, bacteria, and any airborne particles with a size of 0.3 microns (µm)
HIPEC	Hyperthermic intraperitoneal chemotherapy
HMP	Hazardous medicinal product
HMP spill	A spill of HMPs or related wastes
HMP waste	Waste contaminated with HMPs or metabolites – it includes any residual HMP that remains following patient treatment and any materials or equipment potentially contaminated with HMPs.
HMP-OSH	Occupational safety and health (OSH) policies and practical measures for the prevention and control of hazardous medicinal products (HMP) risks
HR	Human resources
HSE	Health, safety and environment
HVAC	Heating, ventilation and air-conditioning
IATA	International Air Transport Association
IMDG Code	International Maritime Dangerous Goods Code

[292] Taken from Questions & answers section of the ECHA website: Will medicinal products need to be classified and notified to the Classification and Labelling Inventory? Substances and mixtures which are in the finished state and intended for the final user and which are medicinal products within the scope of Directive 2001/83/EC on the Community code for medicinal products for human use, or veterinary medicinal products within the scope of Directive 2001/82/EC on the Community code relating to veterinary medicinal products are on the whole exempted from the provisions of the CLP Regulation, i.e. they do not have to be classified, packaged, labelled and notified to the C&L Inventory. However, in cases where a manufacturer or importer supplies substances and mixtures, e.g. active pharmaceutical ingredients (APIs) or excipients, that are not yet in the finished state, this manufacturer or importer will have to classify, package and label these substances and mixtures in accordance with CLP. In addition, if these substances are placed on the market, they will also have to be notified to the C&L Inventory. The exemption from the provisions of the CLP Regulation does not distinguish between active and non-active pharmaceutical ingredients: it applies to any substance or mixture used in medicinal products, e.g. excipients, which is in the finished state and intended for pharmaceutical use. Source: https://echa.europa.eu/de/support/qas

[293] WHO, (2010), WHO good manufacturing practices for pharmaceutical products containing hazardous substances, Annex 3. WHO Technical Report Series, No. 957.

[294] Directive 2004/37/EC, Article 2

Term	Definition (for the purposes of this guide)
Immune system	System of cells and special proteins throughout the body that serves to resist and overcome infection, and attack foreign matter (for example – transplants) and abnormal cells (for example – early cancer)
Immuno-suppressive	Relating to a substance or procedure that lessens or prevents adequate response of the immune system
Infusion	Therapeutic introduction of a fluid other than blood into a vein
Ingestion	A route of exposure – taking in HMP or waste through the mouth
Inhalation	A route of exposure – breathing in HMP or waste in aerosol or powder form
Injection	A sterile fluid preparation of a medicament to be used parenterally (such as – by injection, subcutaneously, intramuscularly, intravenously or intrathecally)
Inland TDG	Inland Transport of Dangerous Goods (2008/68/EC) Directive 2008/68/EC of the European Parliament and of the Council of 24 September 2008 on the inland transport of dangerous goods
Intralesional administration	Injection directly into a lesion on or immediately below the skin
Intraperitoneal	Administered by entering the peritoneum
Intrapleural	The cavity that lies between the two layers of the pleura, a thin membrane that surrounds the lungs and lines the internal surfaces of the chest cavity
Intrathecal injection	Injection into the fluid-filled space that surrounds the spinal cord
Intravenous (IV) infusion	Introduction of a liquid into a vein through a hollow needle or flexible tube over a period of time
Intravesical installation	Introduction of liquid through a hollow needle or tube into the urinary bladder
IARC	International Agency for Research on Cancer
Isolator	Provides a perfectly hermetic and secure containment area. It is a piece of equipment for the protection of aseptic preparations.
ISOPP	International Society of Oncology Pharmacy Practitioners
IV	Intravenous
LEV	Local exhaust ventilation
Limit value	Any binding or non-binding limit value for exposure, contamination or concentration in a biological medium or its metabolite, or an indicator of effect, set in legislation, another source or derived internally
Lipophilicity	Able to dissolve much more easily in lipid
Luer-lock	A standardised system of small-scale fluid fittings used for making leak-free connections between a male-taper fitting and its mating female part on medical and laboratory instruments
MAB	Monoclonal antibody
MDI	Metered-dose inhaler
Metabolites	What a substance changes into when acted upon by the normal chemical processes that go in a person's body
Mutagen	Defined in the CMRD as "a substance or mixture which meets the criteria for classification as a category 1A or 1B germ cell mutagen set out in Annex I to Regulation (EC) No 1272/2008" [295]
NIOSH	National Institute for Occupational Safety and Health
Non-porous	Not permeable to water, air, or other fluids

[295] Directive 2004/37/EC, Article 2

Term	Definition (for the purposes of this guide)
Occupational exposure	Exposure to HMPs during a work activity
OEB	Occupational Exposure Band
OEL	Occupational Exposure Limit
Oncology	Relating to cancer treatment
Oral	A method of administration – usually in the form of tablets or capsules
OSH	Occupational Safety and Health
OSH FD	Occupational Safety and Health Framework Directive (89/391/EEC) Council Directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (89/391/EEC)
Parenteral	Administration of HMP by methods other than through alimentary canal, such as intravenous (IV), subcutaneous, intramuscular, intrapleural, intraperitoneal, intravesical
PDE	Permitted daily exposure
PDR	Prescriber's digital reference
Personal protective equipment (PPE)	All equipment designed to be worn or held by the worker to protect him against one or more hazards likely to endanger his safety and health at work, and any addition or accessory designed to meet this objective.[296] Personal protective equipment can include, for example, protective gloves, gowns/coveralls, respiratory protective equipment, and eye protection equipment
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIPAC	Pressurised intraperitoneal aerosol chemotherapy
PPE	Personal protective equipment
PPED	Personal Protective Equipment Directive (89/656/EEC) Directive 89/656/EEC Council Directive of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace
PPER	Personal Protective Equipment Regulation (2016/425) Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 on personal protective equipment and repealing Council Directive 89/686/EEC
Preparation of HMPs	Preparing HMPs upon delivery from the manufacturer for administration to a patient – includes, for example, reconstitution and dose preparation
Prevention	All the steps or measures taken or planned at all stages of work in the undertaking to prevent or reduce occupational risks[297]
Pregnant worker	A pregnant worker who informs her employer of her condition, in accordance with national legislation and/or national practice[298]
Protective	HMP-protective
PWD	Pregnant Workers' Directive (92/85/EEC) Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding

[296] Adapted from Directive 89/656/EEC, Article 2. For the full definition, see Council Directive of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace (third individual directive within the meaning of Article 16 (1) of Directive 89/391/EEC) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01989L0656-20191120

[297] Directive 89/391/EEC, Article 3

[298] Directive 92/85/EEC, Article 2

Term	Definition (for the purposes of this guide)
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (1907/2006) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
Reconstitution	Adding a liquid diluent to make a specific concentration of liquid
Reprotoxic substance	Defined in the CMRD as "a substance or mixture, which meets the criteria for classification as a category 1A or 1B reproductive toxicant set out in Annex I to Regulation (EC) No 1272/2008" [299]
Respiratory protective equipment (RPE)	Equipment that is designed to prevent inhalation of contaminated air
RiFaS	Pharmaceutical Substances Risk Assessment (Risico instrument Farmaceutische Stoffen, RiFaS) developed by the Royal Dutch Society for the Promotion of Pharmacy (KNMP)
Risk	The likelihood that the potential for harm will be attained under the conditions of use and/or exposure
Risk assessment	Evaluation of the probability that an adverse health effect may occur under the conditions that are likely to develop
Risk management	Analysis and judgment that uses the results of risk assessments to produce decisions about actions to be initiated to avert risks
RPE	Respiratory protective equipment
Safety data sheet (SDS)	A document that describes, amongst other information, the identity, properties (that is to say chemical and physical properties and health hazard and environmental hazard information), uses, precautions for use, safe handling procedures and safe disposal procedures of a substance or mixture. These are an integral part of Regulation (EC) No 1907/2006 (REACH).
SC	Subcutaneous
SDS	Safety data sheet
SEG	Similar Exposure Group. Group of workers having the same general exposure profile for the HMPs
Session	A period of time where a process or series of processes are performed with the same operational conditions such as personnel, process, and environment
Sharp	Article capable of piercing skin, such as a used needle or fragment of broken glass that has been in a health care setting
SmPC / SPC	Summary of product characteristics
SOP	Standard operating procedure
Spill	An unintended release of an HMP from a system such as a primary package of HMP, a syringe, an infusion-set or waste
Standard operating procedure (SOP)	A set of instructions or steps to be followed to complete a job safely and in accordance with legal, operational and company or institutional requirements. SOPs should be written for any processes an individual or group performs
Sterile	Free from living organisms
Systemic	Affecting a person's inner organs

[299] Directive 2004/37/EC, Article 2

Term	Definition (for the purposes of this guide)
TACE	Transarterial chemoembolisation
Telophase	The last of four stages in the division of a single body cell into two identical cells
Teratogenicity	Ability to cause harm to an embryo or foetus to produce birth defects
Topical	Method of administration on the body, typically (but not exclusively) through the skin using creams and ointments. Inhalation is dealt with as a separate category in this guide.
TTC	Threshold of toxicological concern
Unit dose	A sealed single-unit container so designed that the contents are administered to the patient as a single dose, direct from the container
Vial	Small glass jar with a stopper that contains one or more doses of an HMP for injection
WHO	World Health Organisation
Worker	Any person employed by an employer, including trainees and apprentices but excluding domestic servants.[300] In this guide, this includes casual, agency, or temporary workers.
Workers' representative (with specific responsibility for the safety and health of workers)	Any person elected, chosen or designated in accordance with national laws and/ or practices to represent workers where problems arise relating to the safety and health protection of workers at work[301]
Worker who has recently given birth	A worker who has recently given birth within the meaning of national legislation and/or national practice and who informs her employer of her condition, in accordance with that legislation and/or practice[302]
Worker who is breastfeeding	A worker who is breastfeeding within the meaning of national legislation and/or national practice and who informs her employer of her condition, in accordance with that legislation and/or practice[303]
Young worker	Any person under 18 years of age having an employment contract or an employment relationship defined by the law in force in a Member State and/or governed by the law in force in a Member State[304]
YWD	Young Workers' Directive (94/33/EC) Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work

300 Directive 89/391/EEC, Article 3
301 Directive 89/391/EEC, Article 3
302 Directive 92/85/EEC, Article 2
303 Ibid
304 Directive 94/33/EC, Article 2

Annex 2. Examples of templates for risk assessments

A risk assessment must be conducted regularly, for instance every year and in any event when any change occurs in the conditions which may affect workers' exposure to HMPs. [305] A risk assessment process should include a review of documentation from previous risk assessments, evaluations of incidents, absenteeism and health surveillance, reports on new HMPs introduced, reports on new illnesses or symptoms, proposals for improvement, and any other relevant documentation.

