SAFER HEALTHCARE & BIOSAFETY NETWORK

European Biosafety Network

Presentation by Ian Lindsley at Pharmaceutical Quality Assurance and Technical Services Symposium 2023,International Convention Centre Newport, Wales (ICC), 29 September 2023

The Safer Healthcare and Biosafety Network

The Safer Healthcare and Biosafety Network is an independent forum focused on improving healthcare worker and patient safety and caring for those who care for us.

It is made up of clinicians, professional associations, trades unions and employers, manufacturers and government agencies with the shared objective to prevent occupationally acquired diseases and improve occupational health and safety in healthcare.

The Network was originally founded in 1999 as the Safer Needles Network to protect healthcare workers from needlestick injuries and was key to the adoption of the 2013 Sharps Regulations.

The Network has expanded its agenda to drive awareness and promote a greater range of safer practices and new technology and the role they can play in improving healthcare worker and patient safety standards.

In 2021, the Network set up the Safety for All campaign to improve practice in, and between, patient and healthcare worker safety to prevent safety incidents and deliver better outcomes for all.

New EU legislation

The European Biosafety Network was established in 2010 to ensure the implementation of the Sharps Directive and also campaigns for the prevention of occupational exposure to hazardous drugs, or hazardous medicinal products (HMPs)

New EU legislation passed in March 2022 for the first time includes HMPs and reprotoxins within the scope of the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD) and a broader definition of HMPs which contain category 1A or 1B CMR substances

HMPs, which cannot be replaced or substituted, must be manufactured and used in a closed system, as set out in CMRD hierarchy of control

The CMRD includes a new requirement for training those in healthcare handling HMPs

The fifth revision of the CMRD has just started and the European Parliament recxently voted overwhelminingly to include the definition of HMPs in Annex I. Separately the ETUI list is being used as the basis for agreeing the new EU indicative list of HMPs by the European Commission

New EU guidance on the safe management of HMPs

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- New EU legislation also requires new EU guidance on handling HMPs to be published and disseminated
- The new EU guidance includes the same **broader definition of HMPs** than exists in most existing EU member state guidance and regulation
- 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, including the administration on wards but also in social care and home care and veterinary settings

New EU Guidance on the safe management of HMPs - MABs

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- There is an ongoing debate about whether monoclonal antibodies (MABs) are HMPs.
- In 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.
- A biological mechanism for teratogenicity has been demonstrated at therapeutic doses. 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 and the ETUI list includes MABs in its table 2 based on CLP Classification category 2.

