Why are investors not interested in my radiotracers?

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Chrysalium Consulting

Salzburg, April 10, 2016
We need to know...

The reason: why have RPs never developed liked conventional drugs?

The constraints: Is there still a specific problem with RPs?

The frame: What are the basic recommendations for showing interest to investors?

The future: What will be of interest in 10 years from now?
Introductory statements and considerations

1. In this presentation all conclusions are derived from economical considerations, not technical
2. Very good science is not sufficient to bring a drug on the market
3. Radiopharmaceutical industry (RPI) is now fully mature but does not have (anymore) the funds to fully develop RPs
4. Today Conventional Pharma Industry (CPI) is not (yet) interested in RPs (and absolutely not in diagnostics)
5. Regulatory constraints will not be weaker in the future
6. Awareness about potential and successes of radiopharmaceuticals is very weak
Industries and investors

General misunderstanding

**Investors**
Seeking short and long term profit ≠ **Industries**
Profit based on manufacturing

*Industries can become sponsors (investors) only if they make profit*
Further ...

New molecules to proof biological concepts ≠ New molecules to be used routinely in human
Make your decision now
How?

Turning Radiopharmaceutical Research into Marketable Tracers/Drugs

How to convince industry to invest time and money in expensive clinical trials involving radiopharmaceuticals?

What are the most important criteria to be taken in account in selecting ...  
  • a target indication
  • a biological mechanism
  • a chemical structure
  • and a radionuclide

... that will almost guarantee that the final drug will become a success on the market?
## Industrial evaluation criteria

| Primary criteria | Proprietary molecules (no generics)  
Access to worldwide rights (no local products)  
No 'me-too', no 'me-too+'  
Availability of biodistribution data in man (no early research projects) |
|------------------|----------------------------------------------------------------------------------|
| Market data and competition | Medical need *(at the time of entrance on market)*  
No in-house competition and non-competitive new approach  
Limited competition with non NM modalities  
No future competition with non-imaging diagnosis |
| Technical data | *Modality is not an issue*  
*Type of vectors or indications are not issues*  
Systemic drug, no local applications/therapy  
*Good non-optimized synthesis yields*  
Realistic manufacturing costs  
**Easy access to starting materials involving GMP grade RNs** |
| Non technical criteria | If possible same day imaging  
Reimbursement |
Preclinical research: Biology

No real new constraints

- Choose …
  - the appropriate mechanism of action
  - the best receptor/target
  - the easiest model (in vitro, in vivo)
  - the reference test and reference molecule (if it exists)
- … in which you feel the most comfortable

- Preferably a non competitive new approach
- Work GLP

- Do not spend too much time in preclinical trials as we do not want to cure animals
- Target human as fast as possible – there will be plenty of time later to explore the true mechanism of action
Preclinical research: Chemistry

No real constraints
- Develop the molecule you can afford (in terms of technology and skills)
- With no limitation in terms of modality (SPECT, PET, therapy)
- Covalent vs. chelating chemistry is not an issue
- But be sure to be original and **file patents** – only proprietary molecules are of interest (no generics)
- Protect at a worldwide level (no local products)
- And do not publish before the patent is filed

- **Chemistry**
  - Non optimized synthesis yields above 10-15% ($^{18}$F), 50% (others)
  - Easy access to starting materials
  - Work GLP
## Pipeline and Chances of Success

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic PET/SPECT</th>
<th>Radio-Therapeutic</th>
<th>Conventional Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chances of success (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Phase II -&gt; Market</td>
<td>70-80%</td>
<td>40-50%</td>
<td>15-20%</td>
</tr>
<tr>
<td>End of Tox -&gt; Market</td>
<td>7-10%</td>
<td>5-8%</td>
<td>1-5%</td>
</tr>
<tr>
<td><strong>Budget (M€)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical stage</td>
<td>2-6</td>
<td>2-10</td>
<td>5-20</td>
</tr>
<tr>
<td>Clinical (theoretical)</td>
<td>20-30</td>
<td>50-80</td>
<td>200-300</td>
</tr>
<tr>
<td>Total (realistic)</td>
<td>80-120</td>
<td>120-180</td>
<td>400-600</td>
</tr>
</tbody>
</table>

*These € figures do not include the failures …

… and do not include financial costs, marketing budget and manufacturing tools investments*
NM landscape in 2025
The therapeutic radiopharmaceuticals market takes off with Xofigo, boosting the global nuclear medicine market.

