REVIEW

Assistance Publique - Hôpitaux de Marseille (AP-HM)[1], Service Central de la Qualité et de l'Information Pharmaceutiques (SCQIP), Hôpital de la Conception; Aix-Marseille Université[2], CNRS, ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie ; Assistance Publique - Hôpitaux de Marseille (AP-HM)[3], Service Central des Opérations Pharmaceutiques (SCOP) ; Assistance Publique - Hôpitaux de Marseille (AP-HM)[4], Pharmacie Usage Intérieur Hôpital de la Conception, Hôpital de la Conception; Assistance Publique - Hôpitaux de Marseille (AP-HM)[5], Oncopharma, Hôpital Nord, Marseille, France

Methods to control anticancer chemotherapy preparations ranked by risk analysis

M. Savelli[1], M. Roche[2, 3, *], C. Curti[1, 2], C. Bornet[4], P. Rathelot [1, 2], M. Montana[2, 5], P. Vanelle[1, 2, *]

Received December 21, 2017, accepted March 2, 2018

**Corresponding authors: Patrice Vanelle, Aix-Marseille Université, CNRS, ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS30064, 13385 Marseille CEDEX 05, France patrice.vanelle@univ-amu.fr*
Manon Roche, Aix-Marseille Université, CNRS, ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS30064, 13385 Marseille CEDEX 05, France manon.roche@univ-amu.fr

Pharmazie 73: 251–259 (2018) *doi: 10.1691/ph.2018.7205*

The observed increase in cancer led to a continuous rise in anticancer drug preparations in Hospital Centres. The quality and security of these preparations are essential to ensure the efficacy and to limit the risk of iatrogenic toxicity. Several methods have been described to secure the process of preparation (i.e. non-analytical methods for the control during the fabrication; analytical methods for the final product evaluation). These different methods have been presented in many studies, in particular in descriptive studies, but in practice, selecting a method is difficult and related to needs and hospital priorities. Therefore, we decided to conduct this present review focused on various existing methods allowing enhancement in security of anti-cancer drugs preparation process. A proactive hazard analysis method was applied, considering preparation and control steps, to discuss the choice of a method in terms of quality and security and to identify potential risks of failure. The results show that none method is perfect. Methods with the lowest criticality score are the robotization closely followed by Drugcam® in the case of re-labelling of all containers. According to these elements a University Hospital Centre could consider these risk indexesimplementing control methods.

1. Introduction

Anticancer drugs are involved in complex and individualized treatment protocols, with the emergence of personalized medicine in recent years (Butts et al. 2013; INCa 2012; Institute of Medecine 2017). Because of their narrow therapeutic index (NTI) and iatrogenic risk, anticancer agents are considered as "high alert medications" (Institute for Safe Medication Practices 2017; Carrez et al. 2014). The anticancer drugs production process carries a particularly high degree of risk and medication error in oncology and can have serious impacts on the health of patients (Butts et al. 2013; Carrez et al. 2014; INCa 2012; Institute for Safe Medication Practices 2017; JORF n°0090 2011). Indeed, many studies confirmed that the risks of errors concern all dispensation stages process (prescription analysis, preparation, control, delivery and patient information) and also prescription and administration stages (Ashley et al. 2011; Bonan et al. 2009; Bonnabry et al. 2006; Cairns et al. 2016; Chia-Hui et al. 2012; Christine et al. 2011; Ciofi et al. 2013; Fyhr and Akslsson 2012; Kathleen et al. 2013; Limat et al. 2001; Mattsson et al. 2015; Pongudom and Chinthammitr 2011; Ranchon et al. 2011; Robinson et al. 2006; Tournel et al. 2006; Ulas et al. 2015; Van Tilburg et al. 2006; Weingart et al. 2010). These studies highlight a complex process which involves several trades: physicians, pharmacists and nurses. Many teams mapped the entire process (Chia-Hui et al. 2012; Van Tilburg et al. 2006; Bonan et al. 2009; Robinson et al. 2006; Ciofi et al. 2013), some studies targeted only prescription (Christine et al. 2011) or administration processes (Ashley et al. 2011) and others described the process until patient's home (Kathleen et al. 2013; Bonnabry et al. 2006). A recent review compared non analytical and analytical methods but did not consider robotization in its original SWOT analysis (Bazin et al. 2015).

Actions made to secure the process of preparation of chemotherapies the last decade conducted to the preparation of these drugs in centralized reconstitution units. Thus, pharmacists can contribute to enhance security through the improvement of chemotherapy preparation process. Even though a system allowing the control of anticancer chemotherapy preparations is imposed, the analytical control is not obligatory even if it seems fundamental to ensure patient safety without neglecting the staff and its environment in terms of exposure, often described in the literature (MEWIP studies, Moretti et al.2015, Petit et al. 2017, Nussbaumer et al. 2011; Rekhadevi et al 2007; Sasaki et al 2016; Sessink et al. 2015; Sottani et al. 2012). There are different chemotherapy production or control methods, from simple visual control to robotized compounding. No method was clearly established as a gold standard (Bazin et al. 2015). The choice should take into account the needs and the financial possibilities of each institution. That is why this type of control and production method varies from one hospital to another. Thus, in order to make the whole process secure and to ensure the quality and safety of patient care, proactive hazard analysis method using Failure Mode Effect and Criticality Analysis (FMECA) or Functional Resonance Accident Model (FRAM) can be employed to identify potential chemotherapy process failures (JORF n°0090 2011). These methods are directed towards the analysis of each process, step by step, to identify and to assess potential vulnerabilities. Initially used in the industrial field and expanded in the health care area, these methods are nowadays widely used in risk management in medical oncology. To date,

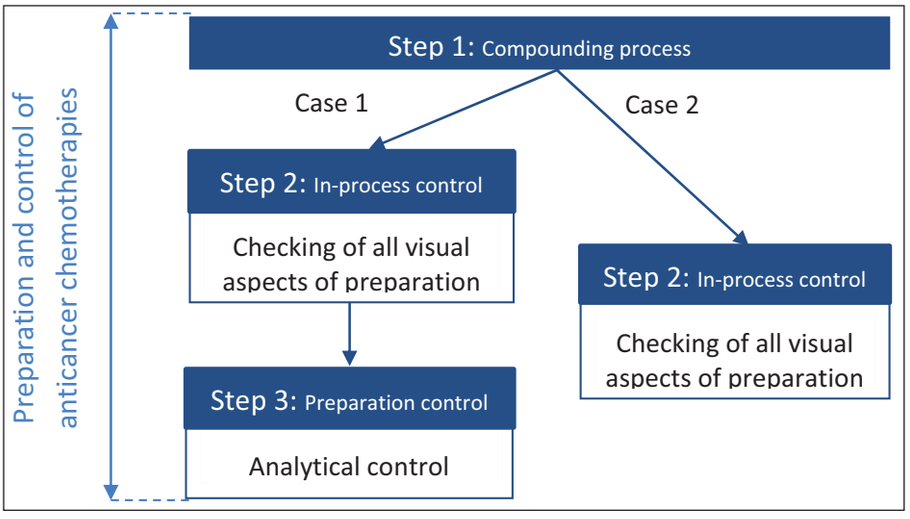
no study has considered proactive risk analysis focused on the methods of anticancer preparation production and control process. The current study focused on various existing methods allowing security enhancement in chemotherapies preparation process and discussing the choice of a method in terms of quality and security, using a proactive hazard analysis method in order to identify potential chemotherapies step process failures.

