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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

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ABSTRACT

The purpose of the study was to perform a comparative analysis of the technical performance, respective costs and environmental effect of two invasive analytical methods (HPLC and UV/visible–FTIR) as compared to a new non-invasive analytical technique (Raman spectroscopy). Three pharmacotherapeutic models were used to compare the analytical performances of the three analytical techniques. Statistical inter-method correlation analysis was performed using non-parametric correlation rank tests. The study's economic component combined calculations relative to the depreciation of the equipment and the estimated cost of an AQC unit of work. In any case, analytical validation parameters of the three techniques were satisfactory, and strong correlations between the two spectroscopic techniques vs. HPLC were found. In addition, Raman spectroscopy was found to be superior as compared to the other techniques for numerous key criteria including a complete safety for operators and their occupational environment, a non-invasive procedure, no need for consumables, and a low operating cost. Finally, Raman spectroscopy appears superior for technical, economic and environmental objectives, as compared with the other invasive analytical methods.

1. Introduction

1.1. Background and purpose

In Western health systems, and in Western Europe in particular, it is widely accepted that healthcare quality and safety are a primary health concern for governmental authorities. Quasi-sacred patient rights are ensured by legislation of a vast scope, covering not only public, semi-public and private health care institutions but also home hospitalization (Law N° 2009-879 of 21 July 2009).

In terms of the level of service, it cannot be argued that it needs to aim for excellence. However, this in turn generates a great fleet of constraints, which are weighing more and more heavily on the shoulders of the medical staff. Objective sources of stress and of reported incidents include the handling and administration of cytotoxic drug solutions for injection, which is a major area of concern. In France, central IV admixtures of chemotherapy treatments are required per law (Decree N° 2005-317 of 24 August 2005). This process is currently performed under pharmaceutical liability, particularly at hospitals. This requirement represents an important step forward in terms of both the quality and safety of care, as well as (a) a strong contribution to the standardization of prescribing practices, (b) a lower exposure of chemicals to caregivers, (c) an improved organization of caregiver workloads

Abbreviations: AQC, analytical quality control; FTE, full time equivalent; HPLC, high pressure liquid chromatography; LabTech, laboratory technician; RS, Raman spectroscopy; TO, therapeutic object; UV/visible–FTIR, coupling of UV/visible light spectroscopic techniques to a Fourier transform infrared spectroscopy detector; UW, unit of work.

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and (d) substantial cost savings (Martin et al., 2004). However, it is currently observed: (a) an increasing number of combined therapies, (b) an increasing number of patients, and (c) more individualized and more complex therapeutic regimens. In this multifaceted context, the development of effective tools for the analytical quality control (AQC) of therapeutic objects (TO) is highly relevant. A therapeutic object is the product resulting from a compounding process, which is performed by a specialized staff, i.e., (a) an active principle in solution or in suspension in an appropriate medium, which is usually diluted in normal saline or 5% dextrose solution, and (b) an immediately labeled package that is potentially pre-connected to an infusion set. The presence of secondary packaging may complete this definition.

The goal of pharmaceutical preparations is to ensure a high and stable quality for the benefit of patients, caregivers and the environment. Furthermore, a systematic analysis of the production process revealed several critical points; these abnormalities may dangerously weaken the validity of the process. In the course of pioneering studies, which began 12 years ago at the Gustave-Roussy Institute (Villejuif 94805, France), we demonstrated the importance of linking the physical product resulting from a TO, to the flow of information (Bourget et al., 2003; Bouligand et al., 2004, 2005; Gravel et al., 2005).

In this context, an AQC process was designed and applied, as systematically as possible prior to administration. This pre-delivery AQC was applied to the three following key parameters: identity, purity and nominal concentration of an active pharmaceutical ingredient. However, such an objective must not be envisaged at the expense of the health safety of production operators and analyst technicians or their respective occupational environments. Yet the analytical techniques commonly used today require the systematic extraction of a fraction of the TO required for the analysis; they are invasive methods. This additional pre-delivery AQC step exposes the production operator who is in charge of manufacturing the therapeutic objects and who performs the extraction (puncture of the TO) to a cytotoxic risk, as well as the analyst who subsequently is in charge of the analytical check. In addition, as there is a risk of environmental exposure, a dedicated system should be introduced for the management of hazardous waste.

