Future US Supply of Mo-99 Through Fission Based LEU/LEU Technology

James S. Welsh, MS, MD

Disclosures

- United States Nuclear Regulatory Commission
  - Member, Advisory Committee on the Medical Uses of Isotopes
- Fermi National Accelerator Laboratory
  - Medical Director, NIU Institute for Neutron Therapy at Fermilab
- American College of Radiation Oncology:
  - President-elect
- American Society for Radiation Oncology (ASTRO)
  - Chair – NRC Subcommittee
- Nuclear Oncology Medical Care, LLC
- Colossal Fossils
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- **Coquí RadioPharmaceuticals Corp**
  - **Board member**

Some Basics

- None of the major reactors were dedicated to Mo-99 production
  - Radioisotope production remains an after-thought or secondary aim
- Were not based on viable business models for Mo-99 industry
  - Mo-99 cost is only a few percent of final price of most radiopharmaceuticals
- No new reactors have been designed or built exclusively for medical isotope production

Some Basics

- Mo-99 shortage discussed at ACMUI/NRC and national medical meetings
- Coqui was formed in 2009

Mo-99 production technologies

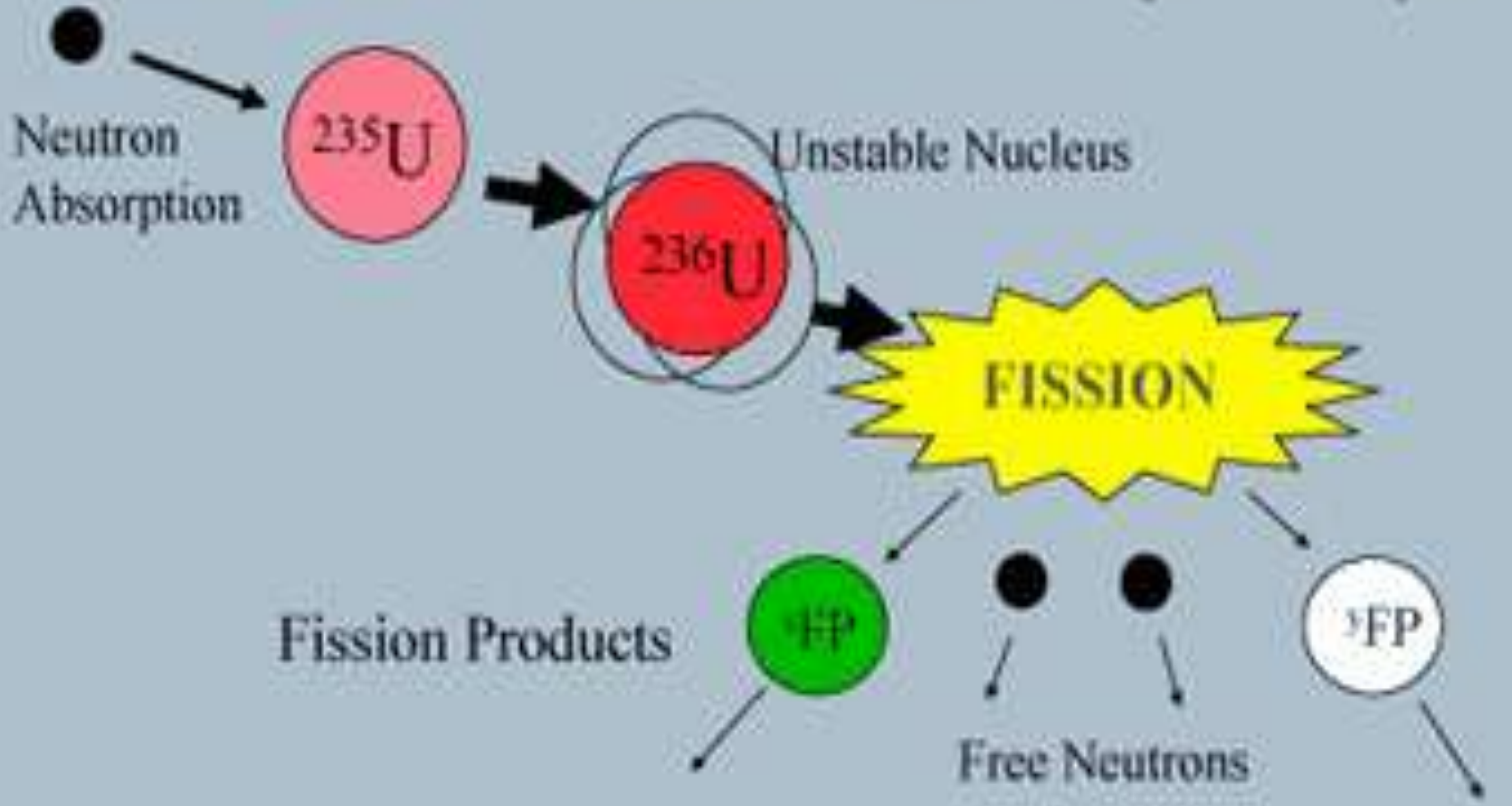
- Novel concepts and new technologies are materializing
- Can these novel alternatives meet the needs?

