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Opinion Paper

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Centrally Prepared Cytotoxic Drugs: What Is the Purpose of Their Quality Control?

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Abstract: To assess the quality of centrally prepared cytotoxics a global approach is being implemented by pharmacists. A risk analysis is performed, and then many in-process controls are proposed. The aseptic process and the material are also fully validated. Moreover the skills of pharmacy technicians are being checked and monitored over time. This short opinion paper discusses the place of in-process quality control within the quality system applied to cytotoxic preparations. It also discusses the pros and cons of analytical control of the final product versus continuous control of each preparation step by eye witness or an electronic device such as a camcorder. Finally the relevancy of controls is discussed in function of different cases and of the human and material resources available in the pharmaceutical technology cytotoxic unit.

Keywords: quality control, cytotoxic drugs, aseptic processing, pharmaceutical release

Nowadays, chemotherapies are prepared by pharmacy technicians in centralized production units under the responsibility of the pharmacists. These products have specific characteristics. First, they are sterile and are thus prepared using an aseptic processing method. Second, their therapeutic margins are often narrow and their toxicity is high. This is why they are prescribed following validated schedules with body-surface calculated doses in most cases. Third, the prescription is usually adapted by taking into account the last biological results of the patient and his or her health status at the time of injection. Thus, the delay between prescription and injection is as short as possible. From the three characteristics above, it is easy to understand that chemotherapy compounding is a risky business.

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In Spain, during the year 1993, a pharmacist team evaluated an overall rate of 6.63% errors (0.33% per controlled parameter) on cytostatic preparations by tracing 20 check points going from the prescription to the administration of the drug to the patients [1]. If one looks only on the error on the concentration of the drug in the drug product the error rate was evaluated to 0.5% over a 7-years period in an University Hospital in the east of France [2]. To lower the risk as much as possible the production process is fully validated: media fill tests are implemented to assess that the process is aseptic and that the operators are qualified, a quality insurance system is used and many controls are implemented at each critical step, which are determined using prospective risk analysis [3, 4].

In fact, the first controls consist to carefully check, at time of arrival in stock, all the materials and drugs that will be used for the compounding process. The biological safety cabinets or the isolators are also qualified and daily controlled by tracing some parameters such as pressure, air-flow velocity, temperature and so on. During the production of a prescribed product many check points are used such as validity of the prescription, type of syringes, drug vials identifications, date of use or identity of solvent.

Then comes the time of effective compounding and at this step the pharmacists has two different choices. Either to only control the final product or to follow each single step of the compounding process by eye witness or an electronic device such as a camcorder or a camera in order to assure that there are no errors in the process and finally that the right drug is given at the right dose in the good vehicle. Finally other controls have to be implemented to check that the drug products is correctly labeled (in order to be taken by the right patient) and that no chemical incompatibilities and particles are present, these last controls are performed by visual inspection (Figure 1). Thus, a choice has to be made for the control procedure during the compounding process: is it better to control the final product by an analytical technique or to follow the steps with eye witness or a camcorder? Some papers already compare the different techniques used in these two cases [5, 6], from those papers it is easy to understand that no universal technical answer is proposed today.

