A Secure Global Supply of Mo-99 and Tc-99m

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Outline

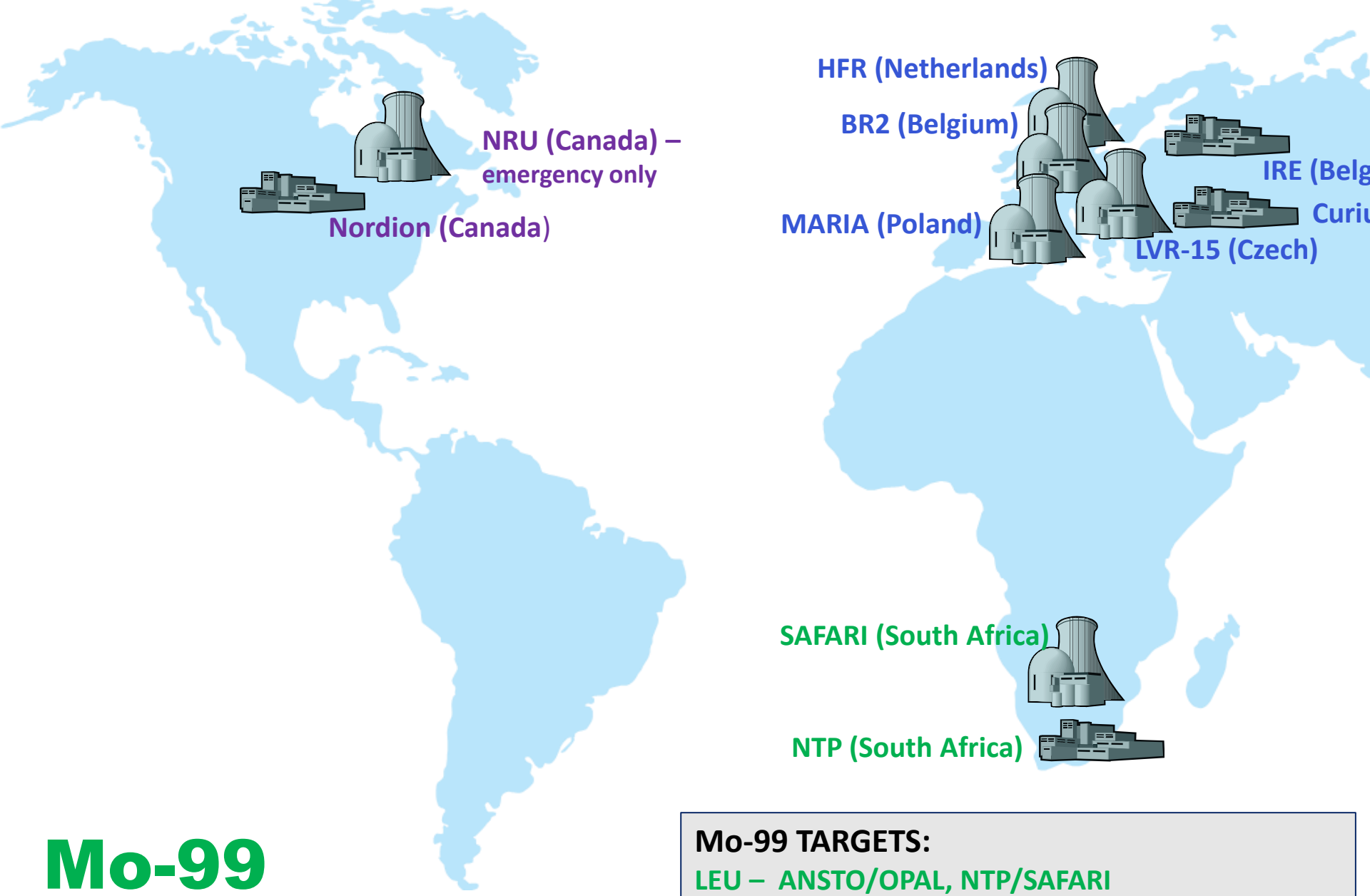
- **Nuclear Medicine**
- **International Mo-99 supply chain (HEU vs. LEU)**
- **North American Supply Matrix**
- **Future Mo-99 Supply Chain**
  - U.S. Domestic Projects
    - S.99 and DOE Cooperative Projects
    - Other U.S. non-HEU projects
  - International Mo-99 supply developments
    - Europe
    - ROW
    - Canada NISP/ITAP
- **Conversion to LEU and LEU Generator**
- **Full Cost Recovery**
- **Mo-99/Tc-99m Supply/Demand**
- **Summary**
- **Lantheus Medical Imaging**

Nuclear Medicine

- **Short-lived radioisotopes**
  - Bond (label) to chemical compounds (pharmaceuticals) with affinity to particular organs
  - Heart, bones, thyroid, liver, brain
  - Injection, oral, or inhalation
- **Diagnosis (imaging): functional vs. structural**
  - SPECT: Tc-99m (myocardial perfusion; 140 KeV gamma), Xe-133 (PE/lung ventilation)
  - PET: F-18 (109 min ½ life; positron; cyclotron), Ga-68 - oncology/tumor imaging, generator
- **Therapy (targeted, short-radius kill)**
  - I-133 (beta), Ra-223 (alpha); Y-90 (beta; radioembolization), Lu-177 (beta/gamma); Sm-153 (palliative)
- **Mo-99 (reactor-produced; 66 hr ½ life) parent Tc-99m (6 hr ½ life)**
- **Tc-99m used in over 80% 35+M NM procedures worldwide**
  - 15M U.S. NM procedures (40-50% cardiac; 35-40% oncology)