2. Methods for the control of chemotherapy preparation: literature research

The two databases used for our literature research were Pubmed and ScienceDirect. We limited the search period from the 2000 to the present. First, an electronic Science Direct search was conducted by selecting publications with general keywords: "anticancer drug preparations" and "control"; "chemotherapies preparations" and "control" in the fields abstract/title/keywords. Secondly, we crossed all techniques with "control". Finally, we used specific keywords for each method in order to obtain more results: for Raman spectroscopy keywords "Raman spectroscopy" and "quality control"; for infrared spectroscopy, "chemotherapies" and "infrared"; for gravimetric control, "weight control" and "cytotoxic drugs" and for high performance thin layer chromatography, "Chemotherapies" and "High performance thin layer chromatography". All the publications on robotization were found on PubMed using a combination of "robotics" and "antineoplastic agents". We also sought data on medication errors linked to anticancer drugs and data on environmental exposure, the former using keywords "medication errors" and "antineoplastic agents" and the latter, "environmental exposure" and "antineoplastic/adverse effects/urine". Finally, we supplemented our search from legislative and regulatory sources.

3. Proactive hazard analysis

The entire anticancer care process could be summarized as: prescription by physicians, preparation and control by pharmacists and administration by nurses. Prescription and administration steps were previously analyzed using the FMECA method, so this study focused only on the preparation and control steps and not considered transport and storage. First, each step in the preparation and control process was discussed by a team of pharmacists qualified and trained in quality assurance, cytostatic reconstitution and control of pharmaceutical preparations. The process was split into 3 steps: step 1: compounding process; step 2: in-process control; step 3: Preparation control. We distinguished a process without the analytical control step and a process combining a visual in-process control followed by an analytical control. All these steps are described in Scheme 1. Finally, the production and control phases were divided into three parts, as noted in Table 1: conventional preparation in an insulator, specific robot items and specific Drugcam® items because of the automatic control in real time by the automat.



Scheme 1: Preparation and control process

Table 1: Preparation and control processes for chemotherapies

Step 1 : Compounding process	
Conventional preparation in an insulator	
Double-control at each stage of preparation	Double-checking during the preparation is carried out by the second preparer: 1. Identification of the different products (active principles, solvents and materials) 2. Patient identification 3. Volumes 4. Quantitative validation of the solution in the vial of active principle before and after the addition in the solvent in comparison with production sheet
Specific robot items	
Compounding process	Axis robotics arm and laser-guides work on the gravimetric method
Specific Drugcam® items	
Compounding process	Preparation realized by operator of each stage of the preparation by following the instructions on a screen placed nearby that signals the vial errors and sampled volumes including labelling of containers in the case of small volume
Step 2 : in process control	
Checking of all visual aspects of preparation	Approximate final volume Clarity and color of the preparation Tightness of the preparation Presence of the clamps on the tube of the diffusers / cassettes / infusion bags Presence of caps at diffuser ends / syringes / infusion bags

Step 3 : Preparation control	
Conventional preparation in an insulator: Analytical control method	
Preanalytical phase	Validation of the method by a pharmacist
	Calibration of the automaton by a pharmacist and laboratory technicians
	Sampling by "unauthorized persons"
	Receiving samples in control laboratory
Analytical phase	By the resident in pharmacy or the hospital pharmacist and laboratory technicians
	Sample processing
	Automaton analysis
Post-analytical phase	Results validated by a pharmacist
Specific robot items	
Control in-process production	Automatic control in real time of key steps of manufacture by the robot
Visual control at the end of the compounding process	Presentation of final product in the loading/unloading chamber and check it by pharmacist. Printing a final report that resumes every step of preparation
Specific Drugcam® items	
Control in-process production	Automatic control in real time of key stages of manufacture by the automaton
Visual control at the end of the compounding process	Analysis by pharmacist of video control, available from an internet platform

Secondly, the same practitioners noted, for each of these steps, all potential failure modes envisaged in a process step previously determined during brainstorming.
Thirdly, for each potential failure mode, occurrence (O) and severity (S) parameters were defined (i.e. risk is defined as a hazard's estimated likelihood of occurrence and the resulting severity of consequences). At the same time, the detectability (D) parameter was added and represents the ability of the method to detect these failure modes before harm is caused. This hazard scoring matrix for occurrence, severity of injury and detection (respectively O, S and D) was derived from a consensus of the same team of experts and was adapted from a study related to proactive risk of errors in prescribing and administering drugs (Lago et al. 2012). Five levels of occurrence, severity and detectability are described with all scores related to these items presented in Table 2.

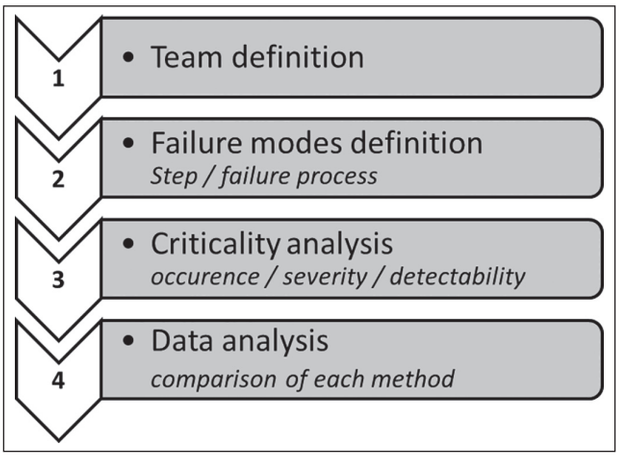
Table 2: O, S, D score (Lago P et al. 2012)

Occurrence of failure mode (O)	Severity of injury (S)	Detection by method (D)
1 Remote : less than once every 5 years	1 No injury	1 detected 9/10 times
2 Low : once a year to once every 5 years	2 Temporary injury needing additional intervention or treatment	2 detected 7/10 times
3 Moderate: one to 4 a year	3 Temporary injury with longer hospital stay or increased level of care	3 detected 5/10 times
4 High: once a month	4 Permanent effects on body functions	4 detected 2/10 times
5 Very high: daily to weekly	5 Death or permanent loss of major body functions	5 detected 0/10 times

Finally, a criticality level was obtained by multiplying the O, S and D scores (minimum, 1; maximum, 125). All criticality indexes determined for each method are included in a table for analysis of the efficiency of the control (production) method(s) in a hospital center. The proactive hazard analysis method is described in Scheme 2.