New EU Guidance on the safe management of HMPs - CSTDs

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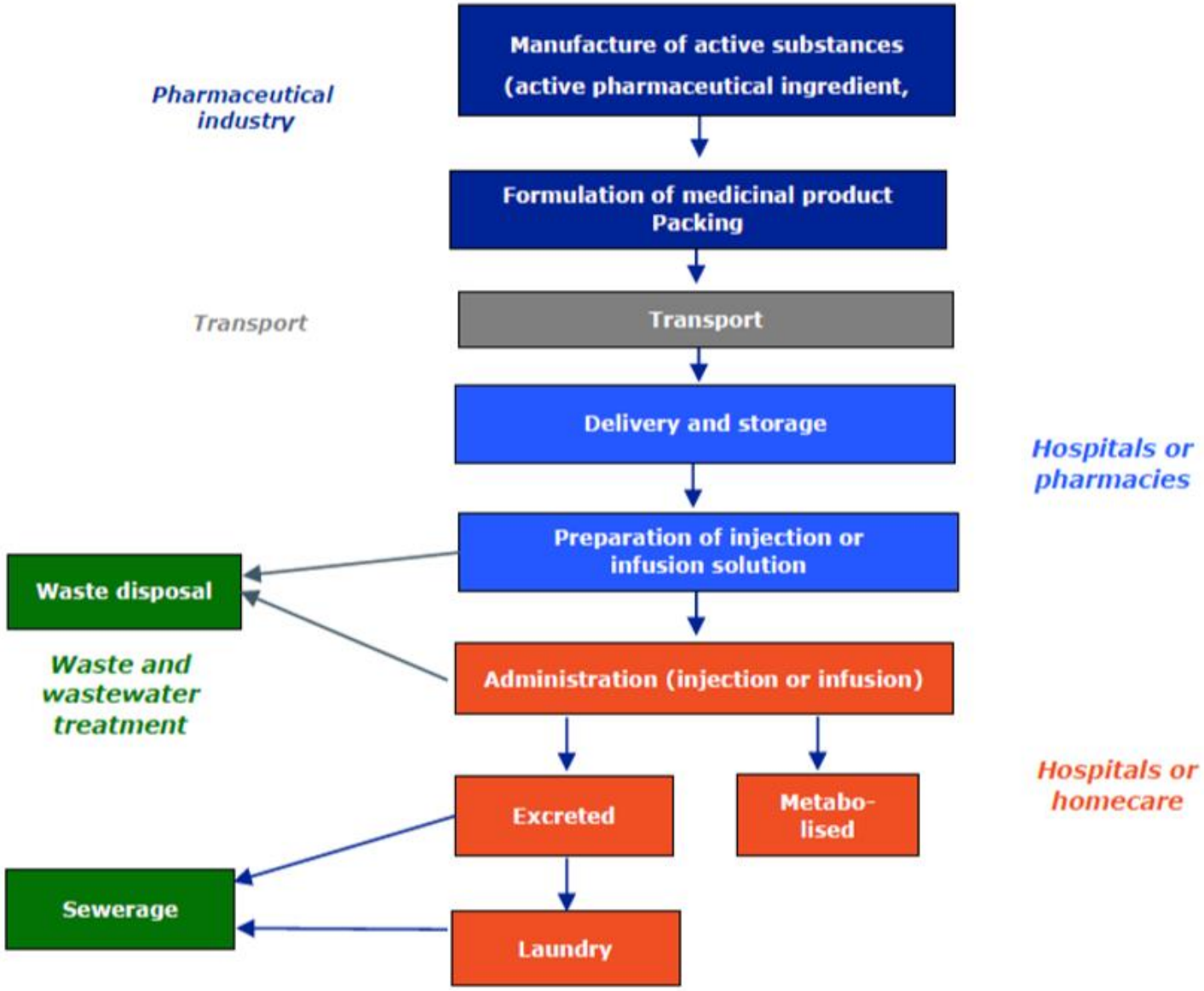
- CSTDs are defined in the guidance as a medicine transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the HMP or vapour concentrations outside the system – NIOSH definition