Alternatives to Conventional Methods

- Accelerator-driven neutrons:
  - $^{235}U\ (n,f)^{99}Mo$
  - $^{98}Mo(n,\gamma)^{99}Mo$
  - $^{100}Mo(n,2n)^{99}Mo$
- The proton-driven reactions:
  - $^{100}Mo(p,pn)^{99}Mo$
  - $^{100}Mo(p,2n)$**^{99m}Tc**
- The deuteron reaction
  - $^{100}Mo(d,p2n)^{99}Mo$
- A photoneutron (γ,n) reaction:
  - $^{100}Mo(\gamma,n)^{99}Mo$
- Photofission:
  - $^{235}U(\gamma,f)\ ^{99}Mo$
  - $^{238}U(\gamma,f)\ ^{99}Mo$

^{235}U Fission

$$^{235}U + {^{1}n} \Rightarrow {^{x}FP} + {^{y}FP} + (2 \ or \ 3)^{1}n$$



Do we really need reactors?

- Are reactors still a viable and competitive method?
- Perhaps a brief historical review can help us determine if reactors are the answer…

A brief history of nuclear medicine

- Joliot-Curies: realized the alchemist's dream of turning one element into another
- Received the 1935 Nobel Prize in Chemistry for their creation of artificial radioactivity
- $^{27}Al(\alpha,n)^{30}P$

A brief history of nuclear medicine

- Ernest O. Lawrence used his cyclotron to bombard a molybdenum sample with deuterons
  - Possibly creating element 43?
  - The material became radioactive
- In 1937 Emilio Segrè and Carlo Perrier studied Lawrence's radioactive product
  - Confirmed it was a new element not found in nature
  - Dubbed it "technetium"

Emilio Segrè

A brief history of nuclear medicine

- In 1936 Dr John Lawrence, using ^{32}P produced in one of his brother's cyclotrons treated a 28-year old leukemia patient
- First time a radioisotope was used in the treatment of a disease
  - marking the birth of nuclear medicine

A brief history of nuclear medicine

- In 1940, deuteron bombardment of carbon-13 led to discovery of carbon-14:
  - $^{13}C(d,p)^{14}C$
- ^{14}C has a long half-life (5770 y)
- Allowed practical scientific investigations of biochemical metabolism

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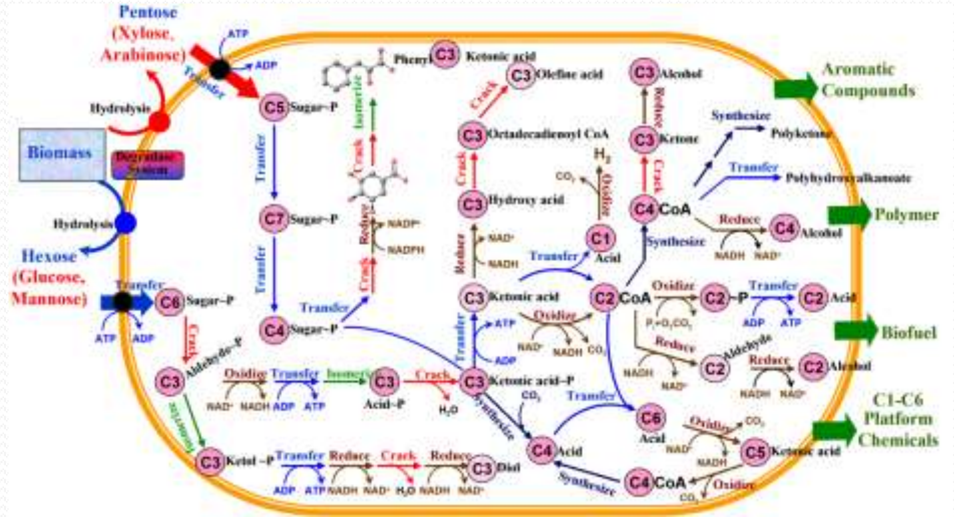