4. Results

Thirty-five publications describing the control methods and fourteen publications on prior risk analysis were obtained. We will first discuss the control/production methods integrating robotization and then turn to the proactive risk analysis.



Scheme 2: Risk analysis process

4.1. In-process production control, non-analytical methods

4.1.1. Visual control

Visual control is one of the most widely used methods in chemotherapy reconstitution units. With its ease of implementation during the preparation of cytotoxic drugs, it can be employed during each major step of preparation (the production step/compounding process and quality control of the finished product). This control increases patient safety but is highly dependent on the human factor (e.g., work interruption, lack of attention), which may lead to a lower quality of the preparation. Different studies evaluated advantages and weakness of this method; all these elements are described in Table 3 (Bazin et al. 2015; Bourget et al. 2012; Facchinetti et al. 1999).

4.1.2. Gravimetric control

Gravimetric control is a simple method which compares the observed weight of the preparation with its expected weight determined by adding the calculated mass of anticancer drugs, the mass of the bag and pharmaceutical devices considering the density of cytotoxics. The method requires little investment by the centralized pharmacy unit, it is fast, universal and widely used for the control of anticancer drugs preparations since the 2000s (Basuyau et al. 2000; Le Garlentezec et al. 2008). Gravimetric

control presents an important drawback: its lack of specificity. It does not allow the identification or quantitation of anticancer drug due to their low variability and the lack of knowledge of densities (not given in drugs marketing authorizations (AMM) and difficult to obtain from pharmaceutical laboratories) (Le Garlantezec et al. 2008; Delmas et al. 2009; Bazin et al. 2014). Densitometers could be used, but this represents an additional and costly investment. Confusion is therefore possible between two active principles, with serious impacts on patient health. In addition, this type of control meets the productivity needs of day hospitals with a limited number of preparations per year. It may also suit institutions unable to purchase other more expensive methods (Le Garlantezec et al. 2008). All criteria related to this technique are discussed in Table 3.

4.1.3. Robotization

In recent years, the robot-assisted preparation of chemotherapy appeared in centralized unit's reconstitutions and in the literature (Palma et al. 2012; Chen et al 2013; Nurgat et al. 2015; Seger et al. 2012). Studies evaluated the qualities of the third generation APOTECAchemo® and the CytoCare® robots. Criteria related to these evaluations are presented in Table 3, considering other methods. According to robotization specific criteria, before starting the preparation, the robot can recognize all the necessary items: drugs, diluent containers and so includes the use of barcodes and digital images (Palma et al. 2012). Confusion between two cytotoxics seems unlikely, but the type of bar code used would need to be specified to ensure its real reliability. Secondly, all the robots operate using a gravimetric method for the control of the final product, thereby entailing the previously described disadvantages of this method (Nurgat et al. 2015).
Production time (5 – 20 min) and mechanical limitations are also described in the literature. The mechanical limitations concerned workflow disruptions (robot downtime); the need to recalibrate the device to accept i.v. bags or syringes, medication vials incompatibility and mechanical issues (e.g., robot arm-clamping failures). An important production time and a reduction or a discontinuation of the activity related to these limitations was not acceptable for hospitals (Chen et al. 2013; Nurgat et al. 2015; Yaniv et al. 2013).
Finally, a study of robotic preparation of monoclonal antibodies was performed with the robot IV.STATION® in 2013 (Peters et al. 2014). The results showed that this preparation is feasible for 3 monoclonal antibodies (bevacizumab, trastuzumab and infliximab) yielding a quality similar to manual compounding. This provided the robotic arm to follow the recommendations of the SPC (Summary of Product Characteristics). The study should be extended to other antibodies used in cancer treatment; the ability to control the robot remains a considerable advantage.

4.2. Analytical methods: Control of the finished product

4.2.1. High-performance liquid chromatography (HPLC)

HPLC coupled with a UV detector like a Diode Array Detector (DAD) is an analytical method widely used (Bazin et al. 2015; Amin et al. 2014; Bourget et al. 2014a; Nussbaumer et al. 2011, Paci et al. 2003). This powerful chromatographic method provides good results in terms of accuracy and precision in the control of monoclonal antibodies (Amin et al 2014; Bourget et al 2014a). However, the drawbacks of the technique include in particular lengthy analysis time, sampling restrictions, environmental exposure and an important investment cost which limits it use in pharmacies. All detailed elements are described in Table 4 (Bazin et al. 2015; Bourget et al. 2014a; Bourget et al. 2014b; Delmas et al. 2009; Paci et al 2003). In addition, concerning iatrogenesis, HPLC is not suited to the intensive production required in day hospitals, which has to be as fast as possible to reduce iatrogenic risk (Covinsky et al. 2003; McDonagh et al. 2000; Shojania KG et al. 2002). HPLC is a technique that requires specialized skills and its implementation calls for the continuous training of personnel. In terms of compatibility with galenic devices, this method is not possible with infusers (physically not possible) and with syringes without considering a mother solution, given the problem of volume (Bazin et al. 2015).

4.2.2. Flow injection analysis (FIA)

FIA is a method of control that differs from HPLC that there is no column (stationary phase) normally allowing compound separation. FIA coupled with an UV detector (DAD) allows the identification of cytotoxics from direct spectral analysis in a considerably lower analysis time (Amin et al. 2014; Bazin et al. 2015). This makes it suitable for the speed imposed in reconstitution units. However, this method has also been linked to a problem with discrimination/identification of molecules, in particular ifosfamide/cyclophosphamide, doxorubicin/daunorubicin, vindesin/vinblastine. As a result, it has to be supplemented with HPLC (Delmas et al. 2009; Nussbaumer et al. 2011), a major drawback. Other limitations described are in particular the scope (exclusion of monoclonal antibodies), the investment cost and the incompatibility with some galenic devices (Table 4).