- 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

Life cycle of HMPs covered by EU Guidance



ETUI list of hazardous medicinal products

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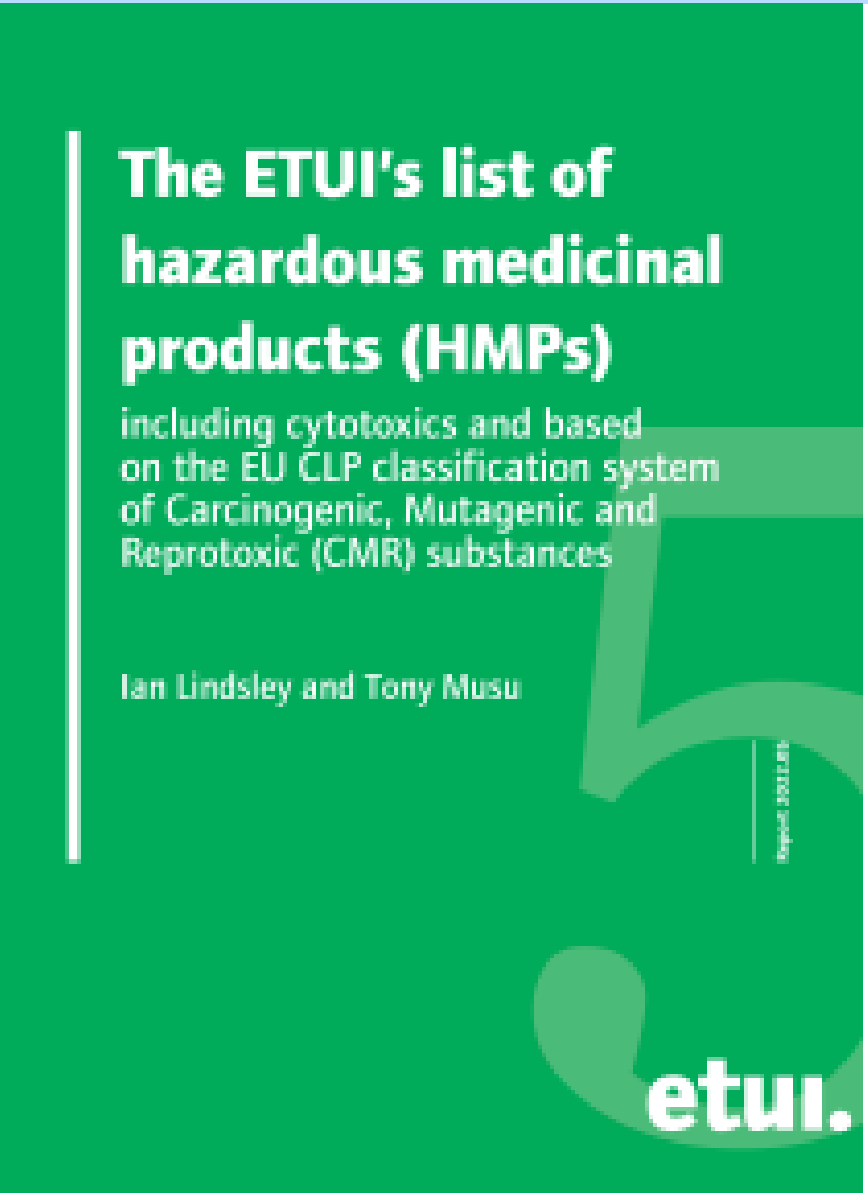
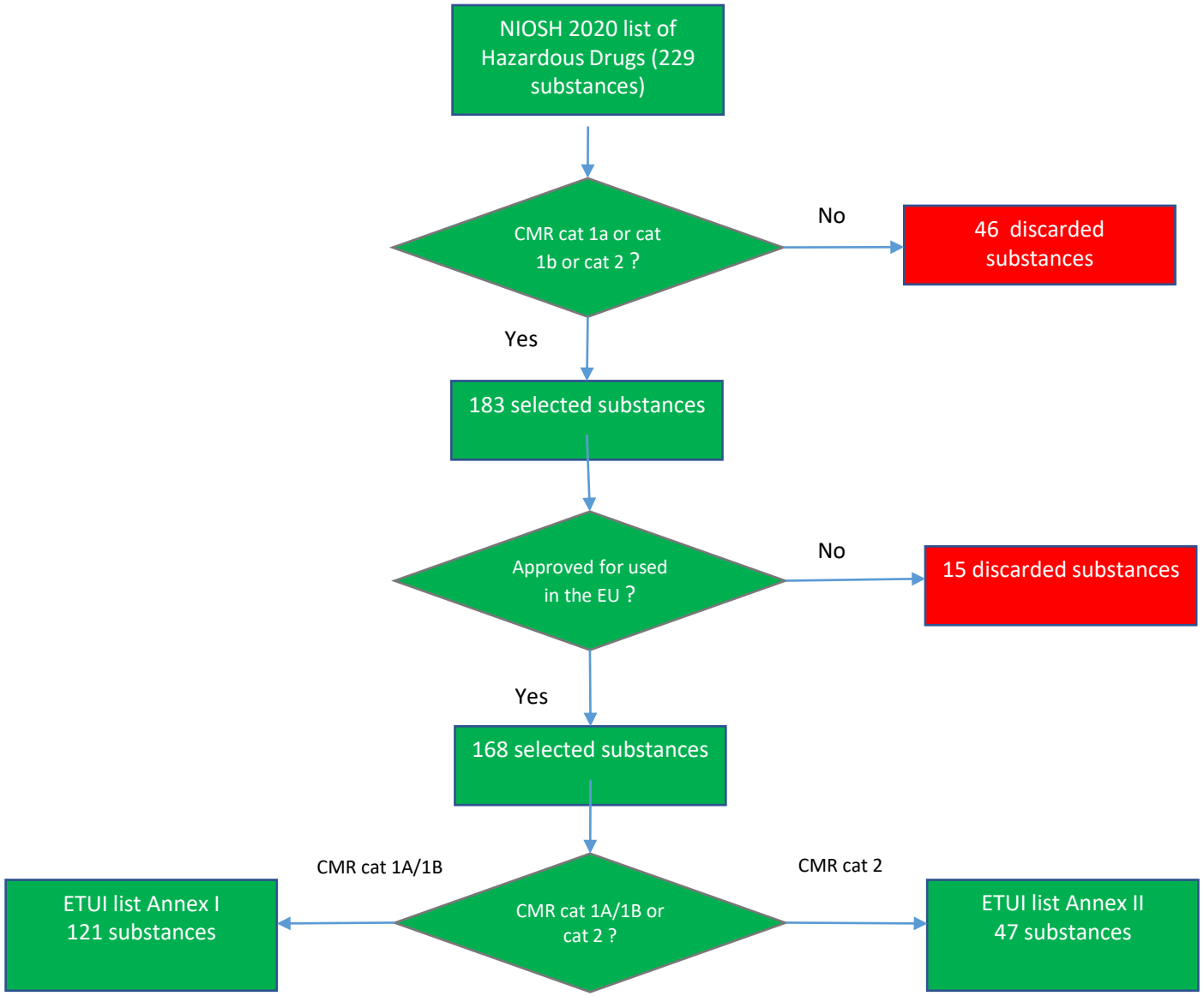


