



European
Biosafety
Network

Safer Cancer Care – HMP EU regulation

**Presentation by Josh Cobb, European Biosafety Network
7th March 2025**



- Established in 2009 by the founding partners, the Spanish General Council of Nursing and the British public services union UNISON



Spanish General Council of Nursing

- The Network is an inclusive organisation made up of national and European professional institutions, representative associations, unions and other interested parties committed to biological and occupational and patient safety in healthcare throughout the European Union

EBN Summit, Polish Parliament, Warsaw

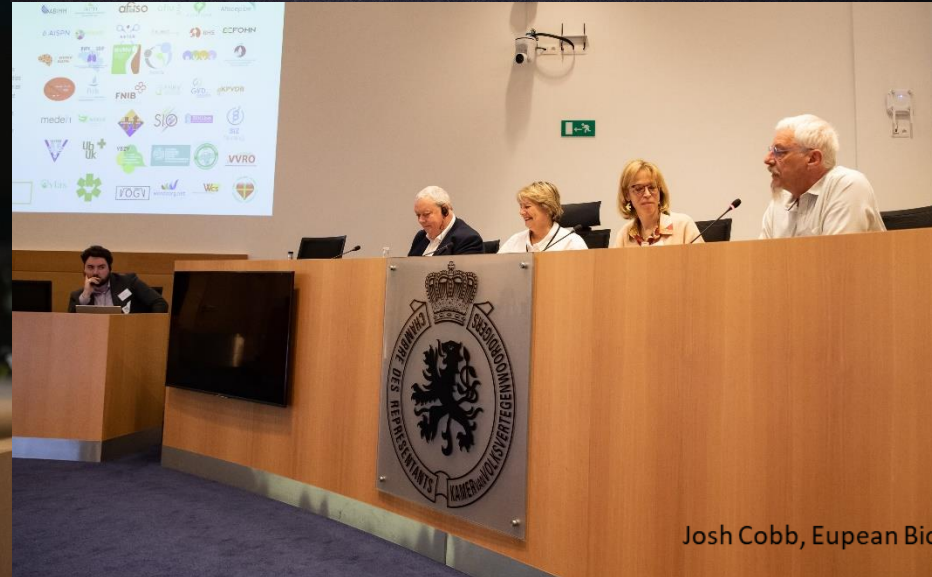
2 December 2013



The European Biosafety Network, Polish Nurses Association and the Czech Nurses Association welcomed over 100 delegates from across the 28 European Member States to the Polish Parliament in Warsaw for the 4th European Biosafety Summit on 2nd December 2013

EBN Summit on HMPs, Belgian Federal Parliament

25 March June 2022



The European Commission published a detailed report on preventing exposure to HMPs: <https://ec.europa.eu/social/main.jsp?catId=148&langId=en>

The report identified almost 1.8 million workers exposed to relevant HMPs in the EU and that number may be as high as **12.7 million exposed workers** in the EU (ETUI, 2020)

The report recommended to add 3 groups of hazardous medicinal products - **antineoplastics, immunosuppressants and antivirals** - and their active substances - to Annex I of the Carcinogens and Mutagens Directive, combined with non-legislative guidance and a list and definition of HMPs

EU Classification of Carcinogenic, Mutagenic or Reprotoxic (CMR) substances

Classification of CMRs in the EU is based on the strength of evidence showing that they present one of the CMR types of hazards to human health.

The EU legislation regarding [Classification Labelling and Packaging](#) of substances – the CLP Regulation 1272/2008 – uses the hazard categories below for substances and for mixtures that contain CMRs. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008R1272>

EU classification of CMR substances	
Category	Criteria
Cat. 1 A	known to have CMR potential for humans, based largely on human evidence
Cat. 1 B	presumed to have CMR potential for humans, based largely on experimental animal data
Cat. 2	suspected to have CMR potential for humans

The key provisions of the CMRD continue to include:

- The employer shall assess and manage the risk of exposure to carcinogens, mutagens or reprotoxic substances. Workers' exposure must be prevented
- The employer shall reduce the use of carcinogens, mutagens or reprotoxic substances by replacing them with a substance that is not dangerous or less dangerous
- 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**
- Where a closed system is not technically possible, the employer shall reduce exposure to the minimum

Transposition of the revised Carcinogens, Mutagens and Reprotoxic Substances Directive (EU) 2022/431



The key new legislative changes affecting pharmacy in the revised Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD) from March 2022:

- Inclusion of HMPs and reprotoxins in the scope of the Directive
- Definition of HMPs
- Requirement for training those in healthcare handling HMPs and CMRs



Must have been transposed into national law in all EU member states by 5 April 2024

<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L.2022.088.01.0001.01.ENG&toc=OJ%3AL%3A2022%3A088%3ATOC>

Definition of HMPs as Category 1A or 1B Carcinogens, Mutagens and Reprotoxic Substances, March 2022

Joint statement of the European Parliament and the Council on the scope of Directive 2004/37/EC – 16 March 2022:

“The European Parliament and the Council share the common understanding that **hazardous medicinal products which contain substances which meet the criteria for classification as carcinogenic (categories 1A or 1B), mutagenic (categories 1A or 1B) or reprotoxin (categories 1A or 1B)**

in accordance with Regulation (EC) No 1272/2008 fall under the scope of Directive 2004/37/EC. All requirements of Directive 2004/37/EC apply to hazardous medicinal products accordingly.”

<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L.2022.088.01.0001.01.ENG&toc=OJ%3AL%3A2022%3A088%3ATOC>