4.2.3. High-performance thin-layer chromatographic (HPTLC)

The method is an automatic and accurate version of thin layer chromatography. It consists of a silica gel plate with a fluorescent indicator coupled with a densitometer to sweep the fluorescent zones. Several studies assessed the use of HPTLC for chemo-

Table 3: Non-analytical methods for the control of chemotherapies during production

	Control in-process production		
Criteria	**Visual control**	**Gravimetric control**	**Robotization**
Accuracy	Depends on the preparer	No improvement[b]	Sufficient
Human factor	High	High	Low
Risk of occupational exposure to cytotoxic	No reduction	No reduction	Low risk
Traceability	Bad	Good	Good
Professional training	Low	Low	Intermediate (high in case of failure)
Cost	Low[a]	Low	High
References	Bazin et al. 2015; Bourget et al. 2012; Facchinetti et al. 1999	Basuyau et al. 2000; Bazin et al. 2015; Bourget et al. 2012; Delmas et al 2009; Le Garlantezec et al. 2008; Lecordier et al. 2011	Palma et al. 2012; Chen et al 2013; Iwamoto et al. 2017; Nurgat et al. 2015; Peters et al. 2014; Schierl et al. 2016; Seger et al. 2012; Sessink et al. 2015; Yaniv et al 2013;

[a] None study concerning the economic evaluation of this method has already been conducted to the best of our knowledge, but this system requires no instrumentation and seems inexpensive. However, it is necessary to take into account the direct personal costs of the member staff and its controller. The lack of a reference time for the preparation may explain the absence of economic studies found in the literature
[b] small volume preparations (<5 ml)

therapy production control (Table 4) (Bouligand et al. 2005; Bouligand et al. 2004; Bourget et al. 2001; Bourget et al. 2003; Delmas et al. 2009; Gravel et al. 2005; Paci et al. 2003). It is a very interesting technique allowing the control of anticancer drugs as well as parenteral nutrition preparations. All the publications from 2001 to 2005 found in the literature described how HTPLC, introduced in the 2000s, can be used routinely. The time required for the result is longer than with other methods, i.e. between 12 and 48 hours, which is described as an important limitation (Delmas et al. 2009). Thus, this technique seems inappropriate for a day hospital unit because it requires the chemotherapy to be prepared in advance, which is not always possible, depending on the hospital and the stability of the anticancer agents.

4.2.4. Fourier transform near infrared spectroscopy (FT-NIR)

Fourier transform near infrared spectroscopy (FT-NIR) is described as a fast and easy identification and quantification method of solutions, with a wide scale of detection (Table 4) (Bazin et al. 2015; Lê et al. 2014). The main advantage revealed is the non-invasive nature of the method since the analysis is performed directly through the container. Actually, it is widely reported in the literature that it is impossible to exclude the risk of cytotoxic exposure (Bourget et al. 2012; Basuyau et al. 2000; Le Garlantezec et al. 2008), with the presence of anticancer agents found in the work environment and in particular on the surface of containers, despite strict guidelines for safe handling (Buckley et al. 2014). However, the major problem with FT-NIR concerns the spectral data of the aqueous media dissolving the cytotoxic. This significant problem explains the limited use of the method in chemotherapy production units, or its systematic combination with other control techniques. Finally, this method presents the same limitations as HPLC and FIA in terms of compatibility with galenic devices and is efficient only for single molecules and diluted preparations (Bazin et al. 2015).

4.2.5. UV/visible- IR-FT or Multispec®

Even though Multispec® marketing was stopped in 2011, it remains widely used in cytotoxic reconstitution units (Bourget et al. 2014a). The Multispec® device combines a UV-visible spectrometer with an FT-IR spectrometer allowing both qualitative and quantitative analysis of a large number of molecules. The main advantage of this device is the extension of the detection spectrum to IR, allowing a broader structural analysis than UV-Visible. Therefore, it is possible to discriminate molecules such as ifosfamide and cyclophosphamide or doxorubicin and daunorubicin which represented a significant problem before Multispec® (Bazin et al. 2010). However, because of the device's lack of separation processes, discrimination of epirubicin and doxorubicin remains a problem (Bazin et al. 2014). Another advantage of this method is the opportunity that affords for control of monoclonal antibody preparations (Bazin et al. 2010). However, it should be recognized that Multispec® offers monoclonal antibody preparation control with only 35% correct recognition if the spectral library provided with the camera used. The development of a new library could lead to 100% recognition, but only for 7 monoclonal antibodies (Bazin et al. 2010; Bazin et al 2015). All advantages, limitations (i.e. sampling volumes, cost…) and criteria evaluated in the literature are described in Table 4 (Bazin et al. 2014; Bazin et al. 2015; Bourget et al. 2014a; Delmas 2009).

4.2.6. Raman Spectrometer: RXN1 analyser® - DXR SmartRaman®

Raman spectroscopy is based on the inelastic scattering of a photon and is widely used as an analytical tool in many research fields. This method involves directing monochromatic light on a medium and analyzes the scattered light. Evaluation of this technique highlighted its strong performance in terms of accuracy and precision, although HPLC's performance remains the strongest (Amin et al. 2014; Bourget et al. 2014) in particular for the analytical control of tablets and capsules (Buckley et al. 2011 Bourget et al. 2003). Other interest like solvent identification (Nardella et al. 2016), analysis without sampling, (Amin et al. 2014; Bourget et al. 2003, Bourget et al. 2012; Bourget et al. 2014), low volumes needed and the possibility of syringes or infusors control have been evaluated (Bazin et al. 2015; Bourget et al. 2012; Delmas et al. 2009). The main drawback here seems to be the necessary investment (Bourget et al. 2014). Another, major disadvantage is that Raman spectroscopy is an unsuitable control method when low concentration infusion bags are involved, due to its lack of sensitivity. This considerably limits the use of this tool, as infusion bags are used in 90% of preparations.

4.2.7. UV/Raman : QC-Prep®

The QC-Prep® automaton is an example of Raman spectroscopy which can be considered as an improved successor to the Multispec® analyser, combining UV and Raman spectrophotometers. The interest of this method is related to the alternate use of two spectrometers: the UV spectrometer to identify and quantify the active substance when it has no Raman spectrum and the Raman spectrometer for compounds not identified by UV. We find most of the advantages of Raman spectroscopy and in particular the facility of this fast method, the identification of solvents, and a large scale (Table 4). No improvements have been realized to the injector device, already described as inadequate with Multispec®. Furthermore, the device's ease of use has been criticized because it requires initial calibration to avoid mistakes (Bazin et al. 2015). Moreover, Raman spectroscopy induces lower sensitivity than IR because of the loss of the visible spectrum. It can be difficult to identify or quantify specific molecules such as monoclonal antibodies or eribulin (Bazin et al. 2015). Like for the Raman Spectrometer, the main drawback here seems to be the cost but the QC-Prep® may have its place in day hospitals thanks to its speed of analysis (less than 2 minutes per sample) (Nardella et al. 2016).

4.3. Video recording in process and after production

Some hospitals combine video control with other control systems in their preparation units. Video recording preparation allows both good traceability and the determination of the exact cause of a potential non-compliance. Video sequences are archived and can be used in a legal framework (Bazin et al. 2015). Although, the lack of qualitative and quantitative analysis means that video control cannot reliably be used on its own, it is efficient when combined with other systems (Table 5).