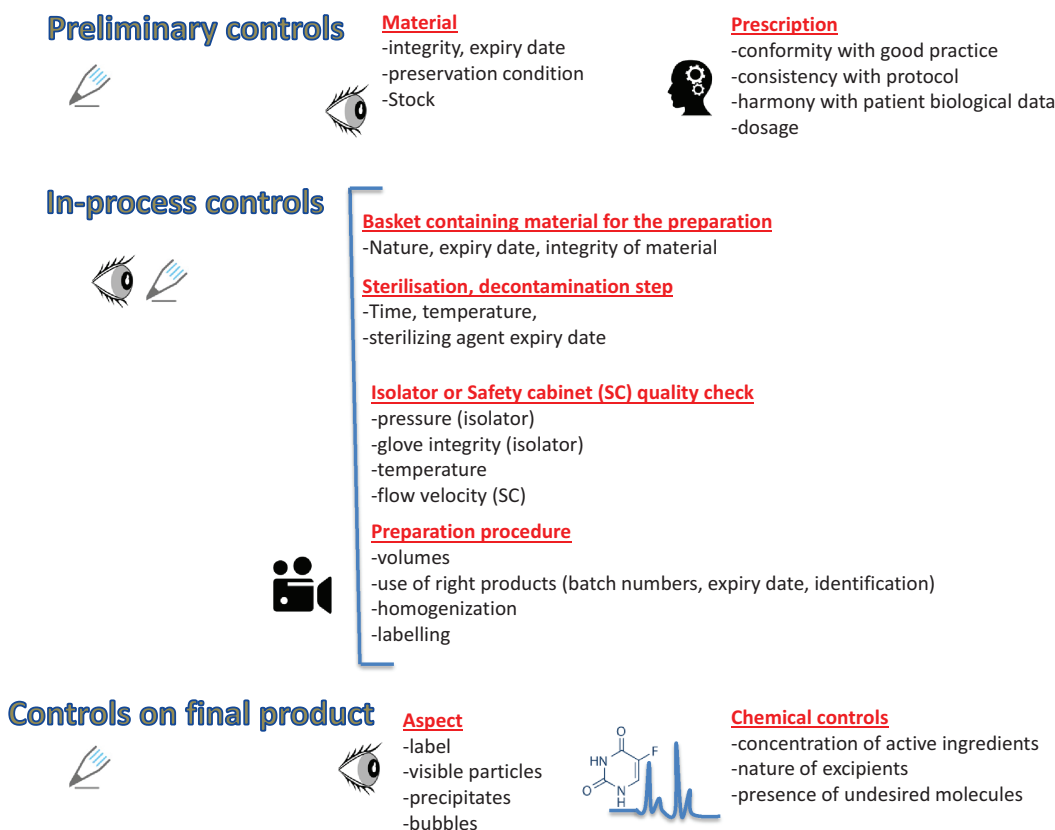


Figure 1: Types of controls implemented in cytotoxic preparation to assess the quality of the final product.

This last decade showed big evolutions of the process of sterile cytotoxic preparation in hospital using standardized doses and more recently robotics both giving great opportunities for securization of the process control. The most significant progress is the possibility of suppressing in-process control by eye-checking by using other more relevant methods such as in-process video recording, gravimetric checks and final analytical control. Different solutions are offered to hospital pharmacists to improve control of the process of compounded preparation. This opinion paper attempts to present the control methods used in hospital pharmacy production of cytotoxic sterile drugs and more generally injectable drugs, while discussing their interests and limits.

Ultraviolet detection is mostly used in the group of the analytical techniques applied to chemotherapy-quality control. Ultraviolet spectrometry can be performed alone (Druglog[®] distributed by Pharmed) or associated to Fourier Transformed Infrared Spectrometry (FTIR) which was called Multispec[®] or to Raman spectrometry (QC Prep+[®], Icônes Services, France) [7]. Ultraviolet detection was also used in quality controls by High Pressure Liquid Chromatography (HPLC) coupled to a

diode array detector (DAD) [8]. Raman spectrometry has also been proposed alone and has the major advantage to determine the analyte without destruction through its container and thus limiting chemical contaminations [9, 10]. The major problem of those analytical techniques is that they are not able to detect and quantify all anticancer drugs. Mass spectrometry would be able to determine all compounds but it had not been proposed yet because it is time consuming and analytical skill to interpret the data is higher. This is why other techniques such as gravimetric control [11] have been implemented in particular when robots are used to prepare cytotoxic drugs. The specificity of this technique is however not good enough if used alone. Finally cameras [12] or video recording (Drugcam[®], Eurekam, France) [13] have been proposed to control all prepared chemotherapies without enhanced risk of chemical contamination due to analyte vial handling and no drug volume loss for analysis. These two points are considered as major advantages of the video system over the analytical procedure (excluding raman analysis).

Each technique has its flows. Analytical techniques can only be performed and validated by team having

skills in analytical chemistry; chemical contamination of bench is possible; chemical analysis takes a few minutes and this can be important for long series of prepared products; false non conformity can occur if the drug is not properly homogenized and finally the volume of the analyte is destroyed and not injected to the patient even if some analytical methods can be process with low sample volumes [14]. Analytical control has also the costs of consumables (vials, columns, mobile phases, cleaning or standard solutions) which vary from one technique to another but is often over 1€ per sample, which can be high for big chemotherapy centers.

On the other hand, visual controlled can be biased if the attention of the watching person is not perfect, which can occur after a few hours of work or if the worker is worried by extra professional reasons or even stressed during work this is why this technique is now replaced by video recording. Actually, electronic visual control is consistent during a full day of work but it cannot detect what is not shown to the lens of the camera. In fact, if every step of preparation shown in front of the camera lens is correct the preparation will be validated but if by mistake one additional wrong step is added without showing it in front of the camera, the system may not detect it. Moreover, electronic visual control does not provide any accurate quantification on the drug concentration and vehicle effectively present in formulation that will be injected to the patient. In fact, it can only be postulated that if every preparation step is correct, the concentration and vehicle will be very close to the awaited value but assuming the good quality of the raw material used. Actually, a video recording will not be accepted as a mean to quantify a concentration with a validated standard error according to International Conference of Harmonization (ICH) guidelines on validation of analytical procedure (ICH Q2).