1. ETUI list is the **first and only list** of HMPs publicly available identifying hazardous drugs used in the EU that strictly fall within the scope of the CMRD
2. The application of the European guidance on HMPs to the drugs identified in the ETUI list will **help prevent future occupational exposure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

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

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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 Cate-tory	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	immunosup-pressant	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	antihyperten-sives	-	-	no	2	*1 of 4 consider repro 1B (otherwise 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard*

Hierarchy of Control in CMRD Directive (EU) 2022/431

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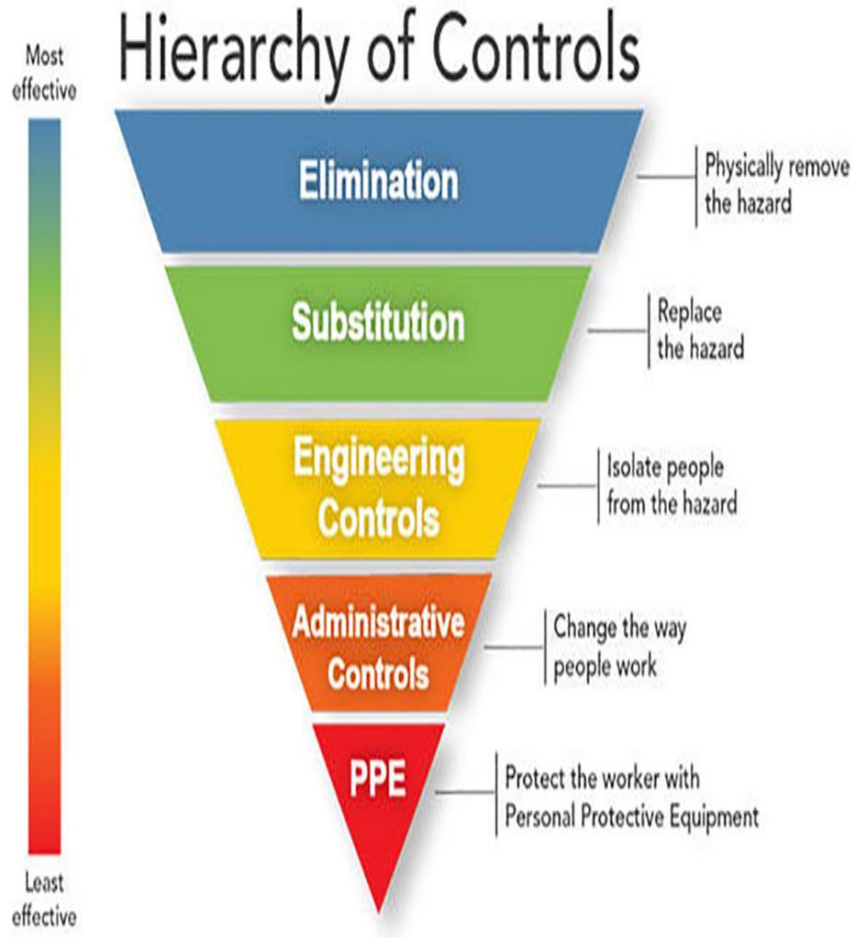
- HMPs, now falling under the scope of CMRD, have to be **manufactured and used**, which means that they must be compounded, prepared, administered, transported and disposed of, **in a closed system**

- 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) and luer lock connectors

- CSTDs include either a physical barrier, air-cleaning technology or a physical barrier with a closed-backed syringe and the fluid pathway is either metal needle or needle free



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CSTDs reduce risk of occupational exposure

Use of the CSTD significantly reduces surface contamination when preparing Cyclophosamide, 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.

