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Introducing Augmented Reality Technique to Enhance the Preparation Circuit of Injectable Chemotherapy Drugs

Sarah Ben Othman[a], Hayfa Zgaya[a], Michèle Vasseur[b], Bertrand Décaudin[c], Pascal Odou[c], Slim Hammadi[a]

[a] Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRIStAL, F-59000 Lille, France
[b] Lille University Hospital- Institut de Pharmacie, F-59000 Lille, France
[c] Univ. Lille, CHU Lille, ULR 7365 - GRITA, F-59000 Lille, France

Abstract

Chemotherapy preparations are often complex and subject to a strict regulatory context. The existing control methods are often limited to Double Visual Control (DVC). In this paper, the preparation circuit of chemotherapy drugs is evaluated through data collection and statistical analysis in order to highlight the difficulties encountered. The results regarding preparation and control times and the number of task interruptions highlight the unreliability of the DVC and its impact on processing time. As a solution, we propose a decision support system "Smart Prep" based on Augmented Reality (AR), co-developed, and commercialized by the Faculty of Pharmacy of Lille, Ecole Centrale de Lille and the company Computer Engineering. This system allows the preparation of chemotherapy drugs according to a step-by-step mode, a traceability of the preparation steps and a reduction of tasks' interruptions.

Keywords:

Augmented Reality, Chemotherapy drugs, Decision Support System.

Introduction

Since 2004, cancer has been the main cause of premature death in France, ahead of cardiovascular diseases. According to the French National Cancer Institute (FNCaI), the number of new cancer cases is estimated to 382,000 per year and the number of cancer deaths is estimated to be 157,400 in 2018 in France [1]. The mortality rate has been steadily decreasing for the past 25 years. However, cancers with a poor prognosis at 5 years represent 31% of cancers for men and 17% for women. Research in the field of cancer is extremely active. Chemotherapy Drugs Preparations (CDP) are sterile pharmaceutical preparations according to the Good Practices in Preparation (GPP) [2]. They must be carried out in Controlled Atmosphere Zones (CAZs) with controlled microbiological and particulate air contamination to ensure the quality of the prepared drug. They also may contain substances harmful to the staff and the environment. It is therefore necessary to implement protective and isolation measures to reduce the risk of chemical contamination [3, 4]. In addition, identification and traceability of the different batches and vial numbers must be carried out. Currently, at the central pharmacy of Lille University Hospital (LUH), CDP requires two pharmaceutical technicians: one who prepares the drug, and another who ensures a second control of the procedure. LUH central pharmacy is not equipped with the methodologies and tools needed to support decision-making and management that are adapted to the requirements of its operating environment. The only information system the operators use during CDP is the software CHIMIO® of Computer Egineering company. It contains information about chemotherapy circuit including preparation protocols. In this paper, we present an evaluation of the current CDP circuit in the central pharmacy of LUH in order to highlight the difficulties encountered. Then, we propose a preparation and control assistance tool "Smart Prep" using AR, co-developed by the Faculty of Pharmacy in Lille, Ecole Centrale de Lille and the company Computer Engineering. "Smart Prep" is an Android application that can guide the pharmacist in the preparation of chemotherapy drugs: it fetches the preparation instructions from the CHIMIO® webservice database, then displays them on the screen of the glasses during the preparation. The glasses must ensure real-time control of CDP as well as traceability.

Method

Preparation of chemotherapy drugs: Current circuit at the central pharmacy of LUH

At LUH, the preparation circuit includes several steps:

Prescription of chemotherapy by the physician which is done in 2 formats: a printed format consisting of a pre-filled prescription specific to each drug, and a digital format on CHIMIO® software for the drugs prepared by the Centralized Cytotoxic Preparation Unit (CCPU) of the pharmacy.