A new approach to cytotoxic production control was recently developed with an intelligent video control system, the DrugCam® system. Only one publication described this innovative safety approach in two French Hospital Centers (Benizri et al. 2016). In real time, the Drugcam® assist module performs an automatic control of production through object recognition (vials, syringes and labels). This makes it possible to identify the active principle and check syringe volumes. If an error is observed, the production process is blocked before the preparation can be dispensed. This system has the advantages of visual control but not the drawbacks because it eliminates the human factor. Recognition of vials is reliable and accurate. This method has been described as an efficient method with a significant specificity and sensitivity with small volumes recognition (paediatric formulations) (Benizri et al. 2016). Similarly, with another module called Drugcam® control, it is possible to control preparations after production with video recording, which the pharmacist can view during the validation step. No system is perfect and the DrugCam® system also has its limits. This is not an analytical method, so there is no control of the final concentration of the final product. In addition, there is no automatic detection of the solvent if they are not previously identified by relabelling solvent containers. Furthermore, dark colour anticancer drugs like mitoxantrone are difficult to detect. Moreover, this system requires significant training of preparers

Table 4: Analytical methods for the control of the finished product

	Analytical control of the finished product						
Criteria	**HPLC**	**FIA**	**HPTLC**	**IR-FT**	**UV/Visible-IR-FT**: Multispec®	**Raman spectrometry**: *RXN1 analyser®- DXR SmartRaman®*	**UV/Raman**: QC-Prep®
Sensitivity	Intermediate Poor discrimination between: ifosfamide/cyclophosphamide doxorubicin/daunorubicin epirubicin/doxorubicin		Not specified	Not specified	Efficient[d]	Efficient but limited (exclusion of molecules without Raman spectrum)	Intermediate: problem with preparations of low concentrations
Analytical target	AP[b]		AP[b]	In primary packaging: AP[b]	AP[b]+ Solvents (except in aqueous media)	In primary packaging : AP[b] + Solvents	AP[b] + Solvents (except in glucose media)
Galenic devices	Syringes, infusion bags		-	-	Infusion bags	Syringes, diffusers	Infusion bags
Invasive ou non-invasive method	Invasive		Invasive	Non-invasive	Invasive	Non-invasive	Non-invasive
Sampling step[a]	Yes		Yes	No	Yes	No	
Sample volume	250 à 500 µL		10 à 1000 nL	Not specified	1,2 mL	Not specified	
Risk of occupational exposure to cytotoxic	High		High	Low	High	Low	
Analysis time	3 min[c]	30 s	-	Not specified	4 min	2min	
Control time	Too long	-	12 à 48h	Not specified	2 min	-	-
Professional expertise	High		High	Low	Low	Nothing	Low
Control of monoclonal antibodies	Yes	Yes	No	No	Yes	No	No
Apparatus cost	€50,000: DIONEX® chain		€14,000	Not specified	End of commercialization in 2011	>€30,000	> €90,000
Analysis cost	€3.6	€2.5 per control	€1.5	Not specified	€3.5	€1.10	€12
Maintenance cost	€15,000/year		Not specified	Not specified	12 to 15% of the amount of the purchase	~0	~0
Consumables	Yes : €13,000/year* (* number of analyzes not specified)		Yes	Yes	Yes	No	No
References	Amin et al. 2014; Bazin et al. 2015; Bourget et al 2014a; Bourget et al 2014b; Delmas et al 2009; Nussbaumer et al 2011; Paci et al 2003	Amin et al. 2014; Bazin et al. 2015; Delmas et al. 2009; Nussbaumer et al. 2011	Paci et al. 2015 ; Bourget et al. 2001 ; Bourget et al. 2003; Bouligand et al. 2005; Gravel et al. 2005	Lê and al. 2014; Buckley et al. 2011	Bazin et al. 2015 ; Bazin et al. 2014; Bazin et al. 2010; Delmas et al. 2009	Bazin et al. 2015; Amin et al. 2014; Bourget et al. 2014; Bourget et al. 2003; Bourget et al. 2014; Bourget et al. 2012; Buckley et al. 2011	Bazin et al. 2015; Nardella et al 2016

[a] increases the risk of technician exposure to cytotoxics and contamination of the working environment
[b] AP: Active principle
[c] variable with the studies
[d] the near-infrared absorption spectrum of water complicates the control of some products, epirubicin and doxorubicin for example

to avoid system crashes at each non-compliance. All details are described in Table 5.

Table 5: Analytical methods for control in process and after production

	Control in process and after production	
Criteria	**Video control**	**Drugcam®**
Analytical target	AP[a] + Solvent	AP[a] + Solvent
Human factors	Yes	Yes
Risk of occupational exposure to cytotoxic	No risk	Yes
Traceability	Good	Good
Professional training	Nothing	High
Cost	Low cost	€45,000 for one work-station
References	Bazin et al. 2015	Benizri et al. 2016

[a]AP: Active principle

5. Criticality analysis

For each step in the chemotherapy production and control process, the team identified potential risks. 11 failure modes were listed during brainstorming: 5 in step 1 and 6 in step 3. As concerns step 2, the experts identified several risks related to analytical methods: errors in method validation, errors in sampling or the degradation of reagents ... But these risks do not have a direct impact on the patient, apart from delaying medical care, so they were excluded from the study. The team did not consider video control analysis because this method is systematically combined with other methods and is of no interest used alone. All risks are described in Table 6 with their occurrence and severity.

Error detectability was analyzed for each method of control. A criticality level was obtained by multiplying the O, S and D scores; results are presented in Table 6. The sum of the criticality indices for the different control methods is 74 for visual control, 133 for gravimetric control, 54 for robotization, 84 for HPLC, 98 for FIA, 93 for HTPLC, 79 for UV/Visible-IR-FT, Multispec®, 136 for Raman Spectrometry, 79 for UV/Raman, QC-Prep and 95/67 for Drugcam® method. The lowest scores were obtained with visual control and robotization, the methods showing the lowest criticality score being robotization (54) followed closely by Drugcam® (67) in the case of the re-labelling of all containers. This is as expected, because these methods have recently been developed to reduce the risks attributed to preparation of chemotherapies. The two methods with the highest criticality score are Raman spectrometry (136) and gravimetric control (133), the problem in both cases lying in the characteristicsof the antineoplastic agents. Actually, Raman spectrometry is not appropriate for the control of chemotherapies because many antineoplastic agents do not have a Raman spectrum. The problem about gravimetric control it is that a few antineoplastic agents have the same density. These two last methods do not reduce most of the identified risks and will not prevent a wrong dose. Visual control achieves a good criticality score and combined with other methods, it allows additional control, in particular for the control of expired products where no method, except Drugcam®, is effective. The analytical methods, except for Raman spectroscopy, reduce the risk of wrong doses since they are based on assay methods. However, only the HPLC method solves the problem of the wrong active principle. None of these methods makes it possible to check whether the container is right, and only the QC-Prep® and the Multispec® checking whether the solvent is right. Global analysis of criticality confirmed that no method could be considered perfect, including the recently developed robotization and Drugcam®. But if two methods are associated (analytical and non-analytical) it is possible to reduce the risk or bringing it closer to zero. In addition, other promising methods, not described here, may be developed for anticancer chemotherapy control, LC-MS/MS or capillary electrophoresis with UV detection for example (Nussbaumer et al. 2010; Guichard et al. 2018).

