Combining multi-product commercial production in a GMP environment with Clinical & R&D activities

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Introduction

Radiopharmaceutical facilities mostly provide [^{18}F]FDG and are progressively evolving into multi-product sites to support new developments and R&D programs. In this paper, three successful sites in Europe handling both routine production and R&D activities will be described.

Methods

In order to combine all the activities in a safe way, a risk-assessment should be designed and implemented. There a several methodologies such as FMECA, FMEA etc. One of the critical steps in the radiopharmaceutical production is the synthesis. The use of a fully automated (minimum human intervention) synthesizer with disposables cassettes; easy to use (training, SOP, software); reliable and robust is an essential component to mitigate the risks.

Results

The Medical Imaging Center of University of Groningen, in the Netherlands, is one of the most active centers in Nuclear Medicine. The center has been producing routinely a wide range of radiopharmaceuticals since 1992; [^{18}F]FDG, [^{18}F]FDOPA (electrophilic), [^{18}F]NaF, [^{18}F]FES and [^{18}F]PSMA, [^{68}Ga]DOTATOC, and also [^{11}C]choline, [^{11}C]methionine, [^{11}C]PiB, and [^{13}N]NH_3. The center combines the routine production with an intense program covering basic research, pre-clinical and clinical research studies in several areas (basic radiochemistry, neurology oncology, and cardiology). The most Frequent produced ^{18}F-tracers are [^{18}F]FDG, [^{18}F]NaF, [^{18}F]PSMA and [^{18}F]FEOBV. They are all produced on dedicated Synthera® synthesis modules. Currently, [^{18}F]FDOPA (nucleophilic) and [^{18}F]FES are under development using the same type of Synthera® platform.

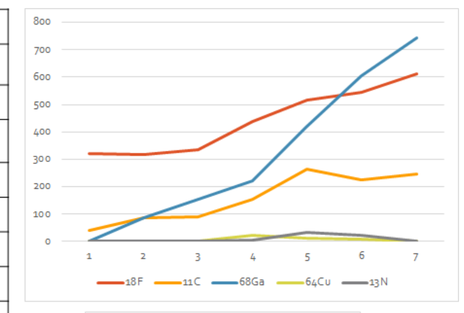
Picture of the UCMG facility in Groningen/NL

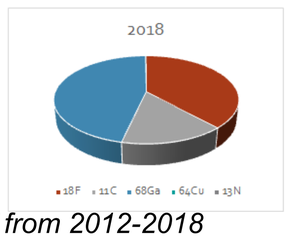
Nr.		2018	2017	2016	2015
1	$H_2{}^{15}O$	1	-	-	38
2	^{18}F-FDG	255	228	247	240
3	$^{13}NH_3$	26	16	42	41
4	^{18}F-Dopa	46	44	66	64
5	^{11}C-Tyrosine	-	-	-	-
6	^{11}C-Choline	17	32	47	55
7	^{11}C-Methionine	41	23	26	20
8	^{89}Zr-tracers totaal**	48	42	69	40
9	^{11}C-Raclopride	5	15	-	-
10	^{11}C-HTP	-	-	-	-
11	^{68}Ga-Dota-Toc	113	108	93	37
12	^{18}F-FES	34	34	38	35
13	^{18}F-FLT	-	-	-	-
14	^{68}Ga-PSMA-Hbed	158	92	15	-
15	^{11}C-PK11195	29	18	17	10
16	^{11}C-Verapamil	-	-	-	-
17	^{11}C-PIB	33	33	34	20
18	^{18}F-NaF*	6	40	37	3
19	^{11}C-MDL	-	-	-	-
20	^{11}C-Acetate	-	-	-	-
21	^{18}F-FDHT	15	16	19	25
22	^{11}C-DASB	-	2	5	27
23	^{11}C-SA4503	-	-	-	-
24	^{18}F-FEOBV	36	22	3	3

List of tracers produced at UCMG from 2015-2018

ICNAS is a research unit of the University of Coimbra in Portugal that hosts a GMP-compliant PET production facility, which supports clinical and pre-clinical R&D programs and supplies RPs to nearby hospitals. The unit is in operation for distribution since 2012 and currently has 5 radiopharmaceuticals (RPs) authorized in the market ([^{18}F] FDG, ([^{18}F] FCH, [^{18}F]NaF, and [^{68}Ga]DOTA-NOC and [^{68}Ga]PSMA). All produced with the Synthera® platform, which in total represents over 5000 cycles. An extensive R&D program is in place with production of other tracers based on ^{18}F (F-DOPA), [^{13}N]NH_3, ^{11}C (Methionine, Raclopride, Flumazenil, PK11195, β-CIT and PiB) and ^{64}Cu -ATSM.

	2012	2013	2014	2015	2016	2017	2018
^{18}F-FDG	322	309	280	337	429	484	517
^{18}F-NaF			3	20	19	14	14
^{18}F-Colina		7	49	75	55	26	33
^{11}C-PiB	40	37	35	87	131	119	178
^{11}C-CITFE				3	45	69	38
^{11}C-PK11195			12	15	52	18	24
^{11}C-Raclopride		41	22	27	26	3	
^{11}C-Metionina			12	8	12	10	13
^{18}F-DOPA				3	14	20	49
^{13}N-Amónia				6	32	22	3 3
^{68}Ga-DOTANOC		85	154	220	354	351	400
^{68}Ga-PSMA				3	65	254	343





List of tracers produced and evolution at ICNAS/PT from 2012-2018

The PET centre of the KU Leuven has been operating for 28 years producing several radiopharmaceuticals for routine use; such as: [^{13}N]NH_3, [^{18}F]FDG, [^{18}F]-FET, [^{15}O]H_2O, [^{11}C]methionine, [^{11}C]-PiB. The PET center has a strong cooperation with several pharmaceutical companies (Merck, J&J, UCB among others) supporting their drug development mainly in the CNS area. Recently, the center has built GMP laboratories to meet the evolving strict pharmaceutical regulations. Besides, the non-GMP lab is used for radiochemistry and radiopharmaceutical research and tracer production for non-clinical applications.

Conclusion

The three centers described have demonstrated that the combination of routine GMP production of multiple radiopharmaceuticals and a busy research program can be successfully achieved. The synthesizer is a key element to be considered. In summary, pros and cons are listed by the users for the synthesizer used in most of these facilities.

Synthera®+ platform: (from left to right) Synthera®+ synthesized with IFP loader, Synthera® synthesizer, Synthera®+ HPLC & Synthera® Extension

PROS

- Reliable and robust
- Small and easily fit in the hotcell
- Short preparation time
- Software is easy to understand (fast learning, fast to operate)
- Software intuitive to develop new sequences (open platform)
- Synthera® platform is flexible(different IFPs for different tracers, easy to adapt the software program & modular concept with versatile Synthera® Extension and HPLC systems)
- New version comes with the electronics outside & possibility to install the automatic IFP loader (to load the cassettes automatically)

CONS

- Vacuum pump needs attention & maintenance with the previous versions
- RFID reader issue in the previous versions

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