

DOSE CALIBRATORS QUALITY CONTROLS IN SWITZERLAND: SIX YEARS OF EXPERIENCE

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Abstract

In Switzerland, the legal use of open radioactive sources in nuclear medicine and the general requirements for quality controls are defined in a federal ordinance. The metrological traceability is guaranteed through a directive of the Swiss metrological office (METAS) that requires each instrument to be monitored at least once a year through either a verification or an intercomparison. The verification is performed onsite by an accredited laboratory with a set of three gamma sources (Co-57, Cs-137 and Co-60) and – if applicable – a beta source (Sr-90/Y-90). The intercomparison is made through conventional mail. A source of I-131 or Tc-99m is measured both in the nuclear medicine department and in an accredited laboratory. The maximum tolerated error is 10% for gamma sources and 20% for beta sources. This methodology guarantees that the instruments have a correct response for most of the energy range used in practice. Not all nuclides are systematically probed and manufacturers are ultimately responsible for the calibration factors. The precision of the measurements performed in Switzerland is satisfactory with only about 6% of the measurements out of the tolerances. This monitoring also allowed us to improve the skills of the personnel and update the park of instruments by getting rid of dose calibrators displaying old units.

1. Introduction

Measuring the activity of radiopharmaceuticals before patient injection is an essential monitoring procedure in nuclear medicine [Wastiel 2005]. Together with the producer's surveillance of the radioactive isotope (test for radionuclidic purity) and the labeling (test for radiochemical purity), it guarantees a safe use of radiopharmaceuticals in nuclear medicine. Activity measurement in nuclear medicine departments is therefore part of good laboratory practice [Santri 1998] and is being slowly integrated into national legislations. It is usually performed locally with a dose calibrator using the original vial provided by the producer if the whole preparation is to be injected. However, a direct measurement of the injection syringe is to be preferred because it evaluates the solution actually injected thus eschewing the problem of the activity adsorbed into the vial walls.

Recently, a group of 24 European calibration and metrological laboratories proposed a project (Guidance for Radio-pharmaceuticals Assay in NUclear Medicine: GRANUM) which aims at networking metrologists and practitioners to share information on existing guides, organizing

inter-laboratory tests involving laboratories in charge of quality controls, and promoting a minimum level of common best practice in nuclear medicine departments through a common guide.

The goal of the present paper is to describe the methodology adopted in Switzerland since 1999 and the results obtained. Section 2 describes the Swiss legal basis and the metrological traceability, with a special emphasis on the beta-emitters used for verification. Section 3 is devoted to reporting the main findings of the verifications and inter-comparisons carried out in the country in recent years; the key lessons are highlighted. The last section summarizes the central points of this paper.

2. Method

2.1. Verification and intercomparison

The legal basis for monitoring a dose calibrator used in nuclear medicine in Switzerland lies in a federal ordinance [Ordinance 1997; Art 30 and Appendix 4]. From this, the Federal Office for Accreditation and Metrology established a directive [Directive 2004] that defines the conditions in which verifications and intercomparisons are performed.

Before a dose calibrator is first used, it has to be verified onsite by an accredited laboratory. The reference value of the long-life source used for stability checks is established during this exercise. At the same time, calibration factors for all potentially utilizable nuclides are checked using this long-life source.

After this initial verification, the nuclear medicine laboratory must demonstrate every year that the instrument is working properly by either asking for a verification or by taking part in an intercomparison also organized by an accredited laboratory. The laboratory can choose which type of monitoring it wants to undergo, but it must perform a verification at least once every three years.

The verification is performed onsite with three reference gamma-emitting sources, 5 ml solutions of Co-57, Cs-137 and Co-60 in a 15 ml penicillin vials. The maximum acceptable deviation is $\pm 10\%$. Although these radionuclides do not have common radiopharmaceutical applications their energies are such that they cover most of the useful range. Since 2004, if beta emitters are measured with the instrument, a reference beta-emitting source of Sr-90/Y-90 must also be measured. The maximum acceptable deviation for this type of source is $\pm 20\%$.