Closed System Transfer Devices – USP<800> standard

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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.

USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, 2017

Closed System Transfer Devices

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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 CTSD?
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/aperformancetestprotocolforclosedsystemtransferdevices.pdf

Examples of CSTDs

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Barrier technology

Chemolock

PhaSeal

Equashield

Filter technology

ChemoClave

Tevadaptor

EAHP Special Interest Group on HMPs

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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

“The United Kingdom does not have a classification system for HMPs. Handling of carcinogens and mutagens are covered by the Control of Substances Hazardous to Health (COSHH regulations 2002 (as amended), but for classification, like in Ireland the NIOSH list is used.”

Closed System Transfer Devices – EAHP Survey on HMPs

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.

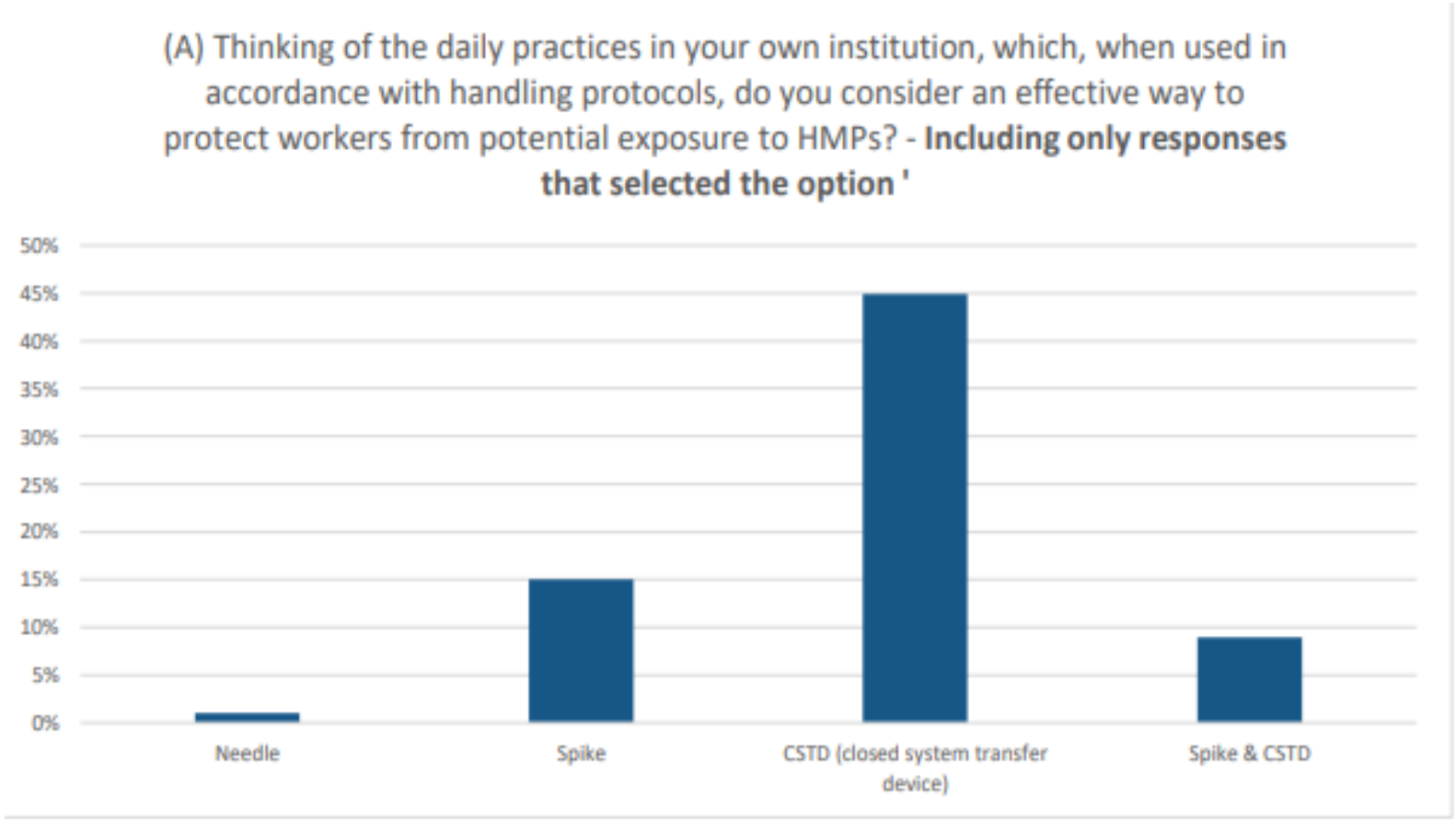

Figure 12 - Percentage of responses by chief pharmacists (N=292) to question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that selected the option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

Closed System Transfer Devices – EAHP Survey on HMPs

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.