A brief history of nuclear medicine

- Radioiodine (^{131}I) accumulation in thyroid
- ^{131}I could be used to diagnose thyroid disease
- High-dose radioiodine therapy shortly followed
- In patients with thyroid cancer, distant metastases could be identified by scanning the whole body

A brief history of nuclear medicine

- “Radioisotope scanning”
- “Atomic medicine”
- Today all of these isotopes are considered ‘reactor-produced isotopes’
- NRC “byproduct material”

A brief history of nuclear medicine

- “Radioisotope scanning”
- “Atomic medicine”
- Today all of these isotopes are considered ‘reactor-produced isotopes’
- NRC “byproduct material”
- *But obviously none were reactor produced at that time…*

Large-scale production of radioisotopes

- First commercial medical cyclotron was installed in 1941 at Washington University, St. Louis
- But soon there wasn't enough cyclotron capacity to meet the rising demand for isotopes

Manhattan Project

- Significant growth in radiation research and expertise
  - Expansion of applications of radioisotopes in nuclear medicine
- Medical isotopes began to be produced in nuclear reactors
- Radioisotopes soon became plentiful

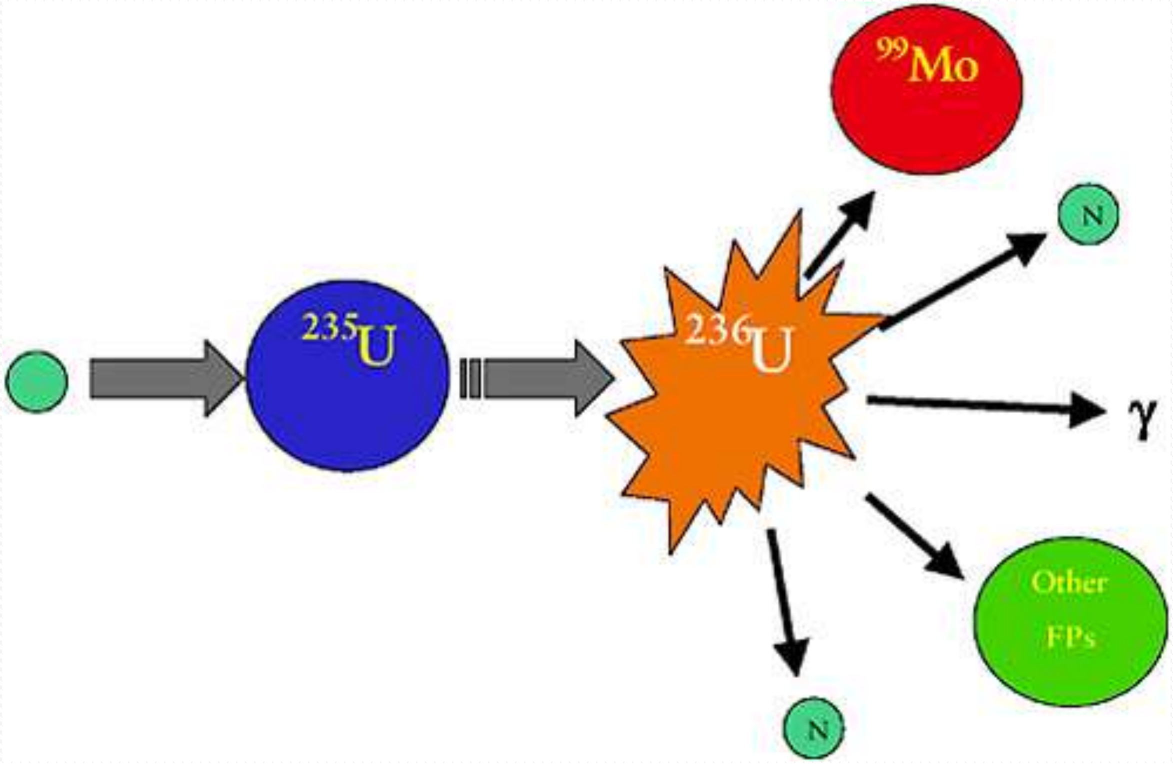
Manhattan Project Isotopes

- All under the strict secrecy of the Manhattan Project