A risk assessment should be conducted in a series of interrelated steps focusing on:

- Identification of hazards and risks
- Identification of limit values for the HMPs
- Assessment of the key exposure routes (e.g. dermal and inhalation exposure)
- Determine if exposure is exceeding the limit values
- Identification of existing control measures and compliance with use
- Analysis of gaps in current control measures
- Implementation of (additional and/or new) control measures
- Evaluation of effectiveness of control measures

Below are examples of templates for risk assessment for the following life cycle stages:

- Administration
- Cleaning
- Laundry

It should be noted that these are only examples. Other approaches exist. In addition, these templates should be read in conjunction with the remainder of this guide, including the information on the hierarchy of controls in Directive 2004/37/EC (CMRD) and Directive 89/391/EEC in section 4.4.1.

[305] Directive 2004/37/EC, Article 3

Annex 2.1 Administration

Step 1. Identification of hazards and risks

- What HMPs are being administered?
- Identify the hazardous properties, classification and labelling of HMPs in use
- Where are the HMPs being administered?
- Which administration procedures are in use at the administration location?
- Which techniques are used in the administration procedures?
- Which workers are at risk (including workers at particular risk)?
- Which patients are being administered HMPs?
- Which exposure risks can be identified for each HMP, with:
  - Techniques used?
  - Patient care?
  - Handling excreta?
  - Cleaning?
  - Handling hazardous waste?
  - Handling laundry?
  - Maintenance?
  - Incidents?

Step 2 Establish whether there are limit values for the HMPs or derive them

Step 3 Assessment of dermal and inhalation exposure

- What is the nature, degree and duration of the exposure for each group of workers (similar exposure group)?

Step 4 Determine if exposure is exceeding the limit values (if these are available)

Step 5 Identification of existing control measures and compliance with them

- Which technical, organisational, and personal control measures are in place to prevent exposure and are they complied with, during:
  - Administration?
  - Patient care for the specific HMP?
  - Handling excreta?
  - Handling hazardous waste?
  - Maintenance?
  - Incidents?
- Which training and procedures and control measures are in place to prevent potential spreading of HMPs, during:
  - Administration?
  - Patient care for the specific HMP?

- Handling excreta?
- Handling hazardous waste?
- Maintenance?
- Incidents?

Step 6 Analysis of gaps in current control measures

- Which control measures should be in place to prevent exposure, during:
  - Administration?
  - Patient care for the specific HMP?
  - Handling excreta?
  - Cleaning?
  - Handling hazardous waste?
  - Laundry?
  - Maintenance?
  - Incidents?
- Which training and procedures and control measures should be in place to prevent potential spreading of HMPs

Step 7 Implementation of control measures

- Decide which control measures should be implemented, taking into account the hierarchy of controls in section 4.4.1
- Decide when the control measures should be implemented
- Appoint the responsible person for implementation of the control measures
- Implement the control measures
- Communicate information about the use of the control measures to the workers who need to know about them

Step 8 Evaluation of control measures

- Periodically evaluate the use and effectiveness of the control measures in preventing exposure to HMPs
- Review and revise the control measures based upon the evaluation

Annex 2.2 Cleaning

Step 1. Identification of hazards and risks

- Where are the HMPs being administered (day-care or nursing wards)?
- What HMPs are administered at the identified location?
- Identify the hazardous properties of the HMPs in respect to cleaning
- Which workers are at risk (including workers at particular risk)?
- Which exposure risks can be identified per location:
  - Administration room?
  - Rinsing areas?
  - Sanitary rooms?
- Are the administration rooms identified?
- Are the surfaces that are potentially contaminated with HMP's identified?
- Are the rinsing areas where HMP contaminated excreta from patients are handled (toilets – bedpan washer) identified?
- Are the sanitary rooms for HMP treated patients (wash rooms – showers – bath rooms) identified?
- Is there designated cleaning equipment only to be used in potentially HMP contaminated areas?

Step 2. Establish whether there are limit values for the HMPs or derive them

Step 3. Assessment of dermal and inhalation exposure

- What is the nature, degree and duration of the exposure for each group of workers (similar exposure group)?

Step 4. Determine if exposure is exceeding the limit values (if these are available)

Step 5. Identification of existing control measures and compliance with them

- Which technical, organizational, personal cleaning procedures and control measures are in place to prevent potential exposure to HMPs during:
- Cleaning of administration rooms
  - Are the administration rooms identified?
  - Are the surfaces that are potentially contaminated with HMP's identified?
- Cleaning of sanitary rooms
  - Are the sanitary rooms for HMP treated patients (wash rooms – showers – bath rooms) identified?
- Cleaning of rinsing areas
  - Are the rinsing areas where HMP contaminated excreta from patients are handled (toilets – bedpan washer) identified?
- Is there designated cleaning equipment only to be used in potentially HMP contaminated areas?

- Which training and cleaning procedures and control measures are in place to prevent potential spreading of HMPs during:
  - Cleaning of administration rooms
  - Cleaning of sanitary rooms
  - Cleaning of rinsing areas

Step 6. Analysis of gaps in current control measures

- Which (additional) control measures should be in place to prevent exposure during:
  - Cleaning of administration rooms
  - Cleaning of sanitary rooms
  - Cleaning of rinsing areas
- Which training and cleaning procedures should be in place to prevent potential spreading of HMPs during:
  - Cleaning of administration rooms
  - Cleaning of sanitary rooms
  - Cleaning of rinsing areas

Step 7. Implementation of control measures

- Decide which control measures should be implemented, taking into account the hierarchy of controls in section 4.4.1
- Decide when the control measures should be implemented
- Appoint the responsible person for implementation of the control measures
- Implement the control measures
- Communicate information about the use of control measures to the workers who need to know about them

Step 8. Evaluation of control measures

- Periodically evaluate the use and effectiveness of the control measures in preventing exposure to HMPs
- Review and revise the control measures based upon the evaluation

Annex 2.3 Handling laundry

Step 1. Identification of hazards and risks

- What HMPs are administered and can be expected to contaminate laundry?
- Identify the hazardous properties of these HMP's?
- In which areas is HMP contaminated laundry to be expected?
- Which workers are at risk (including workers at particular risk)?
- Which exposure risks can be identified with collecting HMP contaminated laundry?
- Which exposure risks can be identified with handling HMP contaminated laundry?
- Which protocols are in place to prevent potential exposure to HMPs?

Step 2 Establish whether there are limit values for the HMPs or derive them

Step 3. Assessment of dermal and inhalation exposure

- What is the nature, degree and duration of the exposure for each group of workers (similar exposure group)?

Step 4. Determine if exposure is exeeding the limit values (if these are available)

Step 5. Identification of existing control measures and compliance with them

- Which technical, organizational and personal control measures are already in place to prevent potential exposure to HMPs during collection and handling of laundry?
- Are potentially HMP contaminated clothes or bed-linen identified?
- Is HMPcontaminated laundry collected in special, identifiable laundry bags?
- Are the routes and/or trolleys for HMP contaminated laundry separate from those for normal laundry?
- Are the trolleys for HMP contaminated laundry stored separately from the trolleys for normal laundry?

Step 6. Analysis of gaps in current control measures

- Which control measures should be in place to prevent exposure during collection and handling of HMP contaminated laundry?

Step 7. Implementation of control measures

- Decide which control measures should be implemented, taking into account the hierarchy of controls in section 4.4.1
- Decide when the control measures should be implemented
- Appoint the responsible person for implementation of the control measures
- Implement the control measures
- Communicate information about the use of control measures to the workers who need to know about them

Step 8. Evaluation of control measures

- Periodically evaluate the effectiveness of the control measures in preventing exposure to HMPs
- Review and revise the control measures based upon the evaluation

Annex 3. European List of Waste (LoW) codes

Table A3-1: LoW codes for healthcare waste (360 Environmental, 2022)

LoW Code	Description	Classification
Chapter 18: Healthcare waste		
Sub chapter 01: Natal care – diagnosis – treatment or prevention of disease in humans		
18 01 01	Sharps (except 18 01 03)	Non hazardous
18 01 08*	Cytotoxic and cytostatic medicines	Hazardous
18 01 09	Medicines other than those mentioned in 18 01 08	Non hazardous
Sub chapter 02: Research – diagnosis – treatment or prevention of disease involving animals		
18 02 01	Sharps (except 18 02 02)	Non hazardous
18 02 07*	Cytotoxic and cytostatic medicines	Hazardous
18 02 08	Medicines other than those mentioned in 18 02 07	Non hazardous
Chapter 20: Municipal Waste and Similar Materials from Commerce and Industry		
Sub chapter 01: Separately collected fractions (except 15 01)		
20 01 31*	Cytotoxic and cytostatic medicines	Hazardous
20 01 32	Medicines other than those mentioned in 20 01 31	Non hazardous

Source: 360 Environmental (2022) Online Waste Support EWC Search facility available at: http://www.wastesupport.co.uk/ewc-codes/

Annex 4. Personal protective equipment (PPE)

Risk assessment

The terms 'PPE' and 'personal protective equipment' in this document are used in the sense of Directive 89/656/EEC. The risk assessment that each employer shall carry out will determine the choice of PPE and the exact type needed in each particular case with regard to the risks they provide protection against.

A task-based risk assessment should be carried out to determine the protective measures for each specific task.[306] According to Article 3 of Directive 89/656/EEC, personal protective equipment must be used when the risks cannot be avoided or sufficiently limited by technical means of collective protection or by measures, methods or procedures of work organisation. This annex summarises what PPE is advisable in the different situations pertaining to HMPs. In this context, account needs to be taken of any applicable national rules in implementation of Article 6 of Directive 89/656/EEC.

The duration of exposure should always be as short as possible, for example by adequately preparing and organising the task, and limiting the number of people exposed as much as possible, for example, by placing a warning not to enter the room.

PPE requirements under Regulation 2016/425 and Directive 89/656/EECPPE requirements

The requirements for the design and manufacture of PPE and its use are set out in Regulation (EU) 2016/425[307] and Directive 89/656/EEC[308] respectively.

PPE in the sense of Regulation 2016/425 must meet the essential health and safety requirements set out in Annex II to Regulation (EU) 2016/425 which apply to it. PPE which is in conformity with harmonised standards the references of which have been published in the Official Journal of the European Union shall be presumed to be in conformity with the essential health and safety requirements set out in Annex II covered by those standards.[309]

Manufacturers have the obligation to assess the conformity of the product, which in the case of PPE category III includes the intervention of a notified body in both design and production phases.[310]

PPE or, when not possible, its packaging and the documentation accompanying the PPE, must have a CE marking followed by the four digits identification number of the notified body involved in the production control phase[311].