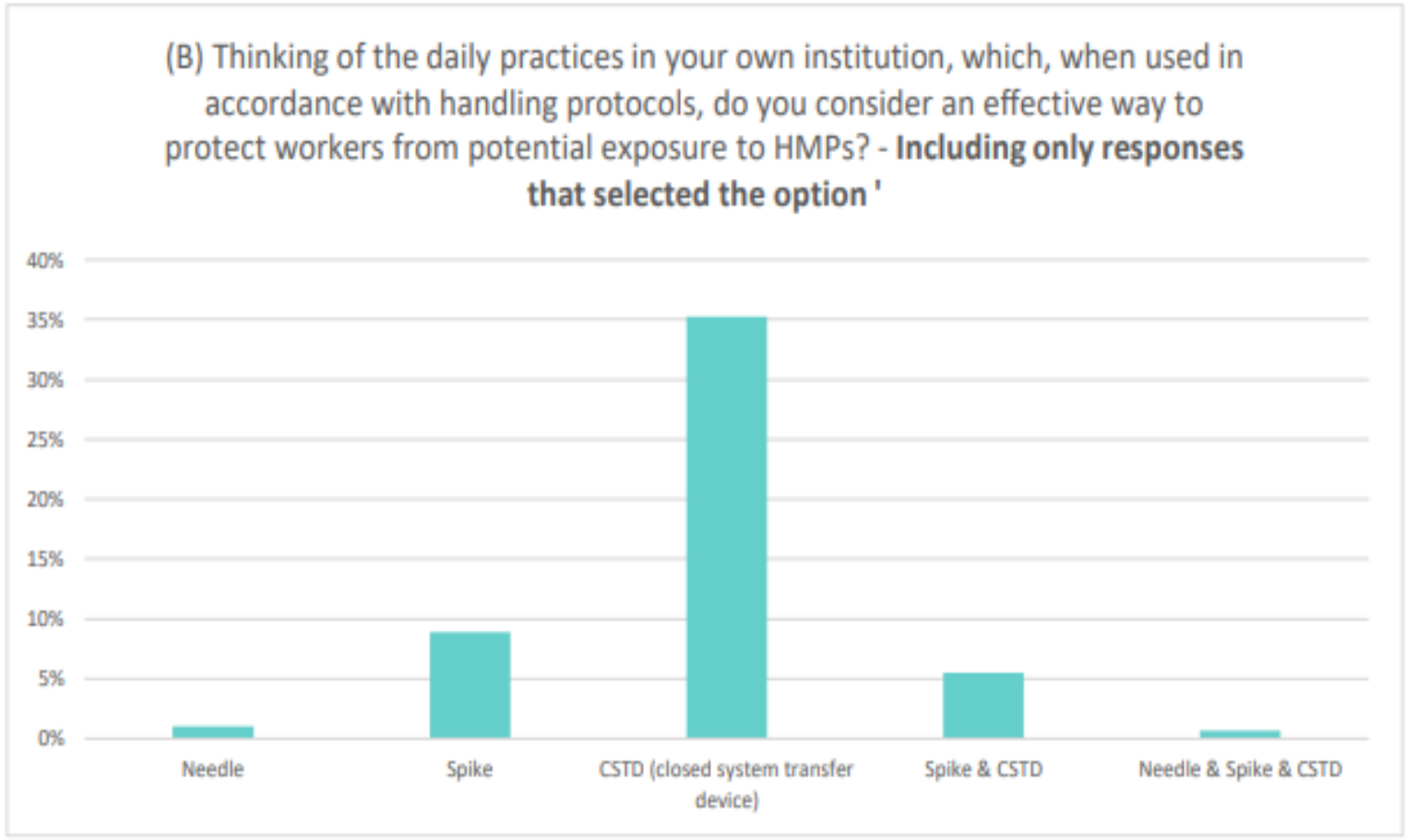

***Figure 13** - Percentage of responses by chief pharmacists (N=292) to question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that selected the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

Closed System Transfer Devices – EAHP Survey on HMPs

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.