As for the intercomparison, it is made by conventional mail. It consists in measuring a given source both in the nuclear medicine laboratory and in the verification laboratory. Depending on their needs, nuclear medicine laboratories may choose between Tc-99m and I-131. They can also opt for measuring a source prepared by the verification laboratory (type A intercomparison) or else prepare the source themselves (type B intercomparison). The choice of Tc-99m or I-131 for the intercomparison serves to complement the verification approach with radionuclides that are frequently used in practice. Whatever the type of intercomparison, the maximum acceptable deviation with the reference value is $\pm 10\%$.

The metrological traceability of the activity measurements of all other nuclides used in nuclear medicine laboratories is not directly monitored by these verifications and intercomparisons. Our approach only ensures the stability of the calibration factors entered in the instrument, while their actual values are the responsibility of the manufacturers. This is justified since all instruments of a given type have the same calibration factors and because the verification probes the responses for gamma-emitting nuclides covering most of the energy range of interest. It is therefore unlikely that the response of an instrument would vary discontinuously for one given nuclide only.

The responses to other nuclides are nevertheless specifically checked by other intercomparisons as this was done recently for several beta-emitting sources [Wastiel 2005].

Apart from the annual monitoring performed by external laboratories, the nuclear medicine departments must perform a series of checks listed in Table 1.

Table 1: Mandatory dose calibrator checks

Frequency	Monitoring
Daily	Measurement of the background Measurement of the long-life stability source
Weekly	Measurement of the instrument response for all potentially utilizable nuclides with the long-life stability source
Half-yearly	Check of the linearity of the instrument with an appropriate source

2.2. Metrological traceability

All reference sources used for these operations are directly traceable to the Swiss national metrological institute in charge of activity measurement (IRA-METAS), which is a signatory of the Mutual Recognition Arrangement (MRA). The degrees of equivalence of our values and the internationally accepted reference values can be found on the BIPM website [BIPM 2006]. Table 2 shows that the maximum deviation of our values from their BIPM reference counterparts is 0.5%.

Table 2: Discrepancies between IRA-METAS activities and BIPM reference values.

Nuclide	Deviation from BIPM reference value
Co-57	- 0.4%
Co-60	- 0.3%
Cs-137	- 0.3%
Tc-99m	+ 0.5%
I-131	- 0.3%

2.3. Special case of the Sr-90/Y-90 source

The beta-emitting source used for the verification of the dose calibrators is a liquid source of Sr-90/Y-90 at secular equilibrium. These nuclides were chosen because Sr-90 has a large half-life (29.1 y) and because the global beta spectrum covers a wide energy range. However, most of the commercial dose calibrators have a calibration factor for Y-90 alone and not for the mixture Sr-90/Y-90. In order to test the correctness of the calibration factor of Y-90 with a source of Sr-90/Y-90, it is necessary to correct the measurement for the extra-contribution of Sr-90.

A Monte Carlo simulation of a commercial dose calibrator (Veenstra VDC 405) was performed [Laedermann 2004] for this purpose. Figure 1 shows the deposited beta energy in the instrument sensitive volume for Sr-90 and Y-90. The areas of these spectra are proportional to the contributions of the current measured by the instrument. Because of the lower sensitivity of the instrument to lower energies, the contribution of Sr-90 is significantly smaller than that of Y-90. The signal produced by a Sr-90/Y-90 source is higher than the response to a Y-90 source of the same activity by a 1.117 factor. Therefore, the calibration factor of Y-90 should be divided by a 1.117 when using a Sr-90/Y-90 source.

