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CYCLOTech - An Innovative Approach for the Reliable Production of ^{99m}Tc - Technetium

"Go to the Market Plan"

CYCLOTech Project

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Documento Técnico submetido para suporte à Candidatura ao Título de Especialista no Grupo 7 – Saúde e Protecção Social / Área de Estudo 72 – Saúde / Área de Educação e Formação 725 – Tecnologias de Diagnóstico e Terapêutica / Medicina Nuclear

Porto, 20 de Maio de 2013

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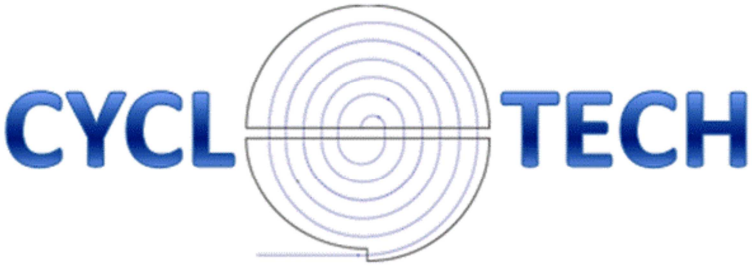


An Innovative Approach for the Reliable Production of Technetium99-metastable

Abstract

CYCLOTech is a high-tech Project, related with an innovative method for direct production of a radioactive pharmaceutical, used in excess of 85% of 35 Million Nuclear Medicine procedures done yearly, worldwide, representing globally more than 3 Billion Euros. The CYCLOTech team has developed an innovative proprietary methodology based on the use of Cyclotron Centers, formally identified as the Clients (actually, there are around 450 of this Centers in function worldwide), to directly produce and deliver the radiopharmaceutical to the final users, at the Hospitals and other Health Institutions (estimating at around 25.000, worldwide). The investment still need to finish Research and Technological Development (RTD), Industrial, Regulatory and Intellectual Property Rights (IPR) issues and allow the introduction in the Market is 4,35 M€, with a Payback of 3 years, with an Investment Return Rate (IRR) of 81,7% and a Net Present Value (NPV) of 60.620.525€ (in 2020).

Resumo

CYCLOTech é o nome que designa um Projecto eminentemente tecnológico, relacionado com o desenvolvimento de um método inovador para produção directa de um medicamento radioactivo (^{99m}Tc-Tecnécio), usado em mais de 85% dos cerca de 35 Milhões de exames efectuados em Medicina Nuclear anualmente, representando globalmente mais de 3 mil milhões de Euros no Mercado Global. ***CYCLOTech*** representa o desenvolvimento de uma metodologia inovadora própria, baseada no uso de Centros equipados com Ciclotrões (existindo cerca de 450 Centros deste tipo pelo mundo) para produção directa do ^{99m}Tc e distribuição aos utilizadores finais, nos Departamentos de Medicina Nuclear existentes nos Hospitais (e que são cerca de 25.000 distribuídos pelo mundo). O investimento necessário para garantir as condições para finalizar a pesquisa e resolver as questões industriais, regulatórias e as inerentes à Protecção dos Direitos de Propriedade Intelectual e Industrial e à introdução no mercado é de cerca de 4,35 M€, com um Payback de 3 anos, uma Taxa Interna de Retorno (TIR) de 81,7% e um Valor Actual Líquido (VAL) de 60.620.525€ (em 2020).

1 Executive Summary

Nuclear Medicine is an autonomous Medical Specialty where low doses of radioactive materials are used for diagnosis, by imaging and non-imaging techniques, as well as for therapy in many disease processes (WHO, 1960). Over 85% of Nuclear Medicine Imaging procedures uses Technetium-99metastable (^{99m}Tc), an artificially produced radioisotope, as the imaging component for labeled compounds, making it the most widely used medical radioisotope in the world.

^{99m}Tc is the daughter nuclide of another radioactive material, Molybdenum-99 (^{99}Mo), whose natural process to reach stability, forces it to decays into ^{99m}Tc. To make this isotope available for medical application, pharmaceutical companies developed a biomedical device - ^{99}Mo/^{99m}Tc generators - that allow them to provide ^{99m}Tc to Nuclear Medicine Departments worldwide, based on that Nuclear Physics phenomenon. There is no way to produce generators without ^{99}Mo, and without them there will be no ^{99m}Tc available for Nuclear Medicine Departments worldwide.

World production of ^{99}Mo is based on Nuclear Fission very specific processes, that uses "Nuclear Weapons grade" Highly Enriched Uranium-235 (HEU), occurring in just 5 Nuclear Reactor plants and only 4 Processing Facilities.

The problem consists on the fact that all of them were built in the late 50's, early 60's, being old and subject to an increasing number of problems and service interruptions, implicating long repair times and with consequent supply disruptions. As a logical result, there is no reliable solution for supplying ^{99m}Tc and all the already identified possible solutions have pitfalls and critical issues to solve. Nevertheless, the demand is continuously rising, increasing the international dependency on actual providers.

The "End-Users" of ^{99m}Tc are more than 30.000 Nuclear Medicine Departments (NM Departments) worldwide, which use it as the imaging - radioactive - agent for labeling around two tens of distinct molecules, indispensable to perform over than 35 million procedures worldwide every year. By definition, those NM Departments aren't prepared for the radiopharmaceutical production (only labeling), and so this role has to be assumed by other specialized players, adequately prepared and trained (and regulatory approved): the Cyclotron Centers. Those will be the Global Market, for the CYCLOTech Company, which is expected to grow from the existing 400 to 450 Cyclotron Centers worldwide, to around 600 by 2015[1].

CYCLOTech approach relies on the direct production of ^{99m}Tc, using a stable, non-radioactive precursor material (^{100}Mo, in contrast to HEU), being transformed through distinct approaches in Cyclotrons instead of Nuclear Reactors. Cyclotrons are widely disseminated throughout the world (actually circa of 450, in contrast to just 5 Nuclear Reactors), producing almost no radioactive waste, since the precursor material consists on stable atoms

[1] Source: IAEA – International Atomic Energy Agency, IAEA-DCRP/2006

(in opposition to a process that originates in excess of 99,5% of highly radioactive, thus very dangerous and costly to handle, waste).

CYCLOTech concept is so that CYCLOTech's main products can be described as the License and the sub-products to supply the Technological Solution. The Licensing, in the form of a "Non-Exclusive License", will be contractually agreed accordingly with the specific customer nature.

Worldwide recognized experts consensually agree that the prices of ^{99m}Tc will rise, mentioning multiplying factors between four and ten in comparison with the current figures. They also agree that the Technology based on the use of Cyclotrons to directly produce ^{99m}Tc is the one that should implicate the smallest raise in the final prices, as it is admitted, since the first Panel of Experts, assembled under the designation of "Committee on Medical Isotope Production without Highly Enriched Uranium" (that produces their final report in 2009, the document named "Medical Isotope Production Without Highly Enriched Uranium", to be founded in <http://www.nap.edu/catalog/12569.html>) as well as in all the documents related with the supply of Medical Radioisotopes produced by the "OECD/NEA High-level Group on Security of Supply of Medical Radioisotopes" and many others after them.

CYCLOTech Pricing Strategy is based on the need for the Cyclotron Centers to find its products attractive, so it has been planned to support it, essentially, through an "Entry-Fee" (at the moment of Licensing Contract signature) and 15% royalties of the billed amounts of ^{99m}Tc. Calculations were done using the factor "**2X**" (so admitting that ^{99m}Tc prices, in the "worst case scenario", will only double the present figures) what, by itself, should constitute a very interesting advantage, once prices will stabilize.

From the promotional point of view, this is a typical "B2B"model. The chosen approach will be personalized, based on the direct contact with Cyclotron Center owner's, starting via the professional and personal networking of the CYCLOTech's core members and proceeding with the regular presence on all the relevant International Events. In the meanwhile, scientific and technical articles will be produced and published on the main specialized media. Potential clients might be invited to visit the "Show-Room" Demonstration Site (to be placed in Portugal) that will also serve for continuing Research and Technological Development (RTD) and for Educational and Training purposes.

The Placement Strategy will be addressed based on differentiated approaches taking into account a pre-established geographical strategy, that will allow the identification of the sites where the Cyclotron Centers (the CYCLOTech's Clients) should be installed to better and most efficiently serve the NM Departments (the clients of the Cyclotron Centers). The specific nature of the Potential Client will be considered, always according with a previously established geographical evaluation, segmenting the Market between "Already existing Cyclotron Centers" and "New Cyclotron Centers". In this last case, the approach will be established via a dedicated channel, to be established and developed directly together with Cyclotron Manufacturers. Under special

circumstances, CYCLOTech Company might consider adequate to participate on pre-existing Cyclotron Centers and/or develop (normally – and always preferably – in partnership with local players) local solutions from the start.

CYCLOTech Company will be based on a multidisciplinary, highly skilled and dynamic group of professionals oriented on the Technological and the Entrepreneurial directions, intending to develop all the mechanisms and strategies to efficiently address and supply the market needs. In both directions, there will always be very competent and experienced members and three Patents have been already submitted to demonstrate its effectiveness, with some members denoting relevant international aspects and experience. Even if there are two distinct fields, the connections and permanent interaction between them are assured by elements able to interface both sides, as it is the case of the Company leader.

CYCLOTech Direct Production System should be able to enter the Market late 2014 or beginning of 2015**,** after solving issues related with Technology development, Industrial Property Rights (IPR) protection and Regulatory Approval considering the EMEA and FDA regulated Markets (EU, USA and Canada).

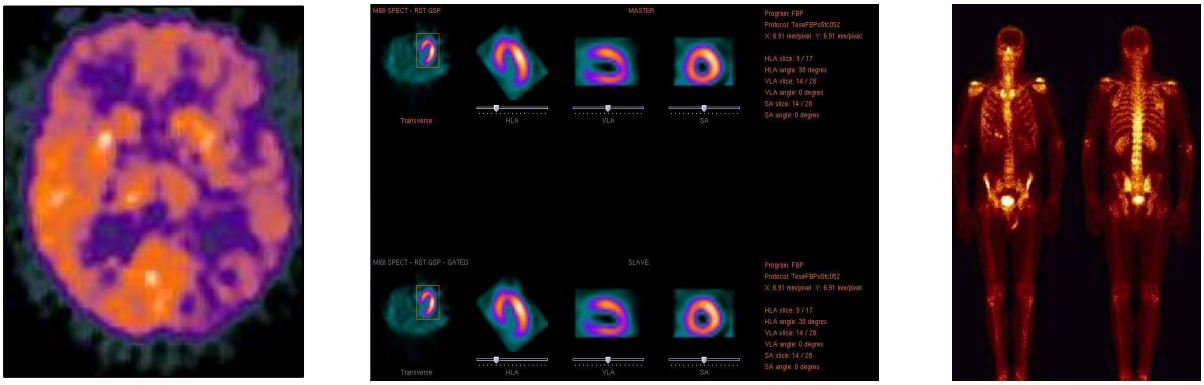
Assuming an Investment of 4.350.000€ until 2018, a Net Present Value (NPV) of 60.620.525€ (in 2020) has been calculated, as well as an Internal Rate of Return (IRR) of 81,7%, while the Payback Period is estimated to be less than 3 years.

*As a "***Quick Summary***", the CYCLOTech Project is intended for Cyclotron Center owners, who already are established on the Market, producing and distributing other medical radioisotopes. The ^{99m}Tc Direct Production System, is an innovative proprietary system developed at the CYCLOTech Project, being an additional Service / Product ready to be offered to the existing and to the new Clients, that can integrate the Cyclotron Center Value Chain and, with a very reasonable additional investment, add one highly profitable new-Product (or "Product-Line") to its Portfolio. Unlike Nuclear Reactor's based actual ^{99}Mo / ^{99m}Tc Production System, this ^{99m}Tc Direct Production System is Reliable, Cheaper, Safer, Cleaner and Easier to spread worldwide in a short-term.*

2 Profiling the Problem

2.1 Problem Identification

The CYCLOTech Project is related with the Nuclear Medicine field. Nuclear Medicine is an autonomous Medical Specialty where low doses of radioactive materials are used for the diagnosis, by imaging and non-imaging techniques, as well as for therapy in many disease processes (WHO, 1960). It is a very relevant medical field, growing steadily at a worldwide rate consistently placed around 8% each year, and the main fields of interest (in 2012) were Oncology (around 55% of the average workflow), Cardiology (around 30%) and Neurology (with a little less than 10%).



Neurology (10%) **Cardiology (30%)** **Oncology (55%)**

Figure 1 – Typical Workflow Partition in a Classic Nuclear Medicine Department

It is common that Nuclear Medicine procedures results on changes on Patient Management in more than 40 to 45% of the cases, demonstrating its more than relevant value and interest, allowing the establishment of a high precision clinical diagnostic, that quite often, is available long before any other modality, so allowing a much more efficient handling and a better prognosis, so benefiting both, the society and the patient himself.

Over 85% of Nuclear Medicine Imaging procedures uses ^{99m}Tc, an artificially produced radioisotope, as the imaging component for labeled compounds, making it the most widely used medical radioisotope in the world. Also, most of the equipments used in Nuclear Medicine are being optimized – already for more than 35 years – for this radioisotope specific characteristics, making it very difficult to replace.