PPE, or when not possible, its packaging or a document accompanying the PPE must also include the contact details of the manufacturer and, when applicable, the importer in a language easily understood by the users.[312]

PPE must be accompanied by the manufacturer's instructions and information in a language easily understood by the users, and either by a copy of the EU declaration of conformity or by the internet address in the manufacturer's

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306 See Articles 4 and 5 of Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01989L0656-20191120&qid=1676368333478

307 Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 on personal protective equipment and repealing Council Directive 89/686/EEC, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R0425

308 Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01989L0656-20191120&qid=1676368333478

309 Regulation (EU) 2016/425, Articles 5 and 14

310 Regulation (EU) 2016/425, Articles 8(2), 19,and Annexes V, VII and VIII

311 Regulation (EU) 2016/425, Article 17

312 Regulation (EU) 2016/425, Articles 8(6) and 10(3)

instructions at which the EU declaration of conformity can be accessed. The EU declaration of conformity must state that the fulfilment of the applicable essential health and safety requirements has been demonstrated.[313]

Member States must ensure the free movement of compliant PPE within the internal market of the European Union and may lay down special requirements for its use.

The use of PPE must comply with Directive 89/656/EEC. Article 4 of Directive 89/656/EEC is reproduced below.

Box A4-1: Article 4 of Directive 89/656/EEC

1. Personal protective equipment must comply with the relevant Community provisions on design and manufacture with respect to safety and health.

   All personal protective equipment must:

   (a) be appropriate for the risks involved, without itself leading to any increased risk;

   (b) correspond to existing conditions at the workplace;

   (c) take account of ergonomic requirements and the worker's state of health;

   (d) fit the wearer correctly after any necessary adjustment.
2. Where the presence of more than one risk makes it necessary for a worker to wear simultaneously more than one item of personal protective equipment, such equipment must be compatible and continue to be effective against the risk or risks in question.
3. The conditions of use of personal protective equipment, in particular the period for which it is worn, shall be determined on the basis of the seriousness of the risk, the frequency of exposure to the risk, the characteristics of the workstation of each worker and the performance of the personal protective equipment.
4. Personal protective equipment is, in principle, intended for personal use.

   If the circumstances require personal protective equipment to be worn by more than one person, appropriate measures shall be taken to ensure that such use does not create any health or hygiene problem for the different users.
5. Adequate information on each item of personal protective equipment, required under paragraphs 1 and 2, shall be provided and made available within the undertaking and/or establishment.
6. Personal protective equipment shall be provided free of charge by the employer, who shall ensure its good working order and satisfactory hygienic condition by means of the necessary maintenance, repair and replacements.

   However, Member States may provide, in accordance with their national practice, that the worker be asked to contribute towards the cost of certain personal protective equipment in circumstances where use of the equipment is not exclusive to the workplace.
7. The employer shall first inform the worker of the risks against which the wearing of the personal protective equipment protects him.
8. The employer shall arrange for training and shall, if appropriate, organize demonstrations in the wearing of personal protective equipment.
9. Personal protective equipment may be used only for the purposes specified, except in specific and exceptional circumstances.

   It must be used in accordance with instructions.

   Such instructions must be understandable to the workers.

Source: Directive 89/656/EEC

[313] Regulation (EU) 2016/425, Articles 8(7), 8(8) and 10(4) and point 1.4 of Annex II

Health and safety requirements should take into account the state of the art, current practice, technical and cost considerations whilst reflecting the seriousness of the harm and ensuring a high degree of health and safety protection for the worker. Member States must ensure free movement on the market but may lay down special requirements for the use of the PPE. Conformity assessment is the obligation of the manufacturer, which applies to imported PPE. PPE must be accompanied by instructions and contact details in the user's language.[314]

Protective gloves

The intact skin is a barrier for substances. This barrier is not absolute and exposure to HMPs can have a local effect on the skin (irritation, dermatitis or allergic reactions) or can pass through the skin. The skin barrier can be affected by skin irritants and skin diseases enhancing dermal adsorption of substances. To avoid dermal exposure of the hands protective gloves should be used.

For protective gloves, the relevant European standards are:

- EN ISO 21420:2020; General requirements and test methods for protective gloves
- EN ISO 374-1:2016; Protective gloves against chemicals and micro-organisms
- EN ISO 374-2: 2019; Penetration
- EN ISO 374-4:2019; Degradation
- EN 16523-1:2015+A1:2018 Determination of material resistance to permeation by chemicals - Part 1: Permeation by potentially hazardous liquid chemicals under conditions of continuous contact:
  - Type A: breakthrough time at least 30 minutes (level 2) against 6 chemicals
  - Type B: breakthrough time at least 30 minutes (level 2) against 3 chemicals
  - Type C: breakthrough time at least 10 minutes (level 1) against 1 chemical
- EN 388:2016+A1:2019; protective gloves against mechanical risks:
  - Abrasion resistance; classification 1
  - Cut resistance, coup test; classification 2
  - Tearing resistance; classification 3
  - Puncture resistance; classification 4
  - Cut resistance, TDM Test ISO 13997:1999; classification B
  - Impact protection; classification P

Protective gloves used during administration, handling excreta, handling contaminated laundry, handling waste containers and cleaning should be tested according to EN-ISO 374-1:2016 and EN-ISO 374-1:2016/A1:2018 (or equivalent) and be at least type B.

Protective gloves used for handling a spillage should be tested according to EN-ISO 374-1:2016 and EN-ISO 374-1:2016/A1:2018 (or equivalent) and be at least type B and, if handling sharp objects or broken glass, puncture resistant (classification 3).

European standards specify a test temperature for gloves of 23 degrees (EN 16523-1:2015+A1:2018) (i.e. room temperature). The equivalent ASTM standard tests at 35 degrees (close to body temperature). As gloves are worn on the body, to protect the body, it would be realistic to test close to that temperature. Although the Declaration of Conformity states that the product is tested to be safe and in compliance with EU regulation, it is good to remember the difference between testing and body temperature that might be of importance for permeation in specific situations.

[314] Regulation (EU) 2016/425, Articles 8(6), 8(7), 10(3), 10(4) and point 1.4 of Annex II

Respiratory protection

There are only a few HMPs with known measurable vapour pressure. The evaporation rate for these HMPs is low. If the procedures described in this guide are properly applied, it is highly unlikely that HMPs will be generated in vapour form in the work environment. If the risk assessment for an individual HMP (for instance the antineoplastic medicinal product Mustine) indicates that inhalation of a vapour is possible then specific respiratory protection is necessary and specialized advise is recommended.

Respiratory protection is needed in case of exposure to dust or aerosols. The following European standards are relevant for the choice and use of respiratory protection devices (masks) for HMPs:

- EN 529:2005; Guideline document for practical use, which contains the basic principles for the selection, use, care, and maintenance of respiratory protection devices
- EN 143:2021; Standard providing the minimum requirements for particle filters (for face masks):
  - P1 filter: Low filter performance (80% efficiency)
  - P2 filter: Medium filter performance (94% efficiency)
  - P3 filter: High filter performance (99.97% efficiency)
- EN 149:2001+A1:2009; Standard providing the minimum requirements for filtering facepieces (FFP) for protection against particles:
  - FFP 1: Low filter performance (80% efficiency)
  - FFP 2: Medium filter performance (94% efficiency)
  - FFP 3: High filter performance (99.97% efficiency)

Respiratory protection for working with HMPs should be at least FFP2 for filtering facepieces depending on the task and FFP3 or facemask with P3 filter in case of an incident with potential exposure to dust or aerosols.

Eye and face protection

Eye and face protectors for HMPs are items of PPE intended to prevent the harmful effects that physical and chemical hazards (such as flying particles, dust and aerosols) may have to the eye and face. The relevant European standards are:

- EN-ISO 16321-1:2022; Eye and face protection for occupational use – Part 1 general requirements
- EN-ISO 19734:2021; Eye and face protection — Guidance on selection, use and maintenance

In case of splashing and aerosols, a face shield is preferred over safety goggles.

Protective clothing

The European standard[315] for clothing protecting against exposure to HMPs is:

- EN 13034:2005+A1:2009; Performance requirements for use in cases of a potential exposure to a light spray, liquid aerosols or low pressure, low volume splashes against which a complete liquid permeation barrier (on a molecular level) is not required

The standard covers both chemical protective suits (Type 6) and partial body protection (Type PB [6]). Chemical protective suits (Type 6) cover and protect at least the trunk and the limbs, for instance one-piece coveralls or two-piece suits, with or without hood, boot-socks or boot-covers. Partial body protection of similar limited performance (Type PB [6]) covers and protects only specific parts of the body, for instance coats, gowns/coverall, and sleeves. This protective clothing (type 6 and PB [6]) can also be used for protection against dust exposure.

[315] Other standards for protective clothing: EN 17491-4: 2008, EN 14605:2005, EN14325:2005, EN ISO 13982-1 and 2:2005 for overalls.

Differentiation in use of PPE

The PPE for single use only is:

- Protective gloves used in preparation, administration, patient care, handling laundry in health care settings
- Respiratory protection against dust and aerosols in health care settings other than incidents
- Protective clothing in healthcare settings (gowns/coveralls)

Prevention of exposure can be done in different ways, for instance in preparation by using Biological Safety Cabinets Class II, isolators, or systems with a physical barrier. In practice, this means that there is a physical barrier between the product and the worker to avoid the inhalation of dust particles or aerosols during preparation. Protective gloves are used to protect the worker from skin exposure from contaminated surfaces, infusion bags, syringes or patient physical care. Protective clothing is used to protect contamination of clothes and skin exposure.

If administration systems with physical barriers between the HMP and the worker are used, for instance primed lines with neutral infusion liquid, multi system lines with valves to prevent HMP-containing liquid from leaking, or administration systems with physical barriers to protect the worker, it is unlikely that aerosols or dust are produced in the breathing zone of the worker, so there is no risk of inhalation. In some cases, patients can self-administer, for instance in oral and dermal applications, avoiding exposure of the worker.

If those systems are not used, then full protection should be used to protect the worker against the possible release of dust, aerosols, and leakage. This means wearing an impermeable gown/coveralls and long protective gloves, as well as respiratory protection and a face shield in case of possible aerosol and/or dust formation and release.

Protective gloves and gowns/coveralls should be used in case of possible contact with contaminated surfaces, infusion bags, or syringes. Double gloving can be used to prevent contamination spread from one aera to another, for example in clean rooms. For protection in administration procedures (oral, IV or injections) normally single protective gloves B are sufficient.

If aerosols are produced in the administration itself (for instance aerosolisation of HMPs in the treatment of lung diseases) respiratory protection should be worn during and for at least 30 minutes after the conclusion of the procedure unless the room is left sooner, which is recommended. A single-use mask FFP2 or FFP3 should be used.

