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Original Article

Long-term quality assurance of [^{18}F]-fluorodeoxyglucose (FDG) manufacturing

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Abstract: Nine years of experience with 2286 commercial synthesis allowed us to deliver comprehensive information on the quality of ^{18}F-FDG production. Semi-automated FDG production line using Cyclone 18/9 machine (IBA Belgium), TRACERLab MX_{FDG} synthesiser (GE Health, USA) using alkalic hydrolysis, grade "A" isolator with dispensing robotic unit (Tema Sinergie, Italy), and automatic control system under GAMP5 (minus2, Slovakia) was assessed by TQM tools as highly reliable aseptic production line, fully compliant with Good Manufacturing Practice and just-in-time delivery of FDG radiopharmaceutical. Fluoride-18 is received in steady yield and of very high radioactive purity. Synthesis yields exhibited high variance connected probably with quality of disposable cassettes and chemicals sets. Most performance non-conformities within the manufacturing cycle occur at mechanical nodes of dispensing unit. The long-term monitoring of 2286 commercial synthesis indicated high reliability of automatic synthesizers. Shewhart chart and ANOVA analysis showed that minor non-compliances occurred were mostly caused by the declinations of less experienced staff from standard operation procedures, and also by quality of automatic cassettes. Only 15 syntheses were found unfinished and in 4 cases the product was out-of-specification of European Pharmacopoeia. Most vulnerable step of manufacturing was dispensing and filling in grade "A" isolator. Its cleanliness and sterility was fully controlled under the investigated period by applying hydrogen peroxide vapours (VHP). Our experience with quality assurance in the production of [^{18}F]-fluorodeoxyglucose (FDG) at production facility of BIONT based on TRACERlab MX_{FDG} production module can be used for bench-marking of the emerging manufacturing and automated manufacturing systems.

Keywords: (^{18}F)-fluorodeoxyglucose (FDG), good manufacturing practice, quality assurance, quality control, total quality management

Background

FDG production site facility was built in reconstructed building of Slovak metrological institute, Bratislava within the years 2001-2004 when various quality assurance systems were introduced, the pharmaceutical quality in particular [1-7]. In our country no precedence existed in the field of radiopharmaceutical production. Still, our "specific" investor, which was the Slovak Office of Standards, Testing and Metrology, to receive our future licensees and clients' credit required the user request specification and the design qualification in compliance with all more or less relevant European and world quality management standards [8, 9], stressing the rules of Good Manufacturing Practice (GMP), Good Automated Manufacturing Practice (GAMP), Good Practice of Control Laboratories (GPCL) and Good Distribution Practice (GDP). Quality management system of company according ISO 9001 standard has been certified since 2007 by the Lloyd's Register EMEA (Prague Office).

Our experience of FDG commercial manufacturing may be useful for benchmarking and evaluation of improvements in this field. Principal decisions on FDG production approach are predictable in near future due to a paradigm shift and competition between central manufacturing and in-house preparation schemes, reducing size and complexity of equipment required and the process cost, but still encountering

Table 1. Radioactive purity of ^{18}F

Nuclide	Half-life	Activity calibrated at EOB					
		Irradiated water		Recovery water		Bulk FDG solution	
		Bq/g	ppb	Bq/g	ppb	Bq/g	ppb
F-18	110 m	6.3×10^{10}	-	6.5×10^{10}	-	4.5×10^{10}	-
Cr-51	27.7 d	5113	81	747	12	<10	<0.22
Mn-52	5.59 d	1479	24	958	15	<2	<0.03
Mn-54	312 d	80	1.3	60	1	<2	<0.03
Co-55	17.5 h	6657	106	14003	215	<0.6	<0.01
Co-56	7.73 d	1562	25	2074	32	<2	<0.04
Co-57	272 d	743	12	1119	17	<2	<0.04
Co-58	70.9 d	9428	150	12104	186	<2	<0.04
Ni-57	1.48 d	3477	55	4641	71	<2	<0.05
Tc-95	20 h	709	11	N.D.	N.D.	N.D.	N.D.
Tc-95 m	60 d	100	1.6	N.D.	N.D.	N.D.	N.D.
Tc-96, 96 m	4.28 d	317	5	N.D.	N.D.	N.D.	N.D.
Re-181	1.27 y	141	2	<47	<0.7	<1.7	<0.04
Re-182, 182 m	19.9 h	269	4	<90	<1.4	<5.0	<0.11
Re-183	2.67 d	134	2	<79	<1.2	<4.2	<0.09

N.D. - not detectable.

GMP demands of parametrically controlled aseptic production and pharmaceutical quality control.

Clean rooms

Clean rooms were designed by company BLOCK (Prague/Valašské Meziříčí, Czech Republic).

The dilemma of the operator protection by under pressure in the area of radioactive source and overpressure of clean air around the devices for pharmaceutical processing was solved during the design qualification. Class III/IV tightness (ISO 10648-2:1994) shielded cells with closed synthesis modules, were adjusted for class "C" (ISO class 7) housing. Pressure drop cascades in production area [10] ensured radiation protection against radio aerosols transfer from shielded boxes to operation rooms, and microbiological and particulate contamination from class "D" to class "C".