The world global Technetium related Market yearly potential value is calculated above three billion Euros, with the part directly corresponding to the main radiopharmaceutical, ^{99m}Tc, evaluated at almost 1.150 Million Euros per year.

^{99m}Tc is the daughter nuclide of another radioactive material, Molybdenum-99 (^{99}Mo), whose natural process to reach stability, forces it to decay to ^{99m}Tc and ^{99}Tc (figure 2).

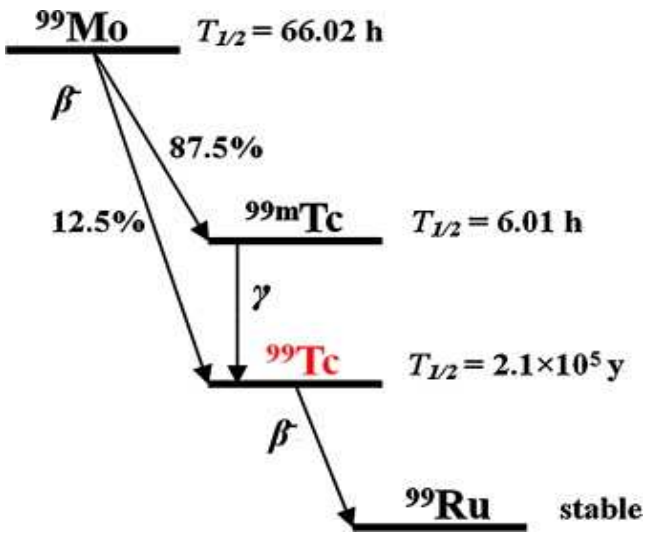


Figure 2 – Decay Scheme of ^{99}Mo [From (Shi et al., 2012)]

As it came out from research studies at the Brookhaven National Laboratory (BNL) done in 1958, (figures 3 and 4) the decay reaction of Technetium can be adapted as a very elegant and practical tool for medical diagnosis and, to make this isotope available for medical applications, pharmaceutical companies take profit from BNL initial work and developed a biomedical portable device – the ^{99}Mo/^{99m}Tc generator – that allowed them to provide ^{99m}Tc to Nuclear Medicine Departments worldwide.

Figure 3 – Image representing the first Molybdenum-99 / Technetium-99m Generator, unshielded (1958). A Tc-99m pertechnetate (^{99m}Tc) solution is being eluted from Mo-99 molybdate (^{99}Mo), bounded to a chromatographic column.

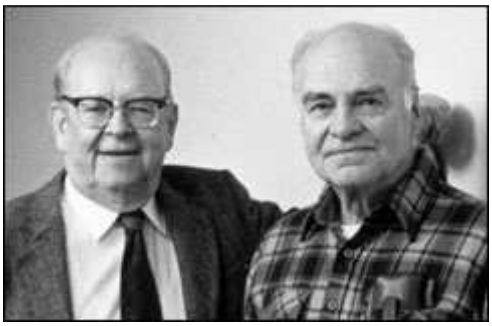


Figure 4 – Walter Tucker and Powell Richards, scientists from the U.S. Department of Energy, Brookhaven National Laboratory, the inventors of the $^{99}Mo/^{99m}Tc$ Generator. (from: http://www.bnl.gov/bnlweb/history/tc-99m.asp)

Using the generators, "freshly produced" ^{99m}Tc is chemically extracted from a probe of ^{99}Mo (figure 5), bound to suitable large molecules (aluminum oxide in this specific case) and administered intravenously to the patients. Then, the 140 keV γ-photons – the gamma photons emitted during ^{99}Mo decay process – are externally detected with specially designed medical devices – the gamma cameras – mapping the body distribution of blood and/or the organ uptake of the radioactive agent. It allows to trace many distinct physiological processes, as for instance regions with low or absent blood supply, for example after a stroke, or highlight spots with enhanced metabolism, identifying potential sites of infection, fractures or even tumors. Importantly, the energy of the gamma photons and the lifetime of ^{99m}Tc are just so that such an exploration does not produce too high radiation exposure and it can be done in a very reasonable time.

Figure 5 – Production line of Technetium Generators at one from the biggest suppliers, with pre-assembled generators awaiting for being loaded with radioactive ^{99}Mo, adsorbed onto alumina columns, a process that takes place in the shielded facility at left (behind green windows). (Courtesy from: David Parker / Science Photo Library)

The situation is such that, currently, there is no way to produce generators without ^{99}Mo, and, consequently, there will be no ^{99m}Tc available for Nuclear Medicine Departments worldwide (figure 6).

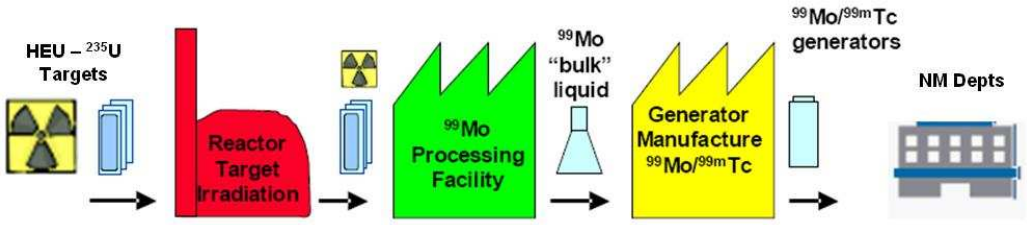


Figure 6 – 99Mo Global Production and Supply Chain [adapted from (Ponsard, 2010)]

The world production of ^{99}Mo is based on nuclear fission very specific processes that use "Nuclear Weapons Grade" Highly Enriched Uranium–235 (HE^{235}U, or just HEU, or even HEU-^{235}U), essentially occurring in just five Nuclear Reactor plants and only four Processing Facilities (figure 7).

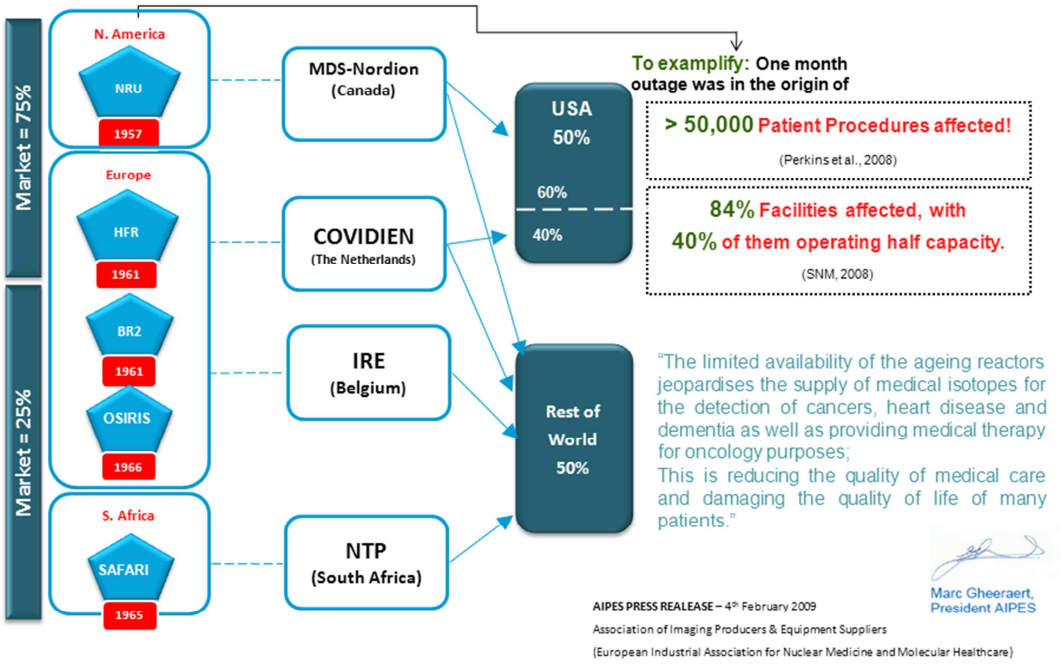


Figure 7 – Nuclear Reactors and Processing Facilities Worldwide Distribution (2009)

Those only five Nuclear Reactors, have all been built during the late 50's or begin 60's, so becoming clearly obsolete and getting more and more fragile with age, approaching the end of their shelf-life, reason why they are being shutdown more and more frequently, with increasingly longer periods for repair, making that it is more and more frequent to have problems with the supplying of ^{99}Mo, "THE" crucial element - since it is the precursor, the parent radionuclide of Technetium - on the ^{99m}Tc production chain. That is greatly disturbing Nuclear Medicine Departments routine and it is decreasing their efficiency very drastically, obliging them to performance indicators of – sometimes - less than 50% of the normal values.

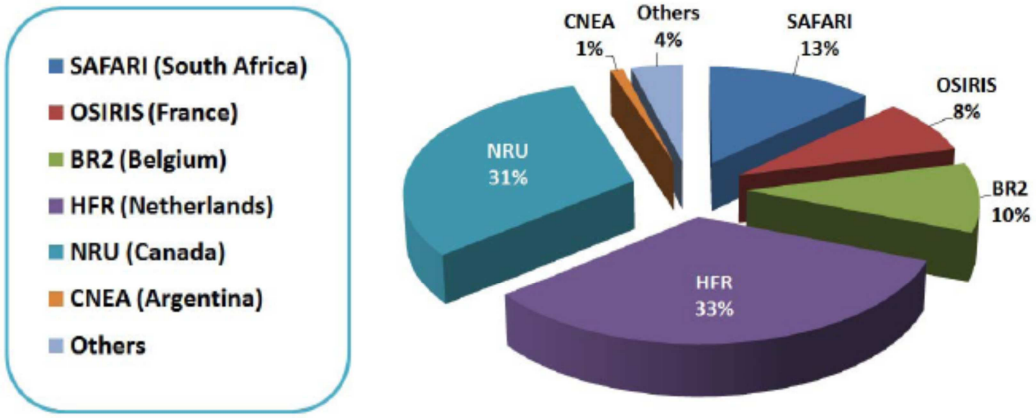


Figure 8 – Nuclear Reactors Relative Contribution to Worldwide 99Mo Production (OECD/NEA, 2011)

The actual ^{99}Mo global supply chain – the way to produce ^{99}Mo/ ^{99m}Tc Generators and to provide ^{99m}Tc to NM Departments – is based on six essential steps:

1 - **Nuclear Reactors** are irradiating HEU "*weapons grade*" ^{235}U **Targets** during about 7 days to produce **^{99}Mo**, which will naturally decays into **^{99m}Tc**;

2 - **Shipment** of the irradiated Targets to the Processing Facilities;

3 - **Processing Facilities** are recovering the **^{99}Mo** by dissolving the irradiated targets;

4 - **Shipment** of the bulk **^{99}Mo** to the Generator Manufacturers;

5 - **Manufacturing of ^{99}Mo/^{99m}Tc Generators**;

6 -**Shipment** to the NM Departments in Hospitals (or firstly to Central Radiopharmacies, whenever that might be the case).

Grosso Modo, after the irradiation of the HEU targets, there are three shipment steps and two different kinds of processing facilities (and corresponding distinct operations) before the NM Departments (or Central Radiopharmacies) may count on the ^{99m}Tc they need to perform their tasks in Nuclear Medicine.

2.2 The Opportunity

^{99m}Tc is by far the most important radioisotope used in the Nuclear Medicine field. Currently there is no reliable supply of ^{99m}Tc, worldwide. It is consensual that there is an urgent need to find solutions. All authorities and related entities agree on that, but there is still no consensus about the best approach to conveniently address this issue.

All over the world, recognized panels of experts and institutions are developing efforts to create possible alternatives; between them – and until the present moment – the most promising seem to be:

- to build new multipurpose research reactors;
- to build a Dedicated Isotope Facility (DIF);
- to include in the Radioisotope Supply Chain other Research Reactors with that potential and eventually still available worldwide;
- to use Photo-Fission methods based on Accelerators technologies;
- to use ^{100}Mo transmutation processes to produce ^{99}Mo, using Accelerators technologies;
- to use ^{100}Mo to directly produce ^{99m}Tc, using low energy Cyclotrons.