1. After checking its conformity, the printed prescription is used to allocate and dispense the vials required for the preparation.
2. The vials are transferred and received after microbiological decontamination in the preparation area of the CCPU. The vials are then stored and packaged while awaiting pharmaceutical validation.
3. At the pharmaceutical validation station, the pharmacist/pharmacy intern carries out the computerized entry of the vials into stock as well as the pharmaceutical validation. Once the validation has been carried out, a printed manufacturing sheet is edited in the storage area.
4. The operator performs the preparation kit which is placed in a basket according to the instructions on the

printed manufacturing sheet, and initials the manufacturing sheet. Each basket is double-checked by a third person. The objective is to check the existence of the material necessary for the preparation and the adequate vials.

5. After transfer to the isolator, the operator carries out the preparation following the instructions on the manufacturing sheet. The preparation steps are controlled by a second person (operator, pharmacy extern, pharmacy intern or pharmacist).
6. The preparation is after that transferred to the Quality Assurance Room with the associated preparation sheet and the vials used. The pharmacist or pharmacy intern performs a release check.
7. After checking phase, the Registered Nurse administers the preparation.

Different control points can be identified in the CDP circuit: checking the compliance with the prescriptions, control of preparations by DVC (in pre-process by the double-control of the basket, in process by the double-control of the steps of preparation and in post-process by the control of the vials of both of the active drug used before destruction and the preparation (integrity, expiration, ...) at the time of pharmaceutical release and control by the nurse before administration.

Evaluation and control of CDP circuit at LUH

Given the narrow therapeutic range of anti-cancer drugs, their preparation in a centralized unit is associated with a high risk of errors occurring at any stage of the process (prescription, validation, preparation and administration) [2, 5, 6]. In Bateman's study, the factors perceived to have contributed to errors were explored. The predominant factor was individual error (78.1%), followed by distraction or interruption (4.3%), inadequate training (3.7%), work overload (3.2%) and understaffing (3.1%) [4]. In order to reduce errors, control methods can be adopted for the CDP circuit control such as the DVC which involves a third person to visually control the realization of a preparation step. The inspector checks each critical step performed by the operator during the preparation. This is an in-process control method. The gravimetric control is also used for CDP control. It consists of a control of the preparation by a weighing system using an electronic scale connected to a computer and the preparation software. Unlike the DVC, the operator acts autonomously. A knowledge of the density of the active drug is essential. Another control method is the digital video control that uses a camera system to check the identity of the active drug and the volume of the syringes. Several hospitals use this control system which consists of taking photos of each critical stage using a camera positioned either outside the preparation unit using an articulated arm [5, 6] or inside it [7]. Drugcam® (Eurekam, La Rochelle, France) [8] is a dynamic video surveillance system providing real-time assistance to the operator. It llows the control of risky phases of the preparation by recognizing objects (vials, syringes, labels) and product volumes without having to re-label with datamatrix or barcodes. Moreover, it allows a complete video recording of the manufacturing process [9]. A comparison between these control methods [10, 6, 11, 12] shows tha the DVC is adapted to the control of the preparation with notably an exhaustiveness of the control points but it lacks reliability and robustness. In spite of its reliability, gravimetric control does not seem to be totally adapted to the control of preparations because the density of the active substance is not always known. Regarding the control by digital video system, it allows preparing drugs without the knowledge of the physico-chemical data of the preparation and allows to ensure a posteriori traceability of the preparation steps. However, it is related to the problem of purchase cost and upstream parameterization.

Augmented Reality (AR): A new solution for the control of CDPs

AR can be defined as an interface between virtual data and the real world. It is a technique which overlays reality with its digital representation updated in real time. It thus offers the user possibilities of interaction in real time. This technology is in full development in the healthcare field, and is used, for example, to model the organs and blood vessels of patients in 3D, thus facilitating the learning process and the work of surgeons, in particular to create precise 3D reconstructions of tumors [13, 14]. The AccuVein® scanner is another example. It illuminates the veins on a patient's skin, which helps nurses and doctors to locate them before inserting a needle [15].