The commercial devices dedicated to automated dispensing in air grade "A" (ISO class 5) aseptic environment passed scrupulous design qualification and operational qualification procedures.

Automatic synthesizer

ISO and GMP compliant housing for about 1 TBq positron (PET) radiopharmaceuticals synthesis modules under class "C" was designed as:

- Atmosphere class "C" according EEC GMP, - vertical laminar flow (ISO 14644-3e NSF 49), - airtight doors validated at negative pressure below 10 Pafor 12 hrs (containment enclosure tests for class "2" according to (ISO 10648-2:1994), - particle and microbial monitoring of inner atmosphere is possible, - the inner surfaces should be easily cleaned and disinfected by aggressive disinfection means, desirable also sterilisable (stainless steel AISI 316 preferred), - aeriform waste control, automatic closure of outlet air ducts.

Quality control

Analytical methods were validated and periodically (at least once per year) re-validated to obtain type B standard deviation of method [11], and analytical results were assessed using expanded uncertainty with the coverage factor which is equal appropriately $k(\alpha) = 2$ for probability $\alpha = 0.95$. No out-of-specification (OOS) [12, 13] results were obtained.

Dispensing

The dispensing units available at the European market (year 2003) did not pass the external design qualification whose aim was to avoid terminal sterilization and ensure aseptic filling of radiopharmaceuticals into open vials (without septum puncture), with continuous particle monitoring and microbial probing, and consequently enabling in-situ bubble point tests of sterilization membrane. Further, it was required to enable identification of vials, measure volume and activity of radiopharmaceutical in standard vials, and communicate with production information system both on stage of programming the dispensing regime and at distributing information for radiopharmaceutical certificate.

Under the IAEA technical co-operation project, an isolator type shielded laminar box with dou-

Table 2. Average pharmaceutical quality of Biont FDG from 2286 commercial batches

Specification	Test method*	Limits
Declared activity ^{18}F (%)	IC	90-110
^{18}F half-life (min)	IC	105-115
Radionuclidic purity of ^{18}F	GS	>99.9
Concentration of 2-fluoro-2-deoxy-D-glucose (mg/ml)*	HPLC	≤0.05
Concentration of Kryptofix® 222 (mg/ml)*	colorim.	≤0.22
Radiochemical purity of 2-[^{18}F]-fluoro-2-deoxy-D-glucose, with less than 10% fraction of 2-[^{18}F]-fluoro-2-deoxy-D-mannose (%)	HPLC	≥95.0
Radiochemical impurities of [^{18}F] fluoride and acetylated 2-[^{18}F]-fluoro-2-deoxy-D-glucose and 2-[^{18}F]-fluoro-2-deoxy-D-mannose (%)	TLC	≤5.0
Concentration of glucose (mg/ml)	HPLC	≤0.63
Concentration of acetonitrile (mg/ml)****	GC	≤0.41
Concentration of ethanol (mg/ml)****	GC	≤5
Radionuclide impurities (%)****	GS	<0.1%
Bacterial endotoxins (*EU*/ml)****	LAL	<17.5
Sterility****	Ph.Eur. 2.6.1	No CFU

*IC-ionisation chamber (dose calibrator), GS-gamma-ray spectrometry, GC-gas chromatography, HPLC-high-performance liquid chromatography, TLC-thin layer chromatography, LAL-Limulus Amebocytus Lysate test. **Expanded uncertainty with the coverage factor which is equal appropriately $k(\alpha) = 2$ for probability $\alpha = 0.95$. ***The compliance for the maximum recommended dose $V = 10$ ml. ****The result of test are appended in a due time after the production, the injection may be released for use before completion of this part of analysis.

Table 3. Delivery compliance of commercial batches of FDG

Year	Total	Delayed		Not completed batch dispensing		Cancelled		Total compliance
		Number	%	Number	%	Number	%	%
2006	203	4	2.0	0	0	17	8.4	89.7
2007	259	9	3.5	9	3.5	0	0.0	93.1
2008	244	8	3.3	4	1.6	2	0.8	94.3
2009	176	18	10.2	4	2.3	3	1.7	85.8
2010	336	13	3.9	12	3.6	6	1.8	90.8
2011	230	7	3.0	0	0	1	0.4	96.5
2012	249	8	3.2	2	0.8	1	0.4	96.5
2013	274	2	0.7	12	4.4	1	0.4	94.5
2014	315	14	4.4	26	8.3	3	1.0	86.3
Total	2286	83	3.6	69	3.0	34	1.5	91.9

ble door material transfer system (LaCalhén type) was constructed. Its construction materials should withstand the hydrogen peroxide vapours (VHP) and a laminar flow protects the dispensing unit housing also in open state.

