HHS Public Access

Author manuscript

J Oncol Pharm Pract. Author manuscript; available in PMC 2021 February 19.

Published in final edited form as:

J Oncol Pharm Pract. 2019 January ; 25(1): 148–162. doi:10.1177/1078155217726160.

Survey of guidelines and current practices for safe handling of antineoplastic and other hazardous drugs used in 24 countries

Patricia I Mathias, **Barbara A MacKenzie**, **Christine A Toennis**, **Thomas H Connor**

Robert A. Taft Laboratories, National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services, Cincinnati, USA

Abstract

Purpose: A survey of guidelines and current practices was conducted to examine the safe handling procedures for antineoplastic and other hazardous drugs that are used in 24 countries including the Americas, Europe, the Mideast, Far East, and Australia.

Methods: Subject experts were asked to complete a brief survey regarding safe handling guidelines and practices for hazardous drugs in their countries. Questions addressed practices for handling monoclonal antibodies, the use of closed-system transfer devices, medical surveillance practices, and measurements of compliance with existing guidelines.

Results: Responses from 37 subject experts representing 24 countries revealed considerable variation in the content and scope of safe handling guidelines and pharmacy practices among the participating countries. Guidelines in the majority of countries used the term “cytotoxics,” while others referred to “hazardous” or “antineoplastic” drugs. The International Society of Oncology Pharmacy Practice standard was cited by six countries, and five cited the National Institute for Occupational Safety and Health Alert. Others cited international guidelines other than International Society of Oncology Pharmacy Practice, or they have created their own guidelines. Approximately half reported that their guidelines were mandatory under federal, state, or provincial legislation. Only 11 countries reported that monoclonal antibodies were covered in their guidelines. Closed-system drug-transfer devices are widely used, but were not specifically recommended in four countries, while one country required their use. Medical surveillance programs are in place in 20 countries, but only in The Netherlands is surveillance mandatory. Nine countries reported that they have completed recent updates or revisions of guidelines, and the measures for their adoption have been initiated.

Conclusions: Although the overall goals in the participating countries were similar, the approaches taken to assure safe handling of hazardous drugs varied considerably in some cases.

Corresponding author: Thomas H Connor, U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1090 Tusculum Avenue MS C-23, Cincinnati, OH 45226, USA. tmc6@cdc.gov.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Keywords

Safe handling guidelines; antineoplastic or cytotoxic drugs; monoclonal antibodies; closed system drug-transfer devices; measures of compliance; medical surveillance

Introduction

Occupational exposure to cytotoxic, antineoplastic, chemotherapy, or hazardous drugs has been a concern for healthcare workers since the late 1970s.[1–3] Over the past three decades, considerable information has been published reporting workplace contamination with these drugs, the carcinogenicity of these drugs, as well as genotoxic and other adverse health effects in workers exposure to them in the workplace.[4,5] Further, adverse reproductive effects have been demonstrated in both patients treated with these drugs and in workers exposed to them.[6–8] Therefore, many countries around the world have adopted or are developing guidelines for safe handling of hazardous drugs. Typically guidance documents are published by professional pharmacy and nursing organizations, while others have been developed by national, state, or provincial governments; their adoption may be mandatory and enforceable at these levels, but most are voluntary guidelines. During the 2014, International Society of Oncology Pharmacy Practice (ISOPP) meeting in Montreal, Quebec, a roundtable of 14 ISOPP member subject experts representing seven countries, was held to discuss issues related to safe handling of hazardous antineoplastic and cytotoxic drugs. The purpose of the roundtable was to survey existing guidelines and pharmacy practices for safe handling of cytotoxic and anti-neoplastic drugs in the seven participating countries. Following the meeting, efforts were made to extend the survey by letters of invitation to 25 additional subject experts. The results of that survey are presented in tabular format with summary comments and discussion.

Methods

At the 2014 ISOPP meeting described above, 14 ISOPP member subject experts representing seven countries described in a roundtable discussion the safe handling practices used in their country, province, or territory based upon responses to nine survey questions (Table 1). Before the meeting, the survey questions had been written and discussed by several members of the later roundtable. Questions addressed the practices for handling monoclonal antibodies, use of closed-system transfer devices, medical surveillance practices, and measurements of compliance with existing guidelines. After the meeting, efforts were made to expand the number of countries represented in the survey. Subject experts were identified from government agencies, private research institutes, universities, and members of professional organizations, such as ISOPP, American Society of Health-System Pharmacists (ASHP), Clinical Oncological Society of Australia (COSA), and Japanese Society of Hospital Pharmacy (JSHPP). A letter of invitation along with same survey questions were sent via email to 25 identified subject experts. Twenty-three additional subject experts representing 17 countries agreed to participate in the survey. In total, 37 subject experts contributing to the survey from 24 countries agreed to be identified as contributors (Table 2). Contributors acted voluntarily as private individuals and were

neither compensated for their participation, nor did they act as formal representative of their respective countries, their current employers or as representatives of any professional organization.