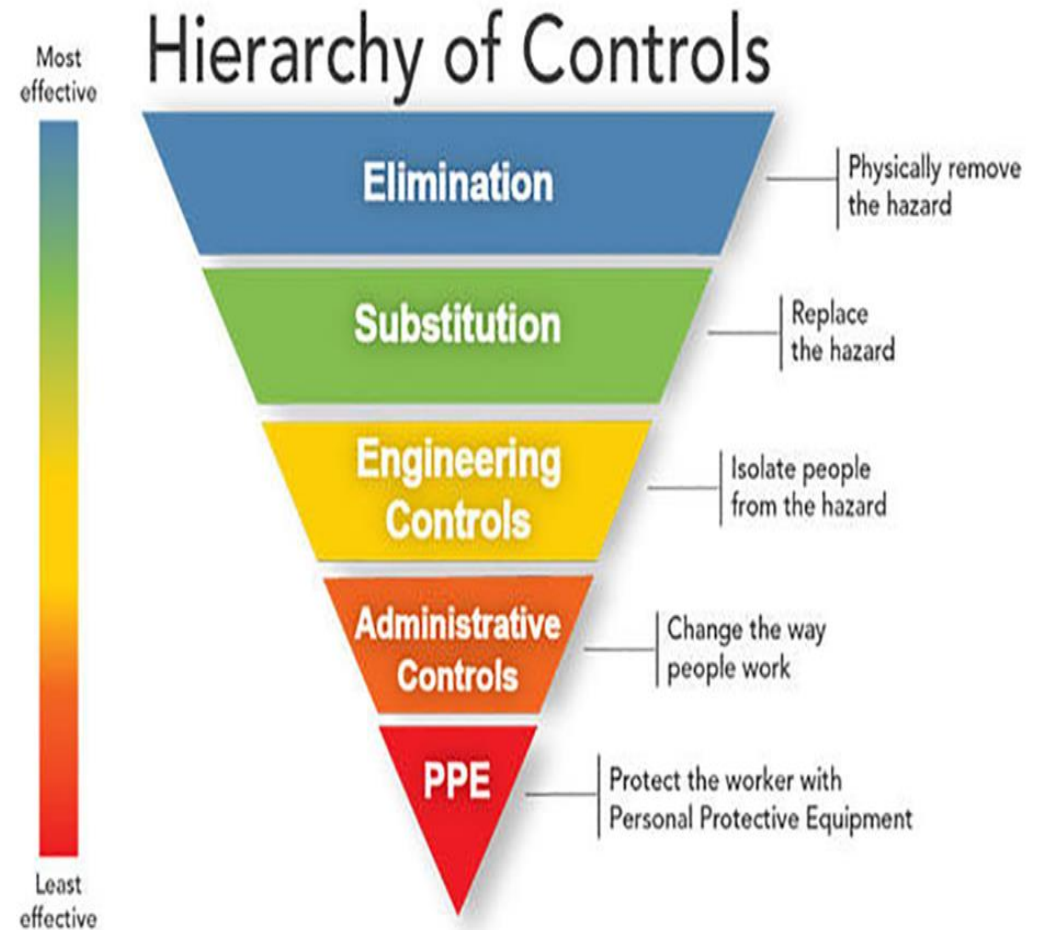


Hierarchy of Control in CMRD

Directive (EU) 2022/431 - amending Directive 2004/37/EC

- Risk assessment and management are at the apex of the hierarchy of control in the new EU legislation – the CMRD
- The first preventive measure in the hierarchy is to replace or substitute the use of carcinogens, mutagens or reprotoxic substances
- In healthcare, it is often not technically possible to replace or substitute HMPs, so the next level of protection for workers is a requirement on employers that a carcinogen, mutagen or reprotoxic substance must be **manufactured and used in a closed system**

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2022.088.01.0001.01.ENG&toc=OJ%3AL%3A2022%3A088%3ATOC



Hierarchy of Control in CMRD

Directive (EU) 2022/431 - amending Directive 2004/37/EC

- HMPs now falling under the scope of CMRD have to be **manufactured and used in a closed system**, which in practice means the use of biological safety cabinets (BSCs), containment isolators and closed system transfer devices (CSTDs)
- Administrative controls, safer systems of work and PPE are at the bottom of the hierarchy of control
- A closed system is defined as “a device that does not exchange unfiltered air or contaminants with the adjacent environment” (NIOSH Alert 2004). Closed systems in healthcare and pharmacy includes the use of biological safety cabinets, containment isolators and closed system transfer devices (CSTDs)
- CSTDs are defined as “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.” (EU Guidance on HMPs 2023)

<https://osha.europa.eu/en/publications/guidance-safe-management-hazardous-medicinal-products-work>

CSTDs reduce risk of occupational exposure

Use of the CSTD significantly reduces surface contamination when preparing Cyclophosphamide, Ifosfamide & 5-FU compared to standard drug preparation techniques

Sessink PJM et al. J Oncol Pharm Pract. 2011; 17:39-48.

CSTDs reduce isolator contamination

CSTD significantly decreases the chemical contamination of barrier isolators compared to standard compounding devices (needles, vented needle free devices and microspikes)

Simon N, et al. PLoS One. 2016; Jul 8:11(7):1-17.

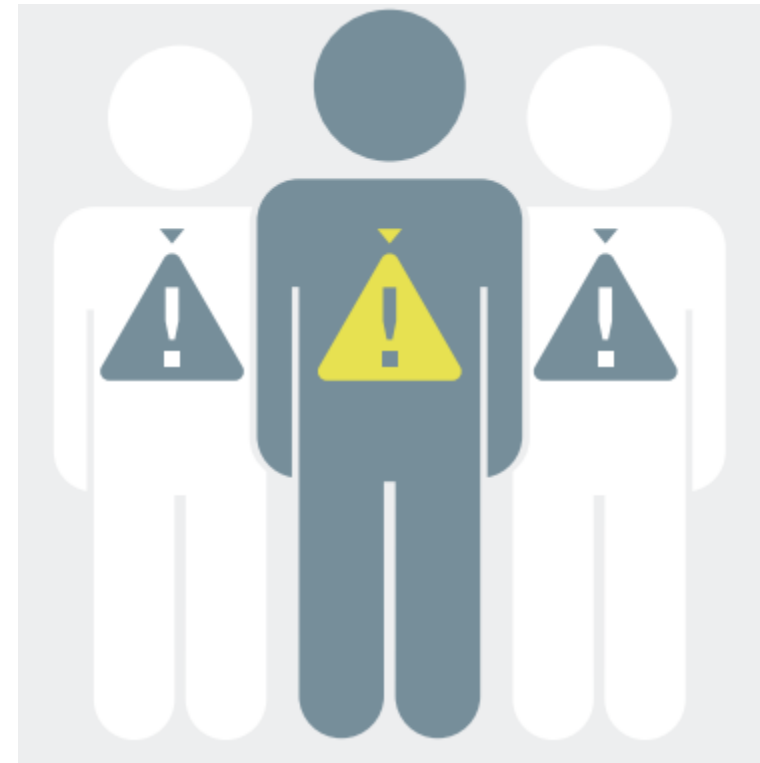
Surface HD contamination from cytotoxic infusion preparation in a pharmaceutical isolator was significant on work and compounded product surfaces

CSTD utilization significantly reduced HD contamination often below the limit of detection making a strong case for CSTD use within isolators

Vyas N, et al. J Oncol Pharm Practice. 2016; 22(1):10-19.



- Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration
- CSTDs should be used when compounding HDs when the dosage form allows
- CSTDs must be used when administering antineoplastic HDs when the dosage form allows
- CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD





Points to consider when choosing a CSTD:

How well does the CSTD prevent HD contamination?

Should a filter-based or vapor-containment system be chosen?

How easy is the CSTD to use?

How many components/manipulations are required to use the CSTD?

What is the cost of the device?

How does the cost correlate with the device's design, components, and quality?

Coyne J. Pharmacy Purchasing & Products. 2018;15(5):36

Consult NIOSH's CSTD testing protocol to help understand the difference between filter-based units and vapor-containment devices.

A Performance Test Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs. NIOSH

<https://www.cdc.gov/niosh/docket/review/docket288a/pdfs/apperformancetestprotocolforclosedsystemtransferdevices.pdf>



The European Association of Hospital Pharmacists (EAHP) published a survey conducted in autumn 2021 with responses from 545 chief pharmacists across Europe and 26 responses of its 35 member associations in 2022

EAHP SIG - FINAL REPORT - Special Interest Group on Hazardous Medicinal Products 2022
https://www.eahp.eu/sites/default/files/final_report_sig_on_hazardous_medicinal_products.pdf

Looking at respondents that selected BSCs in combination with one or multiple of the other options it was observed that 45% (N=131/292) deem BSCs together with CSTDs the most effective way to protect workers followed by 15% (N=44/292) that thought the combination of BSCs and spikes is the most effective. 9% (N=26/292) believed that BSCs used with spikes and CSTDs would offer the best protection from potential exposure to HMPs.