Table 6: Criticality analysis

			Double visual control		Gravimetric control		Robotization		HPLC		FIA		HTPLC		UV/Visible-IR-FT: Multispec®		Raman spectrometry		UV/Raman : QC-Prep		Drugcam®		Drugcam®[1]	
Risks/Failure modes	**O**	**S**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**
Step 1. Compounding process																								
Expired product	1	2	1	2	5	10	2	4	3	6	5	10	5	10	4	8	5	10	4	8	1	2	1	2
Wrong active principle	1	5	1	5	4	20	1	5	1	5	3	15	2	10	2	10	4	20	2	10	1	5	1	5
Wrong dose	3	5	2	30	3	45	1	15	1	15	1	15	1	15	1	15	4	60	1	15	2	30	2	30
Wrong solvent	1	3	2	6	5	15	1	3	5	15	5	15	5	15	1	3	1	3	1	3	5	15	1	3
Wrong container	2	2	2	8	5	20	1	4	5	20	5	20	5	20	5	20	5	20	5	20	5	20	1	4
Step 2. In process control: Checking of all visual aspects of preparation																								
Wrong volume	2	3	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6
Problem in clarity or color of the preparation	2	3	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6	1	6
Problem of tightness	3	1	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3
Absence of the clamps on the tube of the diffusers / cassettes / infusion bags	3	1	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3
Absence of caps at diffuser ends / syringes / infusion bags	4	1	1	4	1	4	1	4	1	4	1	4	1	4	1	4	1	4	1	4	1	4	1	4
Absence of the extension tube for the cassettes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total				**74**		**133**		**54**		**84**		**98**		**93**		**79**		**136**		**79**		**95**		**67**

[1]in the case of re-labelling of all containers the score related to detectability of a wrong solvent and wrong container changes to 1.

Considering hospital priority, the utilization of a combined method should implicate a gain in term of personal intervention limitation, cost or iatrogenic limitations evidences.

6. Conclusion and perspectives

This analysis showed that there is a wide range of methods for the control of anticancer chemotherapy preparations, and that analytical method(s) can be included in the production process. To date, no perfect method of control has been developed to prevent iatrogenic risk. This proactive hazard analysis may help institution's choosing the right control method which is difficult as many parameters have to be considered. While the quality of chemotherapies is the primary aim of such controls, environmental contamination is becoming equally important. With treatment advances in recent years, the control also needs to cover evaluation of monoclonal antibodies. Moreover, the time required for control should be taken into account, since the longer the time spent in a day hospital the greater is the iatrogenic risk. Thus, although not obligatory yet, analytical methods for control of chemotherapy preparations appear vital, in view of the consequences of production errors for patients. However, the cost of an analytical control remains an important criterion under current financial constraints. Using a combined method should offer a gain in real terms for an hospital.

Conflicts of interest: The authors declare that they have no conflict of interest.

References

Amin A, Bouget P, Vidal F, Ader F (2014) Routine application of Raman spectroscopy in the quality control of hospital compounded ganciclovir. Int J Pharm 474: 193-201.

Arrêté du 6 avril 2011 relatif au management de la qualité de la prise en charge médicamenteuse et aux médicaments dans les établissements de santé JORF n°0090 du 16 avril 2011 page 6687 texte n° 14. Available on https://www.legifrance.gouv.fr/eli/arrete/2011/4/6/ETSH1109848A/jo/ Consulted on august 2017

Ashley L, Dexter R, Marshall F, McKenzie B, Ryan M, Armitage G (2011) Improving the Safety of Chemotherapy Administration: An Oncology Nurse-Led Failure Mode and Effects Analysis. Oncol Nurs Forum 38: 436-44.

Basuyau F, Brunelle P (2000) Comparaison de deux mesures physiques rapides pour le contrôle de la dose des préparations injectables de médicaments anticancéreux avant administration : application au 5-fluorouracile. J Pharm Clin 19: 5-9.

Bazin C, Vieillard V, Astier A, Paul M (2010) Contrôle rapide et fiable des préparations de chimiothérapies à base d'anticorps monoclonaux à l'aide de l'automate Multispec®. Ann Pharm Fr 68: 163-77.

Bazin C, Vieillard V, Astier A, Paul M (2014) Implementation of real-time identification analysis and quantification of chemotherapies preparations with a Multispec® analyser. Ann Pharm Fr 72: 33-40.

Bazin C, Cassard B, Caudron E, Prognon P, Havard L (2015) Comparative analysis of methods for real-time analytical control of chemotherapies preparations. Int J Pharm 494: 329-36.

Benizri F, Dalifard B, Zemmour C, Henriquet M, Fougereau E, Le Franc B (2016) DrugCam®- An intelligent video camera system to make safe cytotoxic drug preparations. Int J Pharm 502: 198-207.

Bonan B, Martelli N, Berhoune M, Maestroni ML, Havard L, Prognon P (2009) The application of hazard analysis and critical control points and risk management in the preparation of anti-cancer drugs. Int J Qual Health Care 21: 44-50.

Bonnabry P, Cingria L, Ackermann M, Sadeghipour F, Bigler L, Mach N (2006) Use of a prospective risk analysis method to improve the safety of the cancer chemotherapy process. Int J Qual Health Care 18: 9-16.

Bouligand J, Paci A, Mercier L, Vassal G, Bourget P (2004) High-performance thin-layer chromatography with a derivatization procedure, a suitable method for the identification and the quantitation of busulfan in various pharmaceutical products. J Pharm Biomed Anal 34: 525-30.

Bouligand J, Storme T, Laville I, Mercier L, Oberlin O, Vassal G, Bourget P, Paci A (2005) Quality control and stability study using HTPLC: applications to cyclophosphamide in various pharmaceutical products, J Pharm Biomed Anal 38: 180-5.

Bourget P, Perello L, Demirdjian S (2001) Place et spectre fonctionnel de l'HTPLC dans un programme d'assurance qualité pharmaceutique hospitalier. Pathol Biol 49: 86-95.