TechneLite® Technetium Tc99m Generator

- **Sodium pertechnetate Tc-99m**
  - used in preparation of FDA-approved diagnostic radiopharmaceuticals,
- **Sodium Pertechnetate Tc-99m Injection is used directly for:**
  - Thyroid Imaging
  - Salivary Gland Imaging (Adults only)
  - Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux.
  - Nasolacrimal Drainage System Imaging (Adults only)
- **Low-Enriched Uranium (LEU) Mo-99 for use in the manufacture of TechneLite® approved by FDA in 2010**
  - first Tc-99m generator in US containing ≥ 95 percent LEU sourced molybdenum-99 (Mo-99)



Mo-99 Supply Chain

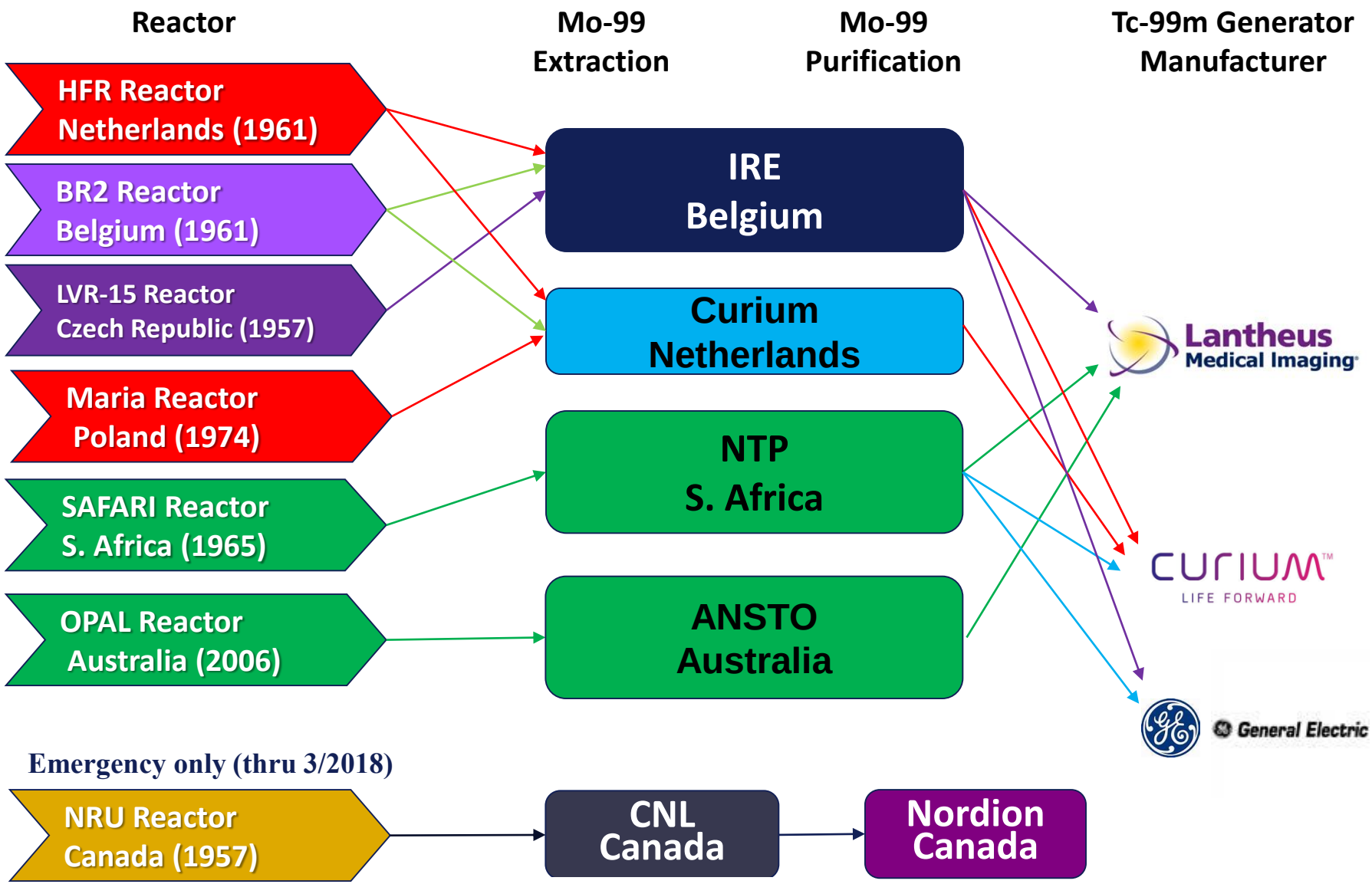
Reactors & Processors

Mo-99 TARGETS:

LEU – ANSTO/OPAL, NTP/SAFARI

HEU – Mallinckrodt w/HFR, MARIA, IRE w/BR2, HFR, LVR-15, NRU

Mo-99 Supply Chain



Major Mo-99 Reactors

SAFARI, NTP, Pelindaba

HFR, NRG, Petten

Opal, ANSTO, Sydney

BR2, SCK-CEN, Mol

LVR-15, UJV, Rez

MARIA, Polatom, Swierk

LEU Mo-99

- **NTP (South Africa)**
  - ~2500 - 3000 6-day Ci/week; mostly LEU
- **ANSTO Health (Australia)**
  - Existing plant: 1800-2250 6-day Ci week (all-LEU)
  - New facility: 3500 6d Ci/week - late 2017

SAFARI, NTP, Pelindaba

Opal, ANSTO, Sydney

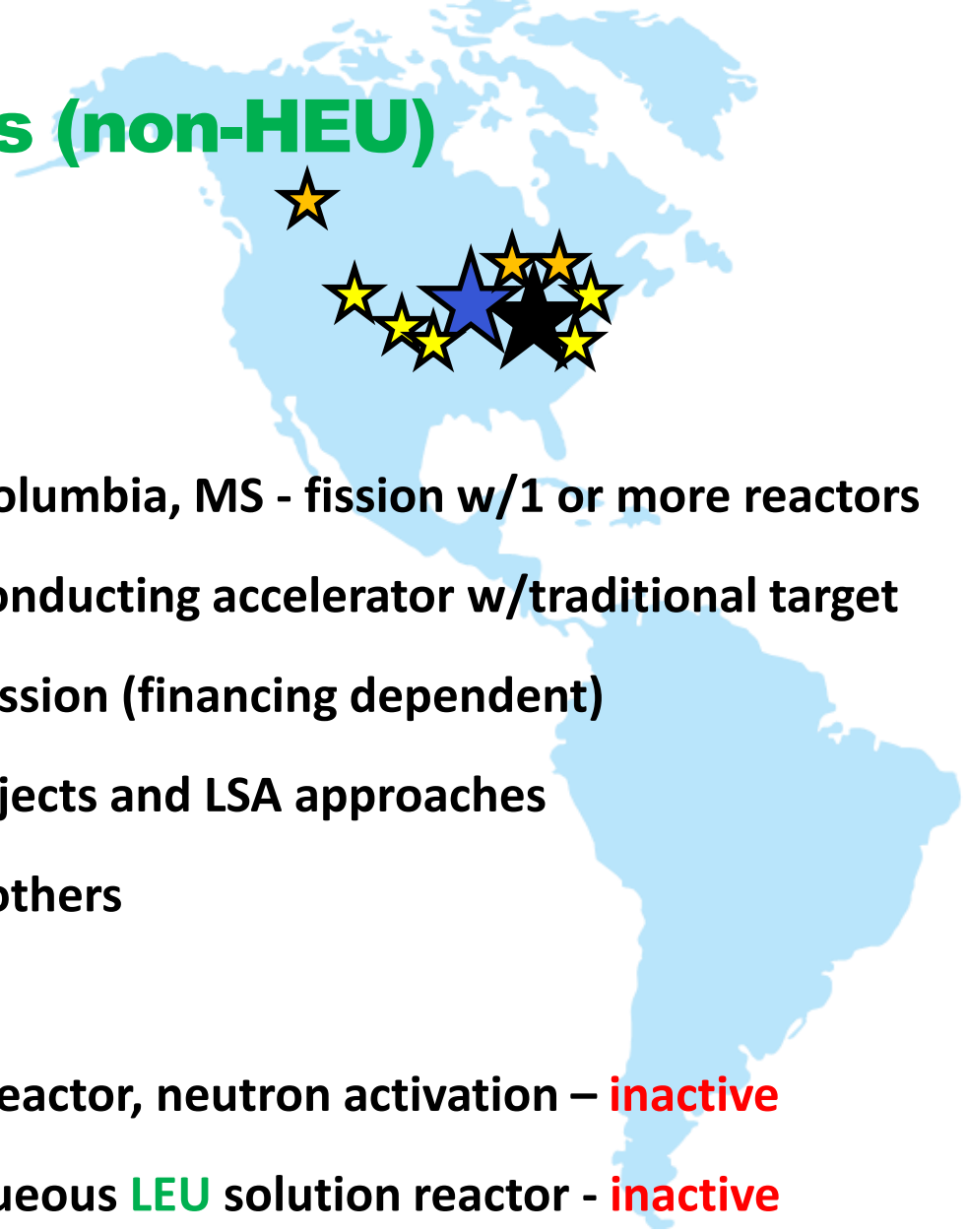
NRU Status

- **NRU reactor ceased regular Mo-99 production October 31, 2016**
  - NRU continues to operate until March 31, 2018; thereafter will be decommissioned
  - NRU and Nordion maintain stand-by capability to restart Mo-99 production in the unlikely event of a Mo-99 shortage
    - back-up production last resort among a range of possible mitigation strategies
- **Government of Canada prepared to activate back-up capability**
  - Communications protocol with AIPES regarding international supply situation