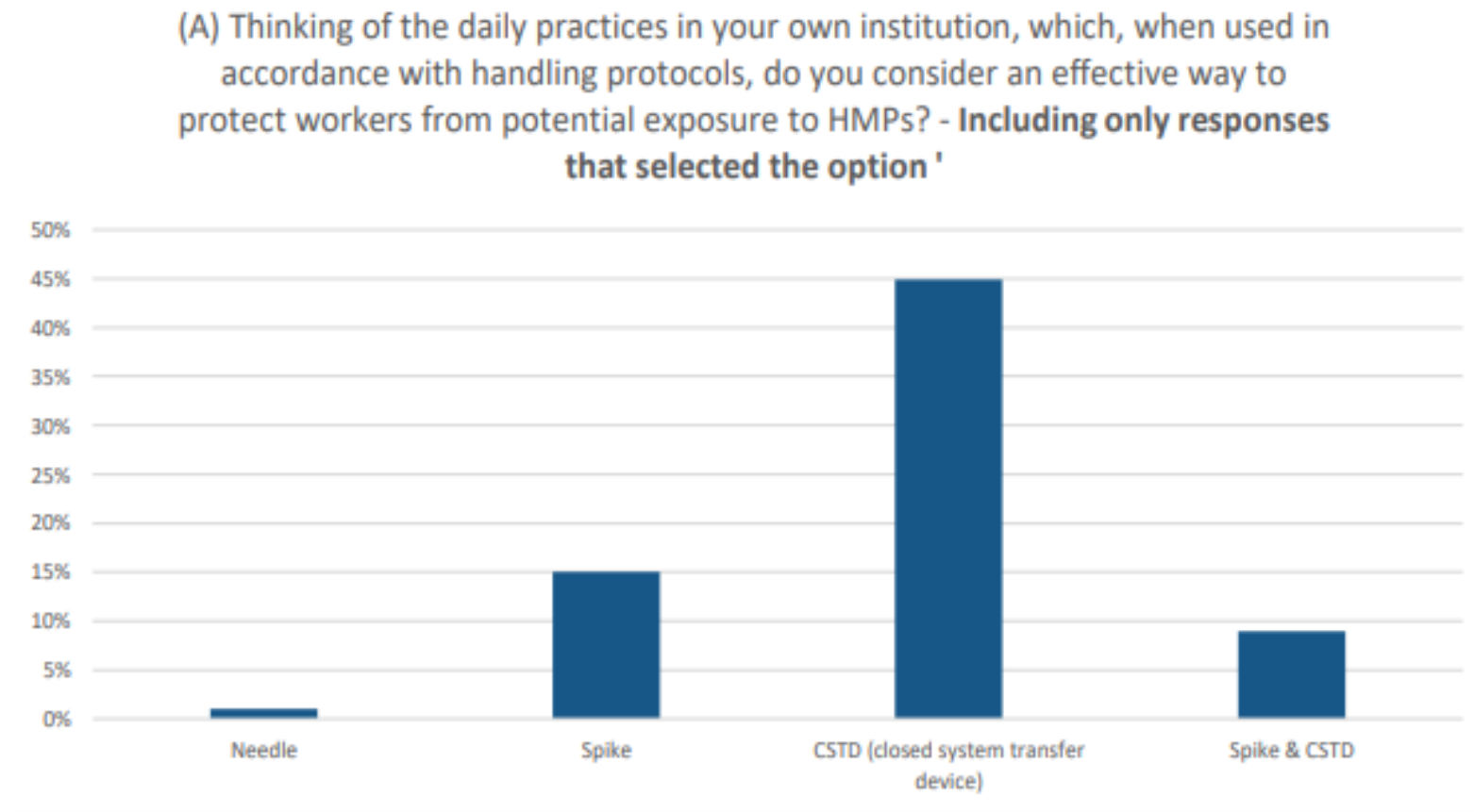


Figure 12 - Percentage of responses by chief pharmacists (N=292) to question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that selected the option 'biological safety cabinet' in combination with the others. (Note that this was a tick all that apply question)

Isolators were considered effective in combination with CSTDs by 35% (N=103/292) of the respondents. 9% (26/292) of respondents deemed spikes when used with an isolator as a good option for offering protection against the potential exposure to HMPs. A small group (5% | N=16/292) also considered isolators in combination with both CSTDs and spikes effective.