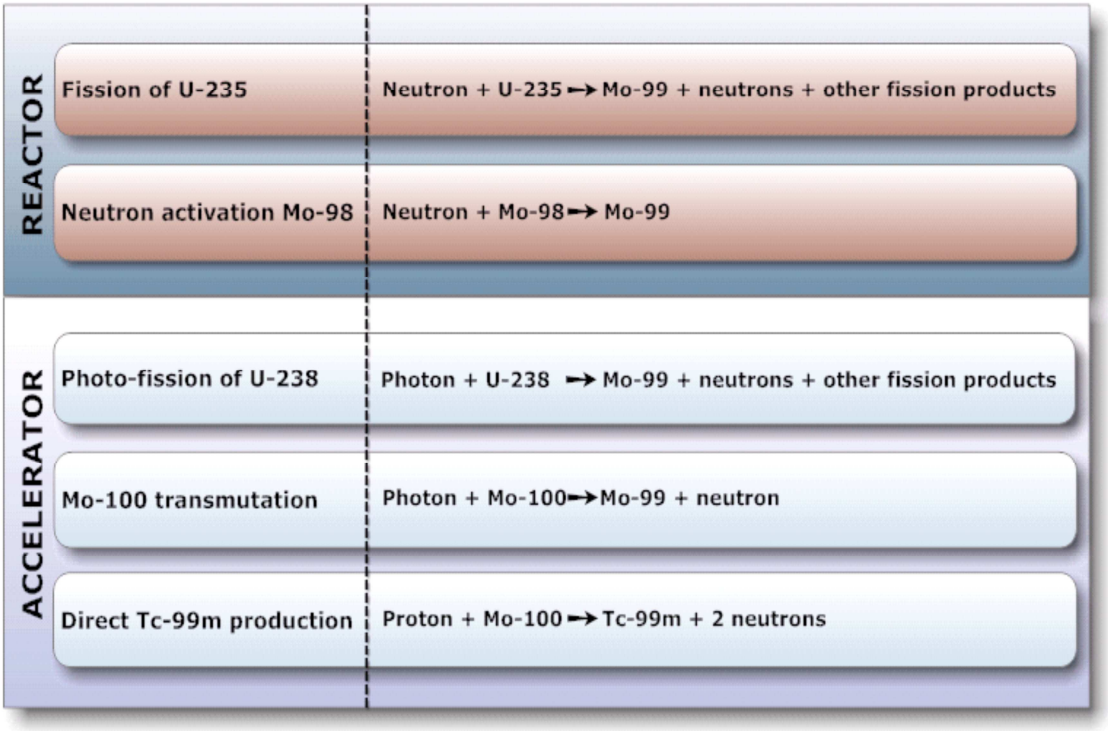


Figure 9 – Most promising technological options identified as "routes" to ^{99}Mo and/or ^{99m}Tc (from OECD/NEA 2009)

During the last years, and yet in this moment, lobbying has been very active – different ones, different goals and directions… – but neither here, none has prevailed clearly and the independent experts involved aren't yet fully convinced about the validity of one or other possible solution.

Cyclotron-based technologies are well positioned, but among the other possible alternatives involving Nuclear Reactors, the use of Low Enriched Uranium to produce ^{99}Mo has been considered quite often, even if – admitting it clearly or not… – essentially because it would allow to maintain the same Production Chain currently existent, thus protecting the interest of the big pharmaceutical companies already in place. Nevertheless, the technology is immature and there are several critical aspects (such as the very low efficiency and the relevant increase on – nuclear – waste production) that need to be conveniently addressed.

Meanwhile, the most relevant governmental entities involved (essentially in the USA, Canada and EU) multiply the efforts (in the form of resources allocated in distinct directions) trying to clarify/further develop the possible technical solutions. Figure 10 shows the relation between the most relevant technological options being actually under discussion.

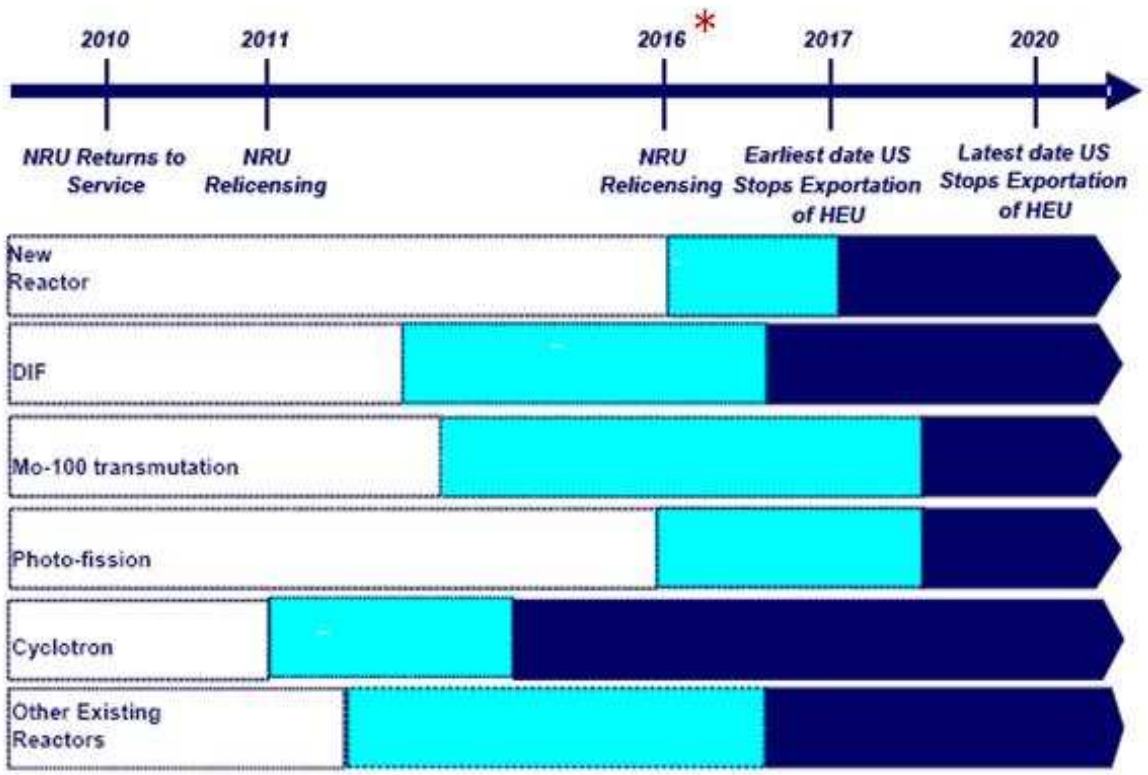


Figure 10 – Timeline for introduction of technology options (where the light blue bar is range for coming on stream, and the dark bar is commercial production). [From (Goodhand et al., 2009)]

* **In 2010 the Canadian Government announced the definitive shutdown of NRU in 2016**

This is also emphasized in figure 11, however, it should be noted that both references demonstrate that experts involved on both situations consensually agreed that "*Cyclotron based Methodologies*" have the potential to be the fastest and the cheapest to introduce, being the easiest to spread and implement worldwide, so inherently with the highest potential to solve the problem in the shortest delay.

Technology Option	Redundancy/Diversity	HEU/LEU	Multi-use	Processing	Environmental and Waste Management	R&D Required	Cost
New multi-purpose research reactor	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology	• No HEU • Designed for LEU targets from outset	• Multi-use facility • Economics improved • Offers broadest spectrum of auxiliary benefits from R&D and other isotopes	• Processing facility needs to accommodate high throughput (LEU) • Process development and optimization may be needed for LEU	• Large amounts of waste with associated costs and environmental concerns	• Limited	• > $500M
DIF	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology • May worsen security of supply by driving out other participants	• HEU • Conversion to LEU required • Costly and difficult	• Single-use facility • High capital and operating costs are not shared • Poor economics	• Processing facility needs to accommodate high throughput (LEU) • Conversion difficult • Some R&D required	• Large amounts of waste with the associated costs and environmental concerns	• Moderate	• $50–250M (without conversion to LEU)
Existing reactors	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology	• HEU • Conversion to LEU required	• May detract from current missions of the reactors	• Processing facility may be far away • Process development and optimization may be needed	• Large amounts of waste with associated costs and environmental concerns	• Moderate	• $50–250M
Accelerator — photo-fission	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • Diversity of technology	• N/A[6]; targets made from natural uranium	• Single-use facility • Facilities would have to be dedicated to Mo-99	• New processing facilities would be required at considerable cost	• Waste with associated costs and environmental concerns	• Significant	• $250–500M
Accelerator — Mo-100 trans-mutation	• Redundancy across supply chain • Diversity of technology	• N/A; targets made from Mo-100	• Single-use facility • Facilities would have to be dedicated to Mo-99	• New generators required • Market acceptance questionable	• No significant waste	• Significant	• $50–250M
Cyclotron	• Redundancy across supply chain • Diversity of technology	• N/A; targets made from Mo-100	• Multi-use facility • Used for R&D; PET isotopes	• Processing R&D required	• No significant waste	• Significant	• < $50M

Yellow: Neutral Green: Positive Orange: Negative

Figure 11 – Comparison between the existing options for radioisotopes production [From (Goodhand et al., 2009)]

The Organization for Economic Co-operation and Development from Nuclear Energy Agency (NEA-OECD) studied the current situation, including past/present trends, structural limits from current methodologies (intrinsic and related with the existing facilities and/or predicted in the field in a near future) and including the capability to react to extra efforts and conclusions are described on figure 12. It can be verified that predicted events as Osiris Shutdown at 2015, NRU shutdown by 2016 and HEU abolition between 2017 and 2020 has major impacts.

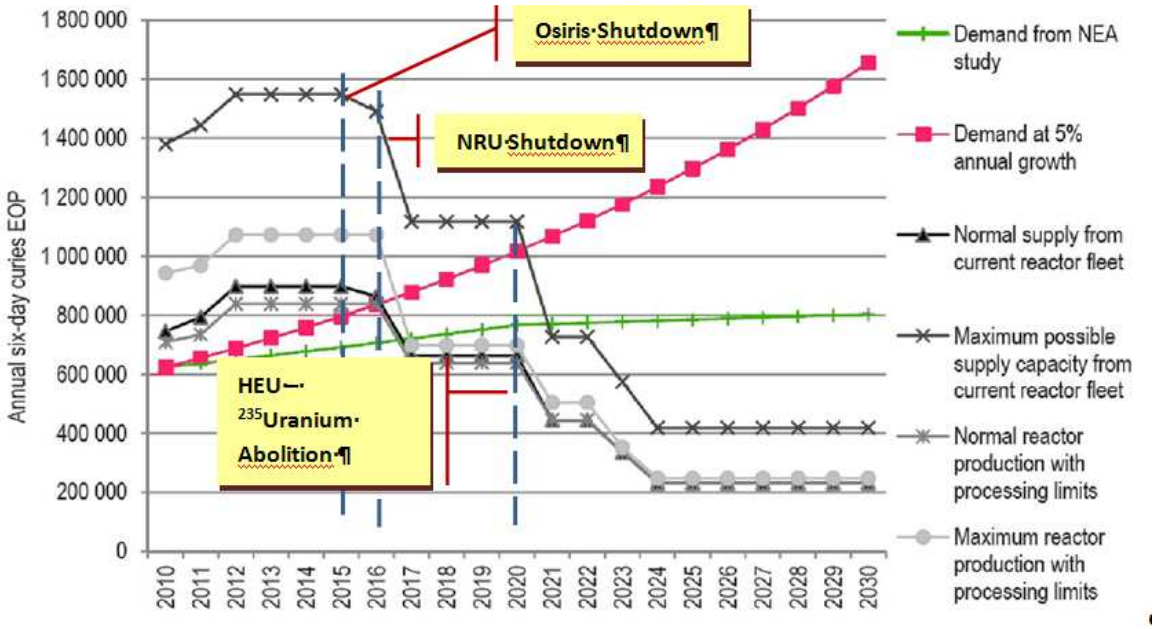


Figure 12 – Current supply versus demand with processing limitations. [From (NEA-OECD, 2010)

As a conclusion, it is clear for everybody involved that there is an urgent need for extra investment and development of other type of solutions, being clearly assumed as the only way to assure the reliability of the supply of ^{99m}Tc.

2.3 The Proposed Solution

The CYCLOTech's technological approach is based:

- **on the Direct Production of ^{99m}Tc using Low-Energy Cyclotrons** (in opposition to the cascade associated to ^{99}Mo-Molybdenum production, to be used in ^{99}Mo/^{99m}Tc Generators, biomedical devices that are distributed worldwide, once a week, and then used to the daily production of ^{99m}Tc in the NM Departments),

- **on the use of a distinct precursor material** (that is the ^{100}Mo – Molybdenum 100, a stable, **non-radioactive**, element, in clear contrast to the "Nuclear Weapons Grade" HEU, a radioactive material that, for distinct reasons – with international political measures concerning the "Non-Proliferation" and "Reduction of Terrorism Threat" in the top of the list – is being more restricted, harder to obtain and transport, and shall be banned in a very near future – between 2016 and 2020 (according to B. Obama's Administration announced decisions),

- **on a different approach using distinct methodologies** (recent and safe low-energy Medical Cyclotrons, in opposition of old and obsolete – so unsafe – Nuclear Reactors),
- **on an existing and widespread available technology** (approximately 450 Cyclotron Centers, in opposition of just 5 Nuclear Reactors),
- on a far cleaner technology producing almost **no radioactive waste**, since based on a stable precursor material (in opposition to the current Process, that is efficient in less than 0,5%, producing very considerable quantities of highly radioactive waste – so very dangerous and costly to handle).

Finally, it is **very easy** and **quick to disseminate worldwide**, in opposition to everything else yet proposed (figure 13).

