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

Cristiana Gameiro[1], Ian Oxley[1], Vasko Kramer[2], Antero Abrunhosa[3], Maria Vosjan[4], Arnold Spaans[4]

[1] IBA SA, Louvain-La-Neuve/BE, [2] PositronPharma, Santiago/CL,[3]ICNAS, Coimbra/PT; [4]BV Cyclotron VU, Amsterdam/NL

Introduction

Mono-product facilities are turning to multi-product to cope with decreasing prices of [^{18}F]-FDG (FDG) and to support R&D programs. The aim is to demonstrate that in the same facility and equipment, a busy research program can be safely integrated into commercial production..

IFP™ disposable cassette (Integrated Fluidic Processor)

Synthera® Platform designed for a GMP environment

Methods

To combine both activities in a safe way a risk-assessment should be designed to identify key control points. The use of a fully automated platform (e.g. IBA Synthera) and its disposable cassettes can prevent human errors, reduce risk of cross-contamination and improve reliability. A production schedule, training and labeling procedures should also be considered.

RANKING SCORE	SEV = Severity of Effect on Patient
1	Minor/No Effect - no consequence to patient safety.
2	Mild Effect - Patient is mildly affected.
3	Significant Effect - Severe impact on the patient. Possibility to kill or severely injure the patient.

RANKING SCORE	OCCURRENCE (OCC)
1	Low Probability. Risk Event extremely unlikely
2	Medium Probability-Risk Event is not frequent.
3	High Probability.Risk Event is/could be a common

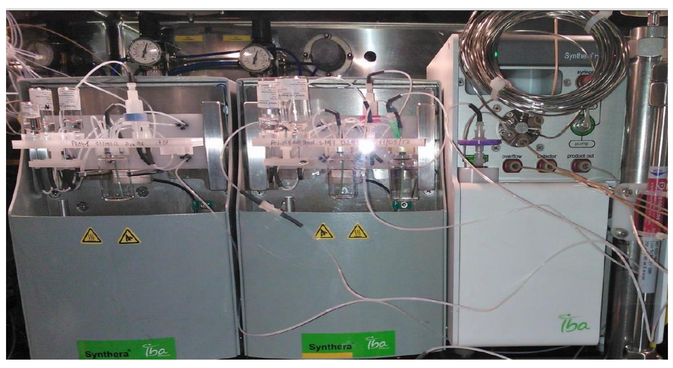
RANKING SCORE	DETECTABILITY DESCRIPTION
1	Risk Event is always immediately detectable.
2	Risk Event is normally detectable.
3	Risk Event may or may not be detected.

Acceptable	ALARP	Not acceptable
1	6	12
2	8	18
3	9	27
4		

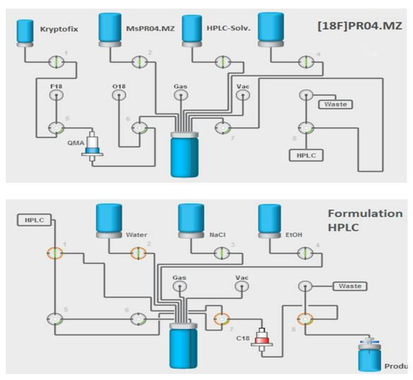
FMEA – Failure Mode and Effects Analysis			ANALYSIS			
FAILURE MODE	EFFECT	CONTROLS	SEV	OCC (Freq)	DET	RPN S x O x D
Mix-ups & cross-contamination: R&D & routine production of several tracers	Business & GMP risk	Use of disposables (line clearance) Appropriate training of the staff Minimize human intervention Well-defined planning SOPs/procedures Labelling ;Quality control	3	2	1	6
Risk of bioburden & endotoxins from starting materials	Business & GMP risk	Work only with qualified supplier Bioburden & endotoxins control at the supplier Periodic assessment of bioburden before filtration etc…	3	1	2	6

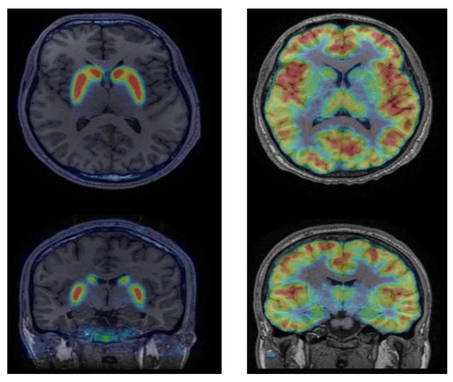
Results

Positronpharma in Chile delivers FDG daily to several hospitals and produced > 1600 Ci FDG in the last 3 years. In addition, [^{18}F]-(FCH, NaF, FET, FLT, F-MISO, DMFP), [^{68}Ga]-DOTA-peptides and PSMA-11 have been implemented as well as two more INDs: [^{18}F]-PR04MZ and MHMZ were translated into clinical studies.