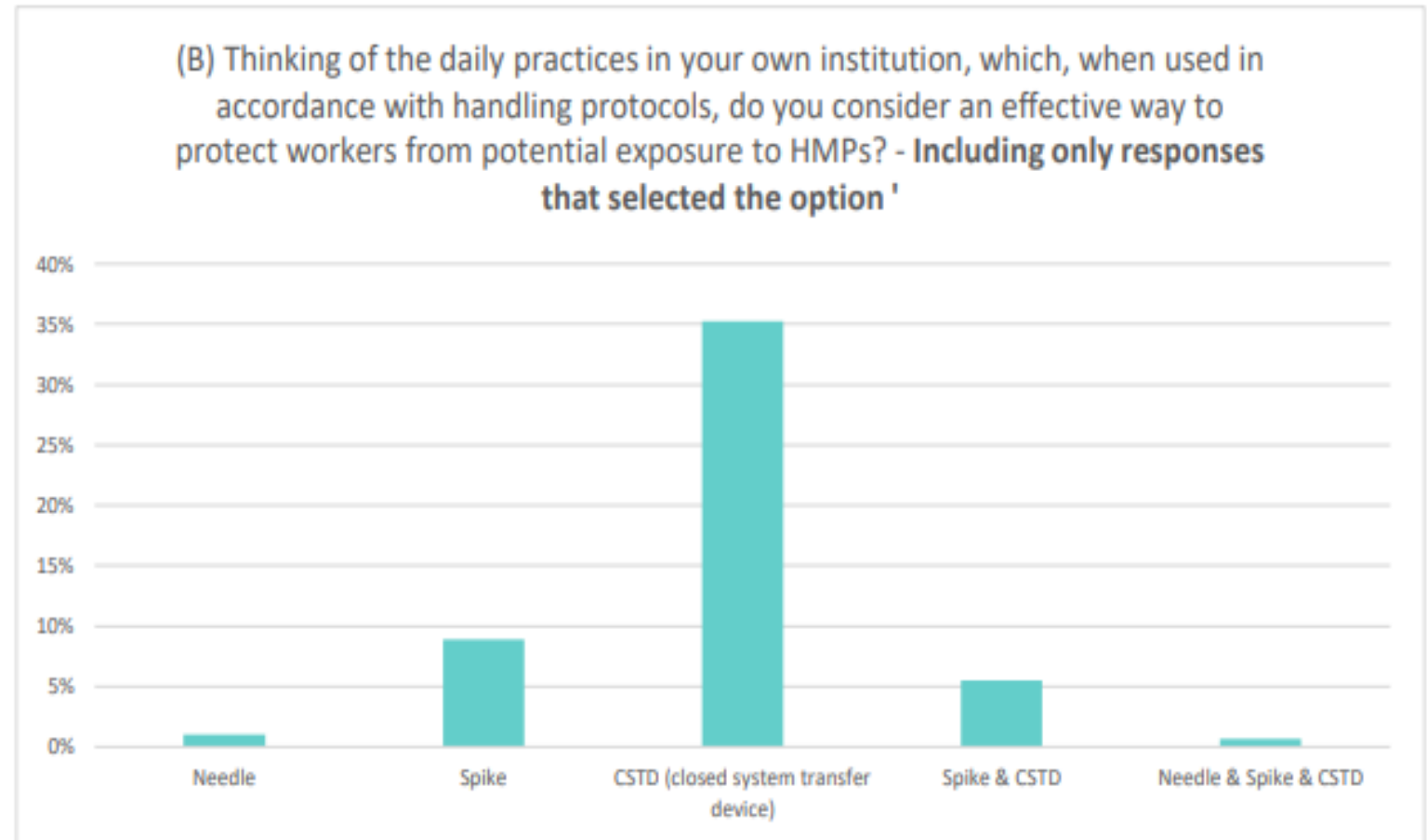


Figure 13 - Percentage of responses by chief pharmacists (N=292) to question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that selected the option 'isolator' in combination with the others. (Note that this was a tick all that apply question)

When assessing the responses to the five options for this question individually, it could be deduced that 14% (N=41/292) of respondents believe that CSTDs offer the best protection against the exposure to HMPs, followed by 10% (N=28/292) selecting isolator and 5% (N=15/292) opting for BSC.

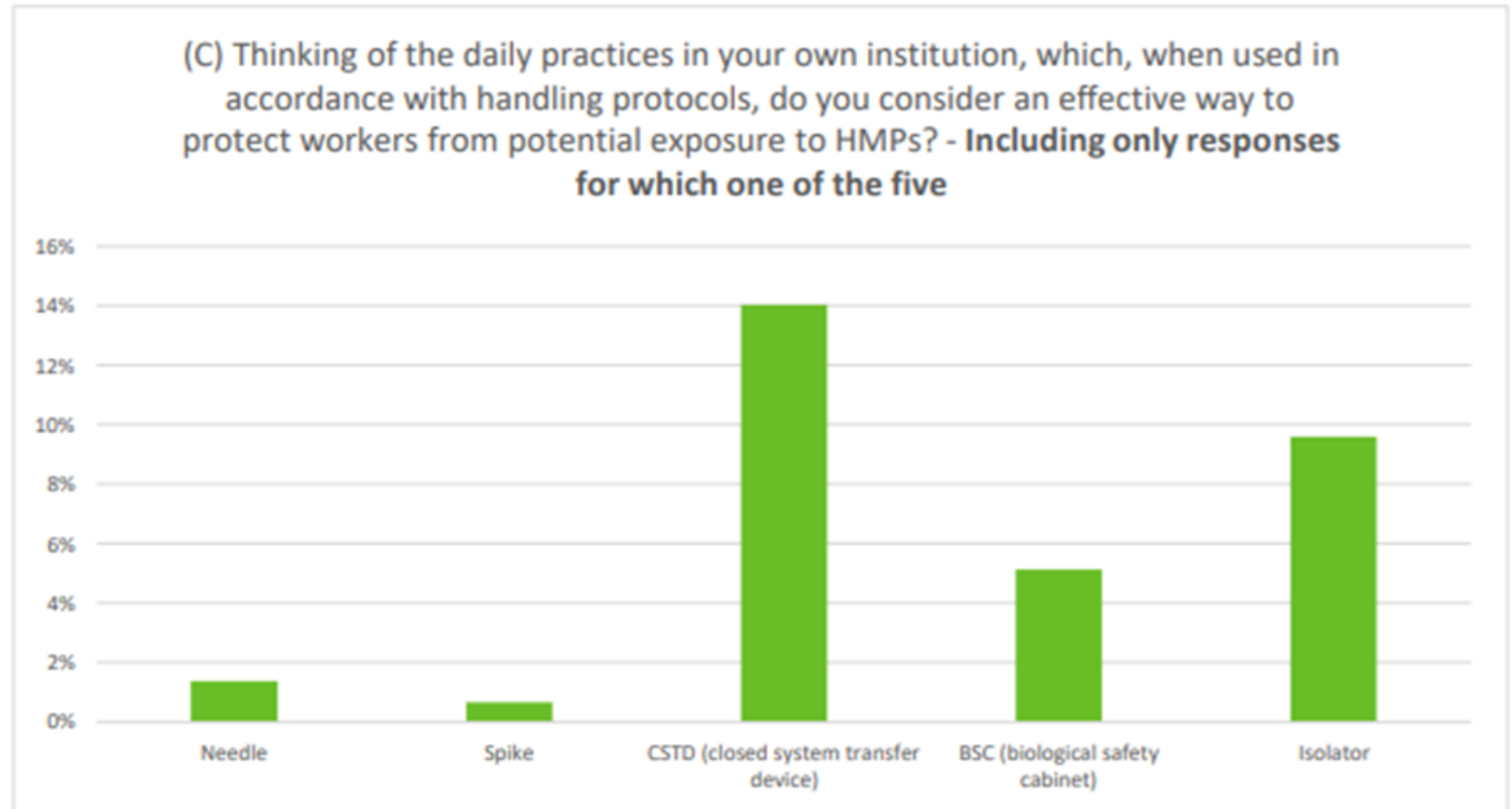


Figure 14 - Percentage of responses by chief pharmacists (N=292) to the question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that ticked only 1 option. (Note that this was a tick all that apply question)

A study published in 2018 evaluated the potential for contamination between four different CSTDs with multiple hazardous drugs that are commonly compounded including ifosphamide, methotrexate, and etoposide (Arminger et al. 2018)

The conclusion of the study was that:

“Barrier-based devices are associated with significantly less HD contamination than filter-based devices.”

“There was significant contamination when using PhaSeal™ with ifosphamide manipulations.”

“Potentially, there are unstudied chemical characteristics of HDs that affect the performance of CSTDs.”

“Compared to all other CSTDs, Equashield® had significantly lower contamination than all other CSTDs tested.”

*Joseph Arminger; Alyson Leonard; Adam Peele; Crystal Peyton. 2018
Cone Health Cancer Center,
Pharmacy Department, Cone Health Cancer Center, North Carolina, USA*

A further study published in 2019, used the NIOSH 2016 draft protocol to assess the containment performance of CSTDs when used for drug preparation and administration (Forshay et al. 2019). The objective of this study was to determine the containment performance of six commercially available CSTDs under a robust vapor challenge. The study concluded that:

“Wipe/pad samplings inside and outside the preparation area were taken during surveillance programs from 2016 to 2021. All samples were analysed for gemcitabine (GEM) contamination. In 2016, the presence of GEM in some samples and the contamination of the operators’ gloves in the absence of apparent drug spilling suggested unsealed preparation systems. In subsequent monitoring, GEM was also evaluated in the vial access device and in the access port system to the intravenous therapy bag of Texium™/SmartSite™ and Equashield® II devices after the reconstitution and preparation steps of the drug. The next checks highlighted GEM dispersion after compounding using Texium™/SmartSite™, with positive samples ranging from 9 to 23%. In contrast, gemcitabine was not present at detectable levels in the Equashield® II system in all of the evaluated samples.”