The user request specification was formulated like follows:

An aseptic robotize dispensing unit housed in a shielded isolator of grade "A" at rest (ISO 14644-1 class 4.8) for automatic formulation (adjustment of strength of sterile radioactive product by dilution with sterile excipient solution up to 1:10) and dispensing in the batch of 15-25 open sterile and apyrogenic 10-15 ml vials (ISO 8362-1:1990), identified by a bar code, preferentially without necessity of final thermal sterilisation of radiopharmaceutical and ensuring its volume radioactivity standard deviation less than 5% and volume accuracy better than 2% with - manipulation with preparation of sterile components without breaking containment (e.g. sleeve system in inner polymethylmetacrylate/polycarbonate glass front door), - a 0.4-0.5 m/s laminar flow of controlled temperature <30°C and relative humidity <60% in working area, - the radiation shielding for a safe work with 220 GBq (6 Ci) of fluorine-18 in automatic dispensing regime, - tightness minimum of class 3 according to ISO 10648-2, internal pressure control, - a standard operation procedure of the sterilization-in-place of the equipment and its housing, desirable with the vapours of hydrogen peroxide (VHP), - performance of the on-line bubble point test of sterilization membrane integrity, - a safe pass-through for input of sterile materials according to ISO 14644-7 (desirable Double Door Rapid Transfer Port, DPTE system), - access sampling points for in-operation microbial and airborne particles monitoring of grade "B" cleanliness, - an output of capped labelled vials without breaking the aseptic conditions in 2 cm lead containers from the front/rear side of shielded cell, - all prophylactic service of isolator available outside the grade "C" operator room.

An offer of Tema Sinergie company was a winner of the IAEA tender among five companies, and the isolator construction was finished under the IAEA technical cooperation program SLR/2/002.

Production monitoring system

A daily batch production is accompanied by the stock of documents, which are similar to those of any large-scale drug production.

The requirements of 21 CFR Part 11, GAMP4 [14, 15] and GAMP5 were implanted in the information system ensuring registration according to GMP and ISO 9001 rules and using encryption algorithms MD5-SHA1 for the on-line processes documentation, starting with the order acceptance till the issues of delivery documents. The system minimizes or controls subjects influence on records, keeping the hard copies down to those required by FDG authorization. Electronic forms of documents are kept under system Alfresco [16].

Yields of FDG were calculated from the activity delivered from target to synthesis module and resulting FDG solution, controlled by certified dose calibrator (Canberra-Packard). Cross-checking of FDG strength was monitored by another certified device in quality control.

Data treatment

A technical graphing program SigmaPlot® 4.0 for Windows (SPSS Inc., Chicago) was used for statistical evaluations and data presentation.

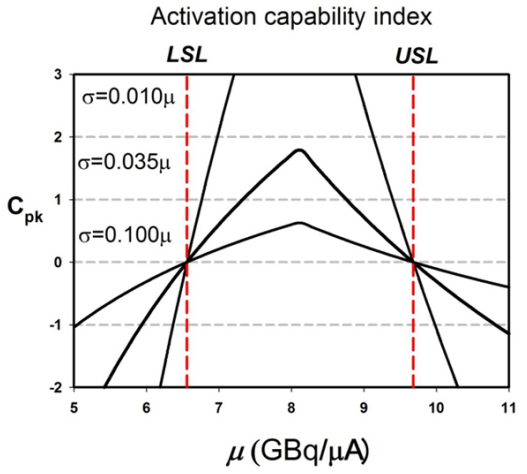

Figure 1. Modelled capability index of activation at specification limit *USL-LSL* = 11σ.

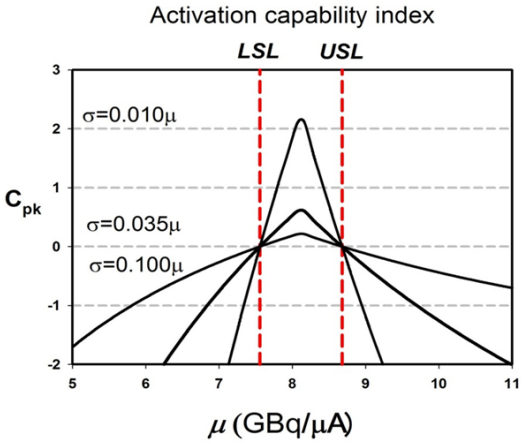

Figure 2. Modelled capability index of activation at specification limit *USL-LSL* = 4σ.

Results and discussion

Activation process

Cyclotron itself is usually not considered as a part of GMP equipment [5], however e.g. in case of FDG its product of activation, ^{18}F is a raw material for ^{18}F-radiopharmaceutical synthesis [7]. We included monitoring of cyclotron in our on-line control as a part of our total quality control [10, 17-19].

As a basic parameter we choose the initial yield of activation *m* (GBq/mA), calculated as

$$\mu = \frac{A_2 e^{\lambda t2}}{I(1 - e^{-\lambda t1})} \quad (1)$$

where A_2 (GBq) is activity of radionuclide (decay constant l) measured at beginning of synthesis (BOS), *I* is beam intensity (μA) during the time of irradiation t_1, and t_2 (the least two being λ-coherent time units) is time between EOB and BOS. Such complex parameter may be influenced by quality of the cyclotron beam and the yield of ^{18}F delivered into synthesis module (and influenced e.g. by concentration of ^{18}O in target water and adsorption of ^{18}F on target and transport capillaries walls or on filterable colloidal particles).