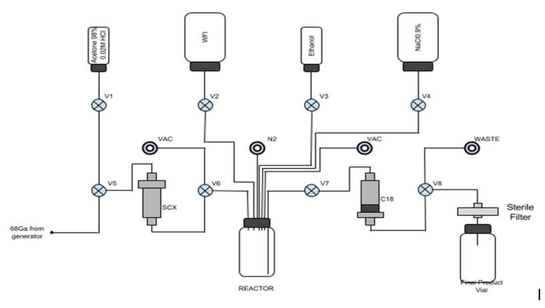
Synthera® set-up in PositronPharma. New Synthera® modules were purchased recently.



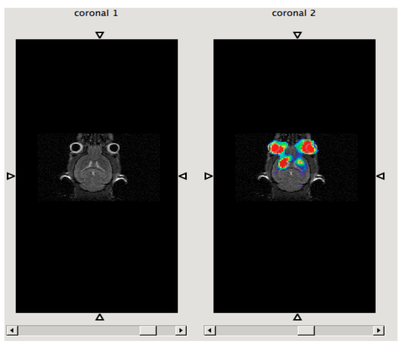


Upper left: Radiosynthesis and formulation after HPLC-purification of ^{18}F-PR04.MZ; **Center:** PET/MRI fusion, transaxial and coronar view of ^{18}F-PR04.MZ binding in striatal region, 15 min frame, 90 min p.i.; **Right:** PET/MRI fusion image of ^{18}F-MH.MZ binding to cortical and subcortical $5HT_{2A}$ receptors.

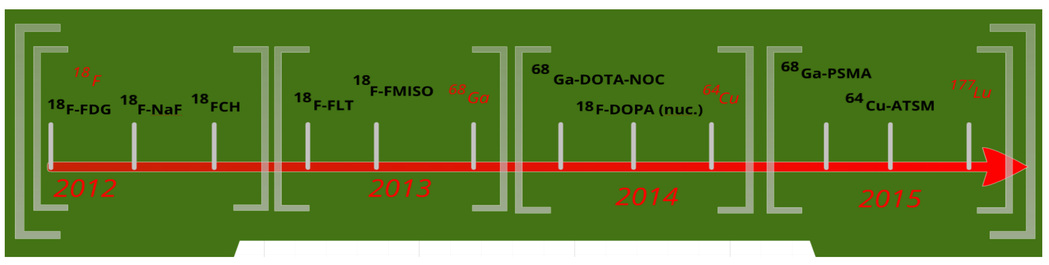
ICNAS a research unit of the University of Coimbra hosts a GMP-compliant PET production facility which supports clinical and pre-clinical R&D programs and supplies RPs to nearby hospitals. Currently it has five RPs authorized in the market (^{18}F-: FDG, FCH, NaF) and ^{68}Ga-DOTA-NOC. All are produced on IBA Synthera and together represent >2000 production cycles since 2012. An extensive R&D program is in place with plans for production of other [^{18}F]-tracers.



^{68}Ga-DOTA-NOC Production

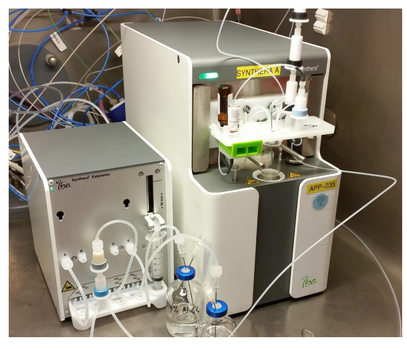


R&D compounds



ICNAS production timeline

BV Cyclotron VU in Amsterdam is a private company with a GMP-compliant PET production facility. Since the 90's FDG is delivered for the Dutch hospitals (annual output of > 7300 patient doses (11 TBq)). ^{18}F-FCH and ^{18}F-FBB (Florbetaben) are also commercially produced with annual output >1400 (1.7 TBq) and >340 patient doses (1.1 TBq), respectively. Besides the commercial productions there is also room for an R&D program, e.g., currently improvement of the production of ^{18}F-FCH is examined.



Synthera® Synthesizer and Extension set-up at BV cyclotron for the optimization of ^{18}F-FCH process.

Conclusion

As a conclusion, the sites described have been functioning for several years and are able to safely combine commercial daily production while keeping a highly active R&D program with more than ten different tracers developed for pre-clinical and clinical applications.