DOE Cooperative Agreements Non-HEU Mo-99

- American Medical Isotopes Production Act of 2012 (AMIPA/S.99)
- U.S. Domestic Projects: 4 active DOE/NNSA cooperative grants (non-HEU projects)
    - SHINE - accelerator-driven LEU solution fission process; 2020 (financing dependent)
        - Lantheus supply agreement (October 24, 2014); also GE agreement
        - Received NRC construction permit approval (Feb. 25, 2016)
    - Northstar – 2 grants: Mo-98 neutron activation at MURR (now) and accelerators w/Mo-100 (later); both LSA using Radiogenix Tc-99m generator - awaiting FDA approval
    - Nordion/MURR/ General Atomics: Selective Gas Extraction; 2H2018 (licensing dependent)

Other U.S. Projects (non-HEU)



NON-DOE PROJECTS

- **Northwest Medical Isotopes: Columbia, MS - fission w/1 or more reactors**
- **Niowave: Lansing, MI – superconducting accelerator w/traditional target**
- **Coqui Radiopharmaceuticals: fission (financing dependent)**
- **Several other fission-based projects and LSA approaches**
  - **Eden, PermaFix, Flibe, others**

TERMINATED DOE PROJECTS

- **GE Hitachi-Clinton – power reactor, neutron activation – inactive**
- **Babcock & Wilcox – MIPS aqueous LEU solution reactor - inactive**

International Mo-99 Supply Developments

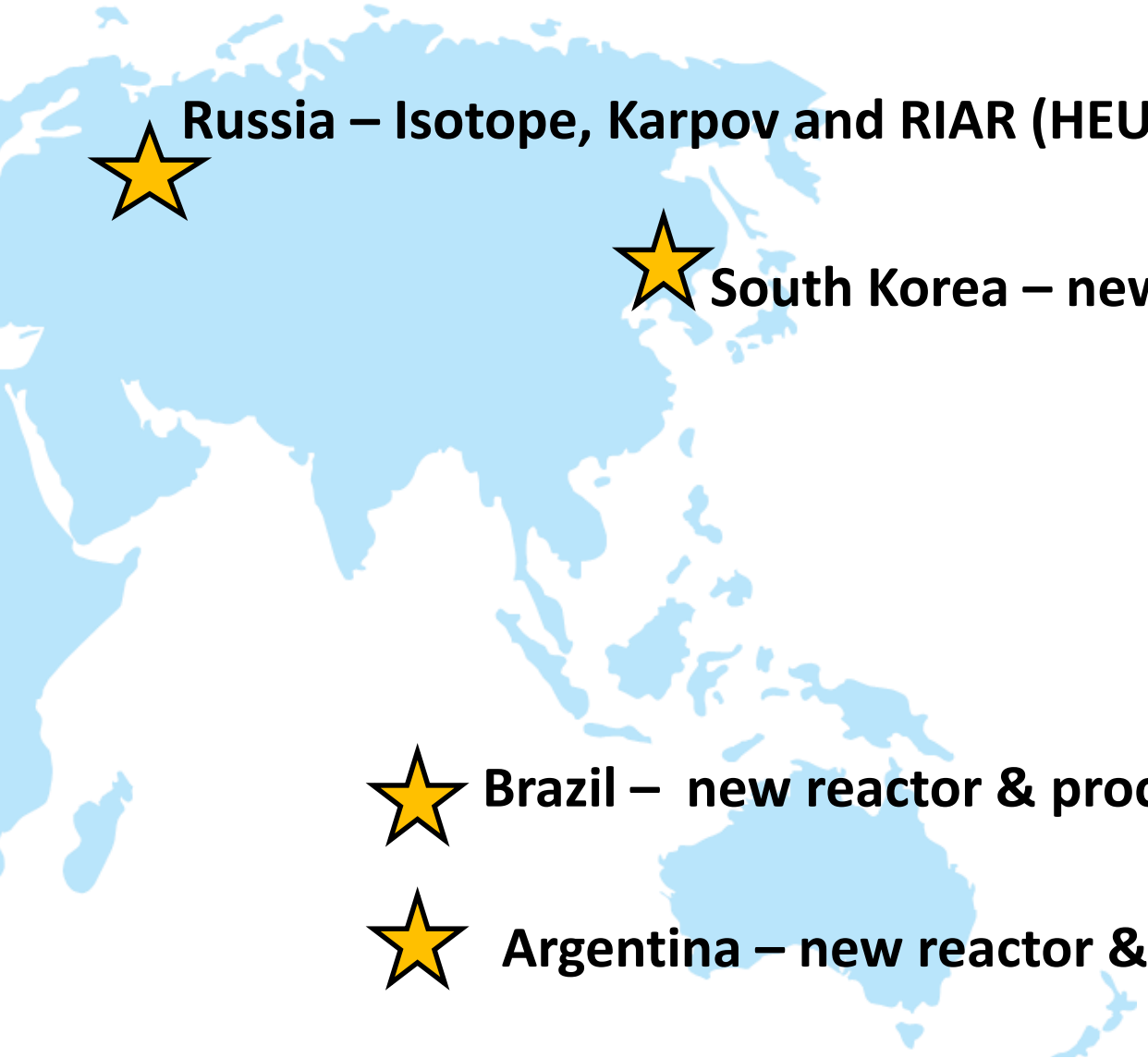
- IRE and Curium conversion to LEU targets – late 2017
  - Nuclear Security Summit 2012 commitment
    - Belgium, Netherlands, France, U.S.
  - IRE – late-2017 commercial LEU supply
  - Curium - end of 2017 LEU conversion
- New European Research Reactors (LEU targets)
  - FRM II Reactor – 2H2019
  - Jules Horowitz Reactor (replace Osiris) – 2022?
  - Pallas Reactor (replace HFR) – 2024 (financing?)
  - MYRRHA (replace BR2) – 2024 (financing?)
- ANM Australia (3600 Ci/week LEU) late 2017 – key project