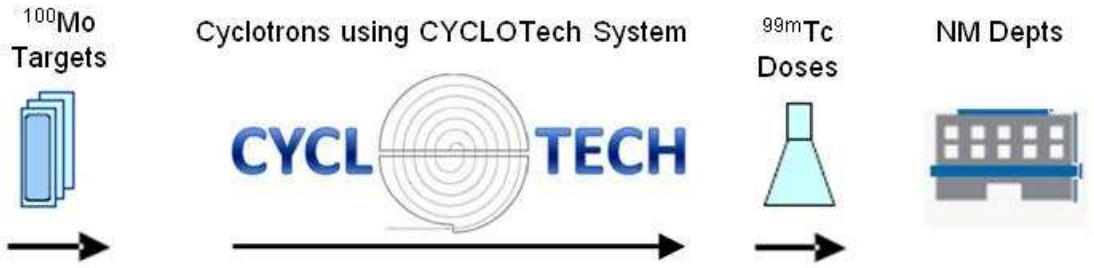


Figure 13 – ^{99m}Tc Global Production and Supply Chain according with CYCLOTech's vision.

2.4 Technical Advantages

The innovative approach developed by CYCLOTech doesn't rely on any of the three critical issues in the basis of the present problems:

- **Precursor Material** – "weapons grade" highly radioactive Uranium *versus* stable Molybdenum,
- **Process** – mandatory preliminary production of ^{99}Mo *via* nuclear fission of HEU ^{235}Uranium, using old and obsolete Nuclear Reactors *versus* direct production of ^{99m}Tc using modern and safe low energy cyclotrons,
- **Very Low Efficiency Process** - 0,5% *versus* 12-15% predicted for the CYCLOTech Process (at the actual state of development; 40 to 45% should be attainable on later stages of technological progress).

2.5 Solution Features and Benefits

The main Product will be a Production and Distribution License, while the second level Products will consist on the complete line of Consumables and Services necessary to keep and assure "*things running smoothly and efficiently*".

CYCLOTech Customers will be the Cyclotron Centers, worldwide. It will be their goal to establish the direct contact with the NM Departments, clearly identified as the "final user" of this technology.

After a relatively small extra-investment, the Cyclotron Centers Owners might find themselves:

- able to add a product to their portfolio, since they already produce and distribute Positron Emitters – essentially ^{18}F-FDG – for NM Departments application in Positron Emission Tomography (PET); with the capacity to produce and distribute ^{99m}Tc, they will be able to offer them also the main product for Single Photon Computed Tomography (SPECT) applications;
- able to gain access to some extra NM Departments (since those NM Departments have no PET, but only SPECT procedures, a specialty that Cyclotron Centers normally don't have any product to offer);
- able to optimize their existing Production and Distribution Chains, while using the same highly specialized (and costly) human resources;

Other possible Customers might be "new concept" Cyclotron Centers, working as well as "Centralized Radiopharmacies". This is indeed a new concept, even if already exists in some countries and that might become more and more generalized or even imposed by local authorities, which may complicate or even, at an extreme situation, will not allow the continuation of activities at the present, usually small and individualized, local departmental radiopharmacies. Whenever that happens, specialized companies entirely dedicated to the Production and Distribution of Radiopharmaceuticals (radioactive medicaments intended to be used in PET, SPECT or Metabolic Therapy) will be forced to appear a little bit everywhere, with each one of them responsible for the production and delivery of radiopharmaceuticals at a radius between 250 to 400kms in the neighborhood of the so-called "Centralized Radiopharmacy".

2.6 How much will consumers be willing to pay?

The most conservative experts predict that prices will rise around four times the actual ones, while others believe that they will rise even more, in the order of ten times the present ones.

In a practical way, and using basic assumptions such as,

- nowadays, at current – May 2013 – level of prices, the minimum amount that Nuclear Medicine Departments spend with ^{99m}Tc supply is approximately 1.500 Euros per week;
- the Cyclotron Center providing ^{99m}Tc charges at least twice the price of generator systems, in a weekly basis;
- this Technology is consensually identified as "the one with the potential to cause the less impressive increase in the prices";
- the Royalties to be payed to CYCLOTech Company for the use of its Production System, could be established at 15% of billing amounts;
- CYCLOTech would start working with 20 Cyclotron Centers worldwide (so less than 5% of the total number of worldwide available Cyclotron Centers);
- each Cyclotron Center would distribute and billed the ^{99m}Tc for 5 NM Departments (so 100 NM Departments in total);

so the CYCLOTech Company should/would expect to receive 45.000 Euros per week, so, assuming 52 working weeks per year, 2.340.000 Euros per year. That are the basis of calculi when prices are assumed that will stays double from actual, because whenever prices rises higher than that, as a factor of four, for instance (so 90.000 Euros per week and 4.680.000 Euros per year), figures will double again …and there are more and more experts mentioning the value of ten (so 225.000 Euros per week and 11.700.000 Euros per year)……..!!

For the moment, it is too soon to clearly see what will happen exactly concerning this more than crucial issue.

2.7 Competitive Advantage

Considering the Market dimension and the key players already involved (some of the biggest pharmaceutical companies), our strategy must be substantially different than just filling and strictly relying on Patents, even if it will always be considered as very important aspect.

It is believed that finishing as quickly as possible the development of our technology, to obtain more precise and complete data to allow fill in "a couple" more Patents (that will be, by definition, each moment more and more precise inter-complementarily, so that will help to "build it together") and to rise enough funds to allow to finish the above mentioned phases, to transfer efforts for industrialization and optimization phases, in order to allow to prepare and submit the corresponding Final Pharmaceutical File, with everything in this order, should be our next steps and all the developmental strategies should be based on that.

Once that initial – but crucial – part is solved and the CYCLOTech System for the "Direct Production of ^{99m}Tc using Low Energy Cyclotrons" is in the market, then the permanent strategy will be based on

- the speed and flexibility (on maximizing the adaptation to the Market),
- the development and optimization of the complete line of necessary consumables for the implementation of the entire System (on a first phase),
- the efficient support to keep it all functioning adequately (second phase) and on
- the creation of a continuous improvement and development system to continuingly improve it (third phase).

CYCLOTech's competitive advantage relies on the fact that the CYCLOTech System is/has been closest to the "final solution" – and so to "the real world" – than anybody else in the world (at least at a certain precise moment…) but it is indeed a race against time, since there are very important and competitive groups busy on the same field and this – theoretical – advantage will be diluted as time goes by.

The multidisciplinary nature of our team is also considered as a strength, since consisting on a point that lacks most of competitor Teams (that are almost exclusively academic). Nevertheless, it is only a matter of time until this will be clearly perceived… and efficiently solved.

3 Value Proposition

3.1 Targeted Customers

- Small medical – low energy – Cyclotron Centers, active at the radiopharmaceutical production and distribution business, that already produce other radiopharmaceuticals such as ^{18}F-FDG, or have the capability to do so, using their – already established – distribution network as a very good and efficient "starting-point" to reach their final customer – the Nuclear Medicine Departments;
- "New Generation" Radioisotope Production and Distribution Cyclotron Centers.

3.2 Description of the Problem

- Currently, ^{99m}Tc is provided in "^{99}Mo/^{99m}Tc Generators", since ^{99m}Tc is a daughter of ^{99}Mo;
- World production of ^{99}Mo is essentially limited to 5 Nuclear Reactor and 4 Processing Facilities;
- Those Nuclear Reactors are old, being subjected to quite frequent service interruptions and long repair times with consequent breaks on supply;
- The Process currently used to produce ^{99}Mo (and thus, ^{99m}Tc) oblige to use "atomic weapons grade" highly radioactive Uranium in a very low efficiency process, responsible for the production of large amounts of highly radioactive waste, so, by definition, a very costly and dangerous waste to handle;
- Demand keeps rising from the last twenty years… and it is predicted to continue that way (even if eventually with slightly shorter figures…) so increasing international dependency on the actual providers;
- There is no reliable solution for Technetium production, worldwide, currently.

3.3 Problem Quantification

- Nuclear Medicine is a steadily and consistently growing Medical Imaging discipline (between 8 and 12% for the last 20 years);
- It provides around 35 to 45 Million diagnostic procedures yearly in clinically relevant areas such as oncology, cardiology and neurology;
- 85% of the procedures relates with the use of a single radioisotope: ^{99m}Tc – Technetium;
- These Procedures represent a worldwide market of over 3 billion dollar yearly.

3.4 The CYCLOTech's System Solution

- **Accessibility:**

  The "Direct ^{99m}Tc Production System" is an additional service to be provided to Cyclotron Centers (existing around 400 to 450 at worldwide level, actual figures). The Cyclotron Centers accessing this System will be able to work on a daily-basis, supplying and distributing the ^{99m}Tc to NM Departments, preventing the risk of disruption;

- **Performance:**

  The "Direct ^{99m}Tc Production System" can add value to the Cyclotron Centers' value chain by allowing the supply of a high demand and high profit new product to their portfolio, with just a small extra investment; so being considered that Cyclotron Centers' efficiency can be increased, since an high percentage of them only use around 20 to 40% of their Production and Distribution capacities;

- **Customization**:

  Working and being delivered on a daily-basis supply, Customers will receive and pay for the exact quantities needed, with the opportunity of maximization and optimization of the usage of their installed scanning equipment and human resources;

- **Risk Reduction:**

  Terrorism: the "Direct ^{99m}Tc Production System" developed is safer, since it relies on the use of a stable material (^{100}Mo – Molybdenum100), instead of the "atomic weapons grade" HEU.

  Environment: The "Direct ^{99m}Tc Production System" is cleaner and more "environment friendly", since it produces almost no radioactive waste.

3.5 Comparison with existing Solutions

- The "Direct ^{99m}Tc Production System" it is an innovative approach to directly produce Technetium, avoiding the use of Nuclear Reactors and the highly dangerous – weapons grade – HEU-^{235}Uranium, as well as preventing the use of a production system characterized for producing in excess of 99,5% of highly radioactive waste (very dangerous and costly to handle).

3.6 Stakeholder Benefits

- Unlike Nuclear Reactor Production, the Direct ^{99m}Tc Production System is safer, cleaner and easier to spread worldwide in the short term, providing a truly reliable solution for Technetium production.

3.7 Value Proposition - Schematic

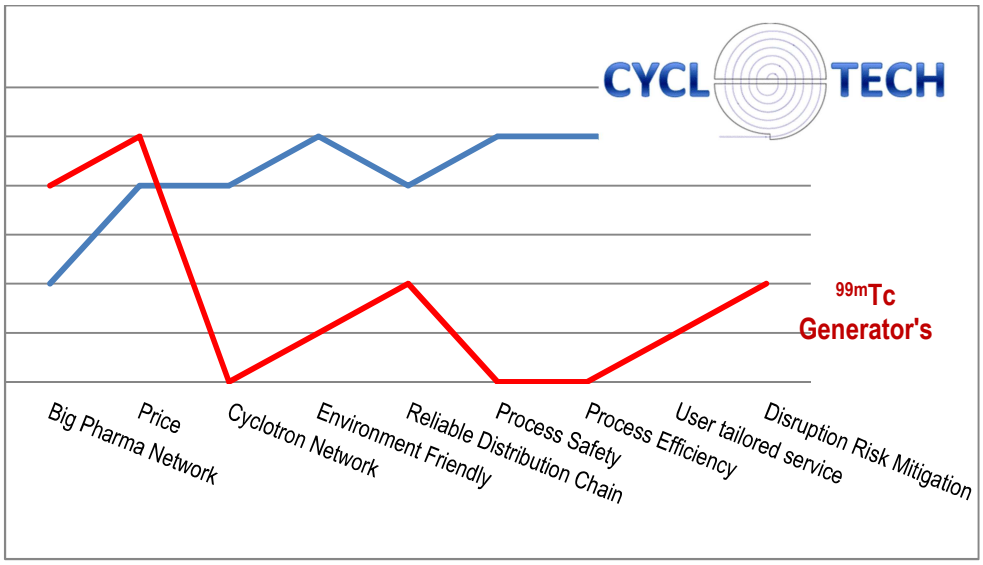


Figure 14 – Schematic comparison between the actual system and the CYCLOTech System.