- **2021**: Second wave of growth with $^{177}$Lu-Lutathera
- **2028**: Third wave of growth with new radiotherapeutics

Source: MEDraysintel (2015)
Global trends

Global market
- The global market is expected to reach US$ 24 billion by 2030 (US$ 5 billion in 2016), showing an annual average growth of 11%.
  - Diagnostic radiopharmaceutical (RP) market is expected to grow by 6% a year mainly driven by volume
  - Therapeutic RP market is expected to grow by 26% a year

Major trends
- Clear split between companies specialized in diagnosis and companies developing therapeutics
- Diagnostics remain in the scope of radiopharmaceutical companies (RPCs)
- Conventional pharmaceutical companies (CPIs) are only interested in therapeutics
- RP companies are transforming in CMOs
Radionuclides: a kind of ‘natural’ selection

1950’s
- Reactor radionuclides: $^{131}$I, $^{32}$P, $^{125}$I, ...
- Only $^{131}$I survived (thyroid)

1960’s
- SPECT $^{99}$Mo/$^{99m}$Tc generator
- Still cheapest RN with the largest number of applications

1980’s
- First ‘exotic’ radionuclides: $^{89}$Sr, $^{153}$Sm, $^{166}$Ho, $^{169}$Er, $^{188}$Re, ...
- Limited by chemistry
- $^{90}$Y and $^{188}$Re still of interest

1990’s
- Small cyclotron: $^{18}$F, $^{124}$I
- Large cyclotron: $^{123}$I, $^{111}$In, $^{67}$Ga
- $^{90}$Y replacing $^{131}$I in RIT R&D

2000’s
- New reactor RN’s: $^{177}$Lu
- New generators: $^{68}$Ga
- $^{177}$Lu replacing $^{90}$Y in R&D
- $^{99}$Mo shortage issue (to be solved by 2018)

Manufacturing capacity (ww) is the limiting factor
Development of New RPs is Limited by Access to RNs

- **Pharmaceutical grade**
  - Generators: $^{99}\text{Mo}/^{99m}\text{Tc}$, $^{68}\text{Ge}/^{68}\text{Ga}$, $(^{82}\text{Sr}/^{82}\text{Rb})$
  - SPECT: $(^{123}\text{I}), (^{111}\text{In}), ^{67}\text{Ga}$, $^{201}\text{Tl}$, $^{186}\text{Re}$, $^{169}\text{Er}$
  - PET: $^{18}\text{F}$, $(^{124}\text{I})$
  - Therapy: $^{131}\text{I}$, $^{90}\text{Y}$, $^{177}\text{Lu}$, $^{153}\text{Sm}$, $^{89}\text{Sr}$, $^{223}\text{Ra}$

- **GMP grade**
  - Generators: -
  - SPECT: -
  - PET: $^{89}\text{Zr}$
  - Therapy: $(^{166}\text{Ho})$

- **Local availability**
  - Generators: $(^{188}\text{W}/^{188}\text{Re})$
  - SPECT: -
  - PET: $(^{15}\text{O}, ^{13}\text{N}, ^{11}\text{C}, ^{64}\text{Cu})$
  - Therapy: $(^{117}\text{mSn})$

By 2020

1. $^{188}\text{W}/^{188}\text{Re}$
2. $(^{64}\text{Cu})$
3. $^{212}\text{Pb}$, $(^{227}\text{Th})$

() brackets: locally available or expensive; blue color: difficult chemistry or limited applications
Development of New RPs is Limited by Access to RNs

- **Pharmaceutical grade**
  - Generators: $^{99}$Mo/$^{99m}$Tc, $^{68}$Ge/$^{68}$Ga
  - SPECT: $^{123}$I, $^{67}$Ga,
  - PET: $^{18}$F, $^{124}$I
  - Therapy: $^{131}$I, $^{90}$Y, $^{177}$Lu

- **GMP grade**
  - Generators: -
  - SPECT: -
  - PET: $^{89}$Zr
  - Therapy: $^{166}$Ho