Bourget P, Paci A, Rey JB, Mercier L, Demirdjian S (2003) Contribution of high-performance thin-layer chromatography to a pharmaceutical quality assurance programme in a hospital chemotherapy manufacturing unit. Eur J Pharm Biopharm 56: 445-51.

Bourget P, Moriceau A, Cassard B, Vidal F, Clement R (2012) La spectroscopie Raman (SR) : un nouvel outil adapté au contrôle de qualité analytique des préparations injectables en milieu de soins. Comparaison de la SR aux techniques CLHP et UV/Visible-IRFT appliquée à la classe des anthracyclines en cancérologie, Pathol Biol 60: 369-79.

Bourget P, Amin A, Vidal F, Merlette C, Lagarce F (2014) Comparison of Raman spectroscopy vs. high performance liquid chromatography for quality control of complex therapeutic objects: Model of elastomeric portable pumps filled with a fluorouracil solution. J Pharm Biomed Anal 91: 176-84.

Bourget P, Amin A, Vidal F, Merlette C, Troude P, Baillet-Guffroy A (2014) The contribution of Raman spectroscopy to the analytical quality control of cytotoxic drugs in a hospital environment: Eliminating the exposure risks for staff members and their work environment. Int J Pharm 470: 70-6.

Buckley K, Matousek P (2011) Recent advances in the application of transmission Raman spectroscopy to pharmaceutical analysis. J Pharm Biomed Anal 55: 645-52.

Butts C, Kamel-Reid S, Batist G, Chia S (2013) Benefits, issues, and recommendations for personalized medicine in oncology in Canada, Curr Oncol 20: 475-83.

Cairns R, Brown JA, Lynch AM, Robinson J, Wylie C, Buckley NA (2016) A decade of Australian methotrexate dosing errors. Med J Aust 204: 10 384.

Carrez L, Falaschi L, Cingria L, Sadeghipour F, Bouchoud L, Bonnabry P (2014) Organisation et sécurisation du circuit des chimiothérapies : Exemple de la pharmacie des Hôpitaux Universitaires de Genève, Pharmactuel 47: 119-124

Chen WH, Hen LJ, Guan RJ, Wu FL (2013) Assessment of an automatic robotic arm for dispensing of chemotherapy in a 2500-bed medical center, J Formosan Med Assoc 112: 193-200.

Chia-Hui C, Chia-Jen C, Pa-Chun W, Hsi-Yen L, Chi-Lan K, Chao-Ton S (2012) Applying HFMEA to Prevent Chemotherapy Errors, J Med Syst 36: 1543-51.

Christine M (2011) Using an enhanced oral chemotherapy computerized provider order entry system to reduce prescribing errors and improve safety. Int J Qual Health Care 23: 36-43.

Ciofi degli Atti M, Paolini V, Cavallin M, Corsetti T, Locatelli F, Trucco P, Raponi M (2013) Proactive evaluation of clinical risk: a FMECA analysis in pediatric chemotherapy. Nuovi Ann Ig Microbiol 25: 15-21.

Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D, Burant CJ, Landefeld CS (2003) Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. J Am Geriatr Soc 51: 451-458.

Delmas A, Gordien JB, Bernadou JM, Roudaut M, Gresser A, Malki L, Saux MC, Breilh D (2009) Quantitative and qualitative control of cytotoxic preparations by HPLC-UV in centralized parenteral preparations unit. J Pharm Biomed Anal 49: 1213-1220.

Facchinetti MJ, Campbell GM, Jone DP (1999) Evaluating dispensing error detection rates in a hospital pharmacy. Med Care 37: 39-43.

Fyhr A, Akslsson R (2012) Characteristics of medication errors with parenteral cytotoxic drugs. Eur J Cancer Care 21: 606-613.

Guichard N, Ogereau M, Falaschi L, Rudaz S, Schappler J, Bonnabry P, Fleury-Souverain S (2018) Determination of 16 antineoplastic drugs by capillary electrophoresis with UV detection: applications in quality control electrophoresis doi: 10.1002/elps.201800007

Gravel E, Bourget P, Mercier L, Paci A (2005) Fluorescence detection combined with either HPLC or HPTLC for pharmaceutical quality control in a hospital chemotherapy production unit: Application to camptothecin derivatives. J Pharm Biomed Anal 39: 581-586.

Institute for Safe Medication Practices. «ISMP's List of High-Alert Medications ». Institute for safe medications practices. Medication safety tools & resources. Available on http://www.ismp.org/Tools/highAlertMedicationLists.asp Consulted on august 2017

Iwamoto T, Morikawa T, Hioki M, Sudo H, Paolucci D, Okuda M (2017) Performance evaluation of the compounding robot, APOTECAchemo, for injectable anticancer drugs in a Japanese hospital. J Pharm Health Care Sci 3: 12 1-8.

Kathleen E, Kathleen M, Douglas R, Colleen B, Joann L (2013) Multisite parent-centered risk assessment to reduce pediatric oral chemotherapy errors. J Oncol Pract 9: 1-7.

Lago P, Bizzarri G, Scalzotto F, Parpaiola A, Amigoni A, Putoto G, Perilongo G (2012) Use of FMEA analysis to reduce risk of errors in prescribing and administering drugs in paediatric wards: a quality improvement report. BMJ 2:e001249.

Le Garlantezec P, Aupee O, Bohand X, Paillet M, Dassé MP, Cannonge B, Edouard B (2008) Choix et mise en place d'un contrôle pondéral libératoire au sein d'une unité hospitalière centralisée de préparation des cytotoxiques. Le Pharmacien Hospitalier 43: 19-27.

Lê LM, Caudron E, Baillet-Guffroy A, Eveleigh L (2014) Non-invasive quantification of 5 fluorouracil and gemcitabine in aqueous matrix by direct measurement through glass vials using near-infrared spectroscopy. Talanta 119: 361-366.

Lecordier J, Heluin Y, Plivard C, Bureau A, Mouawad C, Chaillot B, Lahet JJ (2011) Safety in the preparation of cytotoxic drugs: How to integrate gravimetric control in the quality assurance policy? Biomed Pharmacother 65: 17-21.

Limat S, Drouhin JP, DemesEmay K, Tissot E, Jacquet M, Wonoroff-Lemsi MC (2001) Incidence and risk factors of preparation errors in a centralized cytotoxic preparation unit. Pharm World Sci 23: 102-106.

Mattsson TO, Holm B, Michelsen H, Knudsen JL, Brixen K, Herrstedt J (2015) Non-intercepted dose errors in prescribing anti-neoplastic treatment: a prospective, comparative cohort study. Ann Oncol 26: 981-986.

McDonagh MS, Smith DH, Goddard M (2000) Measuring appropriate use of acute beds. A systematic review of methods and results. Health Policy 53: 157-184.

MEWIP studies. Consultable at http://www.pharma-monitor.de/dyn/php/index.php?id=36. Consulted on 2 November 2017.