Forshay C., Streeter S.O., Salch S.A., Eckel S.F. 2019. Application of the 2015 proposed NIOSH vapor containment performance protocol for closed system transfer devices used during pharmacy compounding and administration of hazard drugs. J. Oncol. Pharm. Pract. 2019;25:1160–1166. doi: 10.1177/1078155218787256.

Performance testing of CSTDs used during preparation and administration of HMPs

- In a study published in 2021 (Piccardo et al. 2021), the effectiveness of two CSTDs in reducing leakage during antineoplastic drug compounding was analysed in a centralised compounding unit as follows

“The study concluded that CSTDs are important supplemental engineering controls for containing the exposure of healthcare professionals and GEM dispersion was found after compounding with the TexiumTM/SmartSiteTM, while the Equashield® appeared to be completely tight and able to eliminate exposure to GEM.”

*Maria Teresa Piccardo ,Alessandra Forlani and Alberto Izzotti. 28 July 2021
Effectiveness of Closed System Drug Transfer Devices in Reducing Leakage during
Antineoplastic Drugs Compounding*

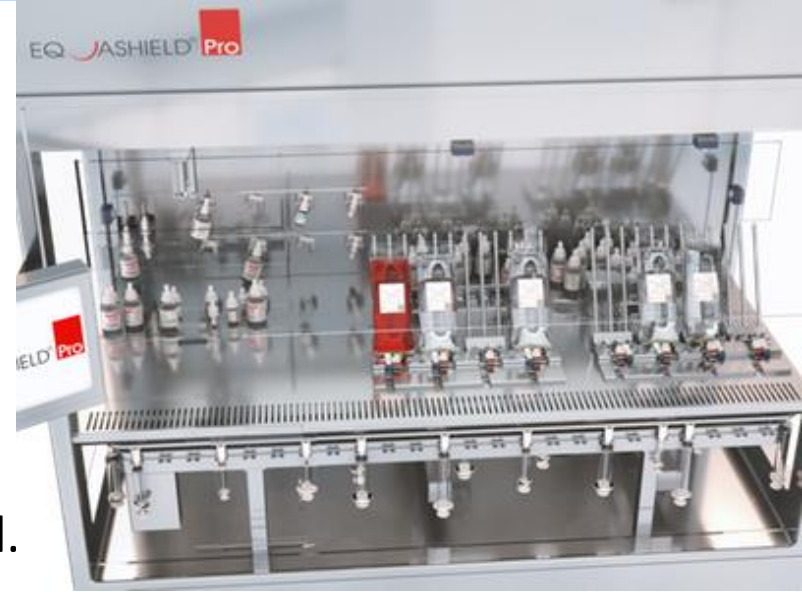


- European hospital pharmacists said that CSTDs are the most effective way to protect workers from the risk of occupational exposure, in combination with isolators and BSCs
- The use of CSTDs is supported by numerous peer-reviewed studies and guidelines in protecting workers and patients from occupational exposure to HMPs and by reducing contamination in the environment
- CSTDs are proven to reduce exposure to HMPs during compounding, preparation and administration and should be used in other areas of the life cycle, where appropriate
- Organisations should choose the CSTD which best suits their needs to prevent the risk of occupational exposure to HMPs to ensure staff and patient safety

- Automation and robotics in compounding of hazardous medicinal products is a revolution in the making of safety, quality and efficiency in the handling of HMPs, to prevent and minimise the risk of contamination, exposure of healthcare workers and medication errors
- Currently, endemic shortages of resources and staff in European healthcare, together with unremitting work pressure, increasing demand and increasing numbers of patients being treated with HMPs, means that reliable automation in compounding is one of the only ways to deal with the workforce crisis
- There is a massive backlog of patients waiting for treatment, particularly in cancer care, owing to workforce shortages, better diagnostics and treatments with new drugs appearing all the time and longer life spans

Automation and Robotics in Compounding

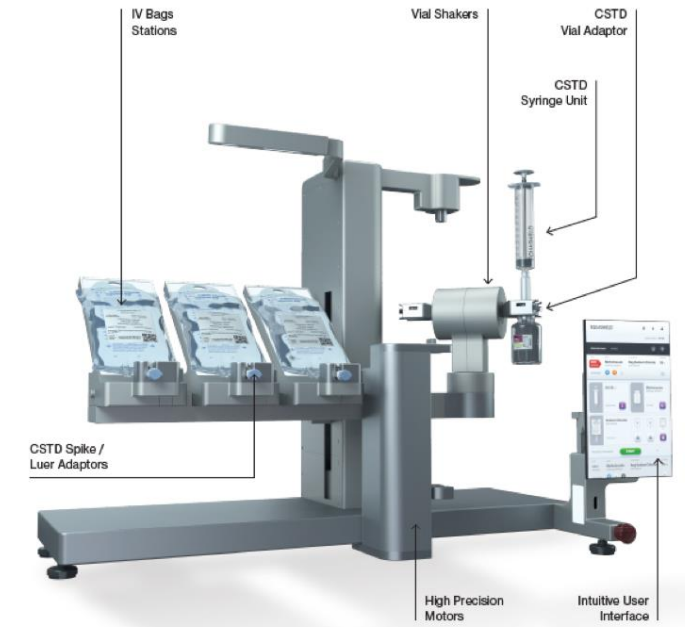
- Robotic IV compounding technology can increase the quality, safety and efficiency of IV compounding to minimise the risks associated with manual compounding for label mix-up, using the wrong drug, calculation and compounding errors. As well as, addressing the growing pharmacy technicians labour shortages and staffing issues
- In 2019, a ‘Multicenter study to evaluate the benefits of technology-assisted workflow on I.V. room efficiency, costs, and safety.’ was published (Eckel et al. 2019). The purpose was to look at the benefits of technology-assisted workflow (TAWF) compared with manual workflow (non-TAWF) on I.V.. room efficiency, costs, and safety at hospitals with more than 200 beds are evaluated. The conclusion of the study was that the use of TAWF in the I.V. room was associated with the detection of 14 times more errors than the use of non-TAWF, demonstrating different frequency of error in the results. TAWF also led to a faster preparation time that had a lower cost for preparation



Stephen F Eckel, Jordyn P Higgins, Elizabeth Hess, Thomas Cerbone , Jennifer B Civiello, Christian Conley , Nilofar Jafari, Shailly Shah , Stephen L Speth , Lynn Thornton. Am J Health Syst Pharm. 2019 Jun 3;76(12):895-901.

