International Journal of Pharmaceutics 494 (2015) 329–336

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Comparative analysis of methods for real-time analytical control of chemotherapies preparations

Christophe Bazin[a,*], Bruno Cassard[b], Eric Caudron[c], Patrice Prognon[c], Laurent Havard[c]

[a] Pharmacy, CHU Angers, 9 rue Larrey, 49933 Angers Cedex 9, France
[b] Pharmacy, Centre Hospitalier Marc Jacquet, 2 rue Fréteau de Peny, 77011 Melun Cedex, France
[c] Pharmacy, Hôpital Européen Georges-Pompidou, 20 rue Leblanc, 75908 Paris Cedex 15, France

ARTICLE INFO

Article history:
Received 18 April 2015
Received in revised form 22 June 2015
Accepted 15 August 2015
Available online 20 August 2015

Keywords:
Chemotherapies
Control
HPLC
FIA
UV/IR
Raman

ABSTRACT

Control of chemotherapies preparations are now an obligation in France, though analytical control is compulsory. Several methods are available and none of them is presumed as ideal. We wanted to compare them so as to determine which one could be the best choice.

We compared non analytical (visual and video-assisted, gravimetric) and analytical (HPLC/FIA, UV/FT-IR, UV/Raman, Raman) methods thanks to our experience and a SWOT analysis. The results of the analysis show great differences between the techniques, but as expected none us them is without defects. However they can probably be used in synergy.

Overall for the pharmacist willing to get involved, the implementation of the control for chemotherapies preparations must be widely anticipated, with the listing of every parameter, and remains according to us an analyst's job.

Contents

1. Introduction

Chemotherapies preparations should be considered as complex preparations and not as a simple reconstitution, performed by pharmacist assistants under the supervision of pharmacists and not by nurses in clinical departments, which implies a full responsibility for pharmacists only. Pharmaceutical centralised units for cytotoxic

* Corresponding author. Fax: +33 2 41 35 40 84.
E-mail address: dr.bazin@gmail.com (C. Bazin).

http://dx.doi.org/10.1016/j.ijpharm.2015.08.041
0378-5173/

drug preparations lead to a staff securisation in terms of exposure (Power et al., 1990; Gallelli 1991; Sessink et al., 1992, 1997; Valanis et al., 1993; DeMeo et al., 1995; Ziegler et al., 2002; Pethran et al., 2003), patient safety (Cazin and Gosselin, 1999; Martin et al., 2004; Baldo et al., 2007), management of good fabrication processes (Favier et al., 1993; Tillett 1999; ASHP, 2000) and costs reduction (Augry et al., 1996; Favier et al., 1996 Legat et al., 2003). Moreover, governmental policies have encouraged their developments (INCa, 2003; MDS 2005). The quality of these preparations is guaranteed thanks to a production in a secure controlled area, process standardization and above all thanks to supervision and quality control systems (Ritter et al., 1996; ASHP, 2000; Basuyau and Brunelle, 2000; Limat et al., 2002). In France, whereas control of preparations is obligatory, analytical control is a compulsory activity for hospital pharmacists. Chemotherapies preparations in particular should not avoid this control. According to us, visual control is not powerful enough to produce satisfying results. Moreover, traceability is difficult to ensure. Consequently it should probably only be used as on line production process or as a substandard process in case of analytical control failure (Watt et al., 2002).

In a global quality insurance policy, whereas the analytical control is not obligatory, it seems to be ethically essential (Pelus et al., 1998; Watt et al., 2002; Havard et al., 2005; Bonan et al., 2009). The major difficulty of this type of control lays on many limiting factors. The first one is the intrinsic hazardous toxicity of these compounds, requesting a protection for the producing staff and the technicians in charge of the control. On the second hand, the lean productions of these preparations leave a very small amount of time available for the control. Finally, the great number of preparations produced each day needs a qualified staff during a large period of time and having at their disposal an adequate material.

The aim of such an analytical control for chemotherapies preparations is to give the most reliable result, but in the smallest time. Indeed, this activity must not become a black hole of which nothing comes out or even worse a useless time, staff and money consuming activity. That is why the pharmacist willing to involve himself into this control must keep in mind the relativity of time: 10 min of production is satisfactory, 10 min for the control is unacceptable.