- Medical isotopes produced at Oak Ridge had to appear as if they had been produced by a cyclotron
- Shipped from Oak Ridge to the cyclotron group at UC Berkeley… From where it was then distributed to the medical centers(!)

End of the first isotope crisis

- So the first shortage of radioisotopes ended when isotopes from Oak Ridge became widely available (in the USA)
- (Globally) accelerators still produced most medical radioisotopes until the 1950s when other countries emulated the US
- ***So the first crisis was solved by reactors (and the United States)***
  - Will the current crisis also be solved by reactors?
  - Or is another solution needed?
  - Will the USA solve the crisis?

$^{235}U(n,f)^{99}Mo$



$^{235}U(n,f)^{99}Mo$: Fission Moly

  - Requires enriched ^{235}U targets
  - Complex chemical processing
  - Requires dedicated processing facility
  - Waste issues
- Produces high specific activity ^{99}Mo
- Familiar technology
- A reliable method with a good track record (until lately)
- High yield

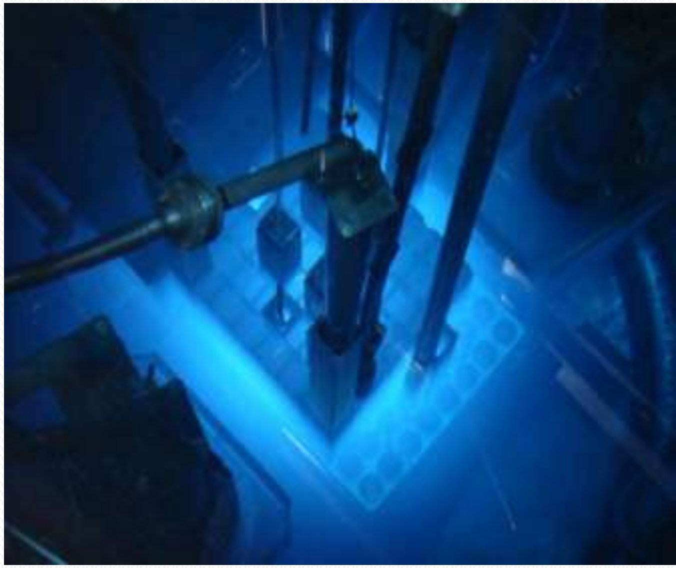
Coquí RadioPharmaceuticals

Coquí RadioPharmaceuticals Corp.

- Primary Goal: Creation of a dedicated Medical Isotope Production Facility in the United States
- Vision is to be a leading supplier, primarily for the USA
- Will not use HEU
- Will use an LEU/LEU reactor-based fission method