- A study on the 'Impact of technology-assisted versus manual sterile compounding on safety and efficiency in a Canadian community hospital.' was published in 2022 (Fan M et al. 2022). The purpose of the study was to look at interventions to improve the safety and efficiency of manual sterile compounding are needed. It evaluated the impact of a technology-assisted workflow system (TAWS) on sterile compounding safety (checks, traceability, and error detection), and efficiency (task time)
- The study concluded that in comparison to manual sterile compounding, use of the TAWS improved safety through more frequent and rigorous checks, improved traceability (via superior documentation), and enhanced error detection. Results related to efficiency were mixed

Mark Fan, MHSc, Danny Yang, MHSc, Becky Ng, MHSc, Jocelyn Jackson, PHT, RPhT, Katherine Bouris, BScPhm, RPh, Sharon Eng, PharmD, RPh, Edith Rolko, BScPhm, RPh, and Patricia Trbovich, PhD. *Am J Health Syst Pharm.* 2022 Oct 1;79(19):1685-1696



The 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

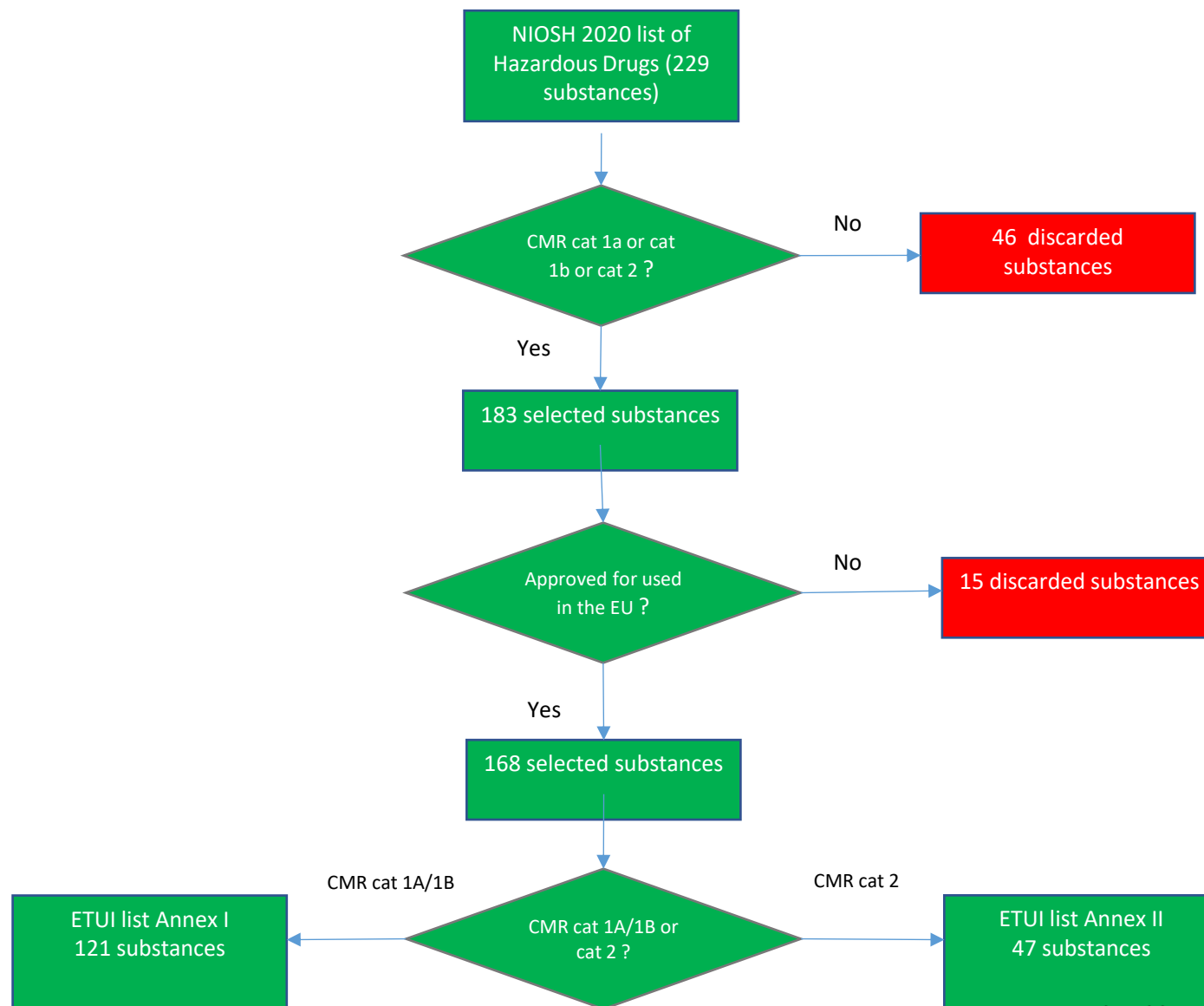
Ian Lindsley and Tony Musu

etui.

1. ETUI list is the **first and only list** of HMPs publicly available identifying hazardous drugs used in the EU that strictly fall within the scope of the CMRD
2. The application of the European guidance on HMPs to the drugs identified in the ETUI list will **help prevent future occupational exposure in millions of workers across the EU**
3. The ETUI list can also be used by the European Commission to help meet its legal obligation to establish by April 2025 an indicative list of HMPs that are CMRs

<https://www.etui.org/publications/etuis-list-hazardous-medicinal-products-hmps>

Methodology and identification of HMPs in ETUI list



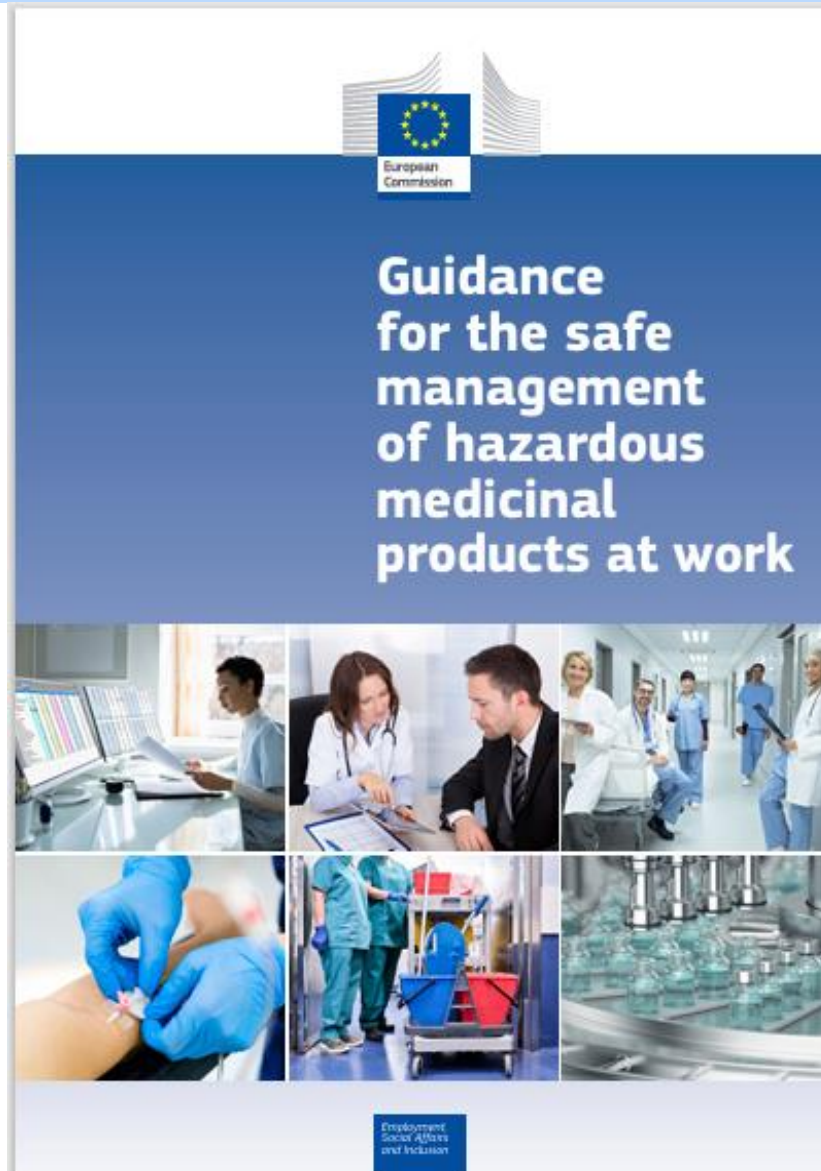
Annex I – 121 HMPs identified as 1A or 1B CMRs under CLP