For assessment of process quality we adopted methodology from the Six Sigma quality system [13, 20], namely applying the "process capability index"

$$C_{pk} = \min\left\{\frac{\mu - LSL}{3\sigma}; \frac{USL - \mu}{3\sigma}\right\} \quad (2)$$

This index is considered as a good indicator of process quality, if C_{pk} is above 1.33 and better above 1.5 (when *USL-LSL*≥6σ). This index strongly depends on the choice of lower specification and upper specification level, *LSL* and *USL* respectively (**Figures 1**, **2**). Choice of *USL* is reasonable to derive from a maximal beam permissible for given target construction and *LSL* can be formulated from practical task to produce required activity in a reasonable time (see also the part „In-time delivery" below). For our assessment their values were based on the first series of cyclotron monitoring when *m* = 8.12 GBq/mA and standard deviation *s* = 0.035 *m* were obtained (relative deviation of *m* 3, 5%). The limits *LSL* = 7.56 and *USL* = 8.68 were chosen, i.e. the width of <*LSL*;*USL*> interval was 4*σ* instead of 6*σ*, because the aim was not to control a high reproducibility of activation yield, which is not of crucial importance here, but to get a suitable indicator for discovery of more serious process deviations and non-compliances concerning beam deformation or targetry state.

The two last year's monitoring of activation process capability (**Figure 3**) indicated high reliability of cyclotron performance, just 12 deviations and non-compliance 2.1% took place.

As an example of exploitation of "warning" capability index there was extra thorough review of the activation exhibiting the most neg-

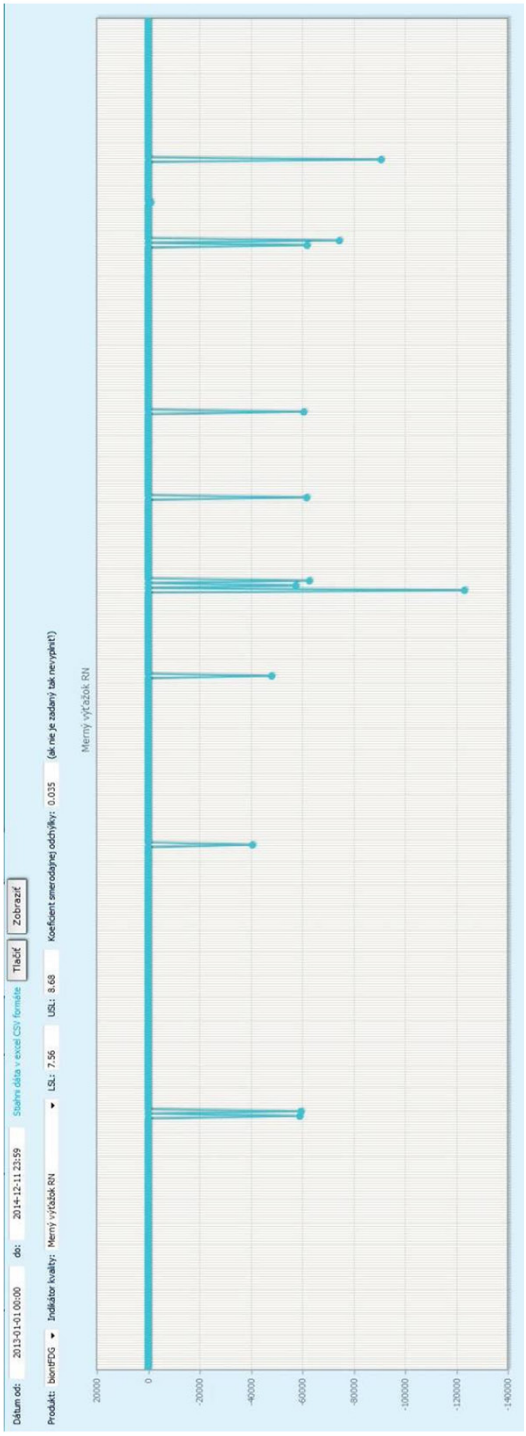

Figure 3. Two-years data for capability index of activation of ^{18}F on Cyclone 18/9 niobium target.

ative value of C_{pk}. It this case the amount of activity prepared for synthesis was as planned, however a non-standard break in irradiation (9 min from 90 minutes of total production time) happened and was reflected in the negative C_{pk} value as a signal of the process declination from a standard procedure of target activation. Though the operator's corrective actions were fully effective in this situation, still some preventive measures should have been considered.

Radioactive purity of ^{18}F

The radionuclide composition of irradiated water in niobium target, and radionuclide purity of recovery water and bulk FDG solution was measured in 2 g samples. The targets with heavy-duty history of foils were chosen to maximise possible impurities content. The samples containing originally 63-65 GBq of ^{18}F were left to for the decay of the latter and measured by HPGe crystal (type GC3519, 35% efficiency, resolution 1.9 keV at 1.33 MeV) and analysed by a DSA-2000/A digital spectra analyser Canberra-Packard with S501/C Genie-2000 and S505 quality assurance software. The activity found was extrapolated to the EOB time. Relative uncertainty of counting was not higher than 20%, and lower limit of impurities detection (LLD) was determined for each uncertain data.

