PREVENTION AND PROTECTION SYSTEM IN HEALTH FACILITIES FOR ACTIVITIES INVOLVING HAZARDOUS NON-ONCOLOGICAL DRUGS

Preparation and administration under current legislation

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SUMMARY

INTRODUCTION

A thorough examination of Italian national legislation in force, i.e., Legislative Decree 81/2008, as amended, which implemented EU Directives on hygiene and safety in the workplace, shows that, with regard to preparation and administration activities, hazardous non-oncological drugs must be considered exposure factors to chemical agents that can cause harm to the health of health personnel, in relation to the provisions of Title IX "Hazardous Substances" of the aforementioned legislation.

Title IX defines hazardous chemical agents (art. 222, paragraph 1, letter b), point 1) as substances and mixtures that meet the criteria for classification as hazardous in one of the physical hazard classes and health hazard categories referred to in the CLP Regulation[1] (Classification, Labelling and Packaging), as well as agents that, although not classifiable as hazardous under the CLP, involve a risk to the safety and health of workers due to their chemical, physical or toxicological properties and the way they are used or present in the workplace, including chemical agents that have been assigned an occupational exposure threshold value, included in Annex XXXVIII of Italian Legislative Decree 81/08, as amended. (Art. 222, paragraph 1, letter b), point 3).

In this regard, it should be noted that for hazardous substances and mixtures to which the CLP Regulation[1] does not apply (e.g., endocrine disruptors, antineoplastic drugs, polymers), but which meet the criteria for classification as category 1A and 1B carcinogens or mutagens in accordance with the provisions of Annex I to the CLP Regulation, the provisions of Chapter II "Protection from carcinogens and mutagens" of Title IX "Hazardous substances" of Italian Legislative Decree no. 81/2008, as amended, apply. The interest aroused by the issue of antineoplastic drugs, which fall into the category of drugs at "high risk or high level of attention" due to their potential toxicity and teratogenicity, as well as the possible mutagenic and carcinogenic effects attributable to some of them, has also led over the years to the publication of ministerial decrees and various documents on the technical application of regulatory provisions at national level.[1-2] They have set out the prevention and protection measures that employers must implement, for workers involved in the handling of antineoplastic drugs, *relating to organisational and productive changes that affect health and safety in the workplace or relating to the level of evolution of prevention and protection technology*, pursuant to Title I, Chapter III, art. 18, paragraph 1, letter z. It should also be considered that the obligations under Title I, Chapter III, Art. 18, paragraph 1, letter l of Italian Legislative Decree 81/08, as amended, of information, education and training (referred to in Title I, Chapter 3 Section 4, Articles 36 and 37 of Legislative Decree 81/08, as amended) and health surveillance of workers are essential to achieve the objective of maintaining occupational exposure to chemotherapy drugs *as low as reasonably achievable*, or ALARA.

1 Regulation (EC) No. 1272/2008 of 16 December 2008 (Classification, Labelling and Packaging, CLP).

2 Decree of the Italian Ministry of Health of 18 February 1999 "*Modificazioni del regime di fornitura dei medicinali antiblastici iniettabili*" (OJ, General Series no. 47 of 26 February 1999) ('Annex 1 "*Farmaci iniettabili antiblastici: motivazioni per la limitazione all'uso ospedaliero*").

3 Provision of 5 August 1999 of the Italian Permanent Conference for Relations between the State and Regions, (OJ no. 236 of 7 October 1999) "*Documento di linee guida per la sicurezza e la salute dei lavoratori esposti a chemioterapici antiblastici in ambiente sanitario*" (record folder no. 736).

4 Document, published in May 2010, by ISPESL "*Le Indicazioni per la tutela dell'Operatore Sanitario per il rischio di esposizione ad antiblastici*".

5 "*Raccomandazione per la prevenzione degli errori in terapia con farmaci antineoplastici*", Italian Ministry of Health (no. 14, October 2012).