- **Local availability**
  - Generators: -
  - SPECT: -
  - PET: $^{15}$O, $^{13}$N, $^{11}$C
  - Therapy: $^{117m}$Sn

By 2025

- $^{188}$W/$^{188}$Re
- $^{212}$Pb, $^{89}$Zr
- $^{188}$W/$^{188}$Re
- $^{64}$Cu
- $^{212}$Pb, $^{227}$Th
- $^{211}$At, $^{225}$Ac

() brackets: locally available or expensive; blue color: difficult chemistry or limited applications
$^{68}$Ga and $^{68}$Ga- labeled tracers

Generic tracers under development
- $^{68}$Ga-DOTANOC – generic – NET imaging
- $^{68}$Ga-DOTATOC – generic – NET imaging
- $^{68}$Ga-Galacto-RGD – angiogenesis
- $^{68}$Ga-PSMA (s)

Proprietary tracers under development
- $^{68}$Ga-BNOTA-BRGD2: Beijing Union Medical College – Angiogenesis – local development
- $^{68}$Ga-Bombesin – Piramal – metastases imaging – development restarted?
- $^{68}$Ga-DOTATATE – AAA/Radiomedix (= $^{68}$Ga-GaTate – Somakit - GalioMedix) – phase II, NET imaging
- $^{68}$Ga-OPS202 (SOMScan) – Octreopharm/Ipsen – NET imaging – phase I started in June 2014
$^{68}$Ge/$^{68}$Ga generators

**Marketed generators**
- **Eckert & Ziegler**: “IGG100” – unique generator with a marketing authorization (2014) – shelf-life: 12 months
- **ITM**: “itG-Ge-68/Ga-68 generator”, GMP – MA expected by 2016
- **iThemba**: sold in Europe by **DSD Pharma** (previously by **IDB**) – GMP
- **IRE**: "Galli-Eo" launched in 2015 - GMP
- **PARS**: "PARS-Gallugen"
- **Obninsk** (and formerly **Nukem**) so far sold by **E&Z** and **JSC** – no MA request filed

**Generators under development**
- **ANSTO** – “GAG-1/RAGIDIS”, combination with a concentrator – still under development, but available as a non-GMP tool
- **LANL** and New Mexico CIM – probably on hold
- **Tenex** – probably on hold
- Others having shown interest: Soreq – and all companies having acquired a 70 MeV cyclotron
Gallium-68

• > six $^{68}$Ge/$^{68}$Ga generators under development
  • maximum capacity 100 mCi
• 2014: E&Z obtains first MA for its $^{68}$Ge/$^{68}$Ga generator
  • 12 months shelf-life
• Generic $^{68}$Ga-PSMA-11 is available (almost) worldwide (*and used*)
  • Limitation: generator + synthesizer
• 2015: ANMI brings the first cold kit for $^{68}$Ga-PSMA-11 on the market
  • Technology can be extended to almost any $^{68}$Ga labeled molecule
• 2015: NCM-US shows possibility to produce $^{68}$Ga with a cyclotron
  • >3 Ci/h high quality – no contamination with $^{68}$Ge
  • IBA and GE develop also an alternative
• 2015 (SNM): FDA informs that $^{68}$Ge/$^{68}$Ga generators do not need MA
  • $^{68}$Ga solutions are to be qualified as API
$^{99}$Mo/$^{99m}$Tc

- By 2018 the $^{99}$Mo shortage issue will be solved
- By 2022 there will be excess of capacity in $^{99}$Mo
- Price of generators may even drop due to competition
- There will be a new shortage issue by 2028-2030, when Petten and Mol reactors will have to close (if not replaced by Pallas/Myrrha)

As a consequence of the limited interest in SPECT in the past 10 years there is a very low number of new $^{99m}$Tc tracers available

But $^{99m}$Tc will remain the cheapest radionuclide and SPECT the cheapest NM diagnostic modality
Radionuclide selection - Summary (2016-2025)

• PET radionuclides
  • $^{18}$F
  • $^{68}$Ga definitely yes
  • $^{89}$Zr could be the adequate substitute for $^{124}$I

• SPECT radionuclides
  • $^{99m}$Tc: urgent to restart research programs
  • ($^{123}$I)

• Therapy
  • $^{177}$Lu (but nca) better profile than $^{131}$I and $^{90}$Y
  • $^{188}$Re, ($^{131}$I )
  • $^{211}$At, and potentially $^{212}$Pb as first alpha emitters
Any new ‘exotic’ radionuclide has a chance to make a breakthrough in the RP market, **only if one has secured global, worldwide, long-term and cheap supply**
Is there a future for new radionuclides?