Results

Safe handling guidelines cited by countries

The ISOPP Standard of Practice was the only world-wide guidance that was identified by participating countries, while other countries cited the guidelines from the National Institute for Occupational Safety and Health.[4,15] The ISOPP standard was cited as the basis for guidelines in Australia, Belgium, Iran, Malaysia, Portugal, and some Canadian provinces (Table 3). The NIOSH 2004 guidelines were cited in part or in its entirety by Malaysia, Spain, United Arab Emirates, the USA, and some Canadian.[4] Chile cited Quapos5 and GEDEFO.[19,20] German pharmacies have developed own guidelines TRGS 525.[21] Thirteen countries have developed their own guidelines and did not cite any specific guideline as a source. Compliance with these guidelines is reported as voluntary in 11 countries and in 12 compliance as mandatory (Table 3). In Canada, occupational health and safety regulations are enforceable at the provincial level, while guidelines from ISOPP, CAPhO, CSHP, or other professional organizations where they have been voluntarily adopted are not enforceable. In Australia, individual states have developed voluntary guidelines based on ISOPP, COSA, SHPA, and other professional organizations.

Drugs included and terminology

In current literature, the terms cytotoxic and antineoplastic are often used interchangeably although each has somewhat different definitions. They are typically used to identify drugs used to treat cancer. The term “cytotoxics” is used in more guidelines than other terms (14/24). However, cytotoxic does not apply to some of the new targeted antineoplastic drugs being developed, such a tyrosine kinase inhibitors.[22] The terms “antineoplastic” (6/24) and “hazardous” (4/24) are also commonly used. Several guidelines defined the term “hazardous drugs” based upon the NIOSH 2004 Alert.[4]

Monoclonal antibodies

Survey respondents reported considerable variations in recommendations for handling monoclonal antibodies (Table 3). This is supported in an article by Crul et al. that found differences between countries and sometimes between facilities within a country for handling monoclonal antibodies.[23] In this survey, 11 of 24 participating countries include monoclonal antibodies in their recommendations, and 12 do not (Table 3). Two countries, the United Kingdom and Australia, have specific guidelines for handling monoclonal antibodies.[14,24] In Germany, the risk associated with the use of monoclonal antibodies is addressed by other regulations issued by the Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services.[25] In The Netherlands and Norway, monoclonal antibodies are not specified in their guidelines, but are managed in pharmacies in a similar manner to cytotoxic drugs. In Canada, safe handling guidelines are issued at the provincial level and vary by provincial health regions, agencies, or by specific facility. Alberta and Manitoba guidelines include monoclonal antibodies. Five provinces, British

Columbia, Labrador, New Brunswick, Newfoundland, and Quebec, reference the NIOSH hazardous drug list, which includes three monoclonal antibody preparations, two that are conjugated (ado-traszuzumab emtansine and brentuximab vedotin) and one unconjugated (pertuzumab) (NIOSH HazDrugList2016).[26]

Closed system drug-transfer devices (CSTDs)

In guidelines where CSTDs are included in the hierarchy of controls, they are designated as engineering controls (Table 3). The U.S. Pharmacopeia (USP 800) recommends them for drug preparations and makes them mandatory for drug administration.[27] NIOSH currently recommends them as supplementing engineering controls (e.g. to be used in biological safety cabinets or compounding aseptic containment isolators). However, in Brazil, Chile, Japan, and the United Kingdom, they are designated as PPE. CSTDs are used in 19 countries. Guidelines in other countries either do not mention CSTDs or they are not specifically recommended for use (Denmark, France, Norway, and some Canadian provinces). In Mexico, CSTDs are not specified, but designated as “protection” in “use of equipment and appliances specialized in compounding.” In Malaysia, CSTDs are reported as generally used when no clean rooms with isolators or safety cabinets are available. In Germany, approximately one half of the facilities use CSTDs. One country, Israel, requires CSTDs for preparation of all conventional antineoplastics, but their position in the hierarchy of controls was not reported.[28]

Requirement for medical surveillance for healthcare workers

Requirements of recommendations for medical surveillance varied considerably from country to country (Table 4). The purpose of medical surveillance is to establish an initial baseline of worker health and then monitor their ongoing health as it relates to potential exposure and disease risk. ISOPP recommends a baseline medical examination and ongoing exams at six month intervals that include a complete blood count with a WBC differential, liver function test with urea, creatinine and electrolytes, and inclusion of a health history including a record of hazardous drug handling.[1] NIOSH further recommends reproductive health exams and biological monitoring.[29] Additional NIOSH recommendations appear in the entry for the United States in Table 4.

Twenty countries reported that their institutions have medical surveillance programs while four reported they did not. The only country that was identified where medical surveillance is mandatory is The Netherlands. The ISOPP safe handling standard was cited by several countries as the basis from their medical surveillance recommendations.[1] In some countries, facilities have detailed mechanisms in place for medical surveillance that included annual laboratory testing, X-ray examinations, and use of general and reproductive health questionnaires on a regular basis. Others have no programs in place or rely on employees and their personal physicians, or on company occupational health physicians.

Measures of compliance to guidelines

In 12 countries, guidelines are mandatory and compliance is measured through yearly or other periodic inspections and audits. In the 12 remaining countries, guidelines are voluntary and compliance rates are either unknown or there were no methods in place to measure them

(Table 5). This may be due in part to the various recommendations that are followed in some countries. Only five countries, Belgium, Denmark, Italy, Sweden, and the US, reported that they conduct environmental wipe sampling on a regular basis. Although compliance with guidelines in the United Sates is voluntary, in half of the states the USP800[27] is enforced. In Spain, compliance is measured as part of medical surveillance and periodic risk assessments. Only one country, Belgium, has detailed data on compliance with existing standards.