6 Technical document of the Standing Advisory Commission for workplace health and safety (approved at the meeting of 28 November 2012) "*Criteri e strumenti per la valutazione e gestione del rischio chimico negli ambienti di lavoro ai sensi del D.Lgs. n. 81/2008 e s.m.i. (Titolo IX, Capo I "Protezione da Agenti Chimici" e Capo II "Protezione da Agenti Cancerogeni e Mutageni"), alla luce delle ricadute del Regolamento (CE) n. 1907/2006 (Registration Evaluation Authorisation Restriction of Chemicals - REACH), del Regolamento (CE) n. 1272/2008 (Classification Labelling Packaging - CLP) e del Regolamento (UE) n. 453/2010 (recante modifiche all'Allegato II del Regolamento CE 1907/2006 e concernente le disposizioni sulle schede di dati di sicurezza*") to which Title IX of Legislative Decree No. 81/08, as amended, refers (external link) (http://sitiarcheologici.lavoro.gov.it/SicurezzaLavoro/Documents/Documento_agenti_chimici_09012013.pdf).

7 Document of the SIFO (Italian Society of Hospital Pharmacy and Pharmaceutical Services of Health Authorities) "*Linee di indirizzo tecnico - La tutela dell'operatore sanitario a rischio di esposizione ai farmaci antiblastici* "(Ed. Il Campano, October 2015).

8 Italian Consensus Document "*Gestione del rischio di esposizione del personale sanitario nella manipolazione dei farmaci antineoplastici iniettabili: gli aspetti di prevenzione e la caratterizzazione delle misure di sicurezza*" (OIC Group Scientific Press, April 2017).

1. HAZARDOUS DRUGS

Some non-oncological drugs have toxic properties similar to those of antineoplastic drugs. Documents from the U.S. National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Agency (OSHA), as well as numerous international studies indicate that, in addition to various antineoplastic drugs, some antiviral agents (e.g., ganciclovir), biotechnological drugs and antibiotics (e.g., chloramphenicol) may also interfere with the cell cycle or DNA synthesis. For some other drugs, toxic effects on reproduction represent the main occupational hazard.

Hazardous non-oncological drugs are commonly used for a variety of clinical indications, from rheumatic diseases to the prevention of organ transplant rejection.

The NIOSH definition of "hazardous drugs" is based on the definition developed in 1990 by the American Society of Hospital Pharmacists (ASHP), now known as the American Society of Health-System Pharmacists.

In 1990, the ASHP revised the "Technical Assistance Bulletin on Handling Hazardous Drugs" (ASHP 1990) and set out the criteria determining the hierarchy of potential toxicity to identify potentially hazardous drugs in order to allow for their handling (from preparation, through administration, to disposal) according to a well-defined procedure to protect the health of professionally exposed workers.

In accordance with the definition formulated by the ASHP, NIOSH defines a drug as being hazardous if it has one or more of the following characteristics:

- *carcinogenicity*, i.e., the ability to cause or promote the development of cancer;
- *teratogenicity*, i.e., the ability to cause congenital foetal malformations;
- *toxicity to the reproductive system*, i.e., the ability to impair fertility (causing miscarriage, foetal death, infertility);
- *genotoxicity*, i.e., the ability to damage DNA, causing mutations;
- *organ toxicity*, i.e., the ability to cause significant toxic effects on organs at low doses;
- *chemical structure and toxicological profile* similar to those of a drug recognised as hazardous according to the above criteria.

Among the various sources cited by NIOSH in its procedures for identifying the toxicity of hazardous drugs is also the classification given by the International Agency for Research on Cancer (IARC). It divides carcinogens into different groups based on their carcinogenicity.[9]

In the 2004 document "*NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings*," the definition of hazardous drugs was expanded to include other characteristics related to additional developmental disorders and reproductive toxicity. The lists of drugs considered hazardous were subsequently updated in the 2010, 2014, and 2016 NIOSH documents and most recently in the 2020 document (*NIOSH List of Hazardous drugs in Healthcare Settings*, 2020), hereinafter referred to as the "*List*," which, though not mandatory for employers, is a guideline for ensuring the safety of workplaces where drugs considered hazardous are handled, according to the criteria set out by NIOSH.

NIOSH formalised the methodology followed for modifying the 2020 list of hazardous drugs as part of the document "*Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures)*" (NIOSH, 2020).