During regular cleaning of administration areas, see section 14.1, the worker needs protective gloves that are changed on a regular base, particularly after direct contact with liquid. Ideally protective gloves should be changed every time a room or area has been cleaned to avoid cross contamination from one place to another. If intensive cleaning is required, for instance such as after a spillage, see section 13, more personal protection is needed.

Correct use of PPE

General remarks

- Tie back long hair
- Keep beards and moustaches short and clean
- Do not wear hand and wrist jewellery, long necklaces, or large earrings (small earrings such as studs are allowed)
- Keep nails short and clean, do not wear make-up, nail varnish, artificial nails, or perfume

- Do not wear jewelry on hands and/or forearms
- Cover wounds with water-repellent plasters
- Wear good removable shoes (no flip-flops, sandals, or high heels)
- Do not wear shorts, short dresses, or shirts with thin straps

General procedure

- Put on PPE before starting the task. Start with protective clothing, then respiratory protection, eye/face protection and finish with protective gloves
- After finishing the task, remove eye/face protection, remove shoe covers, protective clothing, and hair cover, then respiratory protection and then protective gloves. Do not touch clean clothing or skin with gloves during that procedure
- Single-use PPE: dispose of as hazardous waste
- Non-disposable mask, face shield/goggles: clean using protective gloves, detergent and water, and store in a dedicated bag or box in a clean place

Gloves

Use the correct protective gloves, tested according EN ISO 374_2016 and EN-ISO 374-1:2016/A1:2018 (or equivalent), at least type B. The protection of gloves depends on the substance, material of the gloves, thickness, mechanical strength, quality of production, and the contact-time. Stock a range of glove sizes to ensure they fit well and provide workers with the necessary dexterity to perform their work.

For protection against HMPs, the following parameters should be considered in the risk assessment to select protective gloves:

- Degradation: the material of the protective glove should be resistant against the substances that are used for the period that the protective gloves are worn
- Pinholes: microscopic holes in the material allow the substance to move from the outside of the protective glove to the inside. Pinholes are random and related to the quality of the protective glove. The supplier should provide information about the quality of the protective gloves and protection characteristics
- Permeation: the rate at which the substance passes through the glove at a molecular level. The penetration rate should be as low as possible and is defined by the breakthrough time
- Mechanical strength: gloves should protect against sharp objects, for instance in cleaning of a spill with broken glass
- Thickness: if a protective glove of the same material and production quality is twice as thick, a general rule of thumb is that the breakthrough time is four times longer
- Dexterity: if a protective glove is limiting the ability of the worker to perform their task correctly, this might cause mistakes or spillages causing potential exposure

The best way to use gloves

- Make sure hands are clean and dry before putting on the protective gloves. Wet skin under the glove is more likely to cause irritation.
- Use the protective gloves for as short a time as possible. If you wear protective gloves for more than ten minutes, use a cotton inner glove, which absorbs perspiration and thus prevents softening of the skin

- Change a damaged protective glove immediately. The irritating effect of, for example, water penetrating a broken protective glove is increased under the sealing glove
- Remove jewellery and artificial nails and keep nails short

Removal of (single use) protective gloves (doffing)

- Pull off the protective gloves without contaminating yourself, using the pick-and-shove method:
- Basic rule for removing protective gloves: dirt to dirt and clean to clean
- Take the outside of the protective glove near the wrist with your other hand with gloved fingers
- Pull the protective glove down and hold it in the palm of your gloved hand
- Put two clean fingers inside the other protective glove
- Pull the protective glove to the outer side across the other protective glove and throw the protective gloves away
- When working in a care unit: Disinfect hands and wrists after removing the protective gloves

See video[316] with instructions on how to safely put on/take off protective gloves.

Removal of protective face shield/goggles, gown/coveralls, or mask

- Take off the splash face shield/goggles using protective gloves and hold them at one point
- Pull off the protective gown/coveralls in such a way that the clean inside is turned out, roll it up carefully and subsequently put it in the open waste container or bag
- Remove FFP mask taking care to hold the mask only by the elastic bands, first the lower band and then the upper band. Avoid allowing the outside of the mask to touch your face

Disinfecting your hands

- Use your underarm to pump the disinfectant bottle
- Clean the palms of your hands and then your fingers
- Clean the back of your hands and between your fingers
- Grip your fingers into your palms and rotate slightly
- Clean the thumbs
- Rub your fingertips into your palms to clean them
- Clean your wrists

In Table A4-1, the minimum PPE required to protect the worker against exposure to HMPs is listed for different tasks (marked with an **X**). Combinations of tasks and PPE that are not seen as minimum PPE are marked with a /. A risk assessment should be performed to select the correct PPE. The results of the risk assessment should be followed with regard to the cells marked with a /.

[316] How to safely put on and take off gloves in hospitals - YouTube. Video published on 28 September 2020. Video online as of 8 November 2022. Link as text: https://www.youtube.com/watch?v=eBdYI4gQ_9M

Table A4-1: Minimum PPE or other equipment for different tasks (X=minimum equipment)

Task	Glove type B	Glove type A	Surgical gloves (double)	Glove type A & puncture class 3	Face shield / goggles	Gown	Coverall	Hair cover	Shoe cover	Respiratory protection FFP2	Respiratory protection FFP3	Face mask with P3 filter
Manufacturing	/	X	/	/	X	/	X	/	/	X	X	/
Preparation (pharmacy)	X	/	/	/	X	X	/	X	/	X	/	/
Preparation (outside pharmacy)	X	/	/	/	X	X	/	/	/	/	X	/
Transport (handling containers/boxes)	X	/	/	/	/	/	/	/	/	/	/	/
Infusion administration procedures with barriers	X	/	/	/	/	/	/	/	/	/	/	/
Infusion administration procedures without barriers	X	/	/	/	X	X	/	/	/	X	/	/
Aerosol administration procedures	X	/	/	/	X	X	/	/	/	/	X	/
Topical administration procedures	X	/	/	/	/	X	/	/	/	/	/	/
Injection administration procedures	X	/	/	/	X	X	/	/	/	/	/	/
Surgical procedures	/	/	X	/	X	X	/	/	/	X	/	/
Bladder installation procedures	X	/	/	/	X	X	/	/	/	/	/	/
Handling excreta	X	/	/	/	X	X	/	/	/		/	/
Handling laundry after administration procedures	X	/	/	/	/	/	/	/	/	/	/	/
Cleaning administration area/ patient room / surfaces	X	/	/	/	/	X	/	/	/	/	/	/
Cleaning toilets / showers	/	X	/	/	X	/	X	X	X	X	/	/
Maintenance (for instance changing air filters, biosafety cabinets)	/	X	/	/	/	/	X	X	X	X	/	/
Incident handling (small liquid spill)	/	X	/	/	/	X	/	/	X	/	/	/
Incident handling (large liquid spill, powder, with dust or aerosol release)	/	/	/	X	X	/	X	X	X	/	X	X
Disposal of/handling hazardous waste	/	X	/	/	/	/	/	/	/	/	/	/
Transport carts/ boxes/bags with contaminated laundry, hazardous waste	X	/	/	/	/	/	/	/	/	/	/	/
Opening bags with contaminated laundry	X	/	/	/	/	/	/	/	/	X	/	/
Workplace monitoring	/	X	/	/	/	X	/	/	/	/	/	/

Annex 5. Guides reviewed

As this guide was developed, many other guides, articles and other information were collated and reviewed to help with the development of this guide.

During this process, the documents were identified with a unique ID number to make reviewing easier. This ID number consisted of the two digit code for the country where the document originated and a sequential number. These numbers appear at the start of the document name in Table A5-1 below. Some documents are European or International in origin and these begin with the letters EURINT.

Table A5-1: Bibliography of identified guide documents

Country & Title
Australia
AU 02 (2017) SafeWork NSW - Cytotoxic drugs and related waste - risk management
AU 04 (2018) WorkSafe Victoria - Handling Cytotoxic Drugs in the Workplace
AU 05 (2017) Workplace Health and Safety Queensland - Guide for handling cytotoxic drugs and related waste
AU 13 (2013) South Australian Health Services - Safe Handling Cytotoxic Guidelines
Austria
AT 03 (2011) Ministry of Health - Standards für das Gebrauchsfertigmachen, die Applikation und die Entsorgung von Zytostatika
AT 04 (2018) AUVA - Sicher Arbeiten mit Zytostatika
Belgium
BE 01 (2014) M. Haesendonck - G Schuurmans - Cytostatica in een ambulante setting - Veiligheid van de verpleegkundige
BE 02 (2015) K. Briers - Veilig werken met cytostatica voor nieuwe medewerkers
Canada
CA 01 (2015) Easty - Safe handling of cytotoxics: guideline recommendations
CA 10 (2021) saskatchewan.ca – Cytotoxic Drugs Guide
CA 11 (2014) CUPE - hs_factsheet_cytotoxic_drugs_e_march2014
CA 18 (2022) Alberta - Health Services Hazardous Medication Personal Protective Equipment (PPE) Guide
CA 19 (2018) CAPCA - Recommendations for the Safe Use and Handling of Oral Anti-Cancer Drugs
CA 20 (2015) WorkSafeBC - bk153 safe handling hazardous drugs
Croatia
HR 01 (2015) Ministry of environmental protection (MEP) - Ordinance on Medical Waste
HR 02 (2020) Irena Žuntar - Cytotoxic drugs - responsible and safe work
HR 03 (2016) Glavinović Mateja - Guidelines for the use of cytotoxic drugs and practices in Croatia
HR 04 (2013) Croatian Institute for OHS - Guidelines for medical check of workers in regards to toxins
HR 05 (2020) Vuger Velimir - Safety of medical workers and environment in regards to citostatics