• Yes if ...
  • ...an advantage or a **difference with existing** and already available radionuclides can be shown
  • ...the **impurity profile** (chemical and radiochemical) can be improved up to 99%+
  • ...the **irradiation yields** are highly increased (manufacturing batch sizes >> 1Ci)
  • ...the specific chelating chemistry is improved with **labeling yields** > 90%
  • ...the radionuclide **manufacturing price** (eob) remains largely below 10€/mCi

• Examples of non-fulfilled wishes
  • Covalent gamma emitter other than $^{123}$I
  • Combined gamma/positron radionuclide
Worldwide Equipment - Summary

Cameras (estimations 2015) and cyclotrons (real 2015)

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>EU (geogr. w/o Russia)</th>
<th>World (2015)</th>
<th>World (est. 2025)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>12,500</td>
<td>4,380</td>
<td>26,160</td>
<td>29,000</td>
</tr>
<tr>
<td>PET</td>
<td>2,300</td>
<td>920</td>
<td>4,860</td>
<td>7,000</td>
</tr>
<tr>
<td>Cyclotrons (&lt;25MeV)</td>
<td>239</td>
<td>222</td>
<td>1,106</td>
<td>1,350</td>
</tr>
</tbody>
</table>

Source: MEDraysintell (2016)

Trends

• SPECT: slow evolution in Asia and replacement market
• PET cameras: faster growth but due to filling gaps
• Cyclotrons: 50 new units a year (Asia mainly) - saturation of sites

Additional issues

• Limited access to shielded rooms

Chrysalium - 20160410
Economic considerations

- Value of the PET network ($^{18}$F)
  - France or Germany: hypothesis 5 centers - 5M€ in average: € 25 M
  - Extrapolation to Europe x 450/70 = € 160M
  - North American market: approx same size => World > € 400M

- $^{124}$I: about 7M€/site but only 2-4 required worldwide: € 15-25M

- Extension of an existing SPECT/therapy site (e.g. $^{90}$Y or $^{177}$Lu)
  - Estimated 3-5M€/site (2-4 required worldwide): € 10-20M

- Creation of a new site: € 25-40M, up to € 50-160M worldwide
  - Exception $^{123}$I (short half life): >10 sites worldwide = >> € 150M

- Creation of a generator manufacturing unit: € 15-30M
Personalized medicine

- Selection of positive responders for a specific therapy
- Outcome prognosis and follow up of therapy
What's coming next in imaging? (1/4)

Oncology (2016-2020)

- Proliferation
  - $^{18}$F-Fluciclovine (prostate – Blue Earth Diagnostics: 2016)
  - $^{18}$F-FES (generic – 2016)
  - $^{18}$F-FMAU (generic) – $^{18}$F-PMPA (generic)
  - $^{99m}$Tc-MIP1404 (Progenics - prostate - 2018+)
  - $^{123}$I-CLR1404 (Cellectar - colon - 2018+)
  - $^{89}$Zr-Df-IAB2M (Imaginab – 2019)
  - $^{99m}$Tc-EC20 (Etarfolatide) – $^{99m}$Tc-EC0652 (ovarian – Endocyte – 2016+) companion diagnostic
  - $^{124}$I-Redectane (Wilex - kidney – 2019 – development restarted)
  - $^{99m}$Tc-Lymphoseek (Sentinel node detection - Navidea: launched in 2014)
  - $^{68}$Ga-PSMA-11; $^{68}$Ga-PSMA-617 (generics – no official industrial development)

- Hypoxia imaging (PET): $^{18}$F-Flortanidazole (Threshold Pharma - 2015+)
- Angiogenesis imaging (PET): $^{18}$F-Fluciclactide (GEH – 2018+) – $^{18}$F-GD-K5 – $^{18}$F-AP39 – $^{18}$F-FSPG
- Inflammation (long term):
  - Invasion (PET): $^{18}$F-M4-037 (2017+) - BAY $^{18}$F-85-8050 (Bayer - 2018+)
- Apoptosis imaging agents
  - SPECT: $^{99m}$Tc-Annexin V (AAA - 2017+)