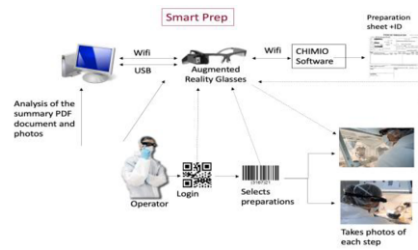

Figure 1: Smart Prep Architecture

In this context, we propose “Smart Prep” (Figure 1), an efficient tool using AR for the safety improvement of injectable CDP process. It is a hands-free tool designed to help the operator in the preparation steps and to record his actions. It consists of a software solution integrated into AR glasses allowing to guide the operator carrying out the preparation in a step-by-step approach. In order to implement “Smart Prep”, several modifications have been made in the preparation circuit: since the presence of datamatrix on the vials and bags is necessary, the vials without datamatrix are relabelled. Regarding the preparation of the basket, as there is no printed preparation sheet, it is based on a computerized checklist obtained thanks to the datamatrix on the manufacturing label. During the preparation, the operator is identified by scanning a datamatrix on a name tag, which ensures computerized traceability of the operator at each step. Then, he scans the preparation label corresponding to the prescription number to access the digital preparation sheet. During preparation, the control steps are modified: the vials and pre-filled bags are controlled by scanning the datamatrix. Only the control of volumes (reconstitution, purging and volume of active drug) is still carried out by DVC by a third person. In order to avoid any omissions in traceability, the DVC steps are traced (identification of the double-controller by scanning the name on the badge). This step has been made necessary and blocking in order to validate the end of the preparation. To avoid the use of generic datamatrix, the glasses are equipped with a voice recognition system activated by key words: "next" (to go to the next step) " photo " (to take a photo), " pause " (to interrupt the preparation in case of preparation with a pause time after reconstitution), " return " (to go back to the previous step). At the end of the preparation, all the photos taken are saved in PDF format corresponding to the batch file of the preparation and archived in the batch file on CHIMIO®. This file allows an a posteriori control of the preparation thanks to the photos taken during the preparation. The different phases of preparation and taking photos can be configured before the preparation in the

CHIMIO® software. The different steps of "Smart Prep" functioning are detailed in Figure 2.

Figure 2: Smart Prep Functioning

Results

In order to evaluate the current preparation and control circuit of injectable chemotherapy drugs, a data collection was carried out in order to highlight the omissions of traceability on the printed preparation sheets, the parameters which influence the time of preparation, the impact of the DVC and the interruptions of tasks during CDP related to the DVC.

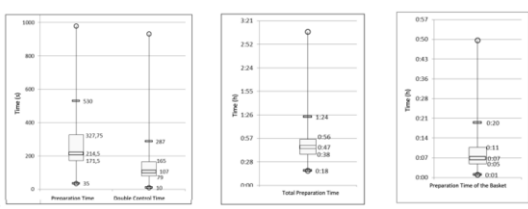

Figure 3: Representation in box plot of preparation and double-control times, total preparation time and basket preparation time

There are two phases in data collection: a first phase of collection for traceability anomalies on the preparation sheets, and a second phase for the observation of CDPs. The first phase of data collection was conducted from 23/01/2020 to 21/02/2020. During this period, 284 preparations were performed at the CCPU. 25 traceability omissions were observed, which represents 8.8% of the preparations. The second phase of the collection extended from 23/01/2020 to 13/06/2020. 134 CDPs were monitored which represents 27 different active drugs. In addition, there were 22% of active drugs requiring reconstitution. Graphical representations were made for all the preparations observed, whatever their characteristics (INPN (International Non-Proprietary Name), reconstitution, packaging) in order to evaluate the distribution of the different preparation times (Figure 3).

Double-control time analysis

For the analysis of predictive factors of the double-control duration, the candidate covariates are studied (Table 1).