Changes in guidance: Current and future issues

Several countries are currently updating or planning to update their safe handling guidelines (Table 6). These include Australia, Finland, Malaysia, Mexico, and the United Kingdom. The German guideline: TRGS 525 "Technical Rule for Hazardous Substances: Hazardous materials in medical care facilities" has been updated and will be adopted shortly.[21] The Netherlands continuously update their recommendations and Israel is planning on new guidance on monoclonal antibodies. In the U.S., several changes and updates are currently in progress or planned. NIOSH updated its list of hazardous drugs in 2016 and will continue to do so every two years. NIOSH is updating its Alert "Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings," which is expected to be published in 2018. ISOPP is currently making revisions and updating its recommendations that will be available in 2018.

Discussion

Although the current survey was not conducted systematically, the 24 countries that participated represent an international cross-section of the world. With the exception of some Canadian provinces, most of North American is included. Brazil, Chile, and Mexico represent Latin America. Twelve countries are in Europe; Israel, Iran, and the United Arab Emirates represent the Middle East, while Malaysia and Japan represent the Far East, and some but not all Australia is included. No African nation participated.

The most commonly used terms used to describe the drugs being considered are "cytotoxic" and "antineoplastic." A broader classification, "hazardous drugs" is used to some extent. The NOSH Alert glossary defines cytotoxic as "a pharmacologic compound that is detrimental or destructive to cells within the body." ISOPP defines cytotoxic drugs more specifically as "chemicals that affect cell growth and proliferation, most of which either bind to genetic material in the cell nucleus, or affect cellular proteins synthesis." ISOPP and NIOSH identify "hazardous drugs" based on one or more of several characteristics: carcinogenicity, genotoxicity, teratogenicity, reproductive toxicity in humans, organ toxicity at low doses in animal models or treated patients. The ISOPP standard includes in the description of hazardous drugs antineoplastic and cytotoxic agents, some hormonal agents, immunosuppressants, antiviral medications, and some monoclonal antibodies. Currently, NIOSH lists one non-conjugated monoclonal and two conjugated monoclonal antibodies as hazardous (NIOSH HazDrugList2016).[29]

Given the different terminology used to identify the drugs considered to be occupational hazards, the various terms used can be confusing and/or misleading. For example, "cytotoxic" does not include the newer targeted therapies used in cancer treatment. Since the

ISOPP Standard[15] is the only international standard that was identified, it may be helpful for the standard to become more universally accepted by defining a recognized term that includes all drugs. The approach taken by NIOSH[4] utilizing “antineoplastic and other hazardous drugs” is more inclusive and covers all types of drugs that may pose an occupational hazard and may be a more informative terminology.

In general, the majority of countries have adopted the hierarchy of controls: engineering controls followed by administrative and work practice controls and then personal protective equipment (PPE). Concerning CSTDs, some countries include them as part of, or as a supplement to, engineering controls while others consider CSTDs as a part of PPE. NIOSH recommends the use of CSTDs in conjunction with biological safety cabinets (BSC) or pharmacy isolators to reduce the risk of occupational exposure to antineoplastic drugs.[4] The USP 800 recommends the use of CSTDs for compounding and administration of chemotherapeutic drugs.[27] A review by Vyas et al. of recent studies indicate that CSTDs are highly effective in reducing surface contamination within pharmacy aseptic manufacturing areas. For this reason, the use of CSTDs in pharmacy drug preparation areas is recommended in the UK.[31] In contrast, Danish reconstitution pharmacies do not use CSTDs. In Danish hospital pharmacies, compliance is measured every two years by environmental swab sampling. The measured levels are compared to a standard based on levels measured at best practice sites that use CSTDs in reconstitution units. The levels measured in Danish reconstitution units are at the same level as those at the standard best practice sites. For this reason, Danish reconstitution pharmacies do not use CSTDs.

Conclusions

Based on this survey, the ISOPP 2007 Standard was the most frequently cited international standard, followed by the 2004 U.S. NIOSH Alert. No single guideline was consistently reported as a source or adopted standard. It would be advantageous if countries around the world adhered to a common set of safe handling recommendations. Similarly, a standardized method or protocol to determine compliance would be helpful to facilities in those countries that do not have a mechanism in place. As expected, individual circumstances in different countries have led to development of diverse recommendations over the years and these are difficult to modify. Further, even within relatively homogeneous geographical and national locals such as the European Union, the United States, and Canada, considerable differences in guidance are noted.

Acknowledgements

The authors wish to thank James M. Boiano and Chun-Yip Hon for their assistance as reviewers in the preparation of this manuscript. The authors alone are responsible for the content and writing of this paper. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH) or the Centers for Disease Control and Prevention (CDC). Mention of company names and/or products does not constitute an endorsement by NIOSH. In addition, citations to Web sites external to NIOSH do not constitute NIOSH endorsements of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these Web sites. All Web addresses referenced in this document were accessible as of the publication date.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Table 1.

Survey questions.

1	What safe handling guidelines for hazardous (antineoplastic, cytotoxic) drugs are followed in your country?
2	What classes/types of drugs are covered?
3	Are monoclonal antibodies covered in your guidelines?
4	In the hierarchy of controls, where do CSTDs fit in if they are used?
	Engineering controls
	Administrative controls
	Personal protective equipment
5	Do you have guidance for medical surveillance for healthcare workers?
	If so, what does it include?
6	Is compliance with guidelines voluntary or mandatory?
7	Do you have any measures of compliance?
8	Do you have any new changes or updates to guidance?
9	Please list any important or relevant information concerning guidance issues.