FRM2 Reactor (Munich, Germany)

Jules Horowitz Reactor (Cadarache, France)

Courtesy of CEA (French Atomic Energy Commission), Cadarache Center

International Mo-99 Supply Developments



Russia – Isotope, Karpov and RIAR (HEU/LEU 2018?)

South Korea – new RR, fission 2022 (LEU)

Brazil – new reactor & processing, 2024 (LEU)

Argentina – new reactor & processing, 2020 (LEU)

Canada: Non-Reactor Technologies

- **Cyclotron-produced Tc-99m (Direct Tc-99m)**
  - 19 MeV PET Cyclotrons (TRIUMF, BCCA, London)
  - 24 MeV Cyclotron (ACSI, Edmonton, Sherbrooke)
- **Mo-99 via accelerator production**
  - Prarie Isotopes (PIPE)
- **NISP $25M (2011-12); ITAP $30M (2013-16)**
- **Proof of principle demonstrated**
- **Health Canada required clinical trial (pertechnetate thyroid imaging) underway**
- **Business model – competitive w/Tc-99 generator?**
  - COGs, production rates, and price per dose
  - Cost comparison may be site dependent

LEU Conversion
Global Threat Reduction Initiative (GTRI)

- **GTRI/Convert goal is to minimize or eliminate the use of Highly Enriched Uranium (HEU) in civil nuclear applications**
  - "Atoms for Peace": U.S. and USSR provided research reactors HEU fuel to support development of peaceful uses of nuclear energy
    - HEU has optimal properties for research reactor fuel and medical isotope irradiation targets (high neutron flux)
    - HEU directly usable in a nuclear weapon (Hiroshima-type)
  - LEU conversion efforts started in late 1970's
    - Reduced Enrichment for Research and Test Reactors (RERTR)
  - Post-9/11 impetus to secure weapons-usable, high-risk nuclear materials; GTRI formed in 2004, U.S.- led international initiative
  - White House/NSC priority: OSTP w/DOE, CMS, other Federal agencies
  - Nuclear Security Summits: Washington (2010); Seoul (2012); The Hague (2014), Washington (2016)

U.S. Government Actions and Programs

Executive Branch and Congressional Actions - GTRI (Convert):

- **American Medical Isotope Production Act of 2011 (AMIPA/S.99) January 2, 2013[4]**
  - Supports development of non-HEU domestic Mo-99/Tc-99m production
  - Establishes DOE fee-based, uranium lease and waste take-back program
    - Waste for which there is no commercial disposition pathway
  - Phase-out HEU exports for medical isotope production over seven years

- **HEU Exports**
  - Reduce exports of HEU that are used for medical isotope production as sufficient supplies of non-HEU-produced Mo-99 are available to the global marketplace
    - HEU exports for medical isotope production made on an annual basis

- **Veterans Administration LEU preference policy[5]**
  - January 3, 2014, Department of Veteran's Affairs issued policy memorandum
  - VA facilities to preferentially procure non-HEU based Mo-99/Tc-99m radiopharmaceutical products as they become commercially available

[4]http://www.asrt.org/main/standards-regulations/regulatory-legislative-news/2013/01/01/congress-passes-medical-isotope-production-act
[5]http://www.hcnmc.org/wp-content/uploads/2014/03/Staples.pdf

CMS Rationale/Intent
Non-HEU Payment Adjustment Policy

- **CMS (Medicare) established a Payment Adjustment Policy for Radioisotopes Derived from Non-HEU Sources[6]**
  - CY2013 Outpatients/HOPPS (NOT for physician offices)
- **Adjustment necessary to ensure equitable payments AND the cost of hospital conversion to non-HEU sources to obtain radioisotopes used in medical imaging**
- **Covers the marginal cost of radioisotopes produced from non-HEU sources over costs of HEU produced radioisotopes**
  - Includes industry transition (especially research reactors) to Full Cost Recovery
- **CMS non-HEU derived Tc-99m is defined as: "Tc-99m that is at least 95% derived from a non-HEU molybdenum source"**
- **<u>CMS reimburses $10 per dose for non-HEU derived Tc-99m dose</u>**
- **Continued in 2014, 2015, 2016, and 2017**

[6]Federal Register /Vol. 77, No. 221 /Thursday, November 15, 2012 /Rules and Regulations 68321