The results of these tests showed clearly that most of the possible contaminants are recovered in the ^{18}O enriched water waste and do not enter into the synthesis process. The activity measurement on the FDG solution is presented for the bulk solution before dilution, the activity level after saline dilution will be even three to seven times lower in the final solution (**Table 1**).

Major activation products in niobium target are isotopes of cobalt (Co-55 and 58) and chromium (Cr-51), and also Mn-52, Ni-57 and Tc-95. Except the lower amounts of Co-56, and Tc-96 (and absence of Cd-109 originated from silver body), the list of impurities relates to the same radionuclides as obtained at activation in a silver target, indicating their origin from Havar alloy foil [21]. Most of radioactivity impurities remain in the solution, which pass the quaternary ammonium resin column for separation of fluorine-18 with impurities of chromium, manganese, technetium and rhenium. The latter are completely removed on the steps of FDG synthesis and purification and do not appear in the bulk solution of FDG product above limit of their detection (LOD), i.e. maximal content of radioactive impurities in resulting bulk FDG solutions was estimated as low as 7×10^{-8} % at EOS.

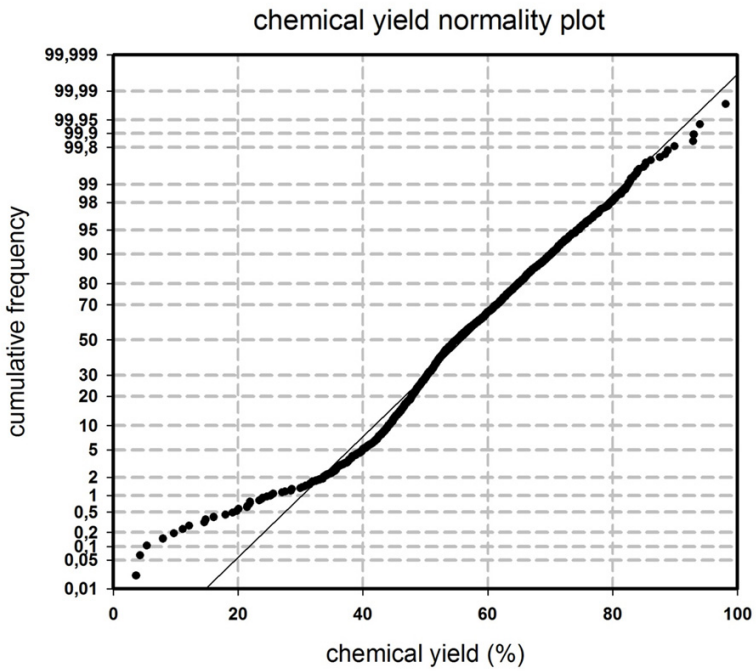

Figure 4. Normality test for corrected (chemical) yield of FDG from TRACERlab MX_{FDG} synthesizer.

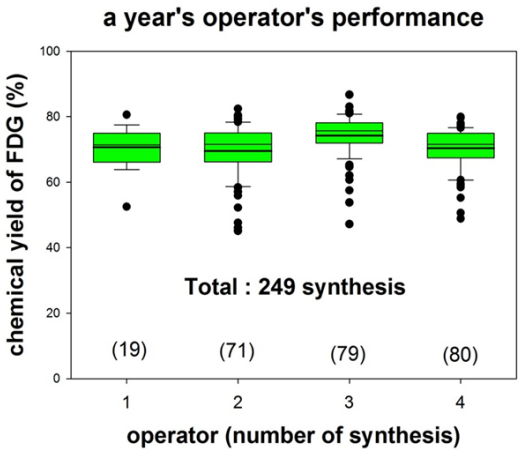

Figure 5. Tukey plot of chemical yield of FDG from TRACERlab MX_{FDG} synthesiser for different operators.

Synthesis yields

The yields corrected on radioactive decay (chemical yields) for the sets of 300-2400 synthesis failed at Kolmogorov-Smirnov normality tests. The mean value and their standard deviation calculated for symmetrical distribution for the first 1320 FDG batches in years 2006-2010 was 68±22%, while the 1082 batches in years 2011-2014, performed at doubled BOS activities (average 221 GBq BOS, compared with 113 GBq of the former set) provided the yield value 50±12%.

Normality plot for total set of data is presented in **Figure 4**. Under conditions of symmetric distribution of all data, the chemical yield was formally 56±11% but the whole set distribution skewness is 3.26 (a long tail to the right of symmetrical distribution for which a skewness is zero) and kurtosis 63.2 (leptokurtic distribution, more "peaked" than a Gaussian distribution for which a kurtosis of 3 is valid). Therefore, further attention was paid to influence of targetry, activity, operators, sets of chemicals (mannose triflate in particular) and disposable synthesis cassettes (**Figures 5** and **6**).

No significant influence of target body (silver or niobium) on chemical yield was observed. Also the losses of activity in target body and PEEK capillary were found to be less than 5%.