Table 2.

Contributing content experts by country, province, or territory.

Country, province, or territory	Contributor
Australia	Susan Kirsa/James Siderov
Belgium	Johan Vandenbroucke
Brazil	Annemeri Livinalli
Canada	
Alberta	Carole Chambers
British Columbia	Joan Fabbro
Manitoba	Marc Geirnaet/Claire Imlah/Barbara Sproll
Newfound and Labrador	Rick Abbott
Chile	Claudio Muller Remirez/Sara Aquayo Ulloa
Denmark	Vagn NeerupHandlos
Finland	Hanna Tolonen
France	Sylvie Crauste-Manciet
Germany	Irene Krämer
Iran	Moham. Javad ZareSakhvidi
Israel	Yaakov Cass
Italy	Roberta Turci/Felice Musicco
Japan	Toshihiro Hama/Hiromasa Ishimaru
Malaysia	Harbans Dhillon
Mexico	Elia Vazquez Rodriguez
Netherlands	Paul Sessink
Norway	Wendy Klem
Portugal	Alexandra Suspiro
Spain	Luis Mazon/Angeles Mendoza/Rosa Orriols
Sweden	Maria Hedmer/Monica Karedal
Taiwan	Shao Chiang
United Arab Emirates	Lyssette L. Cardona
United Kingdom	Stephen Langford/G.S. Sewell
United States	Thomas Connor

J Oncol Pharm Pract. Author manuscript; available in PMC 2021 February 19.

Table 3.

Safe handling guidelines for hazardous drugs by country, classes/types of drugs, inclusion on monoclonal antibodies, and CSTDs.

Country	What safe handling guidelines for hazardous (antineoplastic, cytotoxic) drugs are followed in your country?	What classes/types of drugs are covered?	Are monoclonal antibodies covered in your guidelines?	In the hierarchy of controls, where do CSTDs fit if they are included?
Australia	Individual states have voluntary work-safe guidelines South Australia-Safe Handling of Cytotoxic Drugs and Related Wastes;[9] made mandatory by Policy Directive[10] Victoria-WorkSafe Victoria: Handling Cytotoxic Drugs in the Workplace[11] Queensland—Queensland Department of Industrial Relations: Guidelines for the handling of Cytotoxic Drugs and Related Waste New South Wales—Safe Handling and Waste Management of Hazardous Drugs[12] Others include professional organizations: COSA (clinical), SHPA,[13] ISOPP Guidelines are voluntary, although they are linked by registration body to “good pharmaceutical practice”	Antineoplastic agents	No, they are covered in separate guidelines[14] Yes	Engineering controls were used
Belgium	ISOPP Standards—voluntary Mandatory hierarchic order in prevention and preparation of cytotoxic drugs in pharmacy	Cytotoxics including clinical trial drugs	Yes	Engineering controls
Brazil	RDC n° 220 published by *National* Agency for Sanitary *Vigilance Agency* (Anvisa) in 2004 RDC n° 67 published by *National* Agency for Sanitary *Vigilance Agency* (Anvisa) in 2007, NR n° 32 published by Ministry of Labor and Employment in 2005. Guidelines are mandatory	Antineoplastic and cytotoxic	No	Personal protective equipment
Canada	National—CSHP Guidelines for Sterile Preparation (under revision), CAPhO Provincial: Alberta—Based on ISOPP,[15] CAPhO-Guidelines are mandatory, National Association of Pharmacy Regulatory Authorities (NAPRA) guidance for compounding hazardous sterile drugs informed by USP800 1 February 2016 revised update enforceable. British Columbia—Provincial occupational health and safety regulations—Enforceable; Provincial safe handling standards, College of Pharmacists of British Columbia-Non-enforceable Manitoba—CSHP, NIOSH, British Columbia-Mandatory Newfoundland and Labrador—Provincial occupational health and safety regulations—Enforceable NIOSH list Ontario—Safe Handling of Cytotoxics: Guideline Recommendations[16] Quebec—Order of Pharmacists—Mandatory ASSTSAS	National—CSHP and CAPhO Provincial: Alberta—NIOSH list British Columbia—NIOSH + BCCA addendum Manitoba—NIOSH list New Brunswick, Newfoundland and Labrador—NIOSH divided into cytotoxic and non-cytotoxic, High, low risk HD lists Nova Scotia—cytotoxic drugs Quebec—NIOSH list	Alberta—Yes British Columbia—NIOSH list/BCCA addendum Manitoba—Yes New Brunswick, Newfoundland and Labrador—NIOSH list. Nova Scotia—No Quebec—NIOSH HD list	Engineering controls
Chile	International guidelines, Quapos5 and GEDEFO. Chilean guidelines “general technic norm n°25” of our health ministry. Compliance is mandatory	Antivirals, antineoplasics, cytotoxics, and monoclonal antibodies.	Yes	Personal protective equipment
Denmark	Danish Working Environment Authority guidelines for cytotoxics (December 2004)—Compliance is mandatory. Guidelines developed in collaboration by the Danish Hospital Pharmacies (February 2010) Hospital pharmacy guidelines-Voluntary	Cytotoxics (ATC L01 and medicines having a comparable risk for the operator)	Not directly	Not used
Finland	Finnish Institute of Occupational Health (2007) Guidelines are voluntary	Cytotoxics	No	Not used