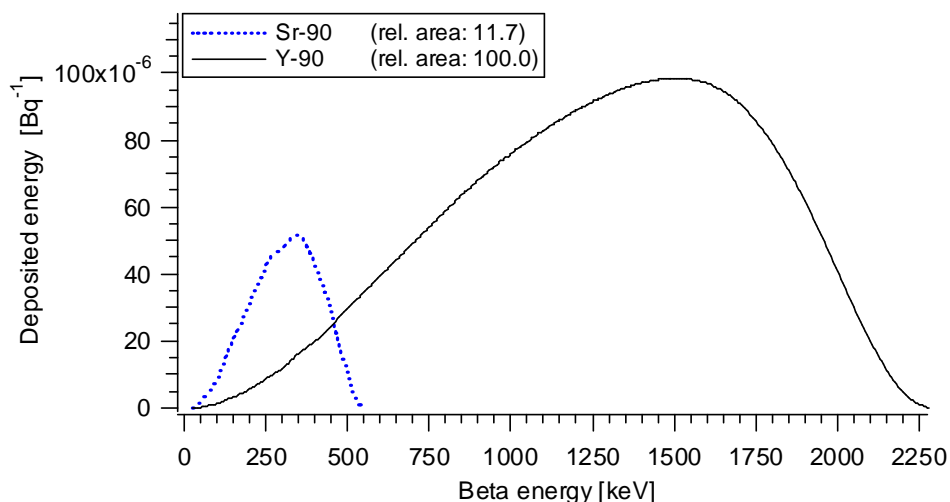


Figure 1: Monte Carlo simulation of the deposited beta energy in the sensitive volume of a commercial dose calibrator (Veenstra VDC 405) for a Sr-90/Y-90 source (Based on the data of Laedermann et al [2004]).

Although Monte Carlo simulation is a useful tool for understanding the physical processes taking place in a measuring instrument, it cannot be directly used in a verification procedure without empirical validation. This was done with a source of Sr-90/Y-90 and a source of Y-90 traceable to national standards for the three most frequently used dose calibrators in Switzerland. The obtained correction factors are shown in Table 3. Surprisingly, for instruments of different makes and types, these factors are sufficiently close to the Monte Carlo simulation to justify using a unique average correction factor of 1.12.

Table 3: Measured Y-90 correction factors when using a Sr-90/Y-90 source.

Type of instrument	Correction factor	Uncertainty [-] (k=2)
Veenstra VDC 405	1.124	± 0.023
Isomed 2000	1.115	± 0.023
Atomlab 100	1.125	± 0.023

3. Results and discussion

3.1. Verifications

All verification results obtained since the introduction of the Sr-90/Y-90 source in 2004 are presented in Figure 2. 40 verifications were performed with the three gamma-emitting and the Sr-90/Y-90 sources and 38 with the gamma-emitting sources only. Except for two measurements of Sr-90/Y-90 sources that were out of the ±20% range, all results were within the tolerances. These results do not however depict reality accurately enough, because instruments out of tolerances are generally adjusted during verification.

The figure nevertheless demonstrates that most of the instruments underestimate the reference value with a median of typically at -4% and a large part of the distribution below the reference value (more than 90% of the Cs-137 and Co-60 measurements and about 75% of the Co-57 and Sr-90/Y-90 measurements).