It is worth pointing out here the conceptual distinction between the terms "antineoplastic" and "cytotoxic": the former covers any agent used to treat cancer (e.g., cytotoxic drugs, hormones, immunomodulants, biotechnological drugs, etc.), and the latter any agent capable of interrupting cell growth and function of both healthy and diseased cells.

The approach in the NIOSH document "*List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016*" considered three types of drugs divided into the following groups:

- Group 1: Antineoplastic drugs (many of these drugs may also pose a reproductive risk for susceptible populations).
- Group 2: Non-antineoplastic drugs that meet one or more of the NIOSH criteria for a hazardous drug (some of these drugs may also pose a reproductive risk for susceptible populations).

9 Group 1: 'Carcinogenic to humans': a category reserved for substances with sufficient evidence of carcinogenicity to humans.
Group 2, divided into two subgroups:
2A: 'Probably carcinogenic to humans': a category reserved for substances with limited evidence of carcinogenicity to humans and sufficient evidence for animals. Exceptionally, also substances for which there is either only limited evidence for humans or only sufficient evidence for animals provided that it is supported by other relevant data.
2B: "Possibly carcinogenic to humans": used for substances with limited evidence for humans in the absence of sufficient evidence for animals or for those with sufficient evidence for animals and inadequate evidence or no data for humans. In some cases, substances with only limited evidence for animals can be included in this group as long as it is firmly supported by other relevant data.
Group 3: "Not classifiable as to its carcinogenicity to humans": this group includes substances that do not fall into any of the other categories.
Group 4: "Not carcinogenic to humans": substances with evidence of non-carcinogenicity to both humans and animals. In some cases, substances with inadequate evidence or no data for humans but with proven absence of carcinogenicity to animals, firmly supported by other relevant data, may be included in this category.

- Group 3: Drugs that primarily pose a reproductive risk to men and women who are actively trying to conceive and women who are pregnant or breast feeding, but do not pose a risk to the rest of the population.

Tables 1, 2 and 3 of the aforementioned document provide the lists of drugs classified as hazardous according to one or more criteria established by NIOSH for Groups 1, 2 and 3 above. The classification assigned by IARC is also indicated for some of these.
In the NIOSH document drawn up in 2020 (*List of Hazardous drugs in Healthcare Settings, 2020*), the breakdown of drugs into categories was changed and they are now divided into:

- drugs that meet the NIOSH definition of a hazardous drug and contain *Manufacturer's Special Handling Information* (MSHI) in the package insert; and/or are classified by the National Toxicology Program (NTP) as "known to be a human carcinogen" or classified by IARC as "carcinogenic" or "probably carcinogenic."
- drugs that meet one or more of the NIOSH definition of a hazardous drug but are not drugs which have MSHI or are classified by the NTP as "known to be a human carcinogen," or classified by the IARC as "carcinogenic" or "probably carcinogenic".

In addition, 16 drugs were added to the tables listing hazardous drugs and five were removed from the list in the previous document. The updated 2020 list took into consideration drugs that were approved or received new safety advisories from the Food and Drug Administration (FDA) during the period between January 2014 and December 2015.

However, the concept of hazardous drug provided by NIOSH cannot be intuitively applied to the toxicity properties associated with some new generation drugs, such as biotechnological drugs. New biologicals act at the molecular level and their interaction with cellular targets and the resulting consequences at the nuclear level are not clearly understood, so the effects of possible prolonged exposure are not fully predictable. Anyhow, in the absence of reliable scientific evidence allowing a thorough risk assessment, current Italian legislation (i.e., Legislative Decree 81/2008, as amended) requires the adoption of the precautionary principle by the employer, by virtue of the priority that is given to workers' health. Therefore, also in view of their increasing use, occupational exposure to biological drugs should be avoided, even in the absence of scientific evidence of the exact type of damage to health.
In any case, in the assessment of occupational risk, the qualitative information related to the intrinsic toxicity of a drug must be complemented by the identification of the risk of exposure, i.e., the quantitative estimate of exposure related to the specific activity carried out in the various healthcare settings and to the way operators performs it.
Therefore, in order to characterise the exposure scenarios, the following should be taken into account:

- the type of formulation and consequent method of handling (tablets/capsules, oral solution, solution for injection, etc.);
- the route of administration;
- the potential route of absorption;
- the frequency of exposure (directly related to the extent of use);
- safety measures already in place and those to be implemented.