3.8 Value Proposition – Summary

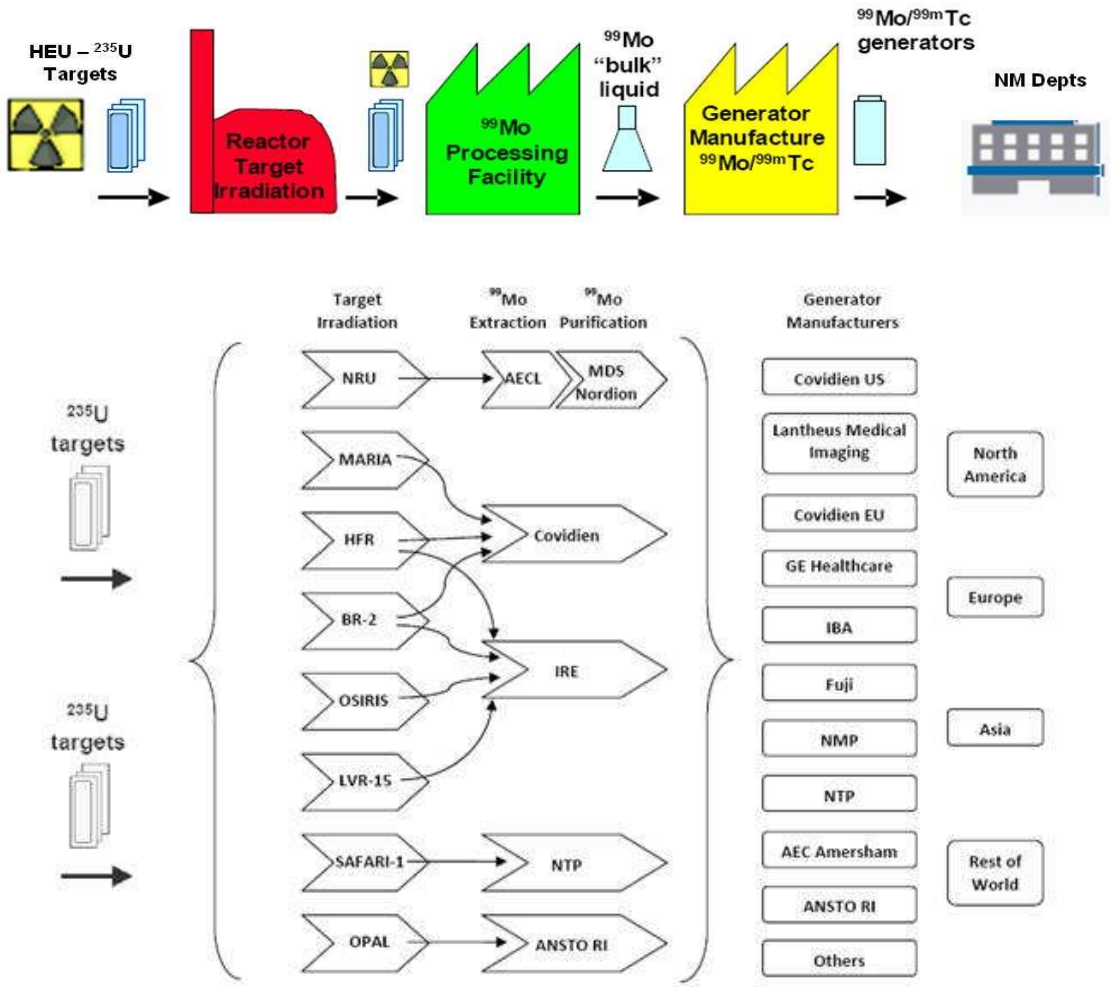
For Small Medical Cyclotron Centers, which already produce other radioisotopes, or have the capability to do so, the "Direct ^{99m}Tc Production System" is an additional service that can easily integrate most of the Cyclotron Centers value chain, adding a high profitable new product to its respective portfolio, which can be customized to fit exactly the correspondent market's demand.

Unlike Nuclear Reactor production, the "Direct ^{99m}Tc Production System" is safer, cleaner and easier to spread worldwide in the short term, as it relies on the well established distribution network used for other radioisotopes, providing a truly reliable solution for Technetium production.

4 Strategic Mapping

4.1 Industry Map

- **Current ^{99}Mo Supply Chain**



- **Direct ^{99m}Tc Supply Chain with CYCLOTech System**

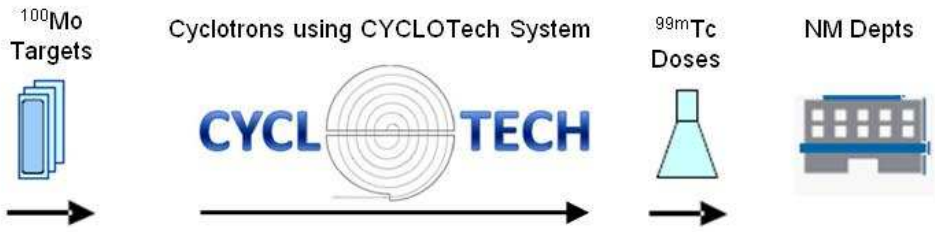


Figure 15 – The Supply Chains Comparison Chart

4.2 Segmentation and Positioning

Considering the Market Segmentation, CYCLOTech System inherent solutions contemplate essentially three (3) distinct approaches,

- firstly considering the existing Cyclotron Centers according to their specific daily workflow (separating the ones with a low/medium level of activity – here considered as "*less than four hours of bombardment time*" - from the ones with a high level of activity – so "*more than four hours of bombardment time*" per day) and
- secondly considering the New Cyclotron Centers.

For each one of them there will be a Specific Complete Package to install and implement the CYCLOTech System for Direct Production of ^{99m}Tc:

- **Already Existent Cyclotron Centers (400 – 450 worldwide):**
  - <4 Beam Hours per day: **CYCLOTech System Package 1** (+/- 200 – 250 candidate centers, with 50 in the USA and the remaining in the RoW[2]);
  - >4 Beam Hours per day: **CYCLOTech System Package 2** (+/- 150 – 200 candidate centers, with 140 in the USA and the remaining in the RoW);
- **New Cyclotron Centers** will receive the **CYCLOTech System Package 3** (150 – 180 candidate centers until end of 2015, according to the IAEA – International Atomic Energy Agency previsions).

Differences between Packages will have to do with practical Production, Preventive Maintenance and Radiation Protection issues. Essentially, it relates with the imperative to deal with distinct (additional) activation phenomena in the Cyclotrons themselves and inside of the Bunkers.

Practically, the different Packages consist in distinct technical approaches considering the conduction of Proton Beam and the Solid Target precise installation and localization. After the Solid Target Holder (itself included) everything is identical in any of the Packages.

[2] RoW - Rest of the World

4.3 Porter's "5 Forces"

Table I - Porter's "Five Forces" Analysis applied to the CYCLOTech System

		Cyclotron Solution		Technetium Generators Solution
Bargaining Power of Buyers	**L**	**Very Low -** Strong need and few options available. Short half-life of radiopharmaceutical limits access to Cyclotron Centers.	**L**	**Very Low -** Strong need and no other options available.
Bargaining Power of Suppliers	**M**	**Medium** to **Low -** Price and availability of precursor material, ^{100}Mo – Molybdenum100, could become a critical issue, but only at a provisory level (increasing the demand will create new opportunities to develop the offer).	**H**	**Very High –** Currently, worldwide, there is no reliable solution for ^{99}Mo – Molybdenum99 production and distribution, since it is based on essentially five old and obsolete Nuclear Reactors and only four Processing Facilities.
Barrier to New Entrants	**M**	**Medium** to **High –** Inherent need to assure the adequate provision of Technical Know-How Resources. Industrial Property Rights and Pharmaceutical Registrations.	**H**	**High –** The Process is highly complex, requiring the production, separation and purification of ^{99}Mo, on a 1st Phase, and generators manufacturing on a 2nd Phase (so at least two distinct kind of infrastructures); Highly capital intensive Project – with Nuclear Reactors at about EUR 1.200 to 1.800 million and a Processing Facility to serve a large market could cost more than EUR 100 million – and very risky since the actual participants are – all of them – very strong, well connected (including strong governmental commitments), well implanted and used to act as a strong international lobby. Industrial Property Rights and Pharmaceutical Registrations.
Threat of Substitutes	**L**	**Very Low –** There is no substitute for ^{99m}Tc and it is not predictable – in fact it is almost impossible, considering all the related aspects… – the appearance of any new entity able to replace it in a short to medium term.	**L**	**Very Low –** There is no substitute for ^{99m}Tc and it is not predictable – in fact it is almost impossible, considering all the related aspects… – the appearance of any new entity able to replace it in a short to medium term.
Rivalry Among Competitors	**L**	**Low –** Short half-life of ^{99m}Tc limits the competition between Cyclotron Centers, reducing it to the only ones occupying the same geographical area and neighborhoods.	**M**	**Medium** to **Low –** Short number of big pharmaceutical companies, used to work together, within the same Market, with the same opportunities and problems, acting the same way at the same time...

4.4 CYCLOTech "Direct 99mTc Production System" SWOT Analysis

Table II - CYCLOTech System SWOT Analysis

Strengths	Weaknesses
• Product and/or Process of Manufacture can be systematically Patent- Protected; • Buyer is a Licensee; • CYCLOTech Team: wide range of expertise and multidisciplinary skills: "good fit" between "Team Skills" and "Project Requirements"; Internal Flexibility: High Level of Efficiency on Adaptability; Good Technical and Business development support.	• Limited knowledge of total Business Costs (especially those from competitors…); • Insufficient knowledge of major Financial Risks in Product Development and Production (some crucial data still missing, waiting for final phase testing); • Insufficient knowledge of major Regulatory Risks in Product Registration (some crucial data will always be missing, waiting for final phase of official submission: only then the official reactions replace the previsions); • CYCLOTech System Technology supports a little range of Product Applications.
Opportunities	**Threats**
• Established Use Dependency of ^{99m}Tc; • There is no reliable solution for ^{99m}Tc production, worldwide; authorities are concerned; • Need to minimize environmental impact and avoiding nuclear waste risks: the actual Process produces in excess of 99,5% of dangerous highly radioactive, costly to handle, waste; the CYCLOTech System almost none.	• Effectiveness of Patent Protection Control Implementation; • Competition – Direct (from ^{99}Mo/^{99m}Tc Generators), as long as they will be able to keep their current price; • New entrants developing similar technology faster and/or efficiently than CYCLOTech.

4.5 Pricing Strategy

CYCLOTech main strategy is based on the differentiation (meaning with this "supplying the same product – ^{99m}Tc – produced using a completely different process") and the reliability of ^{99m}Tc distribution.

Concerning the pricing strategy, it will be based on the establishment of a bilateral contract between CYCLOTech Company and each Cyclotron Center. An "**Entry Fee**" will be honored at the contract celebration moment, which will be distinct for each segment of clients, according and directly related with the respective Technical Package (**CYCLOTech System Package 1**, **2** or **3**) to be received and implemented.

After that moment, and once everything is installed and fully working, i.e. with the CYCLOTech System fully operational and functioning, the remuneration will be related with a monthly payment of **15% of Royalties** based on the billing of the two previous months of the specific Cyclotron Center.

The contract between parts will assure the right and the obligation for the Cyclotron Center to be furnished by the CYCLOTech Company of the necessary and sufficient quantity of consumables, exchange pieces for the System (to assure keeping it functioning smoothly and efficiently) maintenance interventions and consulting that would be considerate adequate. All those items will be priced accordingly.

5 Business Model Marketing Strategy

5.1 Marketing Mix (4 P's)

5.1.1 Product

The Product is based on a proprietary innovative technology (the "CYCLOTech Production System") for the direct production of ^{99m}Tc using (low-energy) medical cyclotrons, meaning with this that the chosen approach will be the establishment of a bilateral contract that will define the basis for licensing any Cyclotron Center in the world that might be interested on the CYCLOTech Production System.

The licensing, in the form of a "Non-Exclusive License", will be done according to the customer specific nature. Directly related to customer segmentation, there will be three Packages available. The common part between them all concerns:

- The Right to Use and benefit from the Pharmaceutical and Regulatory related files;
- All the related Hardware and Consumables for "n" Production Cycles:
    - 1 x Target Holder [TH];
    - "n" "Ready to Use" Targets [Target];
    - 1 x Fully Automatized Transport System from the TH to the Hot Cell [Transport System];
    - 1 x Synthesis/Purification Module [SP Module];
    - "n" Consumables kits [Consumables kit].
- All the related Software to control the System;
- Adequate Education and Training;
- Full Maintenance Package during Warranty Period.

The specific parts for each Pack are related with the technical specifications of each kind of Cyclotron Center, according with the segmentation in three levels already mentioned.

Besides the ^{99m}Tc Direct Production System, the CYCLOTech Company is busy with the preparation and development of the following products:

- ^{99m}Tc Production Kit, including one Ready-to-Use Target plus one Consumables Kit for the SP Module,
- Extra SP Modules, for increased Production situations,

- Distinct Levels of Maintenance Programs to be available after the Warranty Period,
- Continuing Evolution, Debugging and Upgrades for the CYCLOTech System.

5.1.2 Price

There is a strong discussion about this item nowadays. Even if everybody involved – including worldwide authorities, governments and industry– admit that the current prices do not reflect the real costs (so assuming they are definitely not sustainable at a medium or short term), nobody really knows how things are really going to evolve, at what speed and eventually how does it will end. In fact, when experts mention ^{99m}Tc price evolution, they anticipate figures coming from a multiplying factor between four and ten, with an increasing number of experts defending the higher figure.

Here, for CYCLOTech financials calculations, assuming the potential consensually recognized to be the technology with the potential to raise the less the prices, decision was made to use the factor **2X** (so admitting that price, in the "worst case scenario", will only double the actual figures).

Pricing will be based on the establishment of a bilateral contract between CYCLOTech and each Cyclotron Center; under the format of a "Non-Exclusive License". This contract will establish the rights and duties for both parts, mentioning the Royalties to be paid (**15%** of the billed amount by the specific Cyclotron Center two months before) and including an "Entry Fee" to be honoured at the signature moment, which will be distinct for each segment of clients and according with the respective Technical Package (**CYCLOTech System Package 1**, **2** or **3**) to be received and implemented (because of "Financials" easiness of calculation, it will be considered a fixed amount – **150.000€** – with the remaining flexible part corresponding to real costs regarding the specific hardware related with each Cyclotron Center type specificity).