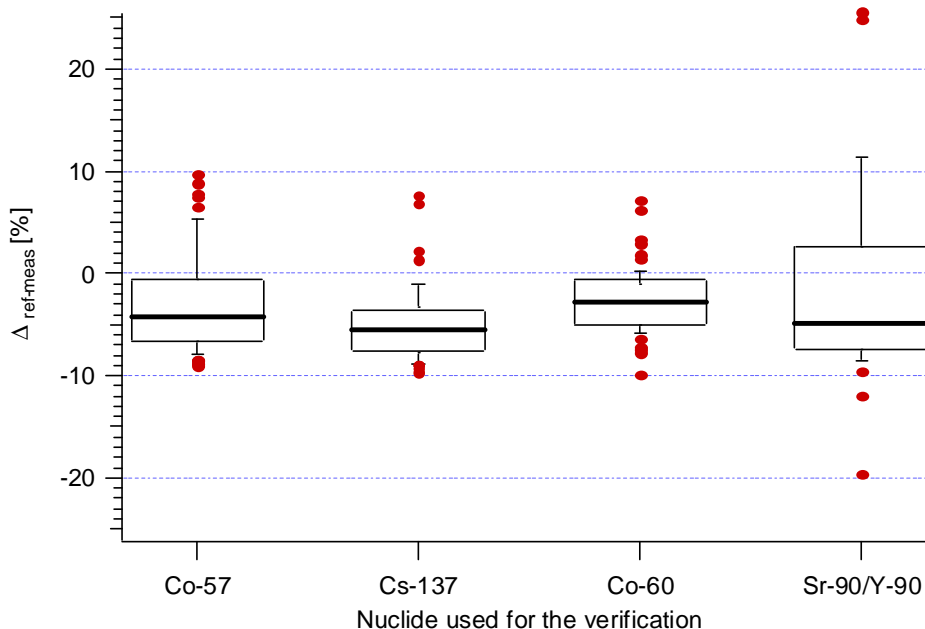


Figure 2: Results of the verifications in 2004 and 2005. For this graph and the following ones, boxes show the two quartiles around the median, the lower and upper whiskers show the extent of percentiles 10 and 90 respectively while the round markers show the individual measurements out of the 10-90 percentile-range. Only markers positioned further than 1.1 times the median-whisker distance are shown on the graph. This latter point implies that measured values very close to the 10th and 90th percentiles but in the periphery of the distribution are not visible in the figure.

3.2. Intercomparisons

A total of 318 intercomparisons were organized from 1999 to 2005. The details per nuclide and intercomparison type are presented in Table 4 which shows that about 6% do not comply with the $\pm 10\%$ tolerance. This performance is the same regardless of the intercomparison type (A or B) or the nuclide (Tc-99m or I-131).

Table 4: Number of intercomparisons and global results from November 1999 to December 2005. In type A intercomparisons the source is provided by the reference laboratory whereas in type B intercomparisons the sources are prepared by the nuclear medicine department.

Intercomparison type	Nuclide	Number of intercomparisons	Out of tolerance
A	Tc-99m	176	10 (= 6%)
B	Tc-99m	72	5 (= 7%)
A	I-131	51	3 (= 6%)
B	I-131	17	1 (= 6%)
Total		316	18 (= 6%)

The time evolution of all the intercomparisons performed from 1999 and 2005 is presented in Figure 3. Most of the measurements (between percentiles 10 to 90) stay within the same range and no trend is visible. An improvement is however visible for the extreme cases (lower and upper 10 percentiles) that are much closer to the reference values since 2003. As for the

verification, the measured values tend to underestimate the reference value; this time with an offset of typically 2-3%.

These results are rearranged by nuclide in Figure 4. Although most measurements underestimate the reference, this is more the case for I-131 than for Tc-99m. The median measurement of Tc-99m is only 1% below the reference whereas it is 2.8% below for I-131. A significant part (36%) of the Tc-99m measurements are above the reference against only 10% for I-131. This suggests a better traceability of commercial instruments for Tc-99m.

Since the calibration factors are defined by manufacturers, it is interesting to plot the results accordingly. This is done in Figure 5 for each nuclide and for the three most used brands in Switzerland.

For Tc-99m, it can be seen that Atomlab instruments are below the reference value with a median at -5.5% and an extension between the 10th and 90th percentiles of 10.5%. The situation is much better for Veenstra instruments: the median is spot on while the extension between the 10th and 90th percentiles deviates only by 8%. There are however some large spreads below the 10th percentile with points going as far down as -70% discrepancy. Measurements performed with Isomed instruments underestimate the reference value – their median deviates by -1.5%.

The same trends obtain for the I-131 sources. Measurements with Atomlab instruments yield rather low estimates with the largest discrepancy at -8% from the reference value. Isomed and Veenstra instruments underestimate the reference value by -2% and -3% respectively. Note that most source activities measured with these instruments are below the reference values (100% of Atomlab, 75% of Isomed and more than 90% of Veenstra).