The first step to ensure the ability of an on-line control is to build the control laboratory next to the production unit, and moreover to be able to establish an easiness of circulation for the samples or preparations as much as communication between the staff members. Another strain which must be kept in mind is the absolute necessity to dedicate a laboratory, the equipment and a trained staff for this activity. The laboratory will also be designed to manage safety toward chemical hazards and waste.

The aim of this study is to determine which method is the most efficient in terms of reliability and cost. To produce a powerful study, methods have been studied in different institutions in terms of size, status and activity and above all managing different cancer types to cover as much cytotoxic drugs as possible.

Chemotherapies control can rely on analytical or non-analytical methods. Gravimetry, video-assisted or simple visual control can be used as non-analytical methods.

Several analytical methods are already available, and others are in development. Three different methods have been studied. Two of them are already used in routine analysis: chromatography with FIA or classical HPLC analysis linked to UV/DAD and spectroscopic apparatus equipped with UV/FT-IR or UV/Raman. We also wanted to compare these methods to Raman spectroscopy because of its potential advantages.

The final aim of our work is the comparison of these control methods thanks to a SWOT analysis used as a benchmarking and prospective approach in order to give information and tools to pharmacists willing to get involved in such an activity

2. Methods and materials

2.1. Non-analytical methods

2.1.1. Visual control and video-assisted control

Simple or double visual control has not been studied because we consider it as difficult to rely on, because of predominance of the human factor, and moreover on the difficulty to ensure a good traceability. However, visual control during each major step thanks to another staff member has been the first implemented control. It can be considered as old-fashioned but remains the most used one because of its easiness of implementation (Breton et al., 2008).

Video recording allows to keep the traceability of this control and moreover to go back afterwards in case of doubt and/or problem. However, this method is very time-consuming and may lead to the necessity to dedicate staff members to that activity, without the insurance that every mistake will be stopped, as everything depends on the human factor. Furthermore the question of archiving numeric video datas on the long term – i.e., 10 years in French law – seems hard to implement and for sure hardware memory consuming.

2.1.2. Gravimetric control

Weighting vials, syringes, and devices is obviously the fastest and simplest way to apply control of chemotherapies preparations. This technique lays upon a sequential control, all the way long the process chain, for instance thanks to CATO® software (Hanke & Horner, Vienna, Austria), allowing a control of the drug volume thanks to its density. Its first advantage is a non-destructive technique. The main outcome of the technique resides in the fact that each step depends on the previous and is a determining factor of the following (Benizri et al., 2007).

2.2. Analytical methods

The aim of analytical control is to identify the molecule in the sample and to determine its concentration (Delmas et al., 2009). The identification of the solvent can be considered a priori as pointless, whereas many incompatibilities have been found, for instance oxaliplatin in sodium chloride (Jerremalm et al., 2004). Indeed, the solvent identity can easily be controlled visually on the bag. Moreover, the analytical identification can only be done thanks to its infrared spectra and not with HPLC.

Analytical methods allow a qualitative and quantitative control. Thanks to these methods, the human factor remains limited. On the other hand, they are more expensive in terms of equipment and staff. They are also much more difficult to carry out than non-analytical methods and obviously need much more time. These limits, financial and technical, lead to very few crews using them on daily routine (Watt et al., 2002; Breton et al., 2008).

Moreover, these methods require an important handling management concerning the preparation. Everywhere this analytical procedure has been set up, the handling and preparation procedures have been adapted to eradicate falsely-negative results. For instance, the bags homogeneity is a decisive factor (Castagne et al., 2011). This major limit for analytical procedures comes from the result being a concentration result and not a total dose. The bag volume comes around with the systematic over-filling produced by the manufacturers whatsoever they are. This fact hales us to measure the exact volume by weighting bags samples on representative batches and adding for each bag an average over-filling volume to the theoretical one. Lower the volume of the bag is, more important this correction can be.

Furthermore, samples must imperatively be obtained after conscientious injection site rinsing and a bag mixing efficient but soft enough to avoid bubble generation or molecules degradation.