5.1.3 Promotion

This is a typical "B2B"model. The approach will be personalized, based on direct contact with Cyclotron Center owners via the professional and personal networking of the CYCLOTech Company members and partners, on a first phase, proceeding with a globalized gradual approach including the official presence (via a dedicated CYCLOTech's Booth) on the most relevant International Events and related Congresses worldwide.

Scientific and Technical articles will be produced and sent for publication in the main specialized media. Potential clients might be invited to visit the "Show-Room" Demonstration Site (planned to be placed in Portugal) that also serves for RTD, as well as Education and Training purposes.

5.1.4 Placement

The Placement Strategy will be dressed taking into account:

- **Already existing Cyclotron Centers:** the approach will be personalized, direct contact with Cyclotron Center owners will be established; dedicated booths and other forms of presence on all the relevant related International Events and Congresses worldwide will be considered;
- **New Cyclotron Centers:** the approach will be established via a dedicated open-channel to be established and developed together with the Cyclotron Manufacturers;
- **Portugal Show-Room Demonstration Site:** it is planned to be the first Show-Room and Demonstration Site.

5.2 Develop an IP Strategy

CYCLOTech is very committed in protecting as efficiently as possible its Industrial Property (IP), and has filled and submitted three Patents:

- **Pt - 104.656** from 1st July 2009, at INPI – Portugal;
- **USPTO** - **12/512,529**, from 30th July 2009 (claiming priority from **Pt-104.656**), USA and
- **PCT/PT2010/000026**, International.

Those were the first Patents submitted until this moment. Currently, more specific Patents are being planned and prepared to be submitted as soon as possible, in the INPI – the Portuguese Patent Agency as well as at the International level and at the USPTO. This is a very important point and CYCLOTech is deeply invested and interested in issuing the next Patent Files as stronger and efficiently as possible.

Investing in the protection of the Trade Mark “CYCLOTech” is actually being discussed and should be considered between the next suitable steps.

Finally, building a good – in the sense of “strong” and “precise” – Pharmaceutical File is assumed as a mandatory subject and it is considered as “**THE ISSUE**”, most probably with even more relevance than the Patents by themselves.

5.3 Investigation on Legal Regulatory Constraints

The most important issues will be related with IP protection but also with all the Regulatory Issues related with the fact that the final product is a **radiopharmaceutical**, so a radioactive medicine, that need to fulfill several legal and regulatory specific aspects, with all of them being strictly mandatory.

A specific Pharmaceutical File should be elaborated, presented and defended until it demonstrates full compliance with all the International Regulations (strategically to be presented via INFARMED, in Portugal, but to be accepted and fully compliant with as well the European Medicines European Agency (EMEA), in the EU, and the Food and Drug Administration (FDA), in the USA).

5.4 Operational Value Chain

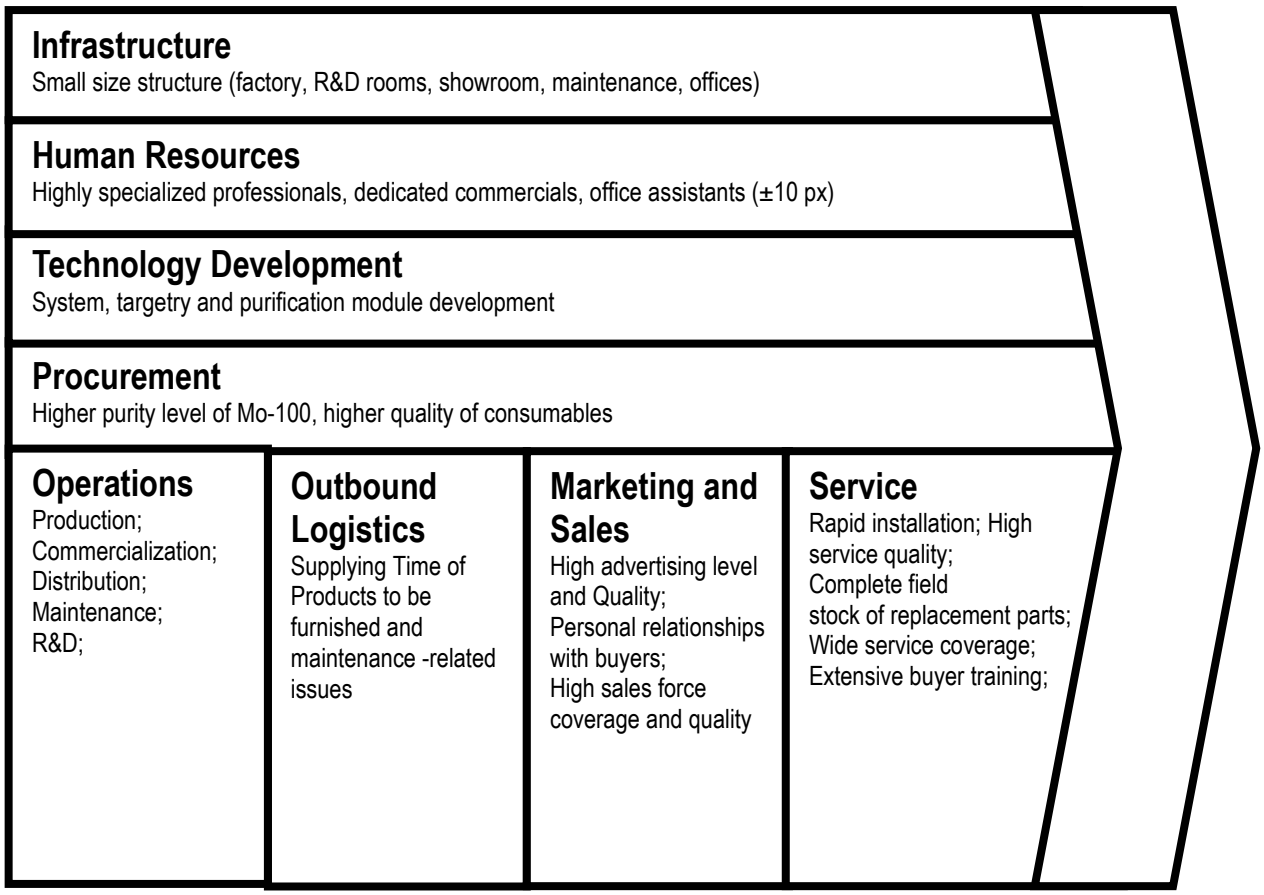


Figure 16 – The Operational Value Chain Scheme

5.5 Revenue Model Cost Model

The Revenue Model presented here is based on several premises, namely what has been considered as "Addressable Market" (please see at **Appendix Section 8.1**) and its evolution (from +/- 5% in the first year to +/- 10% in the last year here considered); also it has been assumed that each Cyclotron Center will provide ^{99m}Tc for five Nuclear Medicine Departments, and, as mentioned before, the pricing strategy developed admits that final prices will be twice the current prices (so 2 X 1.500€ per week per NM Dept) and all the calculations done are based on that.

The relation between the CYCLOTech Company and each Cyclotron Center will be based on a Bilateral Contract establishing a **Non-Exclusive License** to use CYCLOTech Production System, by paying an "**Entry Fee**" and **15% of Royalties**.

The "**Entry Fee**" includes a "package" with all that is necessary to implement and start using the Production System (please see at **Appendix Section 8.3**), that also includes Costs Benefits related.

6 Operations Commercialization Strategies

6.1 Team / Organization Development

The Company will be structured as mentioned bellow, on the following flowchart.

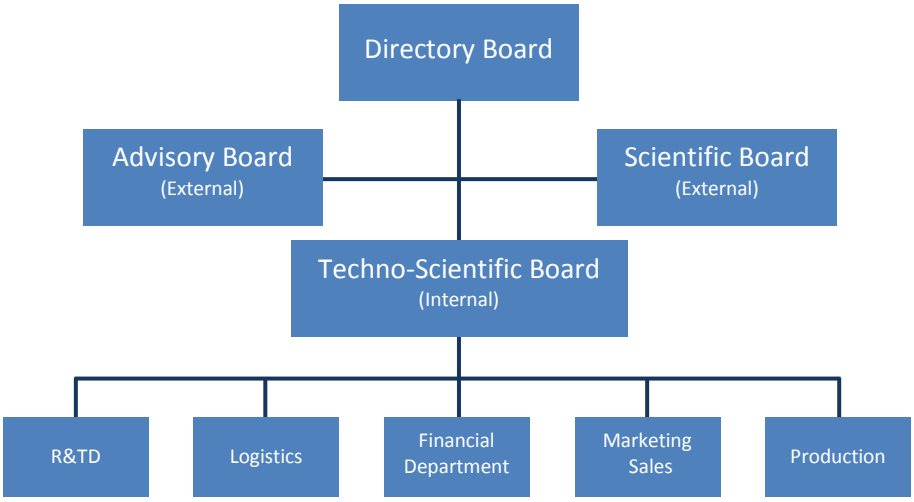


Figure 17 – The Organizational Flow Chart of the CYCLOTech Company

There will be two "Advisory Boards", both external and international, including invited relevant external individualities, with the subjects to be treated divided between "scientific" and "non-scientific". Depending on the Board of Directors specific constitution, there might be a need to implement a "techno-scientific board", intermediary between the five Basic Units/Departments already identified and the Head/Decision Board.

6.2 Current Status and Will Achieve

This Project has started at the 3Q of 2008, based on the recognition of the opportunity that it might constitutes the global weaknesses on the ^{99m}Tc supply and the ***IDEA*** that could/should be possible to find reliable solutions for the direct production of Technetium using low energy cyclotrons. Tending to develop a disruptive solution, it goes clearly against the current establishment, including very strong interests from very powerful governments and (big) pharmaceutical companies and their investments.

Using only internal – personal – funds and the resources of a very limited Team of Researchers, the work has started, efforts had been produced and the first results obtained served to submit the first series of three Patents [the 1st July 2009 (at INPI, in Portugal), the 30th July (at the USPTO, in the USA) and at the 1st July 2010, the PCT, at an international level].

As predicted, it allowed firming a position internationally, but those first series of Patents – as it is normal – aren't as strong and effective as desirable, so the following, to be submitted in the future, should be more concrete and objective, allowing to precise much more, so becoming more effective and reliable.

The Industrial Property Rights (IPR) should be completed with the adequate Pharmaceutical and Regulatory File, ideally to be submitted at INFARMED (Pt) and internationalized via EMEA and FDA concomitantly, while Japanese, Korean and South American markets should deserve our attention directly after.

Quite an interesting path and process has been accomplished until this moment, since all the development (both technical/scientific and the IPR protection being done until this moment) has been achieved with personal effort from all Team Members and the financial personal resources from the co-inventors, so this could easily be defined as our "bootstrapping strategy", definitely "doing a lot with little", …as it is usual at the best Portuguese traditional and most characteristic way!

Now, once this is done, the situation is currently at its (logical and more than normal) limits, so there are already several months that the researches, unfortunately, had been halted, obliged for the lack of financial resources to purchase more reagents, to build new prototypes and to travel abroad to perform some testing that cannot be done internally.

Nevertheless, it might be re-started as soon as the situation will change, continuing at exactly the same point it has been halted (at least if – and when – the opportunity still exists!).

There is just one critical point: competitors – namely other Teams developing the same approach, as it is the case from a Canadian consortium, that had received more than 38,5M CAN$ (Millions of Canadian Dollars) from the Canadian Government at the begin and middle of 2011 – never stopped, and so CYCLOTech is losing way …and the opportunity, while its relative advance is being diluted (if it still exists).

The following chronogram (figure 18) intends to represent a possible way of development from the operations according with the time.

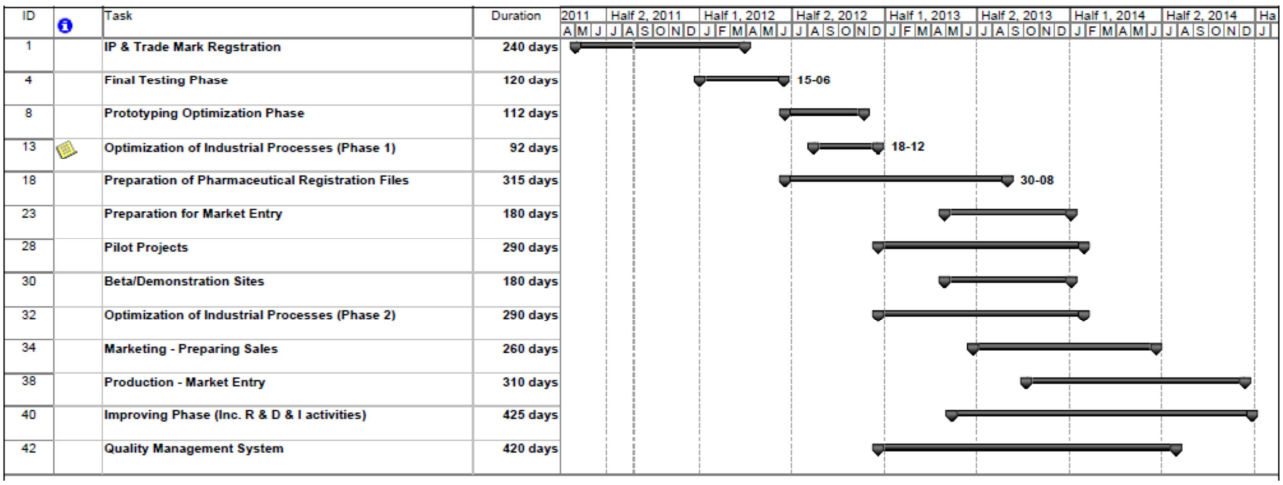


Figure 18 – Timeline representing operations development

With the appropriate resources, between 18 to 24 months should normally be enough to arrive to the market and to perform the first sales.