Country	What safe handling guidelines for hazardous (antineoplastic, cytotoxic) drugs are followed in your country?	What classes/types of drugs are covered?	Are monoclonal antibodies covered in your guidelines?	In the hierarchy of controls, where do CSTDs fit if they are included?
France	(Bonnes Pratiques de Préparation-AFSSAPS JO du 21/11/2007)[17] Guidelines are mandatory	All toxic/hazardous drugs (chemical and biological)	No	Not specifically recommended
Germany	German National law, TRGS 905 Framework directive: 89/391/EEC for occupational safety and health German hazardous substances ordinance German Guideline: TRGS 525 Guideline for handling hazardous drugs in healthcare facilities Guidelines are mandatory Revised by German committee on hazardous substances effective 7/2015	Medicinal products with Carcinogenic, Mutagenic or Toxic to Reproduction (CMR) activity Medicinal products without CMR activity	No	Engineering controls ~50% of facilities
Iran	APHON, ASHP, ISOPP Guidelines are mandatory	Alkylating agents, antimetabolites, hormones, and antagonists	Yes	Engineering controls
Israel	Israeli comprehensive guidelines on safe handling and administration of cytotoxics which is mandatory	Conventional antineoplastic agents	Future guidelines are forthcoming	Personal protective equipment
Italy	*PROVVEDIMENTO 5 agosto 1999*—Documento di linee-guida per la sicurezza e la salute dei lavoratori esposti a chemioterapici antiblastici in ambiente sanitario (Repertorio atti. n. 376) (*Pubblicato sulla Gazzetta Ufficiale n. 236 del 7 ottobre 1999*) "Guidelines for the Safety and Health of Health Care Workers Exposed to Antineoplastic Drugs" Guidelines are mandatory	Antineoplastic drugs, with particular attention to those classified by the IARC	No	Engineering controls
Japan	Aseptic compounding guideline for injectable drugs and antineoplastic drugs—2007 by JSHP Compounding manual for antineoplastic drugs—2008. Guidelines are voluntary and no recommendation by any governmental organization	Antineoplastic drugs	No	Personal protective equipment
Malaysia	NIOSH, ISOPP Guidelines are voluntary	NIOSH list	Yes	Yes. Generally used when there are no clean rooms
Mexico	Regulation for compounding centers-NORMA Oficial Mexicana NOM-249-SSAI-2010, Mezclas estériles: nutricionales y medicamentosas, e instalaciones para su preparación Guidelines are mandatory	Cytotoxics. penicillins, cephalosporins, cytotoxics, hormonals, immuno-suppressing drugs of biological origin and others considered as high risk	No	Yes. Not specifically designated as CSTDs; "use of equipment and appliances specialized in compounding"
Netherlands	EU Directives (chemicals, labor, safety, etc.) Netherlands: labor working conditions, chemicals, safety laws (Arbowet/Arbobesluit) Employer-employee agreements (Arbocatalogus) Protocols Quality Manual Cytostatic Drugs 2011 Compliance to guidelines is mandatory	Hazardous drugs (cytotoxic drugs (primarily), carcinogens, mutagenic drugs, reprotoxic drugs, sensitizing drugs, radioactive drugs.	Yes	Engineering controls
Norway	Law on the work place. (Arbeidsmiljøloven, inkl. forskrift 1355 "forskrift om organisering, ledelse og medvirkning, kap. 14") FOR 2014-02-24-207 forskrift 1357 "forskrift om utførelse av arbeid, kap 3.20 og 3.21"). Ministry of Labour and Social Affairs. Guidelines are voluntary, but compliance is high	Cytotoxic drugs, monoclonal antibodies, hazardous substances for extemporaneous production	No	Not used
Portugal	ISOPP—Guidelines are voluntary	Cytotoxic drugs	No	Engineering controls

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Country	What safe handling guidelines for hazardous (antineoplastic, cytotoxic) drugs are followed in your country?	What classes/types of drugs are covered?	Are monoclonal antibodies covered in your guidelines?	In the hierarchy of controls, where do CSTDs fit if they are included?
Spain	*NIOSH guidelines and specific protocols developed in each hospital.* *Guidelines are mandatory*	Cytostatic drugs, antibodies, antibiotics	Yes	Engineering controls
Sweden	Ordinance in original AFS 2005:5, amendment provision AFS 2009:6, cytostatic drugs and other drugs with permanent toxic effects, The Swedish Work Environment Authority, Stockholm, Sweden, 2005/2009—Guidelines are mandatory	Cytostatic, cytotoxic, and sensitizing drugs	Yes	Engineering controls
Taiwan	Safe handling for anti-neoplastic hazardous drugs: A multidisciplinary consensus guidelines in Taiwan Guidelines are voluntary	Cytotoxic antineoplastic agents, agents for hormonal therapy, small molecular target therapy.	No	Engineering controls
United Arab Emirates	NIOSH—Guidelines are mandatory	Antineoplastics, antibiotics	No	Not known
United Kingdom	No official guidelines—individuals/institutions have developed own guidelines from literature. ISOPP and UK Health and Safety Executive (HSE) HSE is mandatory	Cytotoxic	Yes	Personal protective equipment
United States	Federal OSHA (1995)—can be enforced NIOSH (2004)—Voluntary organizational ASHP (2006)—Voluntary USP 800 (2008)—Enforced by some State Boards of Pharmacy ONS (2011)—Voluntary state Washington (2012) mandatory California (2013) mandatory New Jersey (2017) mandatory North Carolina (2014) mandatory	Federal and organizational (NIOSH, OSHA,USP) Hazardous drugs including antineoplastic drugs State Washington California North Carolina, New Jersey Antineoplastic and other hazardous drugs	OSHA (2016)[18] NIOSH (2016)	NIOSH: Engineering Controls USP 797: Engineering controls Washington, California, and North Carolina follow NIOSH guidelines in 2004 Alert