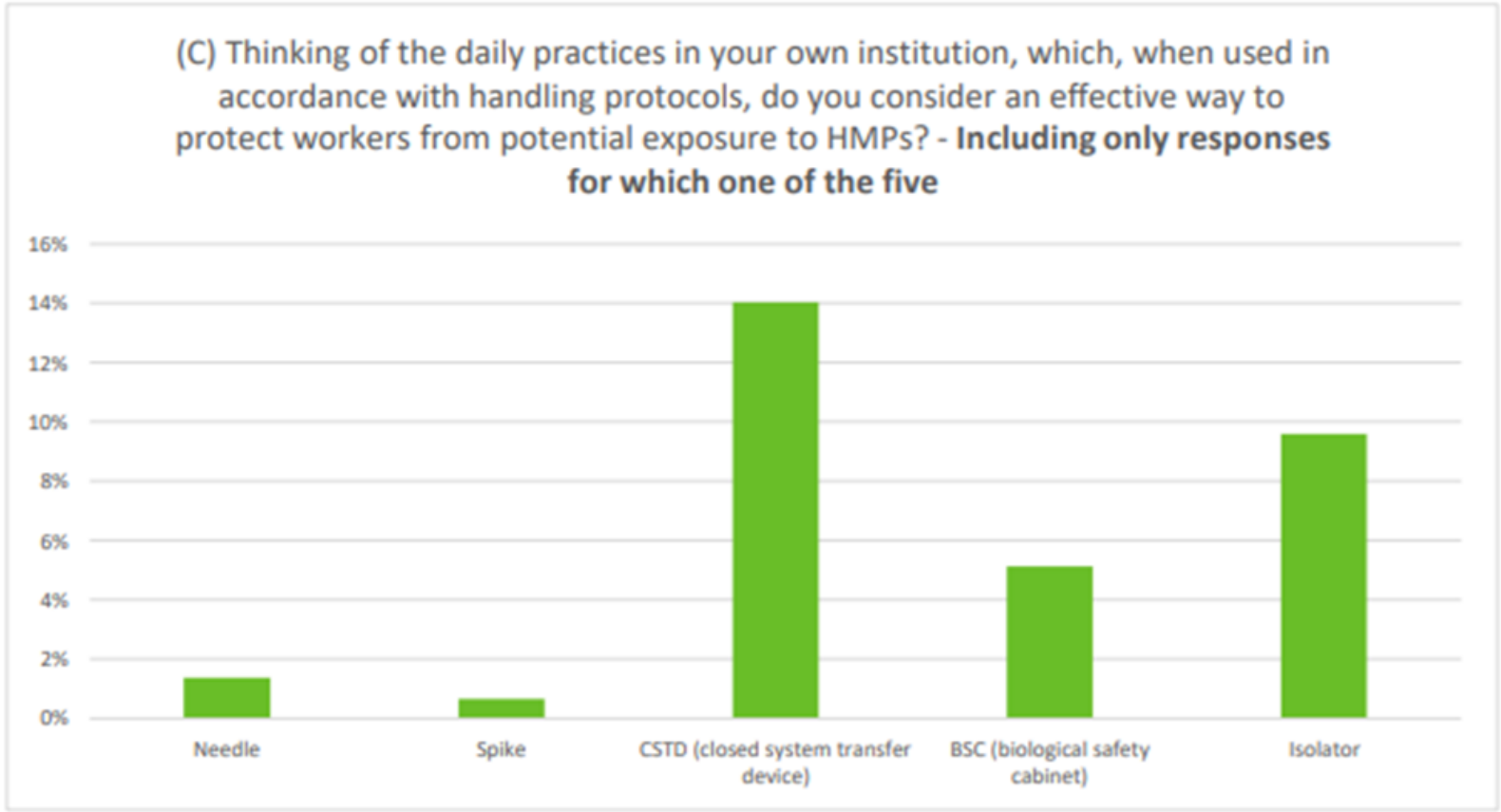

***Figure 14** - Percentage of responses by chief pharmacists (N=292) to the question 16 'Thinking of the daily practices in your own institution, which, when used in accordance with handling protocols, do you consider an effective way to protect workers from potential exposure to HMPs?' that ticked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

Closed System Transfer Devices - Conclusions

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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.

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