It is important to mention that, only to prepare, submit and defend the Pharmaceutical/Regulatory File, around one to one and half years should be necessary, keeping always in mind that this series of documents are strictly mandatory to be obtained **before** getting into the Market, whatever Market the Company might intend to get in. The timing has been calculated being aware of:

A - the need for completing final testing phase;

B - the need for optimization and industrialization phase of testing, development and confirmation;

C - the fact that, after arriving to a certain status/point of development (in the optimization/industrialization phase of testing), the Pharmaceutical/Regulatory Files might be presented already, thus allowing both crucial aspects to evolve in parallel.

6.3 Risks Evaluation and Mitigation

The CYCLOTech Direct Production System and all the things that it involves, the whole “Business Case”, signify something that it is hardly competitive while the situation keeps going in the same way.

It is consensually recognized that, when everything goes right, the actual price and general conditions related with the existing solution – essentially based on ^{99}Mo being produced at no-costs in dedicated Nuclear Reactors,

all of them Governmental, to be processed in just four Processing Units, all of them belonging to big Pharmaceutical Companies, and then incorporated in $^{99}Mo/^{99m}Tc$ Generators distributed worldwide by a small number of very well organized and installed Pharmaceutical Companies – are unbeatable.

Nevertheless, as described schematically at the figure 12, it was demonstrated that the present situation is impossible to maintain and structural changes are not only needed but mandatory. Experts having studied the problem (NEA-OECD, 2010) refer easily prices rising with factors between four and plus than ten times fold the actual ones.

In CYCLOTech's Business Case the factor adopted to calculate prices has been just twice the actual values in the Market, meaning that this is the lowest factor being used until this moment, but still, it is indeed a real obstacle for the adoption of this approach, disregarding the current one.

Nevertheless, once supplying problems will arrive again (and that will happen soon), this method will be directly in the front line, between – if not "THE" – the best, since more reliable, easy and quick to disseminate and cheaper options, as demonstrated, before.

The reasons to follow and support this Project can be summarized in the following aspects:

- The unreliability of the current technology used for ^{99}Mo production, based on essentially five old and obsolete Nuclear Reactors, all within the fifth decade of operation, subjected to frequent problems and expected to be halted in the next years (e.g., the French unit of OSIRIS, responsible for around 15% of the world production, is announced/expected to be halted in 2015 and the Canadian unit of NRU at Chalk River, responsible for more than 55% of the world production, has already announced to stop in 2016, if there will be no – further – safety reason to oblige to halt them before…),

- the "nuclear weapons grade" Highly Enriched ^{235}U-Uranium, because of its intrinsic potential for terrorism uses, hopefully will "disappear in the Market" between 2017 and 2020, the soonest as possible, according with related US Government directives and politics,

- the use of Cyclotrons-based methodology has been recognized (Goodhand et al., 2009) as being

    - the one with the biggest potential to increase the final product prices the least, since the most affordable to develop and implement,

    - the safest on execution and the closest to achieve maturity and arrive in the Market,

    - predicted as the fastest to implement and to disseminate (there are 400/450 cyclotrons worldwide, with the number predicted to increase to 600 in the 2020 horizon),

- by far the cleanest and safest approach to the problem, since it does not produce Nuclear Waste,

- tremendous inefficiency of the Nuclear Process being used, that produces in excess of 99,5% of highly radioactive waste, each day more costly and expensive to be adequately processed. In "*Fukushima Era's*" and the "*general wake-up*" for those kinds of environmental issues, this is becoming a more and more critical issue…

- The Canadian Government is deeply interested in "non-Nuclear Reactors" approaches to this problem, strongly funding different Projects; the ones on this specific direction has received – globally – more than 40 Million Canadian Dollars in the last one and half year (our most direct possible competitors are inside this group of Research Teams..). Since Canadians are consensually considered between the best nuclear experts worldwide, it should mean that, definitely, "*there's something*" here…

- the U.S. Senate has recently approved a special dedicated fund of 163 Million USD dedicated to the subject of "*Production of Medical Isotopes without Highly Enriched Uranium*".

…so it really looks like there might be something interesting in the end of this road!

The "Internal" development risks – to overcome on technical aspects that would need expertise, experience, know-how and/or skills not available inside of the CYCLOTech Team – might happen and will be solved via the strong international network already available via the personal and professional networks of CYCLOTech team.

Nevertheless, the greatest risk, already mentioned, is the lack of enough funding to perform research and development at the adequate level and speed, that can become very critical, since there are other Research Teams, i.e. the Canadian Consortiums already mentioned before, namely the one being based at the Edmonton University and the one with TRIUMF [3] that, having received recent funding support from the Canadian Government of more than 38,5 M CAN$, shouldn't need much more to achieve all the goals. They even recognize our efforts, as it could be seen when, in January 2011, their chosen Team's name ("***CycloTech99m"***) has been advertised… [4]. In 28th February 2013, another 14,0 M CAN$ had been added to the funds already allocated to "*support the development and application of cyclotron and linear accelerator production technologies to improve the security of supply of medical isotopes for Canadians, reduce radioactive waste and meet nuclear non-proliferation goals.*" [5].

As a conclusion, development risks should be essentially related with:

[3] http://www.triumf.ca/nrcan-nisp
[4] http://www.triumf.ca/nrcan-isotopes
[5] http://www.triumf.ca/headlines/funding-announcements/triumf-team-receives-isotopes-investment

- **Technical Aspects**, that can be solved with hard work, time and funding: the less the funding, more time would be needed for similar achievements – and time might become INDEED a critical issue… – and even more hard work will be needed to overcome it;

- **Regulatory Aspects**, that can be solved firstly with hard work and a good and competent professional work elaborating the relevant files, but also, in a second phase, with political work and lobbying to facilitate administrative and regulatory tasks, at national and international levels.

The IP Protection shouldn't be considered a problem neither a development risk, essentially because of the Pharmaceutical File, that really will be the "cornerstone" of all the Process. The first Company to complete and approved the first Pharmaceutical File will have the real advantage, reason why this is the "real race": to have the Pharmaceutical File, that will "legalize" the Process to produce a Pharmaceutical – since, without it, there will be nothing else but an almost useless chemical product – that can be licensed, produced, distributed, sold and used worldwide, for the most important daily benefit of thousands of patients.

6.4 Future Funding Needs Related to Operating Development

Ideally, a first 300.000€ will be used for technical, maintenance and administrative installation purposes (please report to Appendix Section 8.5), corresponding to items 1, 5 and 6 from the Table (to be completed in items 5 and 6 with 10.000€ per year of maintenance, consumables and upgrading). It includes the necessary to incorporate the CYCLOTech Company as well as administrative, general and specific equipment and tools as well as physical adaptation of installations, a small workshop for mechanical, chemical and electronic engineering to be used on prototyping.

It has been calculated that an amount of 400.000€ (item 2, first column) should be enough to finish the testing phase and allow to introduce the "Optimization and Industrialization Phase", that would use an extra 200.000€ in the following year (item 2, second column).

After the start of this Phase, the pharmaceutical and regulatory files (that will cost around 1,750 M€, divided between 750.000€ in the first year and one extra million euros in the second year (item 3, first and second columns), and should last between 12 and 18 months to be achieved) should be ready to be submitted, since some parts of its own specific processes might run in parallel, so allowing to win some time and to create and/or amplify some strategic advantage that might proof its utility in the future.

One should keep in mind that this is indeed a race, a place where the first might win it all and there could be no place for the second… and first place will be defined by the possession of the inherent Pharmaceutical File (and its International (essentially EMEA and FDA) approvals.

The “Optimization and Industrialization Phase” will start with a small technical infrastructure - a kind of “extension” of the workshop already in activity from the previous phase, and it will kept its place for a R&TD Laboratory for the future development of the Company – that should be able to allow the assembling of the first prototypes from what will become later the elements of the Production Chain.

This “Optimization and Industrialization Phase” will be a phase that introduces the “Industrial Production and Maintenance Phase” and will need appropriate infrastructural conditions and equipment to guarantee the production of enough quantities of the distinct products, always assuring and controlling the adequate level of quality.

As a conclusion, and adding all the partials above mentioned, the total amount of Investment will be 4.350.000€ during the first six years of activity.

6.5 Operations Development, Core and Complementary Assets

As stated before, CYCLOTech’s Business Concept relies essentially on the Licensing Contract, to be established on a one-by-one basis and entirely controlled by CYCLOTech, as shown on the figure 19.

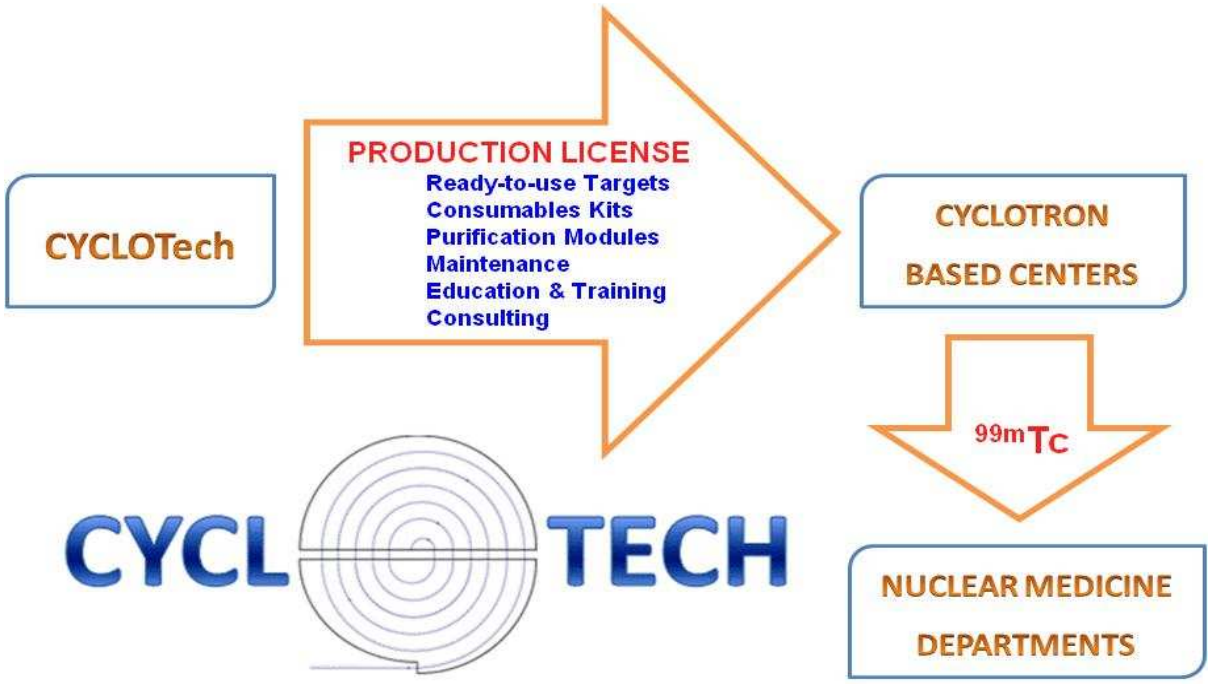


Figure 19 – CYCLOTech Business Concept

CYCLOTech Company will start by previously establishing a geographical strategy that will allow the identification of the specific localizations where Cyclotron Centers (that represent the CYCLOTech Direct Clients) should be installed (meaning both, either “already installed” or “to be installed”…) in order to serve the better and most efficiently the Nuclear Medicine Departments (so the end-users and the beneficiaries from the CYCLOTech System, being themselves the Direct Clients of the Cyclotron Centers).

Considering that the maximum range of action for an adequate distribution in comfortable and efficient conditions should be considered around the 200 to 250 km from the Cyclotron Center, one could easily consider a situation like the one exemplified on the next figure, stating, only as a possible example, the Occidental Europe case (Figure 20).

Considering that each Cyclotron Center can only provide services, producing and distributing ^{99m}Tc, for a maximum number (essentially dependent on the Cyclotron Energy, Beam Current and Beam Time Available) of five to ten Nuclear Medicine Departments, it is evident that it will be happening several situations of more than one Cyclotron Center for the same region, for instance at the entirety of the great metropolitan regions.