APHON: Association of Pediatric Hematology/Oncology Nurses (US) (http://www.aphon.org); ASHP: American Society of Health-System Pharmacists (US) (http://www.ashp.org); ASSTSAS: Association paritaire la santé et al sécurité du travail du secteur affairs sociales (http://www.asstsas.qc.ca/); ATC: Anatomical Therapeutic Chemical Classification System (http://en.wikipedia.org/wiki/Anatomical_Therapeutic_Chemical_Classification_System); BCCA: British Columbia Cancer Agency (http://www.bccancer.bc.ca/default.htm); Berufsgenossenschaft für Gesundeitsdienst und Wolhfahrtspfege (https://www.bgw-online.de/DE/Home/home_node.html;jsessionid=33CB9AC38B8C54DF54163F1795CDFF77.live2); BSC: biological safety cabinet; CaPhO: Canadian Association of Pharmacy in Oncology (http://www.capho.org/); COSA: Clinical Oncological Society of Australia (http://www.cosa2014.org/); CMR: Carcinogen, Mutagenic or Toxic to Reproduction; CSHP: Canadian Society of Hospital Pharmacists (http://www.cshp.ca/); CSPs: Compounding Sterile Preparations; GMPs: Good Manufacturing Practices; IARC: International Agency for Research on Cancer (http://www.iarc.fr); ISOPP: International Society of Oncology Pharmacy Practitioners (http://www.isopp.org); JSHP: Japanese Society of Hospital Pharmacists (http://www.jshp.or.jp/); NIOSH: National Institute for Occupational Safety and Health (http://www.cdc.gov/niosh/); ONS: Oncology Nursing Society (http://www.ons.org); OSHA: Occupational Safety and Health Administration (US) (https://www.osha.gov); PIC/S: The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (http://www.picscheme.org/); PPE: personal protective equipment; SHPA: Society of Hospital Pharmacists Australia (http://www.shpa.org.au/SHPA/ccms.r); SWEA: Swedish Work Environment Authority (https://www.av.se/); USP Chapter 797: (http://www.usp.org/usp-healthcare-professionals/compounding); VPA: Victorian Pharmacy Authority (http://www.pharmacy.vic.gov.au/); WorkSafe BC: (http://www2.worksafebc.com/en/health-care-providers); WorkSafe Victoria (http://www.worksafe.vic.gov.au/forms-and-publications/forms-and-publications/handling-cytotoxic-drugs-in-the-workplace).

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Table 4.

Do you have guidelines for medical surveillance for health care workers? If so, what does it include?

Country	
Australia	Yes. Individual institutions may have their own recommendations and procedures
	Work-safe practices have general guidance for health surveillance of workers
	No specific guidelines for handling chemotherapy
	SHPA Standards of Practice
Belgium	Yes. Yearly medical exam including blood counts, kidney, and liver function test
Brazil	Yes. Any health service is obligated to maintain a Program for Medical Control of Occupational Health.
	It includes periodical clinical evaluation, occupational history, physical examination; Supplementary examinations (medical criteria)
Canada	Provincial:
	Alberta—No
	British Columbia—Yes. Recommended routine medical exam with personal physician, records of preparation, and handling activities
	Manitoba—No
Chile	Yes. Each hospital has a monitoring program of occupational preventive medicine for workers that handle cytotoxic drugs that includes a CBC and physical examination.
Denmark	No
Finland	No
France	Yes. GMPs recommend general medical surveillance for operators, adapted and on a regular basis. Immunologic follow-up, cutaneous, mucous, sensitization risk, genotoxic and reproductive effects. Any injury involving toxic drug is registered in the medical report of the operator.
Germany	Yes, offer preventive health checks and general medical examinations.
Iran	Yes. NIOSH/CDC[26]
Israel	Yes. Regular health checks including yearly X-ray and blood tests.
	Spillage reports entered on the pharmacist's medical records.
Italy	Yes. Medical (including reproductive) and occupational history, and health advice.
	Physical examination if indicated.
	Records of personal exposure.
	Laboratory studies and biological monitoring, including specific analysis for antineoplastic drugs in use (usually cyclophosphamide, 5-fluoruracil, and Pt-compound)
Japan	No
Malaysia	Yes. Usually full blood count, liver and renal function tests.
	Not all hospitals do health surveillance.
Mexico	Yes. Medical examination every six months for compounding staff.
	The examination must include laboratory tests necessary for the surveillance of staff who are in contact with drugs cytostatic.