Legislative Decree 81/2008, as amended, requires that a risk assessment should be carried out and that all safety measures should be implemented. Consequently, as part of the handling of hazardous drugs, the above process requires careful consideration of the inherent and functional properties and characteristics of these drugs, administration procedures, therapy management, and verification of how exposure occurs.
In 2019, the European Biosafety Network (EBN) pointed out that the safe management of the handling of hazardous drugs has not been fully achieved yet in healthcare facilities around the European Union and that, therefore, at-risk conditions of exposure to these drugs have been identified for staff in many healthcare and hospital settings, making it imperative to complete the implementation of all prevention and protection measures in relation to the current technological offering and today's advances in the state of knowledge of the scientific community.
Lastly, with regard to EU legislation in the sector, *Directive 2019/983 EU of the European Parliament and of the Council of 5 June 2019* (Official Journal of the European Union of 20 June 2019) amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work(*transposed into Italian national law, together with EU Directive 2019/130, by Ministry of Labour and Ministry of Health decree of 11 February 2021*) is extremely interesting.
The Directive specifically emphasises the following considerations "[...] *Hazardous drugs, including cytotoxic drugs primarily used for cancer treatment, could have genotoxic, carcinogenic or mutagenic properties. It is therefore important to protect workers who are exposed to such drugs through work involving: the preparation, administration or disposal of hazardous drugs, including cytotoxic drugs; services related to cleaning, transport, laundry or waste disposal of hazardous drugs or of materials contaminated by such drugs; or personal care for patients treated with hazardous drugs. Hazardous drugs, including cytotoxic drugs, are subject to Union measures providing for minimum requirements for the protection of health and safety of workers, in particular those provided for in Council Directive 98/24/EC. Hazardous drugs that contain substances that are also carcinogens or mutagens are subject to Directive 2004/37/EC. The Commission should assess the most appropriate instrument for ensuring the occupational safety of workers exposed to hazardous drugs, including cytotoxic drugs [...]*"

In this regard, in this Directive the Commission had provided (by adding a new paragraph to art. 18a of Directive 2004/37/EC), taking into account the latest developments in scientific knowledge and after appropriate consultation with stakeholders, in particular health professionals, to assess (by 30 June 2020) "[...] *the option of amending this Directive in order to include hazardous drugs, including cytotoxic drugs, or to propose a more appropriate instrument for the purpose of ensuring the occupational safety of workers exposed to such drugs. On that basis, the Commission shall present, if appropriate, and after consulting management and labour, a legislative proposal.*"

2. COLLECTIVE AND INDIVIDUAL SAFETY MEASURES (PERSONAL PROTECTIVE EQUIPMENT, PPE): IMPLEMENTATION AND ROLLOUT IN HEALTHCARE SETTINGS

As illustrated in the paragraph above, it follows that, in order to implement the provisions of the regulations in force and to put in place all the safety measures, it is necessary to carefully consider the provisions of art. 15 "General protection measures", paragraph 1, letter c) of Italian Legislative Decree 81/2008, which sets out "the elimination of risks in relation to the knowledge acquired through technical progress and, where this is not possible, their reduction to a minimum," as well as of paragraph 1, letter z) of art. 18 of said decree that indicates that among the obligations of the employer and manager it is the employer's duty to "*update the prevention measures [...] in relation to the state of evolution of prevention and protection technology.*"

2.1 Hazardous drug preparation environments

It is preferable to allocate dedicated rooms for the preparation of hazardous drugs and, if feasible at the facility, to centralise such preparation as in the case of antineoplastic drugs.
They should preferably be located in the Hospital Pharmacy and in any case fall under the coordination and responsibility of the Hospital Pharmacist.
If it is possible to have a preparation room, it must have negative pressure compared to the surrounding areas of lower class, see for example the "SIFO Standards - Oncological Galenics."
In these rooms it is advisable to make at least six effective air changes per hour (calculated with the recovery time formula) to prevent the concentration of these drugs in the air.