OECD/Full Cost Recovery

- **OECD/NEA became involved in global efforts to ensure a reliable supply of ^{99}Mo and ^{99m}Tc at request of member countries**
- **NEA established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) in 2009**
- **HLG-MR includes experts from governments of major medical isotope producing and consuming countries, the European Commission, the Euratom Supply Agency and the IAEA**
- **OECD/NEA published a series of reports beginning in 2010:**
  - "The Supply of Medical Radioisotopes" (2010) - an economic study
  - "The Path to Reliability" (2011) – policy recommendations
- **OECD "six principles:" Full Cost Recovery (esp. research reactors) , Outage Reserve Capacity (by 2014), implementation by all parts of the supply chain**
- **Series of follow-up reports including supply/demand scenarios, implementation of recommendations**

OECD/Full Cost Recovery

Full-cost recovery

Full-cost recovery means:

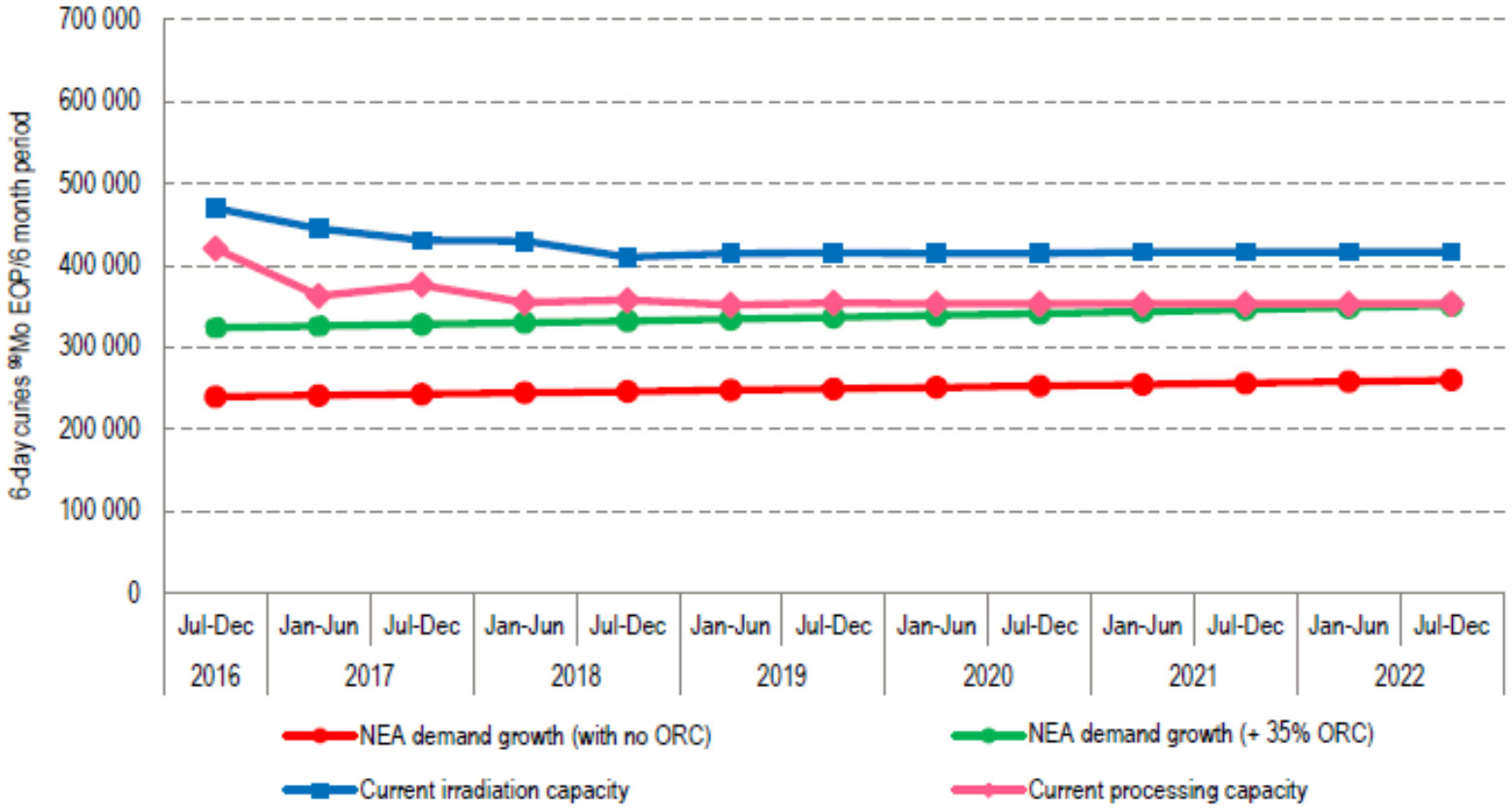
- All costs associated with producing ^{99}Mo are identified and covered through the prices set for irradiation services
- Should include both operational and capital costs:
  - Easily identifiable direct costs
  - Allocated indirect costs
- Methodology provides guidance on how to proportion these costs to ^{99}Mo irradiation services, including indirect costs

Basic steps:

- Identify all costs at reactor/alternative technology facility
- Allocate direct costs for production
- Allocate indirect costs according to agreed methodology