Country	
Netherlands	Yes. Mandatory, but not known how to perform or what is relevant.
	Focus on prevention by area monitoring
	Wipe sampling for cytostatic drugs.
	Contamination criteria after cleaning
Norway	Yes. Company rules.
	Initial checkup to establish a baseline, then followed up by medical checkups every three years.
Portugal	No universal guidance. Occupational health physicians design their own program.
Spain	Yes. Annual medical examinations.
Sweden	No
Taiwan	Yes. Required clinical analyses are complete blood count, creatinine and liver function, and urinary analysis.
United Arab Emirates	Yes. Pre-employment screen, annual medical exam by primary health care physician. Reproductive health surveillance and annual fitness to work screen by occupational health nurse.
United Kingdom	Yes. Follow local guidelines.
United States	Yes. NIOSH/CDC[29]
	Reproductive and general health questionnaires completed at the time of hire and periodically thereafter.
	History of drug handling as an estimate of prior and current exposure.
	A plan to provide initial baseline clinical evaluation, including appropriately targeted medical history, physical examination, and laboratory testing for workers identified as being potentially exposed to hazardous drugs that anticipates their potential toxicities.
	A follow-up plan as needed for workers who have shown health changes suggesting toxicity or who have experienced an acute exposure.
	OSHA (2016)[18]

SHPA: Society of Hospital Pharmacists Australia; GMPs: Good Manufacturing Practices; NIOSH: National Institute for Occupational Safety and Health; CDC: Centers for Disease Control and Prevention; OSHA: Occupational Safety and Health Administration.

Table 5.

Is compliance with guidelines voluntary or mandatory? Do you have any measures of compliance?

Country	
Australia	Compliance is voluntary.
	No measures of compliance
	Last Victorian review of compliance measures done in the early 1990s.
	Victorian Pharmacy Authority inspections include review of engineering controls and cursory review of procedures.
Belgium	Compliance is voluntary.
	Yes. Compliance to preparation in pharmacy (100%).
	ISOPP standards (70%).
	Hierarchic order (50%—but with wide variations).
Brazil	Compliance is mandatory
	No measures of compliance
Canada	Alberta—Mandatory. Yes. Annual certifications for ongoing compliance and individual audits
	British Columbia—Mandatory. Yes. BCCA affiliated pharmacy certification
	Manitoba—Mandatory. Yes. Spot audits, and yearly training
	Nova Scotia—Yes. For cytotoxics
Chile	Compliance is mandatory. Yes. The department of risk supervises this.
Denmark	Compliance is mandatory. Yes. Surface contamination with cyclophosphamide and ifosfamide is measured approximately every second year at all hospital pharmacies. Measured values are compared to a standard based on best practice and deviations from this are discussed and initiatives to change are carried out.
Finland	Compliance is voluntary. No measures of compliance.
France	Compliance is mandatory. Implemented by inspection campaign.
Germany	Compliance is mandatory. Implemented through pharmacy inspections.
Iran	Compliance is mandatory. Yes, as a part of other standard operating procedures.
Israel	Compliance is mandatory. Full compliance as reported in annual relicensing of all hospitals, pharmacies, etc.
Italy	Compliance is mandatory. Periodic surveys are carried out to assess exposure and contamination levels in workplaces.
	Environmental monitoring is the main tool for the collection of exposure data and for effective intervention. Compliance with guidelines is not assessed regularly, especially in small healthcare centers.
	Environmental monitoring usually includes wipe tests and analysis of gloves.
	Biological monitoring commonly means analysis of one or two “reference” drugs.
Japan	Compliance is voluntary. No, because pharmacists understand the risk of exposures, the adherence rate is relatively high.
Malaysia	Compliance is voluntary. No measures of compliance.

Country	
Mexico	Compliance is mandatory. Yes. A survey which is conducted by an Inspector, to approve or decline the license for compounding activity.
Netherlands	Mandatory under European Union directives, Dutch law, and between employer and employee agreements.
	Yes, the Report Health Care Inspectorate concerning preparation and administration of cytostatic drugs in 18 Dutch Hospitals.
Norway	Compliance is voluntary.
Portugal	Compliance is voluntary. No organized or periodic measures for compliance.
Spain	Compliance is mandatory. Implemented in part through medical surveillance and periodic risk assessments.
Sweden	Compliance is voluntary. The SWEA inspects workplaces that handle cytotoxic drugs and cytotoxic agents.
	Use voluntary hygienic guidance values for surface monitoring.
Taiwan	Compliance is voluntary. Compliance not measured.
United Arab Emirates	Compliance is mandatory. No measures described.
United Kingdom	Compliance is voluntary. No measures of compliance.
United States	OSHA, NIOSH, ONS, and ASHP.
	Washington, California, and North Carolina not active
	USP 800 is enforced by approximately one-half of the states

ISOPP: International Society of Oncology Pharmacy Practitioners; BCCA: British Columbia Cancer Agency; SWEA: Swedish Work Environment Authority; OSHA: Occupational Safety and Health Administration; NIOSH: National Institute for Occupational Safety and Health; ONS: Oncology Nursing Society; ASHP: American Society of Health-System Pharmacists; USP: U.S. Pharmacopeia.

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Table 6.

Do you have any new changes or updates to guidance? Please list any important or relevant information concerning guidance issues.

