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New simple and low-cost methods for periodic checks of Cyclone® Plus Storage Phosphor System

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Abstract

The recent large use of the Cyclone® Plus Storage Phosphor System, especially in European countries, as imaging system for quantification of radiochemical purity of radiopharmaceuticals raised the problem of setting the periodic controls as required by European Legislation. We described simple, low-cost methods for Cyclone® Plus quality controls, which can be useful to evaluate the performance measurement of this imaging system.

KEY words: Cyclone® Plus Storage Phosphor System, Quality Control, Background, Uniformity, Linearity, Repeatability, radiochemical purity

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Background

The European Council Directive of 3 May 1989 (89/343/EEC) extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional previsions for radiopharmaceuticals, confirms that "radiopharmaceutical is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose".

This definition refers to all radiopharmaceuticals, excluding radionuclides in the form of sealed sources, to the European Union legislation in the pharmaceutical sector for medicinal products for human use (EU Legislation — EudraLex) [1].

The manufacture of radiopharmaceuticals shall be undertaken in accordance with the principles of Good Manufacturing Practice for Medical Products [2] and the quality of these products must be assured.

According to the present legislation, processes and tools of measurement used in various stages of preparation and the control of radiopharmaceuticals should be periodically checked and calibrated, in order to avoid, "in general, any adverse effect on the quality of products" [2].

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The Cyclone® Plus Storage Phosphor System (Perkin Elmenr, inc.) is currently used in many radiopharmacies for the analysis of thin layer chromatography samples, in the determination of radiochemical purity of radiopharmaceuticals. This device performs filmless autoradiography of samples. Reusable storage phosphor screens capture and store the activity of samples which are exposed.

As suggest by EANM guidelines [3] and by P. Elsinga *et al.* [4], QC equipment, such as the radiochromatogram scanner, should have sufficient sensitivity and spatial resolution for the intended use. Also, the equipment must be regularly checked and maintained, as recommended by the manufacturer. Now, performance specification are indicated by the manufacturer, but no other indications are reported how to perform the instrument's checks and maintenance, and their frequency.

The cGRPP-guidelines, version 2 March 2007 EANM Radiopharmacy Committee, suggest for the thin layer chromatography scanner "determination of background activity each time when used for measurement and regularly verification of detection linearity and accuracy of measurement" [3].

For radionuclide dose calibrators the guidelines prescribe background activity checks every time the calibrator is used. So, constancy should be checked before use for each setting on any day, and linearity check of the dose calibrator-response in a appropriate range of activities should be undertaken at least annually [3].

With the aim to evaluate the scanner status, in line with other quality controls of various measuring instruments in use in nuclear medicine units (e.g. gamma cameras and calibrators), were taken into consideration the following parameters were taken into consideration:

1. Background measurement
2. Uniformity of counting
3. Repeatability of counting
4. Linearity of counting

The purpose of this paper is to introduce a protocol for periodic checks of this instrumentation, which in recent years has become widely used for the quality control of radiopharmaceuticals.

Material and methods

All tests conducted have been carried out between 2009 and 2014. The device used was the laser scanner Cyclone® Plus Storage Phosphor System (Perkin Elmer, inc.) with Multi Sensitive type phosphor screen (12.5 cm × 25.2 cm) and using the software for image analysis OptiQuant™, that displays the results in DLU (Digital Light Unit) or DLU/mm^2.

For Uniformity, linearity as well as the repeatability of counting we used the Co-57 Flood Source by ISOTRAK QSA Global (Product Code C TRF10002; S/N: 12106C; Stated Activity = 666.00 MBq at date = 17/05/2007).

Background measure was carried out 400 times, on a daily basis, scanning the storage phosphor screen after the exposure of the screen to white light for 10 minutes. This practice was performed to minimize any background signal on the screen. After scanning, the displayed image was analyzed applying an appropriate template (CQbackground.tem [Figure 1]). Background values measured in 8 selected equivalent areas, distributed on the surface of the screen, were taken into account.

Uniformity, linearity as well as repeatability of counting were carried out after exposure of the storage phosphor screen to uniform Cobalt-57 (Co-57) Flood Source (666 MBq Flood Source, Active Dimensions: 620 mm × 420 mm).

For uniformity of counting the storage phosphor screen was exposed to the Flood source 50 times for a fixed time depending on the source decay (generally, few tens of seconds) about one time for month. Image analysis was performed applying the same template used for background measurement.

For the repeatability of counting we performed 10 consecutive scans of the source for a fixed time (60 sec.), while for linearity of counting we carried out 9 scans with progressively longer times of exposition. In both cases we applied the template "CQlinearity.tem" (Figure 2) that considers a unique wide counting area (31184 mm^2). Image resolution was 150 DPI.

All the measurements have been performed by E.E, biologist with 7-years experience of Nuclear Medicine quality controls and