Table A5-1: Bibliography of identified guide documents

Country & Title
Cyprus
CY 01 (2016) ΤΜΗΜΑ ΕΠΙΘΕΩΡΗΣΗΣ ΕΡΓΑΣΙΑΣ - ΟΔΗΓΟΣ ΔΙΑΧΕΙΡΙΣΗΣ ΑΣΦΑΛΕΙΑΣ ΚΑΙ ΥΓΕΙΑΣ ΣΤΙΣ ΝΟΣΟΚΟΜΕΙΑΚΕΣ ΔΡΑΣΤΗΡΙΟΤΗΤΕΣ
Czech Republic
CZ 01 (2016) SUKL - LEK-17 Příprava sterilních léčivých přípravků v lékárně a zdravotnických zařízeních
Denmark
DK 01 (2019) Arbejdstilsynet - Arbedje med cytostatika
DK 02 (2021) Sygehusapotekerne i Danmark - Cytostatikapraeparation og arbedsmiljo
DK 03 (2021) Sygehusapotekerne i Danmark - Monitorering af cytostatikakontaminering
Estonia
EE 01 (20XX) Tartu University Hospital (Tartu Ülikooli Kliinikum - TUK) - Keemiajärgsed ohutusmeetmed kodus
EE 02 (2020) Tartu University Hospital (Tartu Ülikooli Kliinikum - TUK) - Tsütostaatikumite käitlemise juhend
EE 03 (2021) East Tallinn Central Hospital (Ida Tallinna Keskhaigla- ITK) - OHTLIKE RAVIMITE KÄITLEMISE OHUTUSJUHEND
EE 18 (2019) Estonian Association of Waste Managers (Eesti Jäätmekäitlejate Liit - EJKL) - Juhendmaterjal. Tervishoiul tekkivate jäätmete käitlus
European and International
EURINT 02 (2022) ISOPP - HS Standards
EURINT 06 (2011) ICRC - Medical waste management
EURINT 08 (2007) ECoVIMCA - Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine
EURINT 10 (2018) ESOP - QuapoS 6
EURINT 11 (2020) FVE - "Veterinary occupational safety and health in veterinary practice" Survey Report
EURINT 14 (2021) ESOP - QuapoS 6 Commentary version
France
FR 01 (2016) French Health Ministry - Best practice of waste in hospitals
FR 02 (2016) INRS - Best practice chemical exposure
FR 11 (2022) SFPC - Pharmacy Best Practice
FR 19 (2001) French Health Ministry - Best Practice Pharmacy hospital
FR 24 (2009) French Vet association - Best practice use of anticancerous drugs
FR 25 (2020) IRSST - Quebec Antineoplastics in hospital pilot study on exposure and prevention
Germany
DE 04 (2010) DGUV - Gefahrstoffe im Krankenhaus Pflege- und Funktionsbereiche
DE 05 (2019) BGW - 09-19-042-zytostatika-im-gesundheitsdienst-data
DE 06 (2016) BGW - 09-19-008-gefahrstoffrechtliche-kennzeichnung-arzneistoffe-tumortherapie-data
DE 7a (2018) BGW - 09-19-042-musterbetriebsanweisung-entsorgung-zytostatika-data

Table A5-1: Bibliography of identified guide documents

Country & Title
DE 7b (2018) BGW - 09-19-042-musterbetriebsanweisung-sicherheitswerkbank-isolatoren-zytostatika-data
DE 7c (2018) BGW - 09-19-042-musterbetriebsanweisung-reinigung-werkbank-zytostatika-data
DE 7d (2018) BGW - 09-19-042-musterbetriebsanweisung-transport-zytostatika-data
DE 7e (2018) BGW - 09-19-042-musterbetriebsanweisung-vorbereitung-zytostatika-data
DE 7f (2018) BGW - 09-19-042-musterbetriebsanweisung-zubereitung-zytostatika-data
DE 09 (n.d) Arbeitsschutz - arbeitsschutz-in-der-tierarztpraxis
DE 12 (2011) - silo.tips_der-praktische-tierarzt
DE 13 (2010) - bevacizumab-praxis-aktuell-data
DE 14 (2011) - hipec-abschlussbericht-data
DE 17 (2022) DGUV - 207-007 Zytostatika im Gesundheitsdienst
DE 18 (2021) DGUV - 213-032 Gefahrstoffe im Gesundheitsdienst
Greece
EL 01 (2019) ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΛΑΣΙΘΙΟΥ - ΕΣΩΤΕΡΙΚΟΣ ΚΑΝΟΝΙΣΜΟΣ ΔΙΑΧΕΙΡΙΣΗΣ ΑΠΟΒΛΗΤΩΝ ΥΓΕΙΟΝΟΜΙΚΗΣ ΜΟΝΑΔΑΣ
EL 02 (2017) Χριστίνα Δεμερτζούδη - ΕΣΩΤΕΡΙΚΟΣ ΚΑΝΟΝΙΣΜΟΣ ΔΙΑΧΕΙΡΙΣΗΣ ΑΠΟΒΛΗΤΩΝ ΥΓΕΙΟΝΟΜΙΚΗΣ ΜΟΝΑΔΑΣ
EL 03 (2011) ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ 'ΛΑΪΚΟ' - ΕΣΩΤΕΡΙΚΟΣ ΚΑΝΟΝΙΣΜΟΣ ΔΙΑΧΕΙΡΙΣΗΣ ΙΑΤΡΙΚΩΝ ΑΠΟΒΛΗΤΩΝ ΓΕΝΙΚΟΥ ΝΟΣΟΚΟΜΕΙΟΥ ΑΘΗΝΩΝ "ΛΑΪΚΟ"
EL 04 (2007) ΕΥΑΓΓΕΛΟΣ ΑΛΕΞΟΠΟΥΛΟΣ - ΕΛΛΗΝΙΚΗ ΚΑΙ ΔΙΕΘΝΗΣ ΕΜΠΕΙΡΙΑ ΕΡΓΑΤΙΚΩΝ ΑΤΥΧΗΜΑΤΩΝ ΚΑΙ ΕΠΑΓΓΕΛΜΑΤΙΚΩΝ ΑΣΘΕΝΕΙΩΝ ΤΩΝ ΕΡΓΑΖΟΜΕΝΩΝ ΣΤΑ ΝΟΣΟΚΟΜΕΙΑ - ΟΔΗΓΟΣ ΓΙΑ ΤΗΝ ΕΚΤΙΜΗΣΗ ΚΑΙ ΠΡΟΛΗΨΗ ΤΟΥ ΕΠΑΓΓΕΛΜΑΤΙΚΟΥ ΚΙΝΔΥΝΟΥ
EL 05 (2017) ΕΘΝΙΚΟ ΣΥΜΒΟΥΛΙΟ ΑΝΑΠΤΥΞΗΣ ΝΟΣΗΛΕΥΤΙΚΗΣ - Παρασκευή και μείξη κυτταροστατικών φαρμάκων
EL 06 (2010) ΚΤΗΝΙΑΤΡΙΚΗ ΣΧΟΛΗ ΑΠΘ - Κατευθυντήριες Οδηγίες Βιοασφαλείας
EL 07 (2012) Υπουργεία Οικονομικών - Περιβάλλοντος - Υγείας - Μέτρα και Όροι για τη Διαχείριση Αποβλήτων Υγειονομικών Μονάδων.
Hungary
HU 01 (2021) OGYEI - Citosztatikus keverékinfúzió és injekció rendelés, készítés, ellenőrzés, szállítás
Ireland
IE 01 (2022) Health Service Executive - Guideline on the Safe Handling & Use of Cytotoxic Drugs
IE 02 (2011) Pharmaceutical Society of Ireland - Guidelines on the sourcing storage and disposal of medicinal products
IE 03 (2010) Health Service Executive - Guide for healthcare waste management
Italy
IT 01 (2017) Lombardi - MANAGEMENT OF THE RISK OF EXPOSURE of healthcare staff in the handling of injectable antineoplastic drugs: prevention aspects and characterisation of safety measures
IT 03 (2021) Lombardi - PREVENTION AND PROTECTION SYSTEM IN HEALTH FACILITIES FOR ACTIVITIES INVOLVING HAZARDOUS NON-ONCOLOGICAL DRUGS: Preparation and administration under current legislation
IT 04 (2014) ISPESL - Il rischio di manipolazione di chemioterapici

Table A5-1: Bibliography of identified guide documents

Country & Title
IT 19 (2014) INAIL - Impiego dei chemioterapici antiblastici per terapie domiciliari
IT 22 (2021) SIFO – Hazardous drugs and occupational risk, the unknown siblings of antineoplastic drugs f
IT 23 (2017): SIFO - Standard tecnici di galenica oncologica
Latvia
LV 01 (2012) Cabinet Regulation nr. 353 - Requirements for the Management of Waste Generated in Medical Treatment Institutions
LV 02 (2015) ZVA/ State Agency of Medicines - Article in the ZVA Newsletter" High risk medicines and safety of chemotherapy"
LV 03 (2018) Olainfarm - Measures to reduce carcinogenic substances in the work environment and risk reduction measures in JSC Olainfarm
LV 04 (2011) Cabinet Regulations nr. 302 - Regulations regarding waste classification and properties rendering waste hazardous
LV 05 (2020) LASUA - Guidlines for medical waste treatment
LV 07 (2018) ESOP - Quality Standard for the Oncology Pharmacy Service
LV 08 (2011) UNDP, Gef - Guidlines for medical waste treatment
LV 09 (2017) SPKC - Recommendations for medical institutions for safe disposal of medical products and injections
LV 10 (2011) UNDP, Gef - handbook for dealing with veterinary waste
LV 11 (2008) Cabinet regulations nr. 803 - Labour Protection Requirements when Coming in Contact with Carcinogenic Substances at Workplaces"
Malta
MT 01 (2022) Malta OSHA - Guidelines use of dangerous substances in the workplace
MT 02 (2022) Malta OSHA - Worker's rights and responsibilities
Netherlands
NL 04 (202?) Dokter Hoe - Geneesmiddelen
NL 06 (2021) IKNL - Handreiking veilig omgaan met cytostsatica v 2.0
NL 07 (2012) RAS - Arbocatalogus & CAO Protocol veilig omgaan met cytostatica voor schoonmaakwerkzaamheden
NL 08 (2022) VVT - Arbocatalogus cytostatica (organisations in homecare and carehomes)
NL 09 (2022) KNMP - Arbocatalogus Apotheken + Risico-instrument Farmaceutische stoffen
Poland
PL 01 (2016) Merks, P., Świerczkowski, D., Cwalina, N., Słomiak, K., Jaguszewski, M. - The disposal of unused and/or out of date medications in the community pharmacy setting in Poland – a challenge for pharmaceutical public health and pharmaceutical care
PL 02 (2017) Farmakopea Polska - Leki sporządzane w aptece (Medicines prepared in a pharmacy), Wydanie XI (9th Edition).
PL 03 (2018) Polskie Towarzystwo Farmaceutyczne - Standardy jakościowe w farmacji onkologicznej Polskiego Towarzystwa Farmaceutycznego (Quality standards in oncology pharmacy of the Polish Pharmaceutical Society)
PL 04 (2010) Olga Fedorowicz, Magdalena Kempczyńska - Postępowanie z lekiem cytotoksycznym w aptece szpitalnej (Proceeding with cytotoxics drug in a hospital pharmacy), Farm Pol, 2010, 66(2): 136-140.