Annex I Drugs which contain one or more substances which meet the criteria for classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B) in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council

Bold denotes medicinal products that moved from Table 1 to Table 2 in NIOSH 2020 list

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Category	MSHI	NIOSH 2020 Table	Supplemental Information
abacavir	1B*	-	2	188062-50-2	620-488-4	antiviral	-	-	no	2	*3 of 45 consider carc 1B, Malignant tumors observed in male and female mice and rats; Genotoxic in vivo micronucleus test.*
acitretin	-	-	1A*	55079-83-9	259-474-4	antipsoriatics	-	-	no	2	*9 of 47 consider repro 1A (otherwise 1B), Only met the NIOSH criteria as a developmental and/or reproductive hazard*
alitretinoin	-	-	1B	5300-03-8	610-929-9	antineoplastic agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
arsenic trioxide (diarsenic trioxide)	1A	-	-	1327-53-3	215-481-4	antineoplastic agent	1	Known to be human carcinogen	yes	1	*Harmonised CLP classification NTP Classification for 7440-38-2 (arsenic)*
azacitidine	1B	-	-	320-67-2	206-280-2	antineoplastic agent	2A	Reasonably anticipated to be a human carcinogen	yes	1	
azathioprine	1A	1A	1A	446-86-6	207-175-4	immunosuppressant	1	Known to be human carcinogen	yes	1	
bendamustine	2	-	1B	3543-75-7	631-540-0	antineoplastic agent	-	-	yes	1	Cytotoxic; Developmental toxicity
bicalutamide	2*	-	1B*	90357-06-5	618-534-3	antineoplastic agent	-	-	no	2	12 of 196 consider carc 2, repro 1A/B
bleomycin	2	1B	2	9041-93-4	232-925-2	antineoplastic agent	2B	-	yes	1	
bosentan	-	-	1B*	147536-97-8	643-099-1	antihypertensives	-	-	no	2	*1 of 4 consider repro 1B (otherwise 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard*

New EU Guidance on Safe Handling of HMPs – April 2023



The European Commission published guidance in April 2023 for the safe management of hazardous medicinal products at work, including cytotoxics, which must be disseminated in all Member States

<https://osha.europa.eu/en/publications/guidance-safe-management-hazardous-medicinal-products-work>

- In order to identify HMPs, the guidance defines HMPs as medicinal products that contain one or more substances that meet the criteria for classification as 1A or 1B CMRs
- This definition of HMPs is much broader than exists in most existing EU member state guidance and regulation, which tends to focus only on cytotoxic or cytostatic drugs
- EU-OSHA said on 20 October 2023 about prevention measures that: “Workers' exposure must be prevented. If replacement is not possible, the employer shall use a closed technological system.”

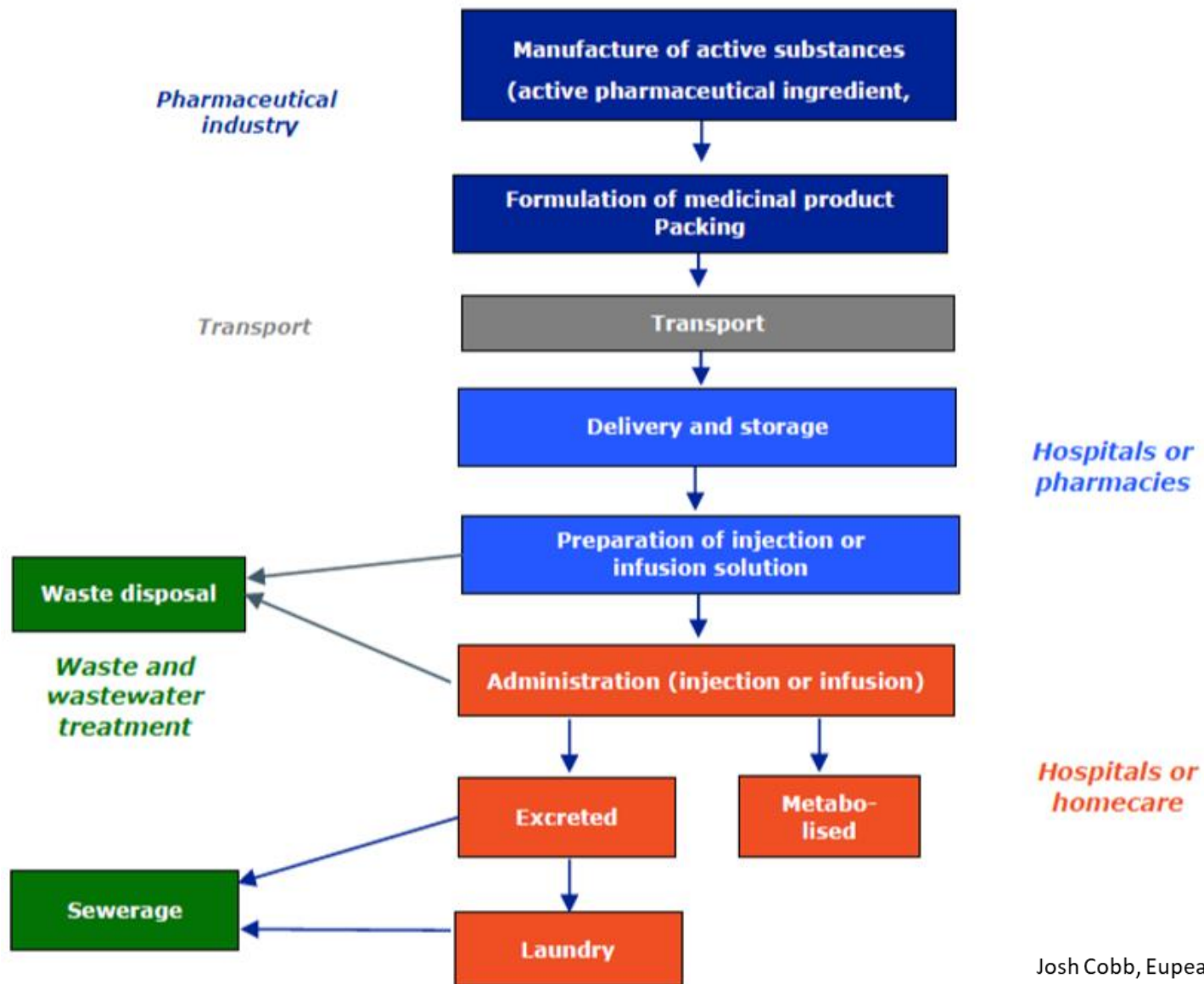
New EU Guidance on Safe Handling of HMPs