By two-ways ANOVA analysis it appeared that the operators skills were found of a minor influence on synthesis yield [13] in opposite to the "stationary" system represented e.g. by TRACERlab FX_{FDG} module [22]. It was difficult to distinguish influence of quality of sets of chemicals and the module disposable cassettes (both ABXadvanced biochemical compounds GmbH). However, by all-pairwise multiple comparison Holm-Sidak method it appeared that the cassettes' quality was almost certainly significant and it was further confirmed by an inter laboratory review. The reason was probably in humidity contents in the cassettes.

It may be remarked, that the statistical approach (the ANOVA analysis and Shewhart diagrams discussed above) and vendors' audit are practically the only way of feasible input materials quality control. Reliable physical testing of small sets of chemicals, cassettes and packing materials is economically not bearable and manufacturer should rely on output quality control at the site of suppliers [10].

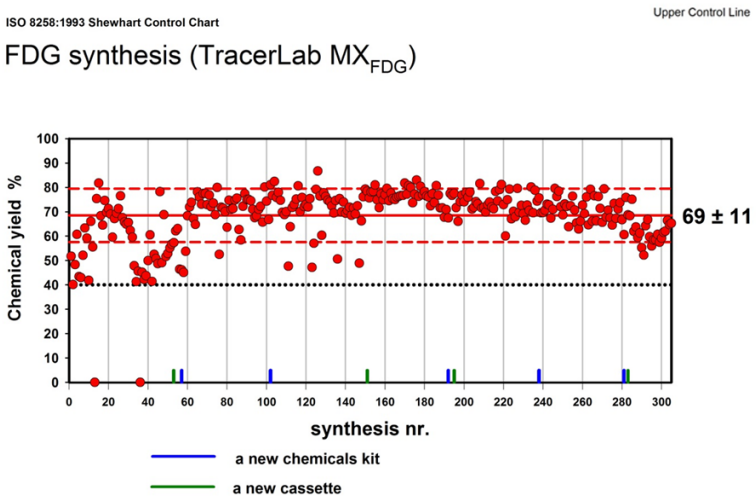

Figure 6. Shewhart control chart.

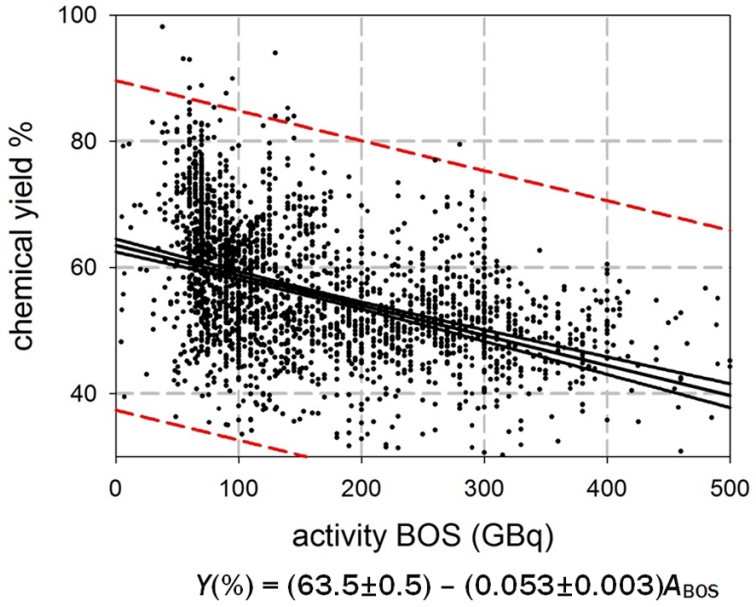

Figure 7. Chemical yield of ^{18}F-FDG as a function of initial (BOS) activity.

Further, influence of activity on the radioactive decay corrected (chemical) yield and radiochemical purity of FDG is demonstrated by **Figures 7** and **8**. As can be expected conferring high radiation stability of FDG [23, 24], the radiochemical purity is not extensively influenced by the activity of fluorine-18 at the BOS. When presented by linear regression, decreasing of radiochemical purity of FDG due to increasing activity at BOS can be expected as low as 0.5 percentage points. At the same time, influence of BOS activity on chemical yield was expressed more strongly and the extrapolated "zero-activity" yield 64% may be diminished to about 38% expectation at the BOS activity 500 GBq. Manufacturer's declared parameters of TRACERlab MX$_{FDG}$ modules are for typical average chemical (decay corrected) yield 70±4%, independent of starting activity level up to 10 Ci, and radiochemical purity better than 99.5% [25].

Quality parameters

Product sterility and apyrogenity, the most important parameters when considering the risk management of diagnosed patient, should have been ensured by manufacturing scheme parameters. During the whole manufacturing period no unsterile product was detected. Also the sensitive apyrogenity test showed that the average bacterial, endotoxins concentration was deep below the pharmacopoeial limit for intravenous applications (**Table 2**).

Increased attention to the FDG quality has been paid at our PET centre yet during manufacturing preparation period, since its purchase delivery from UJF original marketing authorization holder (MAH) from Prague took about 4-5 hours [23, 24].

Routine manufacturing FDG quality was assessed according to European Pharmacopeia [7] and following out-of-specification criteria [12, 19].