Table A5-1: Bibliography of identified guide documents

Country & Title
PL 05 (1996) Ministry of Health - ROZPORZĄDZENIE MINISTRA ZDROWIA z dnia 19 czerwca 1996r. w sprawie bezpieczeństwa i higieny pracy przy przygotowywaniu, podawaniu i przechowywaniu leków cytostatycznych w zakładach opieki zdrowotnej (Dz. U. 1996r., Nr 80, poz. 376) (REGULATION OF THE MINISTER OF HEALTH of June 19, 1996. on occupational safety and health in the preparation, administration and storage of cytostatic drugs in health care institutions (Journal of Laws 1996, No. 80, item 376))
PL 06 (2016) CIOP - ZAGROŻENIA ZAWODOWE CYTOSTATYKAMI I ŚRODKI PREWENCJI (Occupational risks related to cytostatics and prevention measures)
PL 07 (n.d.) CIOP - Wymagania dotyczące pojazdów do przewozu materiałów niebezpiecznych (Requirements for vehicles for the transport of dangerous goods)
PL 08 (n.d.) PIP Państwowa Inspekcja Pracy (National Labour Inspectorate) - CZYNNIKI SZKODLIWE. BADANIA I POMIARY (HARMFUL FACTORS. TESTS AND MEASUREMENTS)
PL 09 (2016) KONSULTANT KRAJOWY W DZIEDZINIE PIELĘGNIARSTWA ONKOLOGICZNEGO (NATIONAL CONSULTANT IN THE FIELD OF ONCOLOGICAL NURSING) - Zalecenia konsultanta krajowego w dziedzinie pielęgniarstwa onkologicznego na temat postępowania pielęgniarskiego w przypadku wynaczynienia leku cytostatycznego (Recommendations of the national consultant in the field of oncology nursing on the nursing management in the event of cytostatic drug extravasation)
PL 10 (2022) KONSULTANT KRAJOWY W DZIEDZINIE PIELĘGNIARSTWA ONKOLOGICZNEGO (NATIONAL CONSULTANT IN THE FIELD OF ONCOLOGICAL NURSING) - OPINIA w sprawie kwalifikacji i kompetencji wymaganych wobec pielęgniarek podających pacjentom leki przeciwnowotworowe (OPINION on the qualifications and competences required of nurses administering anti-cancer drugs to patients)
PL 11 (2013) Maciej AMBROZIEWICZ - Przygotowanie, podawanie i przechowywanie leków cytostatycznych w zakładach opieki zdrowotnej (Preparation, administration and storage of cytostatic drugs in health care facilities)
PL 12 (2016) Sylwia Krzemińska, Emilia Irzmańska, Paulina Chęsy - STOSOWANIE ODZIEŻY I RĘKAWIC PODCZAS PRAC W NARAŻENIU NA KONTAKT Z CYTOSTATYKAMI. Wytyczne dla pracowników narażonych na kontakt z cytostatykami (USE OF CLOTHING AND GLOVES WHEN WORKING IN EXPOSURE TO CYTOSTATICS. Guidelines for employees exposed to cytostatics)
PL 13 (2018) Małgorzata Kupczewska-Dobecka, Anna Pałaszewska-Tkacz, Sławomir Czerczak, Katarzyna Konieczko, Instytut Medycyny Pracy im. prof. J. Nofera (Nofer Institute of Occupational Medicine) - ASPEKTY HIGIENICZNE I PRAWNE OCENY NARAŻENIA ZAWODOWEGO NA CYTOSTATYKI (HYGIENE AND LEGAL ASPECTS OF OCCUPATIONAL EXPOSURE ASSESSMENT TO CYTOSTATICS)
PL 14 (2018) Szpital Specjalistyczny w Krakowie (Specialist Hospital in Krakow) - Procedura postępowania z odpadami i surowcami wtórnymi powstającymi w Szpitalu (Procedure for dealing with waste and recyclable materials generated in the hospital)
PL 15 (n.d.) PIP Państwowa Inspekcja Pracy (National Labour Inspectorate) - Bezpieczna praca w zawodzie pielęgniarki (Safe work in the nursing profession)
PL 16 (2019) Jakub Chojnicki, Grażyna Jarosiewicz, PIP Państwowa Inspekcja Pracy (National Labour Inspectorate) - ABC BHP. Informator dla pracodawców (ABC Occupational Health and Safety. Guidance for employers)
Portugal
PT 06 (2021) SPFCS-MIMOSO - Safe Handling of Citotoxics (Presentation Training)
PT 07 (2018) CHLN - Safe Handling of Hazardous Chemical Products at CHLN (3rd revision)
PT 08 (2017) CHLN - Safe Handling of Citotoxics at CHLN (1st Revision)
PT 09 (2022) CHLN - Procedural Norm #22: Safe Handling of CMR Chemicals at CHULN

Table A5-1: Bibliography of identified guide documents

Country & Title
Romania
RO 01 (2012) EC - Riscurile la adresa sănătății și securității în muncă pentru lucrătorii in sectorul asistenței medicale OHS risks in the healthcare sector / Guide to prevention and good practice"
RO 02 (2013) National Institute for Public Health - OHS Guide on exposure to carcinogens and mutagens
RO 04 (2011) Romanian College of Pharmacists - Legislations and procedures in hospital pharmacies
RO 05 (2018) QUAPOS - Quality standards in oncologic pharmacy
RO 06 (2020) National Institute for Public Health - Carcinogen professional risk
RO 07 (2017) National Agency for medicine - Good practices for manufacturing of medicinal products
RO 08 (2021) National Institute for Public Health - Guidance for the management of medical waste
Slovenia
SI 01 (2018) Oncology Institute Slovenia - Standards of quality in oncology pharmacy
SI 02 (2015) Dejan Peterka - Safe handling of cytostatic medications
SI 03 (2018) ESOP - Quality standards in oncology pharmacy
SI 04 (2021) Government Republic of Slovenia - Waste management programme for Slovenia
Spain
ES 08 (2004) INSHT - NTP_740: Exposición laboral a citostáticos en el ámbito sanitario
ES 19 (2022) SESCAM - Castilla La Mancha Hazardous Drugs
Sweden
SE01 (2005) Swedish Work Environment Authority: cytostatics and other drugs with persistent toxic effect
SE02 (2022) Sweden regions and municipalities: Cytostatics: cytotoxic drugs overview
Switzerland
CH 01 (2004) Suva - Safety in the use of cytotoxics
CH 02 (2018) Suva - Protection measures for the use of medicines
United Kingdom
UK 01 (2013) Department of Health - Health Technical Memorandum 07-01 Safe management of healthcare waste
UK 02 (2014) HSE - Health and safety in care homes
UK 06 (2015) HSE - Handling cytotoxic drugs in isolators in NHS pharmacies
UK 07 (2020) BSAVA - Cytotoxic drugs
UK 08 (2021) HSE - Safe handling of cytotoxic drugs in the workplace
UK 21 (2022) SEPA - Guidance for the storage and treatment of healthcare waste
UK 22 (2022) Environment Agency - SR2008 No 24: standard rules for transfer of healthcare waste
UK 24 (2020) Leeds Teaching Hospitals NHS Trust - Good practice guidance for the safe handling of cytotoxic medicines and cytotoxic waste including spillage management
UK 42 (2022) NICE - Cytotoxic drugs
UK 55 (2019) UK Oncology Nursing Society (UKONS) - Systemic Anti-Cancer Therapy (SACT) Competency Passport

Table A5-1: Bibliography of identified guide documents

Country & Title
United States
US 05 (2019) USP NF - USP General Chapter 800 Hazardous Drugs Handling in Healthcare Setting
US 07 (2018) Smith - ACVIM small animal consensus statement on safe use of cytotoxic chemotherapeutics in veterinary practice
US 11 (2018) ONS - Toolkit for Safe Handling of Hazardous Drugs for Nurses in Oncology
US 12 (2018) ASHP - Guidelines on Handling Hazardous Drugs

Annex 6. Example of the use of occupational exposure bands

This annex provides an approach, which can be seen as an example of good practice but it should be noted that other approaches also exist.

For medicinal products, it is mandatory to determine health-based exposure limits (HBELs) for human and veterinary patients, see EMA (2014) and PIC/S (2018)[317]. These health-based limits (Permitted Daily Exposure or PDE) are derived for facilities where the potential for accidental cross-contamination is a concern, e.g. during manufacturing. Medicinal products provide a benefit to human or animal patients, however, as a cross-contaminant, they may pose a risk. The PDEs are used to prevent unintentional, accidental exposure to medicinal products exceeding the No Adverse Effect Level (NOAEL).

In both EMA (2014) and PIC/S (2018), the data requirements for hazard identification, the identification of critical effects, and the establishment of a NOAEL are prescribed. In the case of active substances with a genotoxic potential without sufficient evidence for a threshold related mechanism, it is considered that there is no NOAEL[318]. A Threshold of Toxicological Concern (TTC) of 1.5 mg/day intake of a genotoxic impurity is considered to be associated with an acceptable lifetime risk. For other active substances, EMA prescribes the procedure for calculating a PDE.

In case no legal limit value (EU or national) for occupational exposure is available, the information of PDEs can be used to establish limit values for workers[319]. These values can be used in the risk assessment as a reference and, in literature and in this annex, they are often referred to in the same way as limit values established by legislation, i.e. Occupational Exposure Limits or OELs (Schenk, 2016).

Occupational Exposure Bands (OEBs) are used to classify substances according to their OELs to identify the control measures to be taken to protect workers. Figure A6-1 shows how OEBs can be related to OELs and in turn how this reads across from Permitted Daily Exposure (PDE) levels for humans (PDE is used in the EU and Acceptable Daily Exposure (ADE) levels in the USA).

HMPs are likely to be classified in OEB 5 or 6 with a PDE 1-10 µg/day or 1 µg/day for band 5 and 6 respectively. According to Figure A6-1, the corresponding derived OEL for HMPs without a legal limit value is therefore <1 µg/m^3.

The PDEs (or TTCs) can also be used to establish threshold values for cleaning residues (for example, on the outside of containers) or for product carry-over.[320]

Besides protection of patients (due to cross-contamination), OEBs can also be used to suggest the appropriate control measures to reduce the risk from occupational exposure to an acceptable level, see Table A6-1.

317 EMA. Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (2014), PIC/S Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (2018).

318 EMA. Guideline on the limits of genotoxic impurities (2006). EMA ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (2018).