*Estimated launch dates mean “not earlier than”*
Diagnostic Cardiology
What's coming next in imaging (2/4)

Cardiology and cardiovascular imaging agents (2016-2022)

- Continuous competition with $^{99m}$Tc-Technetium and $^{201}$Tl-Thallium
- Interest in $^{82}$Rb
- Limited market interest in PET (compared to neurology and oncology), but PET tracers possible by 2018+
  - $^{18}$F-Flurpiridaz (Lantheus - on hold)
  - $^{18}$F-CardioPET (Fluoropharma - 2019+)
  - $^{18}$F-BFPET (Fluoropharma – 2020+)
  - $^{99m}$Tc-DFH12 (Pulmobind – PulmoTech – 2019+) (pulmonary imaging)
- New potential in SPECT (Ischemia)
  - $^{123}$I-Zemiva (2019+)
- High interest in vascular diseases (vulnerable plaque, atherosclerosis, thrombosis):
  - $^{99m}$Tc-Thromboview (2019+)
  - $^{18}$F-VasoPET (Fluoropharma - 2022+)

Estimated launch dates mean “not earlier than”
Diagnostic Neurology
What's coming next in imaging? (3/4)

Neurology (2016-2020)

• Alzheimer imaging agents (all $^{18}$F labeled PET agents)
  • Amyloïd plaques (all launched 2012/2013)
    - $^{18}$F-Florbetapir (Avid Radiopharma/Eli Lilly)
    - $^{18}$F-Florbetaben (Piramal)
    - $^{18}$F-Flutemetamol (GE Healthcare)
  • Amyloïd plaques 2: $^{18}$F-Flutafuranol – (Navidea - 2020+)
  • Amyloïd plaques 3: 24+ new $^{18}$F tracers identified with 12+ different groups
  • Different mechanisms (PBR, tau, tangles, neuro receptors, ...)
    - $^{18}$F-DP-714 (Piramal - 2020+)
    - $^{18}$F-T807/AV1451 (Avid - 2020+)
• More work required until a SPECT agent is available

• Parkinson:
  • $^{18}$F-DTBZ (AV-133 - Florbenazine) (Avid – 2020+)
  • Any other neurodegenerative disorder imaging agent open for research

*Estimated launch dates mean “not earlier than”*
Other tracers of interest
What's coming next in imaging (4/4)

• Other areas of interest
  • Diabetes (interest +++): Pre-diabetic patient identification and Diabetes' progression evaluation - PET and SPECT:
    • $^{18}\text{F} \text{DTBZ (AV-133 - Florbenazine)}$ (Avid – 2020+)
  • Infection/inflammation (++)
  • No additional known tracer under development in this area
High risk of saturation of the worldwide GMP $^{18}$F-manufacturing sites within the next 6-8 years
Radiotherapeutics
The future of NM is in therapy

1946
- Iodine $^{131}$I: Thyroid therapy
  - Cheapest cancer therapy ever

2002
- Launch of $^{90}$Y-Zevalin and $^{131}$I-Bexxar: NHL
  - ww market/year reaching $33M (2013)
  - Rituxan/Mabthera: $4B (USA)

2013
- Bexxar discontinued (GSK)
- Launch of $^{223}$Ra-Xofigo (Bayer)
  - Xofigo: Q1/2014: $49M
  - Expectations:
    - 2014: $158M (US only)
    - 2015: $300M
    - Expected Peak: > $1B

2020
- $^{177}$Lu-Lutathera: NET
- $^{177}$Lu-ATL101: prostate cancer
  - Lutathera: $200+M market
  - ATL101: $>1BM market
Therapeutic agents on the market