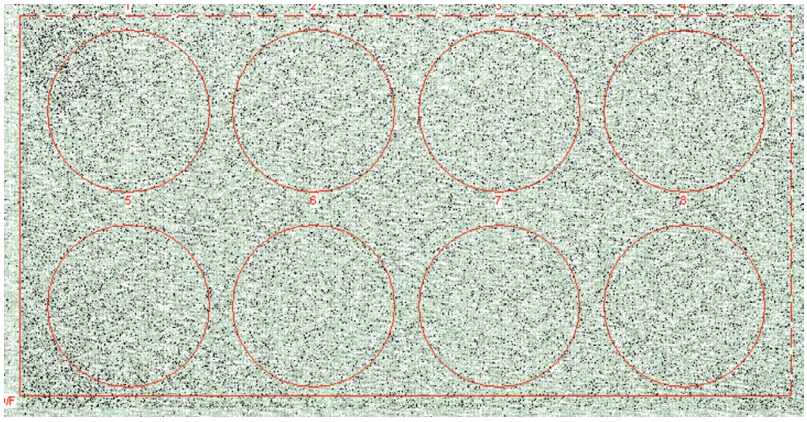

Figure 1. An example of Background measure

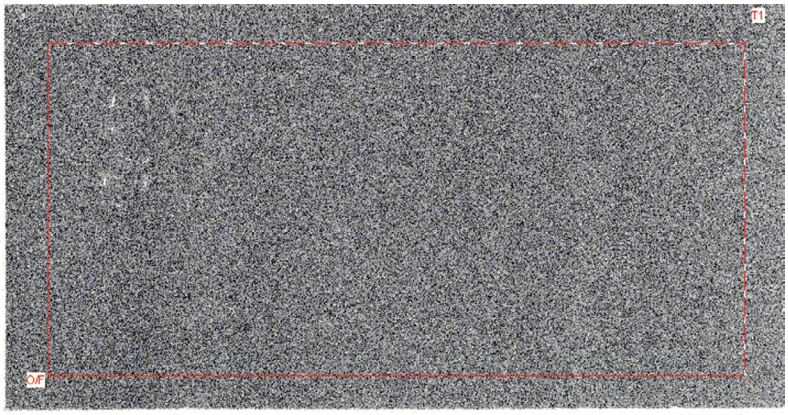

Figure 2. An example of Repeatability counting

M.R.F., medical physicist with 10-years experience of radiopharmacy equipment quality controls.

Results

Background

The average counting of all areas of all scans was 41.9 DLU/mm^2 for the background, with a Standard Deviation of 7 and a range between 28.1 and 74.7 DLU/mm^2. The mean value of the Relative Standard Deviation (% RSD) among the 8 selected areas of the template was 6.98%. Given this, we decided to fix 42 ± 10 DLU/mm^2 as reference range for background, with a maximum %RSD of 10%.

Uniformity

The uniformity of counting was calculated after a single phosphor screen exposition to the Flood source and the calculated exposure values were between 3000 and 6000 DLU/mm^2, with a mean value of 4400 DLU/mm^2. The average variability among the 8 areas of the template was 3.16% RDS. So, we decided to set as the upper limit for the parameter "% RDS Uniformity" at the value of 5%, in the considered range of exposure. Notably, the operating states conditioned the obtained values: in fact, environmental bright conditions can give higher % RDS. The best results, with lower % RDS, were obtained at low lighting level. Therefore, a dark working environment and a high execution speed are the key for the best evaluation of counting parameter.

Repeatability

The repeatability of counting was estimated by the parameter %RSD. %RDS was evaluated among the counting areas obtained after the 10 consecutive scans. Six independent and preliminary scans, with values between 50 × 10^6 and 150 × 10^6 DLU of exposure (mean 114 × 10^6 DLU), gave %RDS value of 3.0%, 1.7%, 2.0% 1.6%, and 1.2% (%RDS mean value = 1.9%).

Linearity

The linearity of counting was calculated after exposure of the phosphor screen to the flood source for progressively longer times (i.e. 60, 75, 100, 120, 150, 180, 200, 230, 250 sec., but we used even longer times in function of source decay). Four pilot experiments provided a good linear trend to data, with a correlation coefficient of 0.9931, 0.997, 0.9987, and 0.996 respectively. In all cases the mean deviation from linearity was 1.5% with a max value of 5.5%.

Discussion

In this paper we propose a cheap, easy method for laser scanner device Cyclone® Plus periodic checks. Instruction Manual of the instrument does not refer how to carry out specific quality controls [5], however, it indicates linearity and uniformity as performance parameters, with an accepted tolerance range over the scan area for uniformity of ± 5% (omitting the specific parameter to be considered) and for linearity standard deviation of ± 5% on the linear dynamic range, which extends over five orders of magnitude [5].

Taking into consideration both the indications of the manufacturer and what is prescribed for other instruments used in Nuclear Medicine, we suggest to evaluate the following parameters: background, uniformity of counting, linearity of counting, and repeatability of counting.

Table 1. Proposal of checks, periodicity and parameters' acceptable limits

Parameter	Periodicity	Acceptable limits
Background	Daily	≤ 10% RDS%
Uniformity	Monthly	≤ 5% RDS%
Repeatability	Annual	≤ 5% RDS%
Linearity	Annual	± 5% max deviation

For the Background measurement we suggest a daily check in order to monitor the screen contamination. As estimating parameter of the Background measure we recommend 42 ± 10 DLU/mm^2 as reference range for background, with a maximum %RSD of 10%.

Moreover we propose a monthly measure of the Uniformity of counting, and suggest to set as the upper limit the value of 5% of RDS.

For repeatability and linearity of counting we consider adequate in both cases an annual monitoring. Our laboratory considers as parameter for good repeatability a value ≤ 5% of RDS. For linearity we taken into account a max deviation from linearity of ± 5%. The periodicity and the limits of the parameters proposed are summarized in Table 1.

Conclusion

The present work described new protocols for periodic checks of Cyclone® Plus Storage Phosphor System, a widely used scanner for the radiochemical purity assessment of radiopharmaceuticals.

In order to ensure a more complete control of the phosphor screen performance, in addition to linearity and uniformity of counting, we suggest to take into account also the background measure and the counting repeatability. All the tests used to check the performance of the phosphor screen are very reliable in the results, simple and low-cost offering a solid platform in the respect of the existent European laws.

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