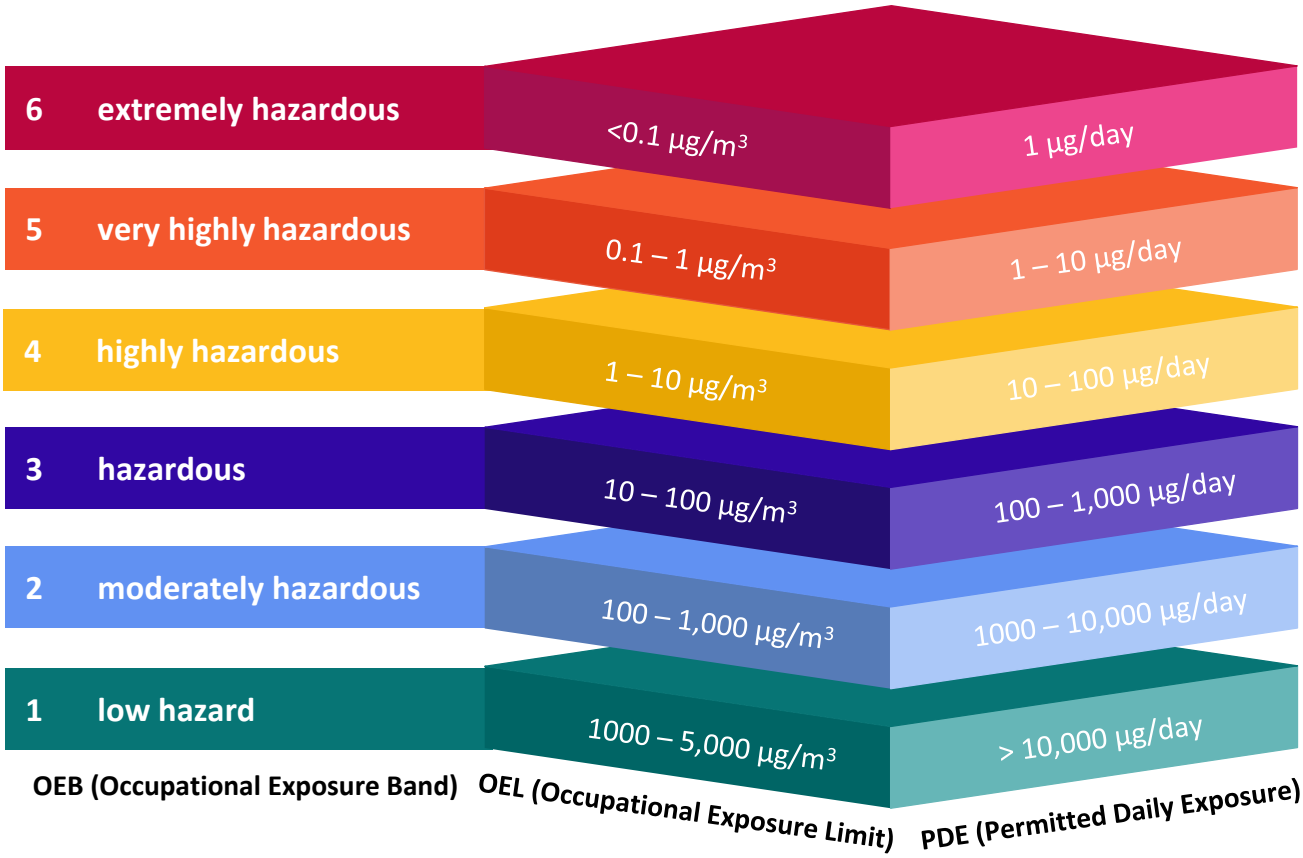
319 Denk, R (2016), The Challenge of cGMP in the Manufacturing of Antibody-drug Conjugates. ADCReview: Journal of Antibody-drug Conjugates. https://www.adcreview.com/articles/the-challenge-of-cgmp-in-the-manufacturing-of-antibody-drug-conjugates/

320 Denk, R (2017), Understanding Containment. Pharmaceutical Technology (March 2017; 80-83)

Although this approach is commonly used in the pharmaceutical industry, a similar approach is useful in all activities with possible exposure to HMPs, e.g. for preparation and administration of HMPs.

The information in this annex should only be used by experts in occupational toxicology and/or hygiene.

Figure A6-1: Occupational Exposure Bands (OEBs), OELs and PDEs, adapted from Denk, R (2016)[321]



Source: Adapted from Denk (2016)

[321] Denk, R (2016) The Challenge of cGMP in the Manufacturing of Antibody-drug Conjugates. ADCReview: Journal of Antibody-drug Conjugates. https://www.adcreview.com/articles/the-challenge-of-cgmp-in-the-manufacturing-of-antibody-drug-conjugates/

Table A6-1: OEBs and corresponding control measures used by the pharmaceutical industry as referenced in section 8.3

OEB Level	OEL range (µg/m3)	Description	Control measures required
1	1,000 – 5,000	The lowest form of containment as substances pose a low risk to workers safety.	Local extraction Ventilation of the room
2	100 – 1,000	Minimal threat to the health of the worker, so steps should be taken.	Dedicated ventilation system for the room
3	10 – 100	The substance is potentially hazardous to the safety of the worker, so measures should be put in place.	Liner systems for containment of waste Glove bags Flexible isolators to provide a barrier
4	1 – 10	Substances hazardous to the safety of the worker. More stringent control measures are required to prevent exposure of the worker.	Physical barriers to separate the worker from the substances Substances handled in dedicated enclosures using glove ports Use restricted access barrier systems
5	<1	Substances are extremely hazardous to the worker. Very stringent control measures should be in place to contain any routes of exposure.	Permanent physical barriers to separate the worker from the substances Substances should be handled in a closed and isolated compartment with access only via glove ports The chamber containing the substances should not be opened
6	<0.1	Highly active or hazardous products. Very stringent control measures should be in place.	Isolator technology: access only via glove ports An airlock system for inserting the highly active substance into the isolator and for removing material and waste High performance filter technology such as a filter cartridge (FiPa) Equipment designed for cleaning on product changeover Regular glove testing/inspection

Sources:

Denk, R (2016) The Challenge of cFMP in the Manufacturing of Antibody-drug Conjugates. Journal of Antibody-drug conjugates, April 2016. From: https://www.adcreview.com/articles/the-challenge-of-cgmp-in-the-manufacturing-of-antibody-drug-conjugates/

Choudhary, Ankur (2018) Pharmaceutical guidelines: Occupational Exposure Bands (OEBs) for Chemicals. From: https://www.pharmaguideline.com/2018/04/occupational-exposure-bands.html

Annex 7. Examples of summary sheets

The summary sheets in this annex are provided as examples – they should not be used directly and must be adjusted to the specific situation and the results of the risk assessment in the relevant organisation.

HANDLING A SPILL OF HAZARDOUS MEDICINAL PRODUCTS – POWDERS

This sheet is a summary that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

AFTER A SPILL, IMMEDIATELY

Contact: Name of person

01234 XXXXXXX

Use spill kit as per instructions

Location: XXXXX

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type A protective gloves (puncture class 3, if needed)

Protective gown/ coverall

Eye protection

Shoe covers

FFP3 mask

STOP THE SPREAD

- Inform the people in immediate surroundings and remove non-essential people
- Ask for support
- Stop people entering the spill area: mark the area and put out signs
- Close windows and doors to avoid air disturbances

CLEAN THE SPILL

1. Put on PPE
2. Cover powder by spraying water mist over the spill. Do not spray water into the spill.
3. Cover spill gently with wet cloths/paper towels
4. Remove powder with wet cloths/paper towels
5. Work from outside to inside and from top to bottom
6. Clean the contaminated area with the recommended detergent
7. Rinse with water
8. Repeat last two steps (Steps 6 and 7) at least 3 - 5 times
9. Remove PPE (gloves last) and wash hands
10. Inform colleagues when the area is free from contamination

WASTE

- Handle used materials with gloves
- Dispose of used cleaning materials and single-use PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

FIRST AID

Skin Contact:

- Rinse exposed skin with hand-warm water
- Wash skin with neutral detergent and rinse with water
- Dry skin carefully by dabbing, no rubbing
- It is advisable to consult a doctor

Eye Contact:

- Rinse eyes with hand-warm water for 15 minutes, or use eye shower or bath, if available
- It is advisable to consult an ophthalmologist

REPORTING

Complete an incident registration form - **LOCATION: XX**

HANDLING A SPILL OF HAZARDOUS MEDICINAL PRODUCTS – LIQUIDS

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

AFTER A SPILL, IMMEDIATELY

Contact: Name of person

01234 XXXXXXX

Use spill kit as per instructions

Location: XXXXX

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type A protective gloves (puncture class 3, if needed)

Protective gown/ coverall

Eye protection

Shoe covers

If aerosols: FFP3 mask

OR

If no aerosols: Face shield

STOP THE SPREAD

- Inform the people in immediate surroundings and remove non-essential people
- Ask for support
- Stop people entering the spill area: mark the area and put out signs
- Prevent spill spreading to a larger area

CLEAN THE SPILL

1. Put on PPE
2. Cover liquids with drying material, e.g. paper towels
3. Work from outside (clean area) to inside and from top to bottom
4. Clean the contaminated area with the recommended detergent
5. Rinse with water
6. Repeat last two steps (Steps 4 and 5) at least 3 - 5 times
7. Remove PPE (gloves last); wash hands
8. Inform colleagues when the area is free from contamination

WASTE

- Handle used materials with protective gloves
- Dispose of used cleaning materials and single-use PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

FIRST AID

Skin Contact:	Clean the skin immediately thoroughly with plenty of water (for 15 min) It is advisable to consult a doctor
Eye Contact:	With the eyelid gap open, rinse under running water for at least 15 minutes, or use eye shower or bath, if available It is advisable to consult an ophthalmologist

REPORTING

Complete an incident registration form - **LOCATION: XX**

ORAL ADMINISTRATION OF HMP – LIQUIDS

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

TECHNICAL AND ORGANISATIONAL MEASURES

- HMPs should only be handled by trained workers
- Use a dedicated spout cup (if possible)
- Ask the patient to self-administer and keep distance (if possible)

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown

Protective face shield or goggles (if indicated by risk assessment)

BEFORE ADMINISTRATION

1. Wash hands and put on PPE
2. Place all equipment (e.g. disposable drink container) within easy reach
3. Place a single-use pad over the surface to protect in case of a spill
4. Open the container with the HMP liquid and pour it into the drink container
5. Use the drink container for administration (by the patient)

AFTER ADMINISTRATION

1. Dispose of the drink container as hazardous waste or clean immediately if re-used
2. Remove PPE: start with gown, then face shield/goggles and finally gloves
3. Wash hands

Remember: patient's excreta (urine, faeces, vomit and sweat) and blood can be contaminated for 7-14 days after administration ends

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: name of person - **01234 XXXXXXX**

Use spill kit - **location: XXXX**

Follow the protocol for handling liquid spills

ORAL ADMINISTRATION OF HMP – TABLETS & CAPSULES

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Include antineoplastics, immunosuppressants, antiviral medicines
- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers

TECHNICAL AND ORGANISATIONAL MEASURES

- HMPs should only be handled by trained workers
- Do not crush, dissolve, and/or otherwise alter without the advice of the pharmacy
- Ask the patient to self-administer (if possible)