- $^{89}\text{Sr}$-Strontium Chloride: bone metastases – pain palliation (Metastron) **GEH** -> generic
- $^{90}\text{Y}$-Yttrium Citrate or silicate: radiosynovectomy
- $^{90}\text{Y}$-Ibritumomab tiuxetan (Zevalin) – **Spectrum Pharma**
- $^{131}\text{I}$-chTNT: Cotara Vivatuxin – **Peregrine - Shanghai MediPharm Biotech** – Lung (China), brain (US, clinical trial)
- $^{131}\text{I}$-Iobenguane (MIBG): pheochromocytoma
- $^{131}\text{I}$-Sodium Iodide: thyroid cancer
- $^{131}\text{I}$-Tositumomab (Bexxar) – **GSK** – withdrawn from market in 2014
- $^{153}\text{Sm}$-Lexidronam (EDTMP/Quadramet)- LMI - generic
- $^{166}\text{Ho}$-Chitosan: **Dong Wha** – brain tumors
- $^{168}\text{Er}$-Erbium Citrate: radiosynovectomy
- $^{177}\text{Lu}$-EDTMP: bone metastases (only Iran, **PARS**) - generic
- $^{186}\text{Re}$-Rhenium Etidronate: bone metastases (only Iran, **PARS**) - generic
- $^{186}\text{Re}$-Rhenium Sulfide: radiosynovectomy
- $^{188}\text{Re}$-Rhenium Sulfide: radiosynovectomy (only Iran, **PARS**) - generic
- $^{223}\text{Ra}$-Radium Dichloride Xofigo (Alpharadin), **Bayer**: bone metastases – pain palliation
What’s next in therapy?

• **High chances to come on the market soon**
  - **NET:** $^{177}$Lu-Lutathera (2017) - $^{177}$Lu-'Onalta' (2019+) - $^{177}$Lu-'SomTher' (2022)
  - **Pancreas cancer:** $^{212}$Pb-Trastuzumab (2020+)
  - **Prostate cancer:** $^{177}$Lu-ATL-101 (2018+) - $^{177}$Lu-PSMA-617 (2020+)

• **On hold** (became generics as a consequence of the long time to find funds to complete clinical trials – expired patents)
  - $^{131}$I-TM-601 - $^{131}$I-Neuradiab - $^{131}$I-ACD101 - ($^{131}$I-Cotara): glioblastoma
  - $^{131}$I-Solazed: melanoma
  - $^{188}$Re-Lipiodol: liver cancer
  - $^{131}$I-Azedra: pheochromocytoma (= nca $^{131}$I-MIBG)
  - $^{90}$Y-Clivatuzumab: pancreas cancer

*Estimated launch dates mean “not earlier than”*
The future of NM is in therapy

**Trends**

- If Xofigo is a success, all conventional pharmaceutical industries will become interested in radiotherapeutics
  - ... but $^{223}$Ra-Xofigo and $^{223}$Ra are an isolated non-reproducible example
- The number of molecules in clinical phase II/III stage remains limited (i.e. marketed before 2022): $^{177}$Lu-Lutathera, $^{177}$Lu-ATL101, $^{212}$Pb-Trastuzumab
- Newcomers: Areva Med, Sanofi, Novartis, Ipsen ...
  - In May 2015, Ipsen Pharmaceuticals acquired Octreopharm and in January 2016, 3B Pharma's radiopharmaceutical pipeline
- $^{131}$I and $^{90}$Y may/will disappear to the advantage of $^{177}$Lu
- Further molecules have a high potential (could be marketed before 2025, if...): $^{117m}$Sn-Annexin (Clear Vascular), $^{131}$I-Iomab, ...
- Alpha radio(immuno) therapy has a high potential, but will be limited to a very small number of radionuclides: $^{211}$At, ($^{212}$Pb), $^{225}$Ac, ($^{226}$Th), ...
Back to the initial problem...

If you think your product is the best and you do not want to develop it yourself (i.e. creating a spin-off, raising funds), then make sure that:

- You are the only one aware about this project
- You are the expert of the domain
- You have patented it (preferably worldwide)
- You can propose a non-expensive solution for all industrialization issues
- You have a clear and realistic idea about the potential market
- You know the potential competition at the time to market

If answer is yes to all, then you can knock at the door of industries or any other investors
Thanks for your attention

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"Why are investors not interested in my radiotracer? The industrial and regulatory constraints in the development of radiopharmaceuticals”
Nuclear Medicine and Biology, 2013, 40(2) 155-166