		Slope	CI95%	p
Sterilization airlock used				**0.01**
Large capacity airlock (entry) Small capacity airlock (exit)		Reference		
		-52	[-93 ; -12]	
INPN				**<0.0001**
	Placebo	Reference		
		64	[4 ; 125]	
	Atezolizumab	-9	[-96 ; 77]	
	Bortezomib	74	[-17 ; 164]	
	Carfilzomib	231	[150 ; 312]	
	Cisplatine	155	[79 ; 232]	
	Daratumumab	107	[45 ; 169]	
	Isatuximab	76	[16 ; 135]	
	MK-3475	111	[50 ; 172]	
	Nivolumab	69	[7 ; 130]	
	Obinutuzumab	272	[148 ; 395]	
	Ro7082859	92	[33 ; 150]	
	Autre			
active ingredient reconstitution		98	[38 ; 157]	**0.002**
Packaging				**<0.0001**
		Référence		
	Syringe Pre-filled bag	28	[-31 ; 87]	
	Empty bag	566	[463 ; 668]	

Table 1: Predictive factors of the double-control time

According to Table 1, the impact of the sterilization airlock used is obvious (p=0.01). For a preparation sterilized in the exit airlock, the double-control time decreased by 52 seconds with a confidence interval CI95% [12; 93]. This could be due to the difference in the type of preparation placed in the two airlocks. In fact, as the exit airlock has a smaller capacity, preparations requiring less material and therefore more rapidly controlled are loaded into it. The impact of the INPN was also revealed (p<0.0001). The double-control time increased for all the INPNs compared to placebo except for Bortezomib. This result is explained by the number of steps to be controlled, which is lower for placebo (no vials or volume of active drug) and Bortezomib (no solvent or tubing). Besides, the effect of packaging (p<0.0001) is clear. The double-control time increases with empty bag packaging. This result can be explained by the large number of syringe volumes to be controlled.

Tasks' interruption analysis

Table 2 shows that for 42%, i.e., 58 observations, the double-control of the preparations was split with an average number of comings of 1.6 per preparation (s = 0.9).

Number of comings	**1**	**2**	**3**	**4**	**5**	**6**
Number of observations	**78**	**39**	**11**	**4**	**1**	**1**
Average Time per coming (s)	**145**	**66**	**36**	**31**	**56**	**15**

Table 2: Number of observations and average time of double-control according to the number of comings of the double-controller

Each preparation is not necessarily controlled twice by the same person, for 9 preparations two different persons controlled different stages of preparation. For 6 of them, it was for active drug preparations requiring a resting time after reconstitution (INPN: Carfilzomib). For the 3 others (1 MSB0010718C and 2 Nivolumab), the cause could be their time of preparation with the shift change (preparation between 11:15 and 12:15: 11:23, 11:56, 12:06). If we consider the familiarity of the operator with the preparations performed, in 93.3% of cases the operator had already performed a preparation with the same procedure. In the 9 cases where this was not the case, the operator had been informed of the procedure in 5 cases (55.6%). In the case of the double-controllers, for 142 cases out of 143 (99.3%), they were familiar with the preparation or had been informed about the

procedure. This analysis shows us the deficiencies of this preparation and control circuit. In order to secure and save time, upgrades have to be implemented.

The CDP "New Process" after the implementation of "Smart Prep".

The aim of the "New Process" is twofold: to improve the security of the entire preparation circuit, including CDP, and to facilitate the implementation of AR glasses as a preparation and control tool.

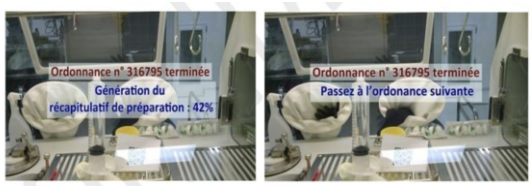

Figure 4: Information displayed on the AR glasses

"Smart Prep" has been connected to CHIMIO® in order to secure the manufacturing process by tracing each step and identifying each element involved in the preparation (vials, active drugs, solvent ...) and to dematerialize the preparation sheets. The printed manufacturing sheet is substituted by a digital preparation sheet displayed on the computer of each workstation. The paper edition is reduced to the printing of the only preparation label with a datamatrix corresponding to the prescription number which will allow to make the link between each step and to identify the content and the procedure of the preparation.