Moretti M, Grollino MG, Pavanello S, Bonfiglioli R, Villarini M, Appolloni M, Carrieri M, Sabatini L, Dominici L, Stronati L, Mastrangelo G, Barbieri A, Fatigoni C, Bartolucci GB, Ceretti E, Mussi F, Monarca S (2015) Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach. Int Arch Occup Environ Health 88: 683-695.

Nardella F, Beck M, Collart-Dutilleul P, Becker G, Boulanger C, Perello L, Gairard-Dory A, Gourieux B, Ubeaud-Séquier G (2016) A UV-Raman spectroscopy method for quality control of anticancer preparations: Results after 18 months of implementation in hospital pharmacy. Int J Pharm 499: 343-350.

Nussbaumer S, Fleury-Souverain S, Antinori P, Sadeghipour F, Hochstrasser DF, Bonnabry P, Veuthey JL, Geiser L (2010) Simultaneous quantification of ten cytotoxic drugs by a validated LC-ESI-MS/MS method Anal Bioanal Chem 398: 3033-3042.

Nussbaumer S, Bonnabry P, Veuthey JL, Fleury-Souverain S (2011) Analysis of anticancer drugs: A review. Talanta 85: 2265–2289.

Nurgat Z, Faris D, Mominah M, Vibar A, Al-Jazairi A, Ewing S, Ashour M, Qaisi SK, Balhareth S, Al-Jedai A (2015) A three-year study of a first-generation chemotherapy-compounding robot. Am J Health-Syst Pharm 72: 1036-1045.

Paci A, Mercier L, Bourget P (2003) Identification and quantification of antineoplastic compounds in chemotherapeutic infusion bags by use of HTPLC: application to the vinca-alkaloids. J Pharm Biomed Anal 30: 1603-1610.

Palma E, Bufarini C (2012) Robot-assisted preparation of oncology drugs: The role of nurses. Int J Pharm 439: 286-288.

Peters BJ, Capelle MA, Arvinte T, Van de Garde EM (2013) Validation of an automated method for compounding monoclonal antibody patient doses. mAbs. 5: 162-170.

Petit M, Curti C, Roche M, Montana M, Bornet C, Vanelle P (2017) Environmental monitoring by surface sampling for cytotoxics: a review. Environmental Monitoring and Assessment 189: 52-66.

Policy Issues in the Development of Personalized Medicine in Oncology: Workshop Summary.Institute of Medicine (US) Washington (DC): National Academies Press (US); 2010. Available on https://www.nap.edu/catalog/12779/policy-issues-in-the-development-of-personalized-medicine-in-oncology Consulted on august 2017

Pongudom S, Chinthammitr Y (2011) Inadvertent intrathecal vincristine administration: report of a fatal case despite cerebrospinal fluid lavage and a review of the literature. J Med Assoc Thailand 94: 258-263.

Ranchon F, Salles G, Späth HM, Schwiertz V, Vantard N, Parat S, Broussais F, You B, Tartas S, Souquet PJ, Dussart C, Falandry C, Henin E, Freyer G, Rioufol C (2011) Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs. BMC Cancer 11: 478.

Rekhadevi PV, Sailaja N, Chandrasekhar M, Mahboob M, Rahman MF, Grover P (2007) Genotoxicity assessment in oncology nurses handling anti-neoplastic drugs. Mutagenesis 22: 395-401.

Robinson DL, Heigham M, Clark J (2006) Using failure mode and effects analysis for safe administration of chemotherapy to hospitalized children with cancer. Jt Comm J Qual Patient Saf 32: 161-166.

Sasaki M, Ishii N, Kikuchi Y, Kudoh Y, Sugiyama R, Hasebe M (2016) Occupational exposures among nurses caring for chemotherapy patients -Quantitative analysis of cyclophosphamide and α-fluoro-β-alanine in urine. Sangyo Eiseigaku Zasshi 58164-72.

Schierl R, Masini C, Groeneveld S, Fischer E, Böhlandt A, Rosini V, Paolucci D (2016) Environmental contamination by cyclophosphamide preparation: Comparison of conventional manual production in biological safety cabinet and robot-assisted production by APOTECAchemo, J Oncol Pharm Pract 22: 37-45.

Seger A, Churchill W, Keohane C, Belisle C, Wong S, Sylvester K, Chesnick A, Burdick E, Wien M, Cotugno M, Bates D, Rothschild J (2012) Impact of robotic antineoplastic preparation on safety, workflow, and costs. J Oncol Pharm Pract 8: 344-349.

Sessink PJ, Leclercq GM, Wouters DM, Halbardier L, Hammad C, Kassoul N (2015) Environmental contamination, product contamination and workers exposure using a robotic system for antineoplastic drug preparation. J Oncol Pharm Pract 21: 118-127.

Shojania KG, Duncan BW, McDonald KM, Wachter RM, (2002) Safe but sound: patient safety meets evidence-based medicine. JAMA 288: 508-513.

Sottani C, Porro B, Imbriani M, Minoia C (2012) Occupational exposure to antineoplastic drugs in four Italian health care settings. Toxicol Lett 213: 107-115.

Synthèse nationale des bilans à un an des 35 sites pilotes. Résultats des expérimentations du parcours personnalisé des patients. INCa, octobre 2012. Available on www.e-cancer.fr/content/download/63469/571061/file/BILEXPPAC12.pdf. Consulted on August 2017

Tournel G, Bécart-Robert A, Courtin P, Hédouin V, Gosset D (2006) Fatal accidental intrathecal injection of vindesine. J Forensic Sci 51: 1166-1168.

Ulas A, Silay K, Akinci S, Dede DS, Akinci MB, Sendur MA, Cubukcu E, Coskun HS, Degirmenci M, Utkan G, Ozdemir N, Isikdogan A, Buyukcelik A, Inanc M, Bilici A, Odabasi H, Cihan S, Avci N, Yalcin B (2015) Medication errors in chemotherapy preparation and administration: a survey conducted among oncology nurses in Turkey. Asian Pac J Cancer Prev 16: 1699-1705.

Van Tilburg CM, Leistikow IP, Rademaker CM, Bierings MB, Van Dijk AT (2006) Health care failure mode and effect analysis: a useful proactive risk analysis in a pediatric oncology ward, Qual Saf Health Care 15: 58-64.

Weingart SN, Toro J, Spencer J, Duncombe D, Gross A, Bartel S, Miransky SJ, Partridge A, Shulman LN, Connor M (2010) Medication errors involving oral chemotherapy. Cancer 116: 2455-2464.

Yaniv AW, Knoer SJ (2013) Implementation of an i.v.-compounding robot in a hospital-based cancer center pharmacy. Am J Health-Syst Pharm 70: 2030-2037.