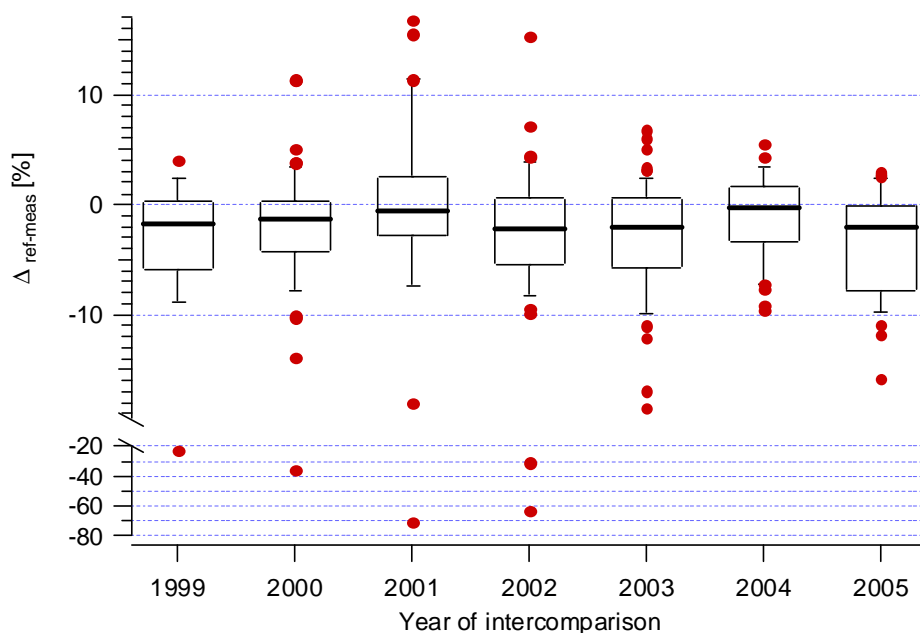


Figure 3: Results of the intercomparisons (pooling of types A and B and of Tc-99m and I-131) across the years. There were 30 measurements in 1999, 56 in 2000, 29 in 2001, 47 in 2002, 67 in 2003, 38 in 2004 and 50 in 2005.

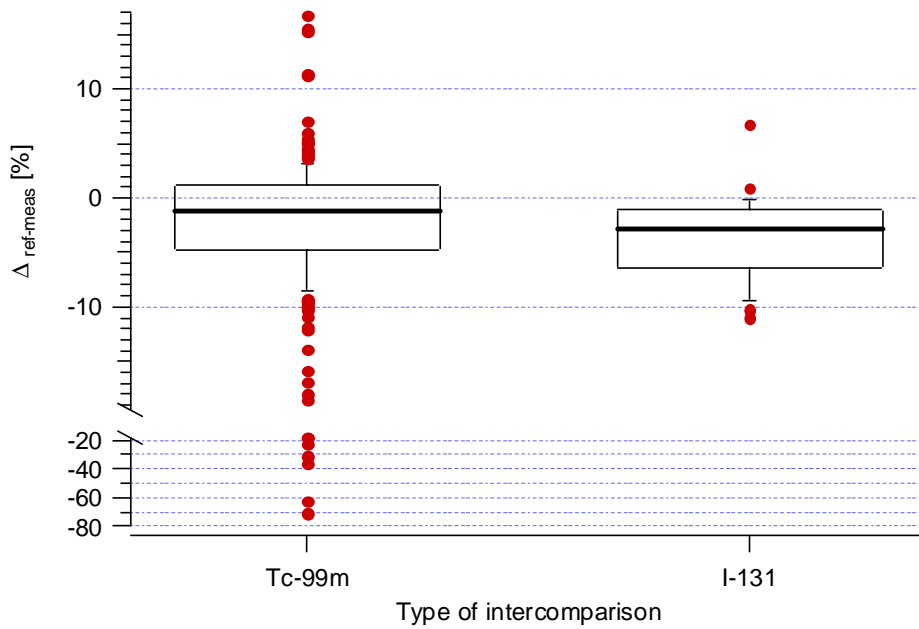


Figure 4: Results by type of intercomparisons for both nuclides of interest. A total of 248 measurements were performed with Tc-99m and 67 with I-131.