2.2 Collective prevention and protection measures

2.2.1 Equipment for Preparation:

2.2.1.1 Healthcare facilities that prepare primarily unclassified and unclassifiable carcinogenic and/or mutagenic drugs

- *Fume Hoods*

Preparation must be carried out under a chemical fume hood, manufactured and installed in accordance with technical standard EN 14175.
A copy of the certification issued to the manufacturer must be requested in order to ascertain the appropriateness of this safety measure in relation to the specific provisions of Italian Legislative Decree 81/2008, as amended.
The fume hood requires periodic maintenance and inspections of its efficiency and performance in order to protect operators, in compliance with the provisions of said technical standard, and the persons carrying out this activity must therefore issue appropriate documentation also certifying the method of execution.
In healthcare facilities, it is usually difficult, for organisational reasons, to carry out any maintenance and periodic checks on the hood at short intervals using the method indicated above; therefore, facilities prefer to channel the exhaust air through ducts to the outside. In the event that the facility has substantial difficulty in implementing such ductwork, periodic maintenance and inspections of the equipment should be carried out at least every 4-5 months.

2.2.1.2 Healthcare facilities that prepare primarily drugs that are classified or classifiable as carcinogens and/or mutagens

- *Fume Hoods*

In healthcare facilities where it is necessary to prepare drugs classified or classifiable as carcinogenic and/or mutagenic (such as in laboratory environments where, for example, formaldehyde and/or other carcinogenic compounds or asbestos fibres are handled) periodic maintenance, both ordinary and extraordinary, particularly with regard to the replacement of filtering units, determines the contamination of the premises, surfaces therein, and various types of materials, devices, instruments and equipment.
It should also be borne in mind that often times, in order to curb costs, these operations are contracted out to so-called global service companies and providers, which may therefore lack specific technical expertise in the management of such equipment, thus causing a more pronounced contamination.
In this regard, considering the aforementioned articles 15 and 18 of Italian Legislative Decree 81/2008, as amended, it should be pointed out that it is possible to use hoods equipped with specific pre-treatment systems for filtering units that can prevent said contamination. This equipment, with valid EN 14175-3 certification for containment, allows that before the filtering units are removed, they are treated with encapsulation technology through which they are impregnated with a suitable solution capable of trapping dust and other substances present on the filters, preventing that they are scattered into the environment. This way, the entire production cycle of a drug under the hood, from start to finish, is adequately managed and monitored, protecting both laboratory operators and maintenance technicians."[10]

- *Isolator*

Currently, equipment called isolators may also be used for the safe preparation of hazardous drugs, particularly in environments where an adequate number of air changes (≥ 6/hour) cannot be achieved. Isolators are currently less bulky and

10 Lombardi R. Risk management: technological innovation for laboratories handling substances and samples containing asbestos or carcinogens-mutagens. Biomed J Sci & Tech Res 2019.17.003069.

more ergonomic than those used in industry, with specific protection requirements for operators. It is necessary to verify that a certificate of compliance with the technical standard ISO EN 14644-7:2004, "Clean rooms and associated controlled environments - Part 7: Separative 12 devices (clean air hoods, gloveboxes, isolators and mini-environments)" has been issued for the equipment (examine a copy of the certificate issued to the manufacturer), to guarantee the suitability of the "closed system". Regarding the ducting of exhaust air to the outside and the periodic maintenance/inspection, consider what has been indicated above for the hood.
Assess, moreover, as a possible aid in making an appropriate choice, if an evaluation by an independent third party (e.g., certification body, university, Public Administration body) competent in the matter is available, which qualifies the equipment as a suitable safety measure according to the legislation in force, i.e., Italian Legislative Decree 81/2008, as amended.

2.3 Administration premises

In premises used only for administration, if the need arises due to intense therapeutic activity and/or the impossibility of preventing concentrations of hazardous drugs from forming in the air, it is advisable to carry out at least 6 effective air changes per hour (calculated using the recovery time formula).