Mo-99 Supply/Demand Scenarios

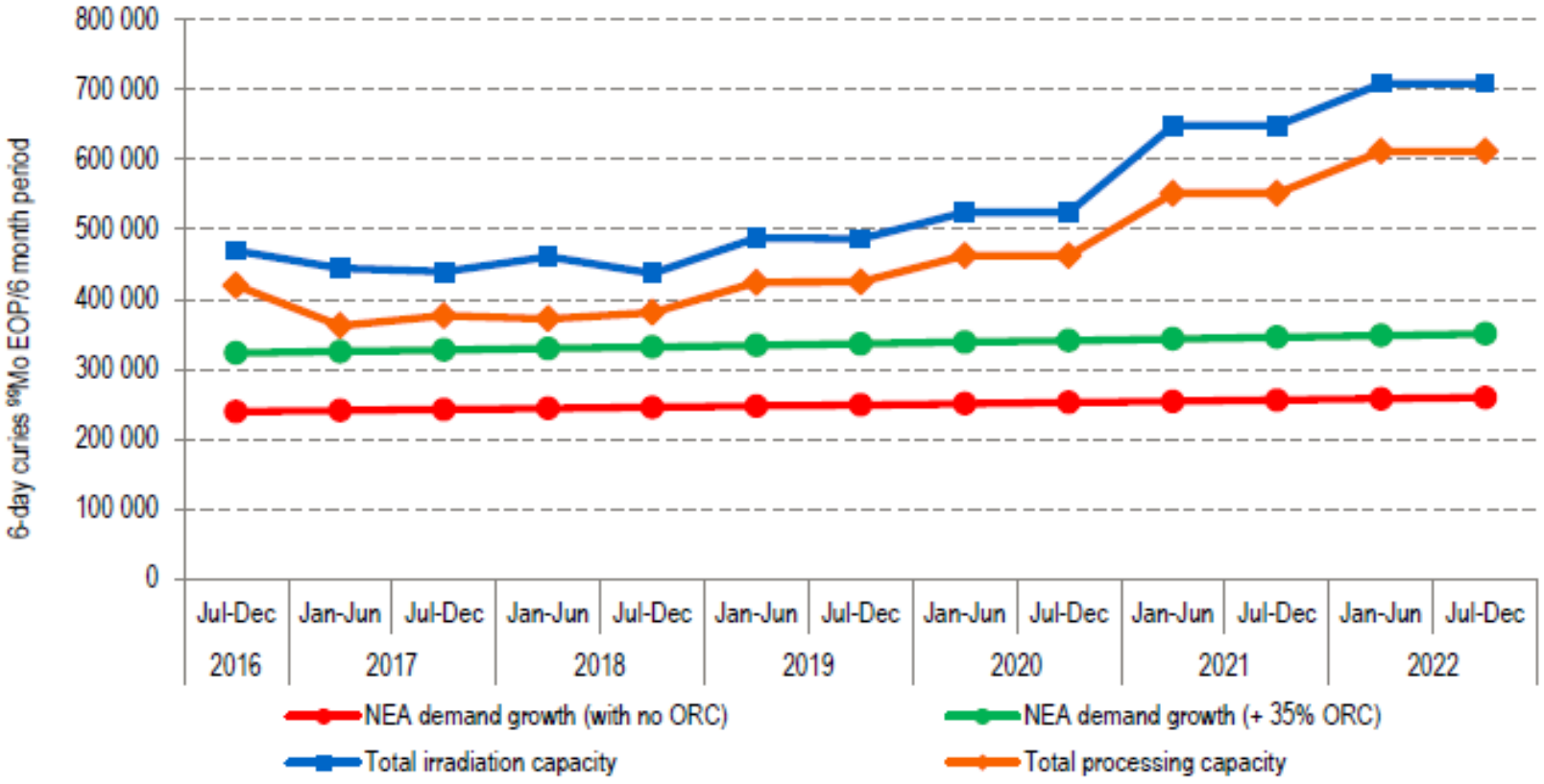
Figure 4.1 Demand (9000 6-day Ci/week) EOP +35% ORC vs. current irradiation and processing capacity, 2017-2022: Scenario A)



Source: OECD Nuclear Energy Agency, "2017 Medical Isotope Supply Review," April 2017

Mo-99 Supply/Demand Scenarios

Figure 6.1 Demand (9000 6-day Ci/week) EOP +35% ORC vs. total irradiation and processing capacity – projects delayed: Scenario C



Source: OECD Nuclear Energy Agency, 2016 Medical Isotope Supply Review, June 2016