PERSONAL PROTECTIVE EQUIPMENT (PPE) – TABLETS & CAPSULES

Type B protective gloves

BEFORE ADMINISTRATION

1. Wash hands and put on protective gloves
2. Place all equipment (small single-use drink container and tablet pot) within easy reach
3. Place a single-use pad over the surface over the surface to protect in case of a spill
4. Open the primary package with the tablets/capsules and add the right number to the tablet pot, preferably by the patient
5. Use the tablet pot for administration (by the patient)

AFTER ADMINISTRATION

1. Remove protective gloves
2. Wash hands

Remember: patient's excreta (urine, faeces, vomit and sweat) and blood can be contaminated for 7-14 days after administration ends

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: name of person - **01234 XXXXXXX**

Use spill kit - **location: XXXX**

Follow the protocol for handling powder spills

INTRAVENOUS (IV) ADMINISTRATION OF HMPs – INFUSION SYSTEMS WITH A PHYSICAL BARRIER

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Include some antineoplastics, immunosuppressants, antiviral medicines
- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers

TECHNICAL AND ORGANISATIONAL MEASURES

- Centralise administration in a dedicated area as much as possible
- Reduce connecting and disconnecting of infusion systems with administration bags to a minimum

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

ADMINISTRATION

1. Connect guard infusion with neutral intravenous (IV) fluid to the patient
2. Place all equipment within easy reach
3. Wash hands and put on protective gloves
4. Place a single-use pad on the working surface
5. Connect infusion line from infusion bag with HMP to the guard infusion
6. Close clips and/or clamps from guard infusion
7. Open clips and/or clamps for HMP administration
8. Remove protective gloves
9. Wash hands

After infusion has ended:

10. Wash hands and put on new protective gloves
11. Close clips and/or clamps and flush with at least 100 ml of neutral IV fluid
12. Disconnect the total infusion set from the patient
13. Dispose of the materials
14. Remove protective gloves
15. Wash hands

Remember: patient's excreta (urine, faeces, vomit and sweat) and blood can be contaminated for 7-14 days after administration ends

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: Name of person - **01234 XXXXXX**

Use spill kit - **location: XXXXXX**

Follow the protocol for handling liquid spills

INTRAVENOUS (IV) ADMINISTRATION OF HMPs – INFUSION SYSTEMS WITHOUT A PHYSICAL BARRIER

IMPORTANT

- If possible, use systems with a physical barrier (such as infusion systems filled with HMP-free solution and connected in the pharmacy or use of a CSTD)
- This sheet is a summary, that should be adjusted to your specific situation. Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Include antineoplastics, immunosuppressants, antiviral medicines
- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers

TECHNICAL AND ORGANISATIONAL MEASURES

- Centralise administration in a dedicated area as much as possible
- Reduce connecting and disconnecting of infusion systems to a minimum

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown

Protective face shield or goggles (if indicated by risk assessment)

ADMINISTRATION

1. Connect guard infusion with neutral IV fluid to the patient
2. Place all equipment within easy reach
3. Wash hands and put on PPE
4. Place a single-use pad on the working surface
5. Connect infusion line to the infusion bag with HMP
6. Fill the line (partially) with the HMP infusion liquid; prevent dripping using a hydrophobic stop filter
7. Check if the drip chamber in the guard infusion is sufficiently filled
8. Connect the infusion line from the infusion bag with HMP to the guard infusion
9. Close clips and/or clamps from guard infusion
10. Open clips and/or clamps for HMP administration
11. Remove PPE: start with gown, then face shield/goggles and finally gloves
12. Wash hands

After infusion has ended:

13. Wash hands and put on new PPE
14. Close clips and/or clamps and flush with at least 100 ml of neutral IV fluid
15. Disconnect the total infusion set from the patient
16. Dispose of the materials
17. Remove PPE: start with gown, then face shield/goggles and finally gloves
18. Wash hands

Remember: Patient's excreta (urine, faeces, vomit and sweat) and blood can be contaminated for 7-14 days after administration ends

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: Name of person - **01234 XXXXXXX**

Use spill kit - **location: XXXX**

Follow the protocol for handling liquid spills

CLEANING IN HEALTH CARE SETTINGS

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Include antineoplastics, immunosuppressants, antiviral medicines
- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers

TECHNICAL AND ORGANISATIONAL MEASURES

- Only use marked cleaning equipment designated for that specific area
- Areas where HMPs are prepared or administered are identified and have a sign
- Specific rooms (sanitary facilities, rinsing rooms) are identified
- Surfaces that need to be cleaned are identified
- Procedures for testing of cleaning efficacy are in place

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown/coverall

Protective face shield/protective goggles (if splashes are likely, f.i. whilst cleaning sanitary equipment)

Class P3 face mask (when risk assessment indicates the use of decontamination agents)

WHEN CLEANING

1. Put on PPE
2. Swipe floor from the relatively clean part of the room (e.g. door) to the back, using standard detergents
3. Clean surfaces from top to bottom, using standard detergents

AFTER CLEANING

1. Discard used water directly after cleaning of a designated room or area
2. Remove PPE: start with gown, then face shield/mask/goggles and finally gloves
3. Leave used cleaning materials at the designated area in a specific storage closet

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF AN INCIDENT – IMMEDIATELY

Contact: Name of person - **01234 XXXXXXX**

Use spill kit - **location: XXXXX**

TRANSPORTATION AND WASHING OF HMP-CONTAMINATED LAUNDRY

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Include antineoplastics, immunosuppressants, antiviral medicines
- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- HMP can be present in contaminated laundry, with urine, faeces, vomit, sweat and blood on bed linen

TECHNICAL AND ORGANISATIONAL MEASURES

- HMP contaminated laundry should arrive in marked laundry bags
- Transport HMP marked laundry bags in a separate lorry
- Wash HMP laundry bags separately from regular laundry

PERSONAL PROTECTIVE EQUIPMENT (PPE) -LAUNDRY

Type B protective gloves

Class P3 face mask (when risk assessment indicates possible inhalation of contaminated dust)

HANDLING LAUNDRY

1. Put on PPE
2. Put laundry bag in the machine
3. Perform cold wash procedure (step 1)
4. Leave HMP laundry bags in the washing machine during the cold wash procedure
5. Remove PPE
6. Follow normal warm wash procedure (step 2)

WASTE

- Dispose of single-use PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use
- Washed plastic laundry bags can be discarded as normal plastic waste

OTHER REMARKS

- Be aware of possible (HMP contaminated) sharp objects (e.g. needles) when handling the laundry

IN CASE OF AN INCIDENT - IMMEDIATELY

Contact: Name of person - **01234 XXXXXXXX**

PREPARATION OF HMPs

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

TECHNICAL AND ORGANISATIONAL MEASURES

- Use a confined and exclusive area with a warning sign outside the room for preparation
- Use leak-proof labelled bags for packaging with secondary package
- Avoid the use of glass ampoules if possible
- Avoid dose fractionation and use single dose mixtures if possible
- Label HMPs appropriately
- If possible, avoid high-risk activities that can generate airborne particles, if this is not possible, consult the risk assessment for additional measures to be undertaken

HYGIENE MEASURES

1. No jewellery, make-up, nail varnish, artificial nails or perfume
2. No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum in the preparation area
3. No mobile phones, personal devices and headphones in the preparation area
4. Tie back long hair
5. Wash hands before putting on and after removing protective gloves

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown/ coverall

Protective face shield, goggles or FFP2/FFP3 mask (if indicated by risk assessment)

WASTE

- Dispose of used single-use material and PPE as hazardous waste, in a closable hazardous waste container
- Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: name of person – **0123 XXXXXXX**

Use spill kit - **location: XXXX**

Follow the protocol for handling powder or liquid spills

VETERINARY PRACTICES – PREPARATION OF HMPs

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

TECHNICAL AND ORGANISATIONAL MEASURES

- HMPs should only be handled by trained workers
- Use the technical measures recommended by your organisation's risk assessment
- Follow your organisation's rules on centralising preparation
- Use a confined and exclusive area with a warning sign outside the room for preparation
- Use leak-proof labelled bags for packaging with secondary package
- Avoid the use of glass ampoules if possible
- Avoid dose fractionation and use single dose mixtures if possible
- Label HMPs appropriately
- If possible, avoid high-risk activities that can generate airborne particles, if this is not possible, consult the risk assessment for additional measures to be undertaken

HYGIENE MEASURES

1. No jewellery, make-up, nail varnish, artificial nails or perfume
2. No food, drink, cigarettes/vaporisers, medication for personal use, or chewing gum in the preparation area
3. No mobile phones, personal devices and headphones in the preparation area
4. Tie back long hair
5. Wash hands before putting on and after removing protective gloves

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown/ coverall

Protective face shield, goggles or FFP2/FFP3 mask (if indicated by risk assessment)

WASTE

Dispose of the following as hazardous waste, in a closable hazardous waste container:

- used single-use material and single use PPE
- housing area materials of treated animals
- animal excreta and blood

Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: name of person – **0123 XXXXXXX**

Use spill kit - **location: XXXXX**

Follow the protocol in the summary sheets for powder or liquid spills

VETERINARY PRACTICES – ADMINISTRATION OF HMPs

This sheet is a summary, that should be adjusted to your specific situation.
Only trained staff should carry out the relevant tasks

HAZARDS

Hazardous medicinal products (HMPs):

- Can have carcinogenic, mutagenic or reprotoxic effects in exposed workers
- Examples include antineoplastics, immunosuppressants, antiviral medicines

TECHNICAL AND ORGANISATIONAL MEASURES

- Use the technical measures recommended by your organisation,
- Follow your organisation's standard operating procedures (SOPs)
- Activities involving HMPs should be supervised by a competent, designated person

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Type B protective gloves

Protective gown

Protective face shield or goggles (if indicated by risk assessment)

ADMINISTRATION

- If the HMPs are from an external source, check for any leakages/damages
- Measures should be undertaken for the comfort and cooperation of the animal patient
- Administration should only be performed under the supervision of a registered veterinary practitioner
- Limit oral administration if possible, use parenteral and injection administration following SOPs
- Use additional precautions for intralesional and subcutaneous administration following SOPs
- All workers involved in administration should wear the appropriate PPE

ANIMAL IDENTIFICATION AND HOUSING

1. Animals treated with HMPs should be housed in a dedicated and labelled area
2. Access to this area should be restricted to essential workers
3. Clearly identify animal patients receiving treatment, e.g. signs on cages
4. Use single-use absorbent bedding and towels
5. For food and water, use single use or non-porous bowls

WASTE

Dispose of the following as hazardous waste, in a closable hazardous waste container:

- used single-use material and single use PPE
- housing area materials of treated animals
- animal excreta and blood

Clean non-disposable equipment and PPE immediately after use

IN CASE OF A SPILL – IMMEDIATELY

Contact: name of person – **0123 XXXXXXX**

Use spill kit - **location: XXXXX**

Follow the protocol in the summary sheets for powder or liquid spills

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