2.4 Administration Procedure

Administration should be done safely, preferably by infusion pump, avoiding accidental spillage. Closed infusion systems are currently available, consisting of: multi-way deflectors with self-sealing bi-directional valves, locking clamp for immediate infusion stop in case of need, downstream injection point with self-sealing valve, for safe administration of drugs in syringe and avoiding manoeuvres that could cause accidental spillage of the preparation.
In the case of drug administration with elastomeric pump, in relation to the relevant indications provided by lawmakers, always inherent in the provisions of Articles 15 and 18 of Italian Legislative Decree 81/2008, it must be composed of a "needleless" system on the loading line to prevent the spillage of the drug in the environment and to make the pump and infusion line system a closed circuit; a non-return valve (one-way) for easy filling of the elastomer avoiding that the solution, pushed by the elastic force of the elastomer, spills when disconnecting the syringe; and a cap with hydrophobic filter at the end of the infusion line, which allows safe priming.
Containers in which to place contaminated materials must be made available. These must be suitable to prevent accidental worker exposure, be designed to facilitate the introduction of these materials, and have an irreversible closure. Suitable sharps containers, or the like, for which a certificate of conformity has been issued as per technical standard EN23907:2013 or other technical standards providing equivalent construction specifications for protection effectiveness can be considered. This also ensures resistance to impact in case of vertical falls, resistance to damage from toppling over and resistance to spillage after toppling over, for suitable operator protection.

2.5 Innovative safety measures

2.5.1 Use of Closed System Transfer Devices (CSTD)

It is necessary to use systems that can be defined as "closed" for the transfer of drugs, during preparation and administration, as per the provisions of Articles 15 and 18 of Italian Legislative Decree 81/2008, as amended (in this regard, please note, among other things, that Article 235, paragraph 2, of the decree indicates the adoption of closed systems for the protection of workers involved in the handling of chemical substances that are carcinogenic or mutagenic); reference should be made to the recent NIOSH definition: "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system." In this regard, NIOSH has proposed a protocol for determining the efficiency of closed systems for vapour containment.
In healthcare facilities, the choice of CSTD system should be made by reviewing available studies to ensure that the system is truly a "closed system" as defined by NIOSH, and by carefully observing the entire system, including its constituent components, to verify that the system as a whole ensures that contaminants are mechanically prevented from entering and leaving the facility.
The Hospital Pharmacy is responsible for examining the technical and scientific documentation and related certification/conformity to select the devices with the best guarantee of protection of the "closed system," in consultation with the other hospital management figures (e.g., employer, Health Director, Medical Director, Health&Safety Officer).

2.5.2 Robotic Systems

As part of preparation, robotic systems are also available today that, for significant workloads, can be used to facilitate the task of healthcare workers. However, it is important to understand that these systems always involve interaction with the operator and the external environment, and that they use "open" dilution and transfer systems (conventional transfer needles) in the preparation phase; therefore, certain collective and individual safety measures are always required, and these must be implemented following a specific risk assessment on a case-by-case basis.

2.6 PERSONAL PROTECTIVE EQUIPMENT (PPE)

2.6.1 Gloves

They must be classified as Category III PPE and have CE marking, in accordance with Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016.
Specifically, the applicable technical standards they must meet are:

- UNI EN 420 - Protective gloves, General requirements;
- UNI EN 374/1/2/3 - Protective gloves against chemicals and micro-organisms

The data sheet must include data on the glove's resistance to permeation by chemicals (EN 374-3:03).
Other parameters to consider are:

- penetration (AQL): from 1 to 3. Level 1 indicates the best performance;
- physical properties (elongation, breaking strength);
- dimensions.