From the text above, one can assess that in-process controls or final analytical control do not give the same amount of information. This is why each pharmacist has to decide what level of information he needs to assure the quality of the prepared drugs. At the end he is the responsible person who will have to justify his choices in case of quality check by external inspectors. In fact, dosing the drug and vehicle by HPLC-DAD, raman spectroscopy, near infrared spectrometry or other techniques gives more information than just checking the steps of the production procedure. For example if the quality of the drug or vehicle provided by the pharmaceutical industry is not good, this can be detected by a final dosing of the prepared chemotherapy. But is it the responsibility of the hospital pharmacist to re-check what has already been released after

many controls in the pharmaceutical industry? In the past a batch was withdrawn from the market after a quality control performed by a compounding hospital pharmacy [15]. Dosing the final product allows also to waive the responsibility of the pharmacist in case of a bad clinical outcome after injection of the chemotherapy. In our hospital, a few toxic outcomes related to methotrexate too high area-under-plasma-concentration *versus* time curve (AUC) were observed. Because our preparations were dosed by combined FTIR/UV (Multispec[®]/Microdom, France), we could prove that the quality of the product prepared by the pharmacy could not be doubted. Thus the high AUC was more related to a pharmacokinetic parameter such as a defect of elimination by the patient.

So can we say that bigger is better and that analytical control should be implemented instead of electronic visual control? Not easily because as said before it requires a good expertise, time, consumables and can lead to chemical contamination of the analytical work bench. It could also be raised that a badly performed or non-fully validated analytical control could give a false green light for the release of the product to the medical wards. The risk of misuse for electronic eye control is much lower as it is much more simpler to understand and to validate. So every responsible pharmacist has to decide if the game is worth the candle, in function of the personal he has, his budget, his expertise in analytical chemistry, the type of chemotherapies he often produces, the quantity of products prepared daily.

However one has to look carefully at the following particular case. Standardized doses of cytotoxic drugs (also called dose banding) have been proposed in order to facilitate a rapid access to the treatment for patients [16] and are now proposed by the National Health Service in England [17]. In this case, series of cytotoxic preparation containing the same amount of drugs are prepared. Thus an error on the concentration of the drug or an error of drug (i. e. cisplatin used in place of carboplatin) can lead to adverse effects in many patients. This is why we think, that in this case, an analytical control should be performed at least on some preparations from the same batch. The time requested by the control is not a drawback because those preparations are produced in advance. It is also important to note that in the case of preparation performed in series, a microbiological stability test or an integrity test should be performed to validate the shelf life of those products.

We thus can propose a first answer to the question raised in the title of this paper: the purpose of quality control is to keep the overall risk at an acceptable level. It should be underlined here that the risk of errors in chemotherapies is not restricted to the pharmacy department

and can be very harmful to the patient [18]. A global approach has thus to be implemented to reduce the risk and enhance the patient safety as much as possible.

A second main reason to perform a quality control is to provide evidence of the quality of the product at the time and in the physical conditions it is released by the responsible pharmacist to the oncology units. To release the product, the pharmacist needs to review all the data from the preparation and to visually check the aspect of the cytotoxic drug. At this step the pharmacist needs some data supporting the quality of the product. Traceability of the process by eye-witness or a camcorder is very useful in this purpose. Camcorder also called electronic eye is the best choice as it is reliable and allows to check all types of preparations including now clinical trials. In the last software versions designed for camcorder controls, the analysis of the video is automatized and the software is validated to check the volumes in syringes according to the preparation protocol.

Finally the purpose of quality control is also to contribute to a databank used to investigate in case of bad clinical in patients. In this last case, for the reason explained above, analytical control is superior to archive video recordings because the concentration of the active drugs is effectively determined in the final product with a validated and known accuracy. However, in case of inquiry the video archives could be very useful if a second determination of the concentration cannot be performed for example for stability issues or because a sufficient volume of the remaining sample is not available.

As a conclusion, we can say that in-process controls, especially video control, which is reliable and allows archiving, are a complement to analytical control of the final product. In function of the level of information he needs, the responsible pharmacist will have to choose between these techniques or associate them. The best way to implement a relevant strategy of quality control is to perform a risk analysis taking into account the local conditions of preparation (i. e. quantity, identity of drugs, target patients ...) and then to decide in function of local expertise and budget. This risk analysis will be documented and can be discussed if the process is audited. As a bottom line we want to emphasize that the field of cytotoxic preparation and its associated technology is greatly evolving. This means that what may be relevant today may not be in the next years. As an evidence of this, it is worth to note that automation is now proposed by several providers to prepare cytotoxics. In this case a gravimetric control is embedded in the process. The average dose error was

evaluated to be around 1% with those systems, which limit human errors in many preparation steps [19].

Conflict of interest statement: The author states no conflict of interest. The author has read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirms that he complies with all its parts applicable to the present scientific work.

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Frederic Lagarce received his PhD in 2004, and has been Professor of Pharmaceutical Technology and Biopharmaceutics since 2012 at the University of Angers in France. Being also a Hospital Pharmacist his research is translational (from bench to bedside) and mainly focused on cancer therapy, especially on bioavailability enhancement by playing on the interactions between drug products (mainly nanosystems) and living tissues. This field involves biological barrier crossing studies but also stability assessment of the active moieties and overcoming the acquired resistances to drugs. In hospital he is in charge of the pharmaceutical technology and quality control unit. Finding new answers to medical needs using innovative drug formulations is what drives him to work every day.