Automatic dispensing

The operation qualification (OQ) of dispensing unit was confirmed by 48 dispensing runs of in-raw dispensing 15-25 ml of sterile physiological solution into 7-10 sterile crimped 10R (ISO 8362-1:1990) vials from 50 total without any fatal (i.e. in-correctable within real time of 10 min) fault, i.e. each batch was dispensed into 7-10 vials, and the crimped vials with sterile

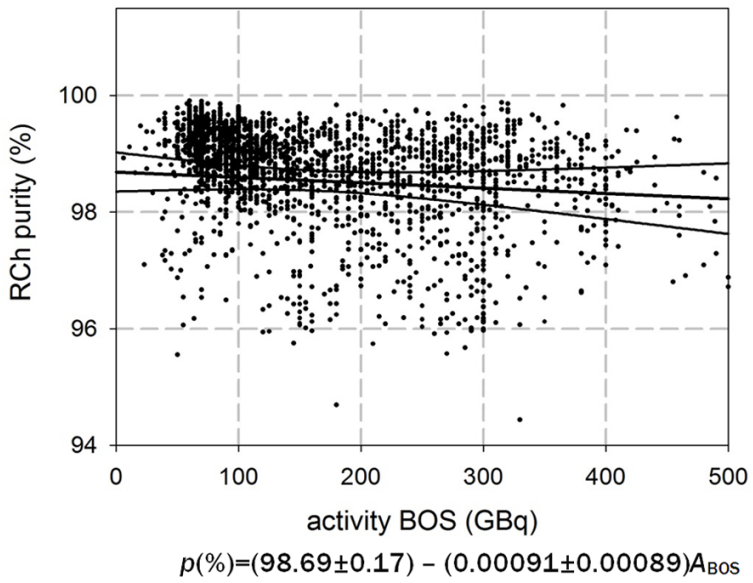

Figure 8. Radiochemical purity of ^{18}F-FDG as a function of initial (BOS) activity.

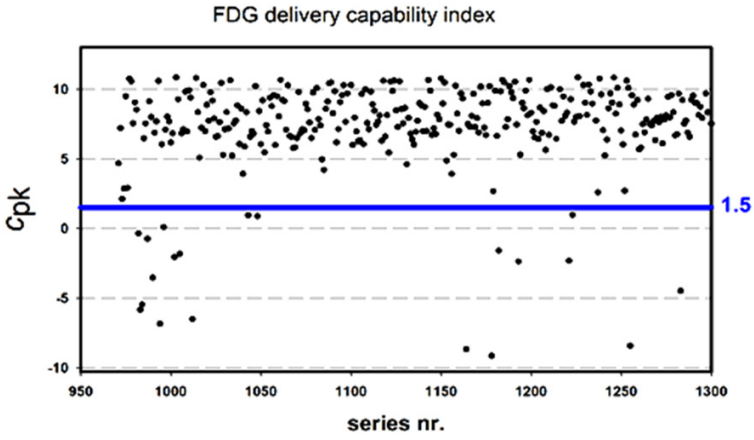

Figure 9. In-time delivery indicator of quality.

solution were delivered to small containers from DMC 3/75 shielded isolator. Apyrogenity test was performed on the day of filling, the sterility test was performed by authorised Slovak company one week after filling, both for the first and last vial from each run. Neither pyrogenic nor non-sterile vials content was found during the OQ.

In-time delivery

In-time delivery is a very important factor for medical clients and their patients, its USL being much below the expiration time of FDG (8-10 hrs from EOS in our case).

We choose reference time for "ready-for-QC" from interval t = <t_1-25;t_1+40> where t_1 is official planned time (min) of finished dispensing according the order for FDG manufacturing. A 40-minutes delay was considered to be acceptable by clients and too early performance, 25 minutes before official time was considered too early and unfavourable due to require excess of raw fluorine-18. Only few of manufacturing cycles 1.6% were outside of these tolerable limits (**Table 3**, **Figure 9**).

Dependability of manufacturing segments

Deviations and non-compliances of basic segments of manufacturing processes:

● Materials supplies, ● cyclotron performance, ● targets and transport capillaries, ● radiation monitoring, ●HVAC, ● shielding boxes, ● synthesisers, ●dispensing unit, and ● delivery

were registered and reported by operators on-line to be subject of correction actions in real time and/or preventive actions in future.

Majority of non-compliances was connected with the mechanical operations in dispensing unit, synthesis modules, shielding boxes and cyclotron (targets and capillaries) (**Figure 10**).