Discussion

The implementation of "Smart Prep" allows a gain in security. However, it requires a financial investment for the purchase of computer equipment (touch tablets for the preparation of baskets, labelling machines, barcodes and datamatrix scanners, computer workstations on each workstation) and for the evolution of the CHIMIO® software. It also imposes a total "dependence" on computer equipment and wifi, which may lead to a daily management of problems that may be encountered by the operator. "Smart Prep" was implemented and connected to CHIMIO® on July 22nd, 2020. As after every implementation, a learning phase is necessary. During this period, data collection cannot be performed to avoid introducing a bias in our data which would make the results unusable. It is preferable to collect data at a distance from the beginning of the project, which explains why the data collection could not be integrated in this work. Nevertheless, the transition to this new version allows us to continue the development of the AR glasses in order to use them for the different injectable drugs preparations. "Smart Prep" has been tested and validated by LUH. This solution also makes it possible to avoid double checking, especially if in the future this technology is associated with an expert alert system. The first tests have proved the efficiency of the different concepts of the proposed solution. Instructions displayed on the glasses are easy to read and do not affect eyesight even through an isolator, the integration of information (preparation protocol to be followed step by step). During the first tests, our solution made it possible to efficiently perform a preparation more quickly thanks to the step-by-step concept, the voice command, and the traceability of the key steps of the preparation by photos. AR glasses allow a secure CDP. They are also of high maneuverability. In addition, they can be suitable for subcontracting activities by allowing remote access to traceability data. With "Smart Prep" we switch from an in-process control to a post-process control (except for the control of the vials). Some of the preparation errors will no longer be detected during the preparation in the isolator but when the preparation is finished. This may entail a need for re-processing that could have been avoided. These reprocessings may lead to the increase of the waiting time for patients, and therefore to patient dissatisfaction and disorganization of the care service. "Smart Prep" can also be used as a control solution for all preparations outside chemotherapy context. In terms of securing the preparation circuit and more particularly the administration of chemotherapy by the registered nurse, currently the administration schedule is in printed form and the traceability of the administration is done manually in the hospital. Administration is done manually in the software. A greater level of security could be achieved by implementing an interconnected identification system. This system allows the computerized verification at the patient's bed, of the adequacy between the patient's identity (by an identification bracelet given to the patient upon arrival) and the preparation administered (via the datamatrix present on the preparation's label) as well as the correspondence with the cycle and the day of administration within the preparation's validity period. In addition, this system enables the administration of the preparation to be validated in real time at the patient's bed, in the CHIMIO® software [16, 17]. The ONCO SAFETY system [17] commercialized by BBraun goes further. It is an administration assistance software for chemotherapy which, after validation of the patient's identity and the preparation, imports the administration protocol directly from the CHIMIO® software and programs the pumps (flow rate, administration time). In return, the pumps feed the CHIMIO® software with real time traceability. This replaces manual data entry and saves nursing time.

Conclusions

In this paper we highlighted the weaknesses of the current circuit for the preparation of injectable chemotherapy drugs, particularly concerning the DVC and its impact on the preparation environment. Our proposed solution consists in the implementation of the decision support system "Smart Prep". This has made it possible to secure part of the CDP circuit, but its impact remains to be assessed. AR glasses are an innovative solution to facilitate the preparation and control of chemotherapy preparations. It adapts easily to the preparation environment while securing the simplest to the most complex preparations. In our future work, in order to assess the impact of the implementation of "Smart Prep", an analysis of the preparation circuit will be carried out.