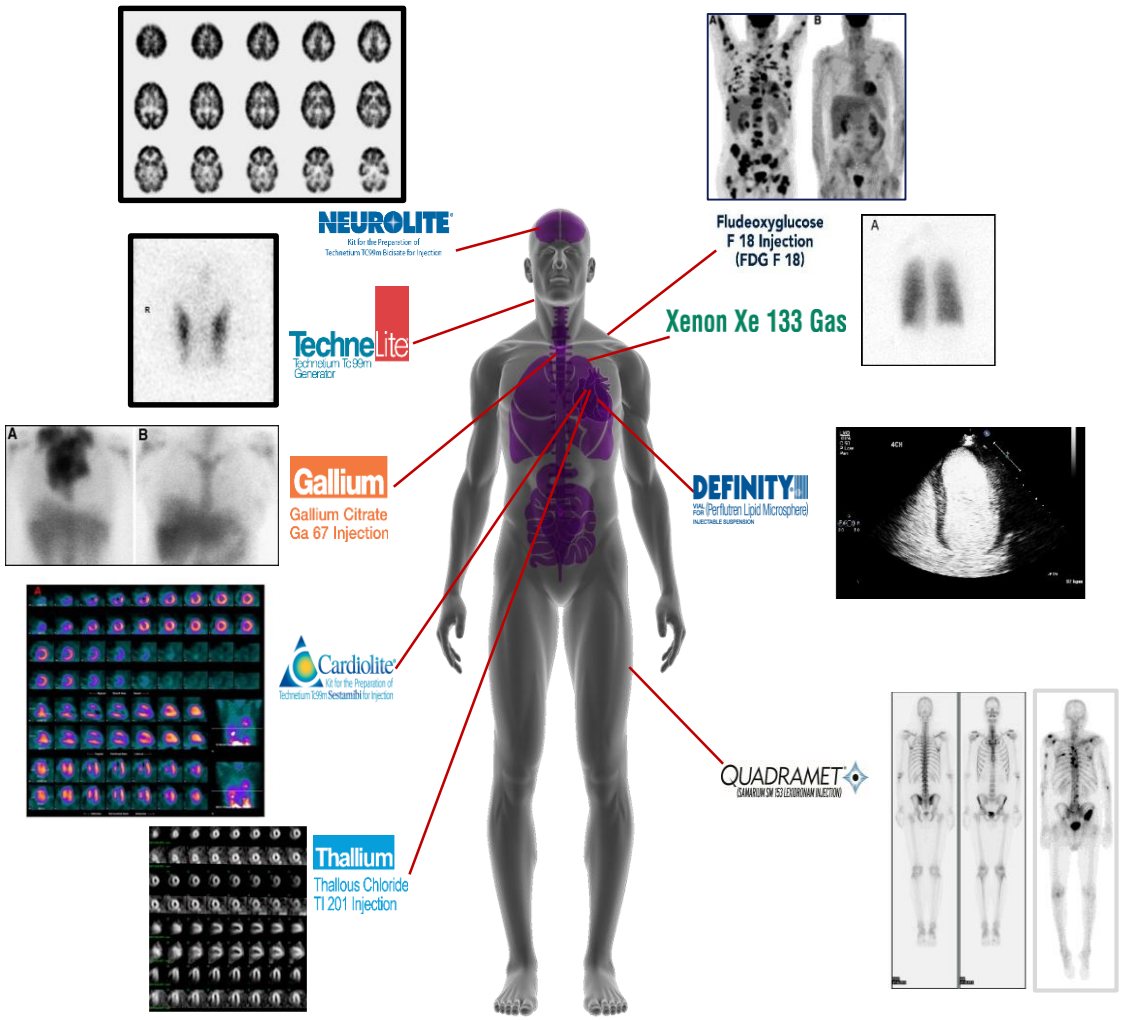
Summary

- Reliable and secure post-2016 Mo-99 supply is achievable
- LEU/non-HEU technologies part of solution to assure future stable and reliable supply of medical radioisotopes
- LEU conversion, together with industry transition to Full Cost Recovery, results in increased costs in supply chain
- U.S. (S.99, CMS add-on, Veterans Adm) and international community committed to LEU/non-HEU Mo-99 supply
- LEU is already important part of global Mo-99 supply
- Further actions underway across the globe to assure future reliable supply and to establish LEU/non-HEU production

Lantheus Medical Imaging

Company Overview	• Lantheus Holdings, Inc. (NASDAQ: LNTH) is the parent company of Lantheus Medical Imaging • A global leader in innovative diagnostic medical imaging agents and products • Products used to diagnose coronary artery disease, congestive heart failure, stroke, peripheral vascular disease and other diseases
Headquarters	• N. Billerica, Massachusetts
Offices Global Presence	• Canada, Puerto Rico • ~400+ employees worldwide
Commercial Products	• Ten
Development Pipeline	• Next-generation product candidates use Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI)

Lantheus - 60 Years of Innovation



Lantheus at-a-Glance

- Pedigree – New England Nuclear (1956), Dupont, BMS Medical Imaging
- Global leader in diagnostic medical imaging
- Develop, manufacture and commercialize essential diagnostic imaging agents and products that help healthcare professionals identify disease and improve patient treatment and care
- Diversified portfolio serving Echocardiography and Nuclear Medicine specialties
  - Lead products include *DEFINITY®*, *TechneLite®* and *Xenon*
  - Dynamic pipeline contains promising next-generation imaging agents
- Worldwide distribution partnerships covering EU, APAC, and LatAm regions
- IPO in June 2015 (Ticker: **LNTH**)

Schematic for illustrative purposes only. Please see Indications and full Prescribing Information on product specific pages of Lantheus.com.