Conclusions

Semi-automated FDG production line using Cyclone 18/9 machine (IBA Belgium), TRACERLab MX_{FDG} synthesiser (GE Health, USA) using alkalic hydrolysis, grade "A" isolator with dispensing robotic unit (Tema Sinergie, Italy), and automatic control system under GAMP5 (minus2, Slovakia) was assessed by TQM tools as highly reliable aseptic production line, fully compliant with Good Manufacturing Practice

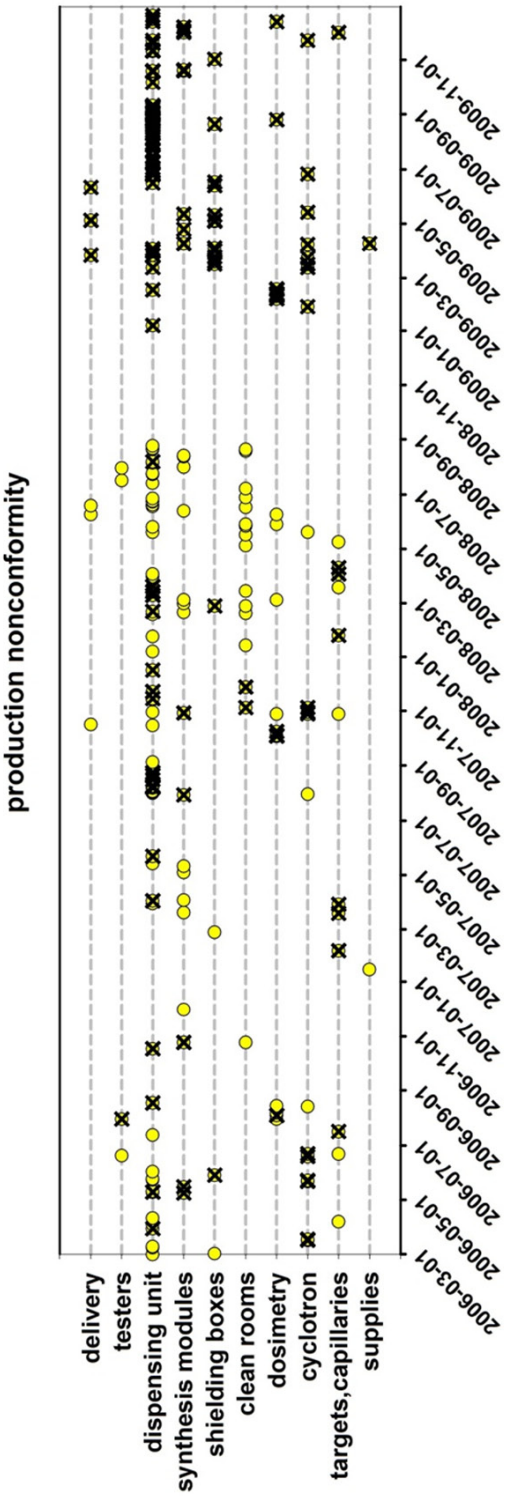

Figure 10. Manufacturing equipment reliability.

and just-in-time delivery of FDG radiopharmaceutical. The stages of nuclear activation and synthesis are not sensitive to operator's performance. Fluoride-18 is received in steady yield and of very high radioactive purity. Its increased activity diminishes the yield of FDG and in much less extent also the purity of last. Synthesis yields exhibited high variance connected probably with quality of disposable cassettes and chemicals sets. Most performance non-conformities within the manufacturing cycle occured at mechanical nodes of dispensing unit.

From 2286 commercial synthesis there was a minimal number of out-of-specification product: one with non-compliant pH value and three times non-compliant radiochemical purity. The in-specification product and total compliance of completed batch and in-time requested deliveries was 91.9 %. Aseptic conditions have been fully preserved during the manufacturing period.

Since the pharmaceuticals production is a strongly regulated industry, some additional merit of further quality systems is usually not envisaged. Still the implementation of total quality management under ISO 9001 introduces higher assurance for quality production performance such as the issues of the management responsibility, customer needs and satisfaction, contractual arrangement, subcontractors' selection and audit, test/inspection methodologies, statistical methodologies, internal audits, job training, personnel competence control, corrective and preventive actions, and also costs evaluation in the area of failures. These features add value and creditability of the enterprises, which are of sophisticated many-sided character and often beginners in the field, like the new radiopharmaceuticals distribution centres in developing countries.

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Disclosure of conflict of interest

None.

Abbreviations

ANOVA, Analysis of variance; BOS, Beginning of synthesis; CFR, Code of Federal Regulations (USA); CFU, Colony Forming Unit; EANM, European Association of Nuclear Medicine; EDQM, European Directorate for the Quality of Medicines & HealthCare; EOB, End of beam (on cyclotron); EOS, End of synthesis; EU, Endotoxin unit; EudraLex, The Rules Governing Medicinal Products in the European Union; GAMP, Good Automated Manufacturing Practice; GC, Gas chromatography; GCLP, Good Control Laboratories Practice; GDP, Good Distribution Practice; GMP, Good Manufacturing Practice; HPLC, High-performance liquid chromatography; ISO, International Organization for Standardization; ISPE, International Society for Pharmaceutical Engineering; LAL, Limulus amebocytus lysate; LSL, Lower specification limit; MAH, Marketing Authorisation Holder; OOS, Out-of-specification; OQ, Operation qualification; PIC, Pharmaceutical Inspection Convention; PQ, Performance qualification; QA, Quality Assurance; QC, Quality control; QMS, Quality management system; TLC, Thin layer chromatography; UJF, Nuclear Physics Institute of the ASCR (Czech Republic); USL, Upper specification limit; VHP, Hydrogen peroxide vapours.

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