Gloves certified as sterile PPE should be used during preparation. Do not wear one pair of gloves over the other.
Replace gloves whenever there is contamination and, compatibly with the permeability of the substance, replace them every two hours of work. It should also be borne in mind, as highlighted by Italian Legislative Decree 81/2008, as amended, that for the sake of compliance with the regulatory requirements for the risk of exposure it is important to examine the reports that indicate the protection properties with regard to hazardous drugs in use at the facility, particularly in the case of drugs classified or classifiable as mutagenic or carcinogenic.
In view of an intense work cycle for the preparation of hazardous drugs, check that the protection class is equal to 4; to allow for appropriate handling, consider the differential thickness and anatomical shape (relevant for the appropriate use of the PPE in accordance with Italian Legislative Decree 475/1992); length 27 cm, marking positioned on the device (as indicated by the Italian Ministry of Productive Activities, referring to paragraph 3 of art. 8 of Italian Legislative Decree 10/97, reiterating that CE marking must be affixed to each device in a visible, legible and indelible manner for the entire foreseeable life of the PPE). If it is impossible and/or there is a technical reason that makes marking each individual PPE glove difficult or uneconomical, it is sufficient for the marking to be affixed to the sales packaging (as confirmed by the Italian State Council - section III - ruling no. 1171 of 25 February 2013.
In the case of handling drugs classified or classifiable as carcinogenic and/or mutagenic in compliance with the above provisions of Articles 15 and 18, it should be noted that sterile gloves made of styrene-based copolymers that are particularly resistant to permeation by antiblastic substances according to the stringent technical standard ASTM D6978-05 "Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs" are available and offer a better guarantee of health protection.
These gloves are also particularly useful in the case of operators with allergies or intolerance to accelerants and other compounds, which are used in the vulcanization of natural or synthetic rubber, so they are to be preferred to traditional nitrile and/or neoprene gloves, also considering that the production process of styrenic devices does not require these chemicals, thus constituting in itself a form of prevention of the known irritating and allergenic potential of these compounds.
Finally, in the administration phase the intraperitoneal perfusion procedure has developed and spread significantly in recent years and, since it has to be considered in all respects a surgical procedure, the operators involved in this procedure should be provided with gloves having the same properties as surgical gloves and in any case be classified as Category III PPE in accordance with Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 and therefore be suitable for protection against hazardous drugs classified or classifiable as mutagenic or carcinogenic. In this sense, all of the considerations made in the previous paragraph on the choice of the appropriate device to ensure appropriate health protection apply.

2.6.2 Protective clothing

Protective clothing must be classified as PPE and have CE marking, in compliance with the general and specific technical standards necessary to ensure protection from chemical agents (UNI EN 17491-4: 2008, UNI EN 14605:2005, UNI EN14325:2005, EN ISO 13982-1 and 2:2005 in the case of overalls) and be classified in category III in accordance with Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016. In addition, as stated above for gloves, it is necessary to examine the reports that must indicate the protective properties by showing that the tests required by the technical standards have been carried out.
In the case of preparation premises classified as *clean rooms*, in which there are fume hoods with the characteristics previously indicated and/or robotic systems, it would be preferable to use sterile PPE overalls suitable for environments classified ISO5.

2.6.3 Respiratory protection equipment

Respiratory protective equipment should be used when preparing in an environment without an appropriate number of air changes, when the fume hood is not functioning properly, and/or in additional circumstances of operator exposure (such as accidental spillage of a hazardous drug and/or when cleaning the fume hood).
A half-mask with dust filter or a dust filtering facepiece, both with appropriate performance properties, should be used by healthcare workers. These devices must have CE marking, be classified as PPE in category III as per Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 and comply compliance with technical standards EN 140 for half-masks (i.e., the supporting structure of the respiratory protective device), EN 143 for the dust filter(s) to be used with the half-mask, and EN 149 for dust filtering facepieces. Without prejudice to the overall prevention system, which must be implemented to protect personnel from the compounds in question, it is considered appropriate that the filters to be used with the half-mask should be class P3 and the filtering facepieces should be class FFP3.

2.6.4 Face protection from splashing liquids and/or other similar material

They must be devices classified as PPE under Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016, of the visor type or equivalent and must have CE marking, in accordance with the technical standard EN 166 "Protection against drops and splashes of liquids".
It is also stressed that all PPE must be properly stored and, in the case of non-disposable devices, must be subject to appropriate hygiene and disinfection procedures. In the latter case, it is recommended that a "personal" protective device be made available to each operator.

2.6.5 Accidental Spillage

In the event of accidental spillage, "emergency kits" that include all of the above PPE must be available for operators and a specific procedure for intervention in the event of accidental contamination must be in place.