- In order to identify HMPs, the guidance **defines HMPs** as medicinal products that contain one or more substances that meet the criteria for classification as 1A or 1B CMRs
- This **definition of HMPs is much broader** than exists in most existing EU member state guidance and regulation, which tends to focus only on cytotoxic or cytostatic drugs
- The guidance is extended to all types of organisation regardless of size, whether public or private, and at all stages throughout the life cycle of HMPs, not just in specific areas like pharmacy or preparation



- CSTDs are defined in the guidance as 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
- The guidance says that the use of CSTDs are the decision of the country/organisation/management/staff in accordance with the risk assessment performed and relevant legislation
- The guidance explains how to create a safe working environment, through risk assessment, exposure assessment, education and training and health surveillance and then divides the guidance up into the life cycle stages of HMPs
- HMPs in the guidance include the following key therapeutic groups: antineoplastics, antivirals, hormones and hormonal antagonists and immunosuppressants and also some HMPs among antibiotics and other therapeutic groups

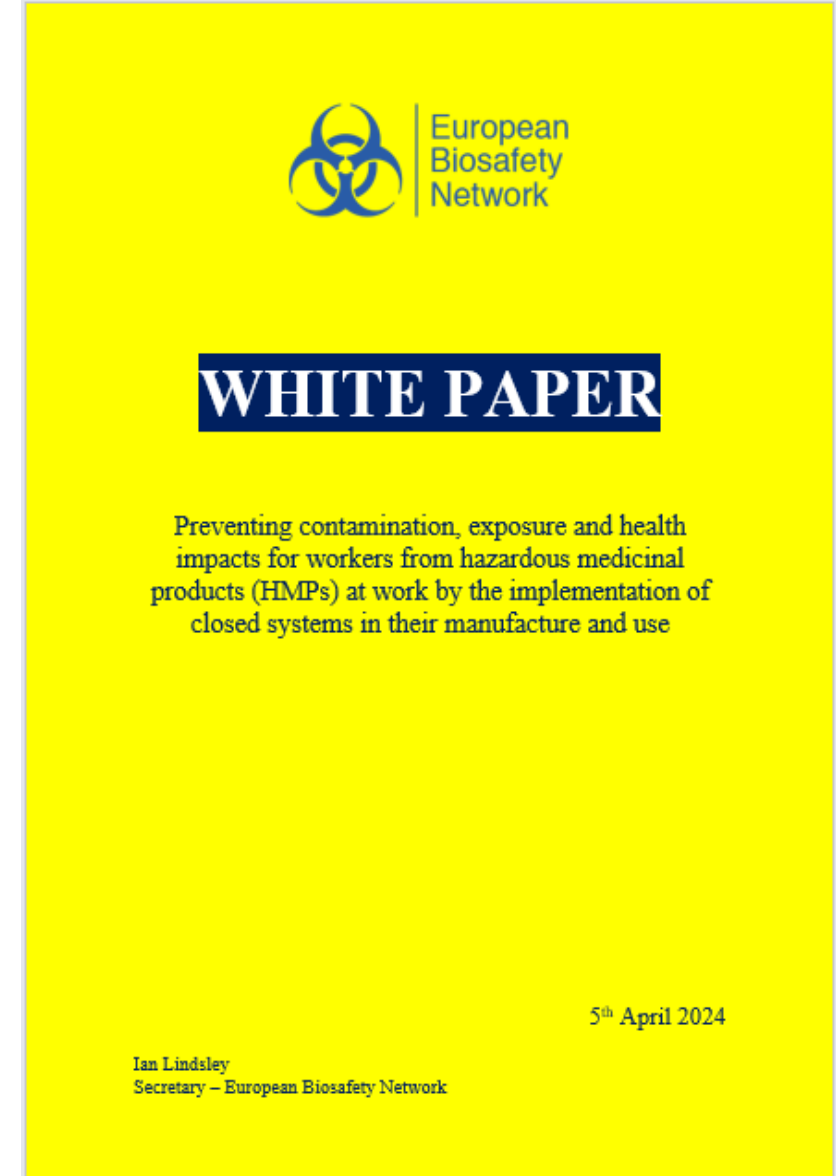
Life cycle of HMPs covered by EU Guidance



EBN White Paper on HMPs – 5 April 2024

- The EBN published a white paper on on 'Preventing contamination, exposure and health impacts for workers from hazardous medicinal products (HMPs) at work by the implementation of closed systems in their manufacture and use'
- The white paper was published on 5 April 2024, the date on which all EU Member States, must have transposed the EU legislative changes in the CMRD from 2022 into national law

<https://www.europeanbiosafetynetwork.eu/millions-of-healthcare-workers-get-protection-from-new-eu-law-today/>



Summary – New EU legislation on HMPs

- New EU legislation passed in March 2022 has to have been **transposed into national law** in all EU member states by **5 April 2024**
- This new EU legislation for the first time **includes HMPs and reprotoxins** within the scope of the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD)
- In the CMRD, HMPs - which cannot be replaced or substituted - must be **manufactured and used in a closed system**, ie BSCs, isolators and CSTDs
- The CMRD includes a new **requirement for training** those in healthcare handling HMPs
- The EU has agreed a **broader definition of HMPs** than currently used as category 1A or 1B substances which are **known or presumed** to have carcinogenic, mutagenic or reprotoxic potential for humans

Summary – New EU guidance on HMPs

- New EU guidance published in 2023 on handling HMPs must be disseminated in all EU Member States
- The new EU guidance includes the same **broader definition of HMPs** than exists in most existing EU member states guidance and regulations
- CSTDs are defined as “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.”
- The new EU guidance states that HMPs belong to a **wider range of therapeutic groups**, including antineoplastics, antivirals, hormones and hormonal antagonists and immunosuppressants, not just cytotoxics
- The guidance is extended to all types of organisation and at all stages throughout the **life cycle of HMPs**, from manufacture to disposal, not just in specific areas like pharmacy or preparation

Why EU countries may not have transposed the legislative changes into national law

- Administrative and bureaucratic delays
- Lack of awareness or understanding
- Legal and regulatory complexity
- Economic and financial constraints
- Resistance from industry and employers
- Enforcement and monitoring challenges

Conclusion

- Exposure to HMPs or hazardous drugs, often used to treat cancer, viruses, chronic inflammatory and other life-threatening conditions, can happen anywhere from manufacture to preparation, administration and disposal, and can cause health impacts from headaches and hair loss to miscarriages and cancer.
- Healthcare organisations in Ireland deploy a range of measures to protect their staff from these risks but much more needs to be done. These changes need to occur systematically for improvements to be seen on the frontlines and organisations must remember that exposure can occur any time during the whole life cycle of HMPs and all those potentially at risk must be protected.



European
Biosafety
Network

www.europeanbiosafetynetwork.eu