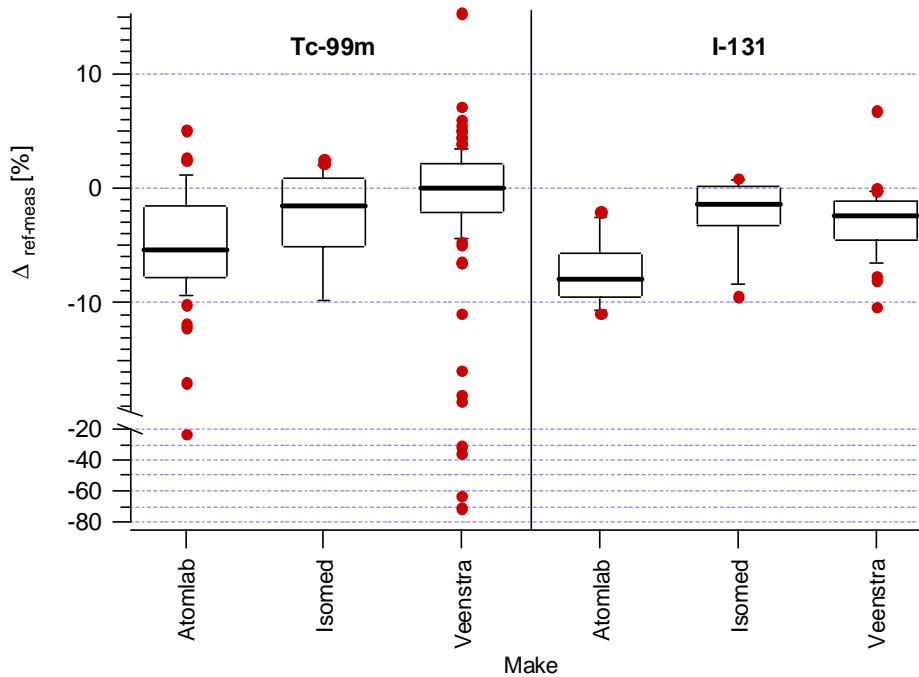


Figure 5: Same results as Figure 4, but tallied by make of instruments. Out of the 248 Tc-99m measurements, 63 were performed with an Atomlab, 24 with an Isomed and 134 with a Veenstra instrument. Out of the 67 I-131 measurements, 13 were performed with an Atomlab, 11 with an Isomed and 41 with a Veenstra instrument.

3.3. Other aspects

At the beginning of the verification and intercomparison campaigns (in 1999 and in 2000), some instruments were still displaying old measurement units (Curies instead of Becquerels) even

though the law had been forbidding their use for half a decade. Official onsite monitoring made it possible to update such instruments or get rid of the most outdated ones.

Making onsite checks also enabled inquiring into the availability and use of long-life stability sources used for daily controls of dose calibrators. In 1999, only about 25% of the laboratories did have such a source. It increased to 75% in the next two years. Since 2002, every laboratory is equipped with such a monitoring source and has been using it systematically.

3.4. General discussion

The accredited laboratory followed up directly every nuclear medicine department with an intercomparison measurement out of the tolerances. Although there were cases of faulty instruments for which maintenance by the manufacturer was necessary, the observed differences were in general due to human errors, since repeating the measurements yielded results within tolerances in most cases. By contrast to I-131, Tc-99m was found to be more prone to such errors, presumably because of its short half-life. Wrong reporting of Tc-99m measurement time alters appreciably the results. Furthermore, when delays in the monitoring procedures occur, the measurements are made at low activities yet the background is not always properly subtracted.

4. Conclusion

It has been more than six years that Switzerland introduced an annual monitoring of dose calibrators for radiopharmaceutical products delivered to patients in nuclear medicine departments. The current situation is quite satisfying since more than 90% of the laboratories tested are within the tolerances and the deviations keep getting smaller.

A strong point of our approach is its complementarity. A verification of the instrument calibration for a wide spectrum of nuclides is performed in the working place. Through the intercomparison we check not only the instrument calibration for the radionuclides in actual use but the working skills of the personnel as well. As shown for Tc-99m sources, this can sometimes lead to large errors.

Its weakest point may be that the calibration factors for most radionuclides in use are not systematically checked and are left to the responsibility of the manufacturers. This can sometimes lead to differences of the order of 5%.

An incidental benefit of the monitoring is to enforce the use of the legal activity unit and up-to-date instruments. More importantly, the enforcement to have a long-life stability source allowed the nuclear laboratories to have independent and regular checks of the stability of the instrument and its calibration factors.

5. References

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