References

[1] L'Institut publie L'essentiel des faits et chiffres des cancers en France (édition 2019) - Actualités [Internet]. [cité 7 juill 2019].
[2] ANSM. Bonnes pratiques de préparation. 2007.
[3] Anthony K, Wiencek C, Bauer C, Daly B, Anthony MK. No interruptions please: impact of a No Interruption Zone on medication safety in intensive care units. Crit Care Nurse. Juin 2010;30(3):21-9.
[4] Bateman R, Donyai P. Errors associated with the preparation of aseptic products in UK hospital pharmacies: lessons from the national asepticerror reporting scheme. Qual Saf Health Care. oct 2010;19(5):e29.

[5] Marchiori M, Menegazzo C, Pedrocca N, Pregnolato S, Rossetti C,Tomaselli G, et al. A gravimetric method for the quali-quantitative control of anticancer drugs. Eur J Hosp Pharm. Avr 2014;21(2):87-90.
[6] Lecordier J, Heluin Y, Plivard C, Bureau A, Mouawad C, Chaillot B, et al. Safety in the preparation of cytotoxic drugs: How to integrate gravimetric control in the quality assurance policy? Biomed Pharmacother. Févr 2011;65(1):17-21
[7] O'Neal BC, Worden JC, Couldry RJ. Telepharmacy and bar-code technology in an i.v. chemotherapy admixture area. Am J Health Syst Pharm. 1 juill 2009;66(13):1211-7.
[8] Benizri F, Dalifard B, Zemmour C, Henriquet M, Fougereau E, Le Franc B. DrugCam ® —An intelligent video camera system to make safe cytotoxic drug preparations. Int J Pharm. avr 2016;502(1-2):198-207.
[9] Le Roch G. Etude de faisabilité de l'installation d'un contrôle vidéonumérique pour les préparations d'anticancéreux au sein de la pharmacie à usage intérieur de l'Institut Universitaire du Cancer de Toulouse. Université de Bordeaux; 2016.
[10] Kolski M, Fouque J, Pichon F, Hurgon A, Escalup L. Validation d'un procédé dématérialisé couplé au contrôle gravimétrique in process lors de la fabrication de préparations cytotoxiques. Groupe d'Evaluation et de Recherche sur la Protection en Atmosphère Contrôlé (GERPAC); 2014.
[11] O'Neil et al. Contrôle pharmaceutique par code-barres. 2010; GERPAC.
[12] Interruptions during nurses' work: A state-of-the-science review - Hopkinson - 2013 - Research in Nursing & Health - Wiley Online Library [Internet]. [cité 7 juill 2019]. Disponible sur: https://onlinelibrary.wiley.com/doi/abs/10.1002/nur.21515
[13] How Augmented Reality is Changing the Healthcare Industry [Internet]. [cité 7 juill 2019]. Disponible sur: https://appreal-vr.com/blog/augmented-reality-for-healthcare/
[14] Réalité augmentée : la chirurgie du futur [Internet]. E-Santé. [cité 7 juill 2019]. Disponible sur: https://www.e-sante.fr/realite-augmentee-chirurgie-futur/actualite/194715
[15] AccuVein Vein Visualization-Improves IV 1-Stick Success 3.5x [Internet]. AccuVein. [cité 7 juill 2019]. Disponible sur: https://www.accuvein.com/
[16] Spahni S, Lovis C, Ackermann M, Mach N, Bonnabry P, Geissbuhler A. Securing chemotherapies: fabrication, prescription, administration and complete traceability. Stud Health Technol Inform. 2007;129(Pt 2):953-7.
[17] La sécurisation des CHIMIOthérapies : une priorité au Groupe Hospitalier | Centre Hospitalier de La Rochelle [Internet]. [cité 13 août 2019]. Disponible sur: http://www.ch-larochelle.fr/ch-la-rochelle/la-securisation-des-CHIMIOtherapies-une- priorite-au-groupe-hospitalier

Address for correspondence

Sarah Ben Othman, LAGIS UMR CNRS 8219, Centrale Lille, Avenue Paul Langevin, 59650 Villeneuve d'Ascq, France, e-mail: sara.ben-othman@centralelille.fr.