Country	
Australia	SHPA Standards of Practice for the Safe handling Guidelines 2005 are being updated[13]
	New monoclonal antibody handling guidelines published
	Changes to clean room design
	Now 4 CSTD in Australian market (PhaSeal, Clave/Genie, Equashield, Carefusion's Chemo Safety System)
Belgium	PIC/S have been established by legislation
	Huge investment costs for all hospitals
	Outsourcing will start
	Frequency of controls and actions in function of wipe sampling
Brazil	New information was published in the last 10 years, we have more monoclonals to treat cancer than before, both intravenous and oral.
Canada	Alberta—Use of robotics, routine workplace contamination monitoring and outsourcing
Chile	New guidance from the Ministry of Health not yet official; local guidance that is continuously revised.
	All staff in cytotoxic preparation areas must use PPE, use proper waste disposal, and follow aseptic procedures.
Denmark	No new guidance planned at this time.
Finland	New guidelines are under preparation.
France	No new guidance planned at this time.
	Specific recommendations are also given for transport of toxic preparations and management of wastes
	Current issues include validation of the cleaning.
	Sometimes guidelines are general and need interpretation from the regional inspection authorities, which can be different from a region to another.
Germany	No new guidance planned.
	Discussions about hazardous character of monoclonal antibodies, flat dosing, and dose banding as measures to reduce pharmacy compounding of ready-to-administer products.
Iran	Hospitals formally should engage such measures in their periodic assessment schedules. There is variation in terms of level of compliance, protection status, and other safety policies across provinces and between governmental and private hospitals.
Israel	Monoclonal antibodies and targeted therapies are planned to be included in the future.
	Current and future issues include home treatment, ambulatory treatment locations, and intrathecal administration of chemotherapy.
Italy	Changes have been made to the original text. The main points are listed below.
	All therapies must be prepared in one central area. The preparation room must be protected by an anteroom. BSCs with high efficiency particulate air (HEPA) filters must be used, if not isolators. Periodic engineering controls must be carried out. Additional equipment, such as closed-system drug-transfer devices, glove bags, and needle-less system must be used. PPE must be worn.
	Written safe working policies and procedures must be developed in consultation with health and safety representatives. Job instruction, information, and training must be provided.
	Health surveillance and exposure assessment including both biological and environmental monitoring are also included.

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Country	
	Periodic assessments must be scheduled to verify compliance with guidelines.
	The main challenges of compliance in this regulatory framework are: a lack of a standardized monitoring system. interpretation of the analytical results from biological and environmental monitoring. a lack of standardized effective decontamination procedures.
Japan	Revision of “Compounding manual for antineoplastic drugs” is in process
	Would be written to conform to ISOPP standards
	“Safe handling guideline of Hazardous Drugs” is ongoing with many challenges
	“Sampling Sheet” method is popular now for environmental measurement compared to traditional wipe testing.
Malaysia	New guidelines are in preparation. At present, the issue is that are no standardized guidelines to follow. The Ministry of Health has their own guidelines, while our Ministry of Education has none.
Mexico	New guidelines are under preparation.
	This standard establishes the minimum requirements for quality in CSP’s by prescription to use for the patients, as well as the minimum requirements that must be met all the establishments engaged in compounding and dispensing. This standard is mandatory for all establishments engaged in the preparation and dispensing of sterile preparations.
Netherlands	Continuous updates on national level based on literature and experience
	Report Health Care Inspectorate (2014)
	Multi-disciplinary approach mainly focused from Occupational Health and Safety perspective
	EU protocol bladder instillation
Norway	New guidelines are under preparation.
Portugal	No changes in guidance.
	The safe handling guidelines are applied only in major hospitals in large cities. In small towns with small hospitals the manipulation of antineoplastic drugs is made under still largely unknown and probably hazardous conditions.
Spain	Yes. Introduction of CSTDs in hospitals and primary health centers as per guidance.
	Level of health consequences in case of unwanted exposures Novedoso Sistema de Abordaje que Hemos Denominado (NICOSEND), which is directly proportional to the frequency of handling antineoplastics in the workplace, and to the possibility of damage depending on the complexity of the task, considering there is no such thing as zero risk.
Sweden	2005 ordinance updated in 2009.
	Many workplaces, e.g. hospitals, have hospital-wide guidelines for the handling of cytotoxic drugs and cytotoxic agents based on the ordinances Statute Book of the Swedish Work Environment Authority/Statute Book of the Swedish National Board of Occupational Safety and Health AFS 2005: 5 and AFS 2009: 6.
	Hygienic guidance values for wipe sampling of antineoplastic drugs in Swedish hospitals can be applied.[30]
Taiwan	Yes, revision to include Types II A2, B1, and B2 as appropriate BSCs
	Reviewing purpose of surgical mask in preparing injectables
United Arab Emirates	Awaiting 2015 updates. There is a need to better describe medical surveillance to determine if clinical urinalysis and blood counts are warranted.
United Kingdom	New guidelines based on ISOPP are under review.
United States	NIOSH updating Alert on Hazardous Drugs (2015)

Country	
	NIOSH hazardous drug list updated (2016)
	NIOSH reformatted the list of hazardous drugs
	Antineoplastic drugs
	Non-antineoplastic hazardous drugs
	Reproductive hazards
	USP 800 HD handling will be removed from Chapter 797 to become USP 800[28]
	OSHA 2016[18]

SHPA: Society of Hospital Pharmacists Australia; CSTD: closed system drug-transfer device; PIC/S: The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme; PPE: personal protective equipment; BSC: biological safety cabinet; ISOPP: International Society of Oncology Pharmacy Practitioners; CSPs: Compounding Sterile Preparations; NIOSH: National Institute for Occupational Safety and Health; USP: U.S. Pharmacopeia; OSHA: Occupational Safety and Health Administration.