Figure 20 – Possible distribution of desirable locations for CYCLOTech Systems implementation.

CYCLOTech Company has the intention to overlook these situations, since it is from outmost interest that the maximum efficiency might occur, but always avoiding as much as possible competition situations that will create unfavorable evolution, with prices and quality of services/products getting lower than desirable.

Once the contract is established, both parts know exactly what they should do and expect from the counterpart. From the Company point of view, so being considered as "Core" and to be produced and entirely controlled indoors:

- "Ready-to-Use" Targets,
- "SP – Synthesis/Purification" Modules,
- ^{100}Mo Recovery System,
- R&TD activities,
- Quality Assurance and Quality Control (both internal and external, via audits),
- Installation, Maintenance, Upgrading and Consulting Services.

To be outsourced, since considered as "Complementary" there will be the:

- Distribution of all products,
- Production of Consumables Kits for the SP Modules,
- Education and Training activities.

Considering the Operational Development, it is believed that things could evolve smoothly from:

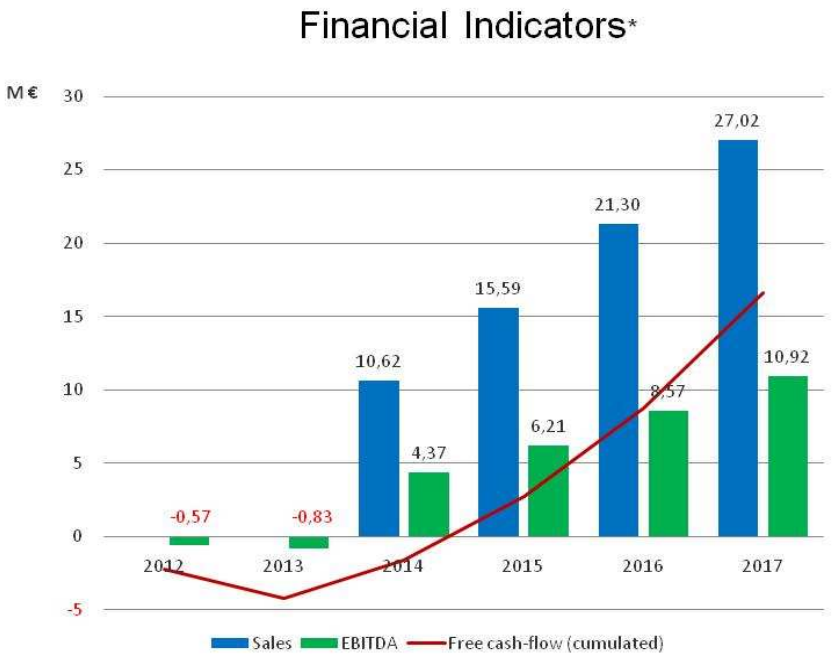
- Establishment of Beta Demonstration Sites (normally, this will be the case for one/two Portuguese Centers that will be the first one/two Cyclotron Centers applying CYCLOTech Direct Production System);
- Permanent Market Surveillance, Marketing and Network establishment, completion and development;
- Procurement Operations, in order to provide the adequate raw material for everything that concerns internal production and adequate outsourcers for everything that relates with externally produced items and/or services;
- Production Operations of all the items from CYCLOTech responsibility, including assembling and integrating operations, always according with timings and quantities necessary to guarantee a normal level of activity, calculating and assuming a strategy based on "JIT – Just in Time" production politics, in order to have a minimal effort concerning product stocking, but always assuring that the client "Cyclotron Centers" will be provided in due time and conditions, with absolutely no delays that might incur in clinical procedures;
- Commercialization Operations, in order to assure an adequate answer to the Market and Clients needs;
- Distribution Operations, even if it is always outsourced, under strict surveillance and permanent control from the Company, in order to guarantee in continuity that the best service is provided to

the clients, while always at the best conditions for the Company. Any deviations will always be considered as an invitation to find better service providers, so clearly assuming a permanent politic of continuous improvement;

- Quality Assurance Politics, including Quality Certification, Assurance and Control Operations, assuming in permanency the Quality Strategy to be adopted for the Company, internally and externally, demonstrated through– internal and external Audits;
- After-Sales Services that will be able to provide an adequate continuity to the previous efforts from the Company, aiming to assure a good level of Client satisfaction as well as the quick and efficient reaction to any unexpected situation that might occur;
- Establishment of an effective and functional R&TD Department assumed as the only way to obtain and assure the maintenance of the CYCLOTech Company position on the field and the best level of Products and Services for future Clients. The CYCLOTech Direct Production System actual positioning results from this attitude and the Company future will do it the same way, since this is indeed a very competitive and quick evolving niche Market, where strong efforts on R&TD are always to be considered mandatory in order to survive among the competitors.
- Establishment of an effective and functionally operational solution for Maintenance, Assistance and Upgrading Services, able to serve the Clients (and the Company interests) on the best way. This is considered as a “Core” activity and should always deserve the maximum attention and level of effort.

7 Financial Model and Funding Requirements

Concerning Sales Forecast, please see at Appendix Section 8.4. The full set of Project Valuation and Indicators has been calculated and results obtained serves as the base for the figure 21, that graphically demonstrate the values and pattern of evolution forecasted.



Investment: 4,35 M€

NPV: 60,6 M€

IRR: 81,7%

Pay-Back: 3 Years

Figure 21 – Financial Indicators

7.1 Assumptions Used for Calculation Purposes

The assumptions on the basis of CYCLOTech Revenue Model are the following:

- The Global Market approach has been considered as "the only Goal", reason why the National Market stands essentially by an unique approach, eventually using a Portuguese Company as a Partner in the development of CYCLOTech technology, that will be responsible by the two Beta/Demonstration Sites that will be the "Proof of Concept", producing and distributing the ^{99m}Tc and providing access to Cyclotron facilities and laboratories, for "Show Room" purposes, as well as for Education and "hands on" Training supporting purposes;

- In "Addressable Market" (please see at Appendix Section 8.1) it has been considered "Cyclotron Centers" as the number of "New Clients" – that purchase one "Entrance Fee" – in each year;

- "Cyclotron Centers Cumulated" numbers are used for "Ready to Use" Targets and Consumables kits forecast;

- For calculation purposes, and related with the average power of the worldwide installed Cyclotrons, it has been considered that each Cyclotron Center is able to supply and distribute ^{99m}Tc to 5 Nuclear Medicine Departments, in average;

- It should be noted that the maximum number of Cyclotron Centers (2017) here used for calculation purposes correspond to only 15% of the number of already installed Cyclotrons (400 to 450) today; if and when considering the forecast for 2017-2020 (around 600/650) then it would make this number correspond to only 10%;

Concerning the line of Products to be commercialized:

- **Product A – Process**: the price was calculated on the basis of 15% of Royalties (please see at Appendix Section 8.2), admitting that final cost for Nuclear Medicine Departments will be 3000€ per week (so twice the current minimal costs), multiplied by 52 weeks per year (so [(3000€ X 52) X 0,15 = 23.400€ per year]. The yearly total revenue is calculated multiplying this value by the total of Nuclear Medicine Departments being supplied.

- **Product B – Targets**: the price estimation is 850€, which takes into account production and raw materials costs. Revenue was calculated considering 1 X Target per Production Cycle, that has been multiplied by 22 working days per month, multiplied again by 12 months a year, once again multiplied by the total Cyclotron Centers (so the so-called "Cumulated" figure);

- **Product C – SP Module**: 1 unit of this product is included on the "Entrance Fee Package" (please see at Appendix Section 8.3). If any Cyclotron Center chooses to use more than 1 production cycle per day, then it will be strongly advisable to purchase another SP Module, which will be extra-charged. Extra safety concerns and redundancy reasons might apply too. Those numbers are unpredictable figures, which, for this reason, haven't been taken into account. The variations can only be positive, so they were not assumed here as relevant;

- **Product D – Consumables kit**: price estimation is 150€ and revenue is calculated using the same premises as **Product B – Target**, as they have the same demand profile and one of each is being used at each Production Cycle;

- **Product E - Entry Fee**: price estimation is of 150.000€ fee to all new contracts, which includes a Package with all the necessary to implement and start using the Production System (with costs of 47.500€), as described in the Tables bellow.

8 Appendix

8.1 Addressable Market

Addressable Market	2012	2013	2014	2015	2016	2017
New Cyclotron Centers per year (n)	0	0	20	15	15	15
Cyclotrons (Total Accumulated)	0	0	20	35	50	65
Nuclear Medicine Dept / Cyclotron	0	0	5	5	5	5
Total Nuclear Medicine Dpt Involved	0	0	100	175	250	325

8.2 Auxiliary Calculations

Product A - Process (15% Royalties)		
Price per Week	3.000,0	
% Royalties	15%	
Weeks in the Year	52,0	
Price per Year		23.400,00
Product C - SP Modules (Extra Package)		
Quantity	1,0	
Price		50.000,00
Product E - Entry Fee		
Price	1,0	150.000,00

Product B - Target		
Week Days	22,0	
Production Cycles	1,0	
Months of Production	12,0	
Price per Cycle		850,00
Product D – Consumables Kit		
Week Days	22,0	
Production Cycles	1,0	
Months of Production	12,0	
Price per Cycle		150,00

8.3 Entrance Fee Package

Entrance Fee Package Contents	Qt	Unit Price	Package Price	Normal Price	Gross Margin
SP Module	1	20.000	20.000	50.000	60%
Target	10	750	7.500	850	12%
Consumables Kit	10	100	1.000	150	33%
Transport System	1	10.000	10.000		
Maintenance/Training	2	2.000	4.000	3.000	33%
Target Holder	1	5.000	5.000		
Entrance Fee Total Cost			47.500		68%
Entrance Fee Purchase Price			**150.000**		

8.4 Income Statement

Unit: Euros

SALES	2012	2013	2014	2015	2016	2017
Increase Rate - Sales	0%	0%	0%	0%	0%	0%

SALES - NATIONAL MARKET	2012	2013	2014	2015	2016	2017
TOTAL	0	0	0	0	0	0

SALES - EXPORT	2012	2013	2014	2015	2016	2017
Product A - Process (15% Royalties)	**0**	**0**	**2.340.000**	**4.095.000**	**5.850.000**	**7.605.000**
Sales	0	0	100	175	250	325
Unitary Price	23.400,00	23.400,00	23.400,00	23.400,00	23.400,00	23.400,00
Product B – Target	**0**	**0**	**4.488.000**	**7.854.000**	**11.220.000**	**14.586.000**
Sales	0	0	5.280	9.240	13.200	17.160
Unitary Price	850,00	850,00	850,00	850,00	850,00	850,00
Product C – SP Module (Extra Package)	**0**	**0**	**0**	**0**	**0**	**0**
Sales	0	0	0	0	0	0
Unitary Price	50.000,00	50.000,00	50.000,00	50.000,00	50.000,00	50.000,00
Product D – Consumables Kit	**0**	**0**	**792.000**	**1.386.000**	**1.980.000**	**2.574.000**
Sales	0	0	5.280	9.240	13.200	17.160
Unitary Price	150,00	150,00	150,00	150,00	150,00	150,00
Product E - Entry Fee	**0**	**0**	**3.000.000**	**2.250.000**	**2.250.000**	**2.250.000**
Sales	0	0	20	15	15	15
Unitary Price	150.000,00	150.000,00	150.000,00	150.000,00	150.000,00	150.000,00
TOTAL	**0**	**0**	**10.620.000**	**15.585.000**	**21.300.000**	**27.015.000**

SALES – TOTAL VALUES	2012	2013	2014	2015	2016	2017
TOTAL SALES - NATIONAL	0	0	0	0	0	0
TOTAL SALES - EXPORT	0	0	10.620.000	15.585.000	21.300.000	27.015.000
TOTAL SALES	0	0	10.620.000	15.585.000	21.300.000	27.015.000
TOTAL SERVICES	0	0	0	0	0	0
TOTAL REVENUES	0	0	10.620.000	15.585.000	21.300.000	27.015.000
VAT	0	0	0	0	0	0
TOTAL REVENUES + VAT	0	0	10.620.000	15.585.000	21.300.000	27.015.000

8.5 Investment Progression

INVESTMENT PROGRESSION	2012	2013	2014	2015	2016	2017
Intangible Fixed Assets						
1 Installation	100.000					
2 RTD	400.000	200.000				
3 IPR + Pharmaceutical and Regulatory Files	750.000	1.000.000				
TOTAL INTANGIBLE FIXED ASSETS	**1.250.000**	**1.200.000**				
Tangible Fixed Assets						
4 Basic Equipment	500.000	400.000	300.000	200.000	100.000	100.000
5 Tools	100.000	10.000	10.000	10.000	10.000	10.000
6 Administrative Equipment	100.000	10.000	10.000	10.000	10.000	10.000
TOTAL TANGIBLE FIXED ASSETS	**700.000**	**420.000**	**320.000**	**220.000**	**120.000**	**120.000**
TOTAL - INVESTMENT	**1.950.000**	**1.620.000**	**320.000**	**220.000**	**120.000**	**120.000**

9 References

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