1.2. Analytical quality control and Raman spectroscopy

Ideally, the purpose of AQC is to enable the analytical certification of the TO prior to its administration to the patient. In terms of hospital organization, the AQC should be fast, reliable, and fully integrated into the production process and treatment. This is particularly relevant for day care units. However, the mandatory withdrawing of a TO fraction for analytical purposes should also be considered in terms of security and safety for operators and their working environment. For some TOs, withdrawal is difficult, and even impossible, e.g., small syringes, autonomous infusion devices (elastomeric portable infusion pumps), and PCA devices. The most frequently used analytical techniques are the following: (a) chromatographic methods coupled with appropriate detection systems, (b) HPTLC (high performance thin layer chromatography) methods, and (c) UV/visible–FTIR. All of the benchmark techniques have two common characteristics: they are invasive and require extraction, and thus, the sacrifice of a fraction of the TO.

In 2008, non-invasive contextual analysis using Raman spectroscopy (RS) enabled the specifications of the pre-delivery AQC to be met as defined above. RS enables the qualitative and quantitative characterization of an active pharmaceutical ingredient and its solubilization matrix, without any risk of alteration. However, among the characterization parameters, both the specificity and reliability of the technique must be demonstrated through experimentation. Furthermore, some molecules are structurally similar (Amin et al., 2010). Further, spectral behavior of packaging layers (of varying number and thickness), their contents, and the potential interferences of their respective signatures, will be systematically studied. For these reasons, the term “contextual analysis” using RS will be used. The Raman effect was discovered in 1928 by C.V. Raman and K.S. Krishnan. It is based on the principle of the inelastic scattering of light within a medium, in particular in the liquid or solid phase. In the absence of any available hospital application, an industrial-scale spectroscope used in study was acquired. In innovation context, the developmental program was complied with the project management principles (Williams, 2008; Shirley, 2011).

It is important to emphasize that quantitative Raman studies undertaken in the field of AQC of TOs are scarce (Mazurek and Szostak, 2006; Bourget et al., 2012, 2014). In other hand, a recent overview of the literature shows that Raman technology is being met with an increasing success and new applications are constantly being discovered (Kallaway et al., 2013; Selvaraju et al., 2013; Bergholt et al., 2014; Wu and Cunningham, 2014); among them, a fast and safe analytical quality control of drugs in a hospital environment is presented here.

The purpose of this study was to perform a comparative analysis of the technical performance, respective costs and environmental effect of two benchmark invasive analytical techniques in the context of pre-delivery AQC: high pressure liquid chromatography (HPLC) and the combination of UV/visible light spectroscopic techniques with a Fourier transform infrared spectroscopy detector (UV/visible–FTIR) vs. a new non-invasive analytical technique: Raman spectroscopy.

2. Materials and methods

2.1. Local technical elements and investigation systems

The injectable manufacturing unit of our hospital opened its doors in March 2009. AQC was deployed with regard to: (a) a list of candidate molecules, e.g., anticancer, antiviral, monoclonal antibodies, immunomodulators; (b) a TO panel, e.g., flexible pouches, syringes, portable infusion pumps; and (c) their respective prescription flows. This production cartography was similar to that of all of the health facilities worldwide that was involved in this type of activity. The opening of this unit was accompanied by the creation of an analytical control laboratory. Several dozens of molecules of interest progressively benefited from the analytical certification using HPLC and/or UV/visible–FTIR.

2.2. Operational qualification: the three analytical configurations

HPLC quantifications were obtained using a Dionex® UltiMate 3000 configuration equipped with a quaternary pump, a variable UV/visible detector, and an autosampler (Thermo Electron, Courtaboeuf, France). Data were recorded; the Dionex Chromeleon® (version 6.80) software was employed for data collection and processing.

Quantification by UV/visible–FTIR was performed using the MultiSpec® tool (Microdom, Taverny, France), which involved the assembly of a UV-visible spectrophotometer coupled to an IR Avatar® 380 analyzer (Thermo Electron, Courtaboeuf, France). The signal was acquired and processed using MultiSpec® Analyses, MultiSpec® Quantification & Librairie. The test sample consisted of ≈1.5 mL per TO.

RS was performed using a RXN1® spectroscope (Kaiser Optical System, Ann Arbor, USA), which was equipped with a laser source emitting in the near infrared (785 nm). Signals were acquired by means of a charge coupled device sensor using the iC Raman®