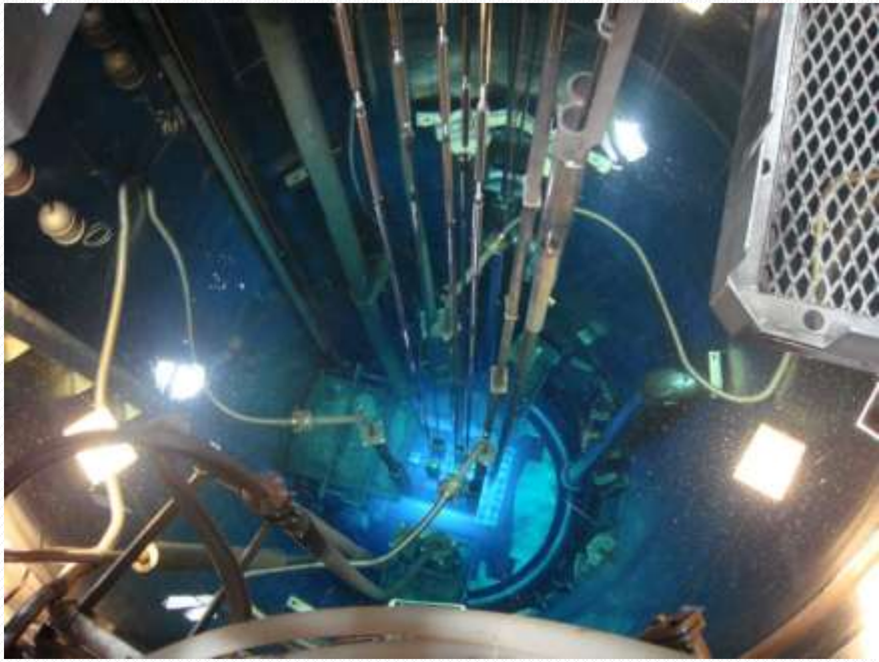
Coquí RadioPharmaceuticals

- Reactor technology that has already been successfully implemented in several countries
- Demonstrated capacity to supply Mo-99 at a commercial scale
- The general technology and process has already obtained FDA approval
  - Targets are the same as those already approved by FDA and have been imported for patient use



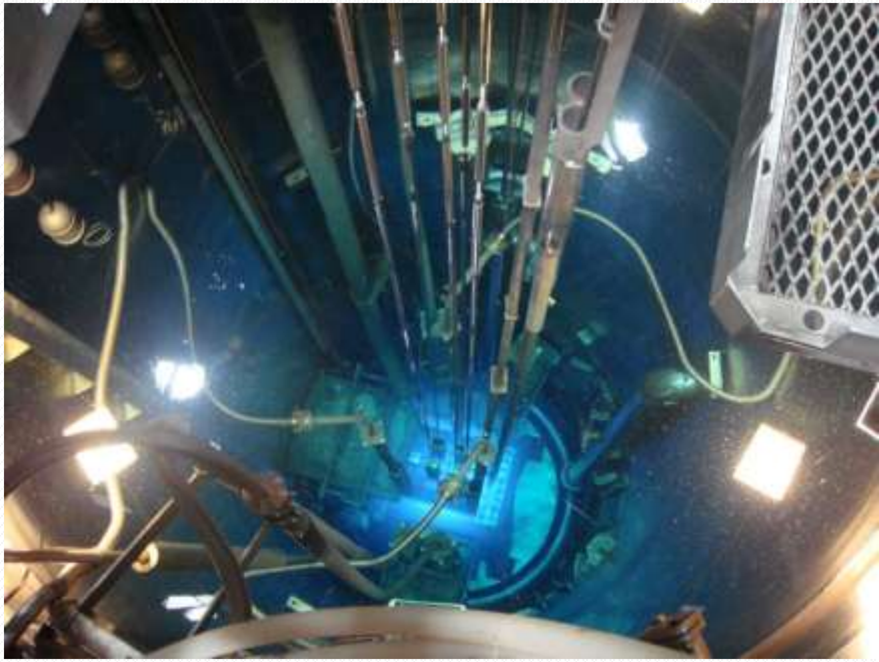
Medical Isotope Production Facility

- Production Goal:
- 7,000 Six-Day Curies per week (100% DOE estimate of U.S. Market)



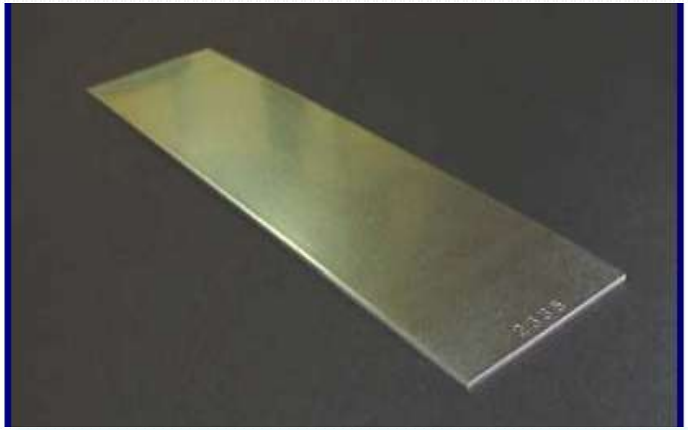
Medical Isotope Production Facility

- Twin production reactors
- Radioisotope processing plant
- Waste management unit
- Support services & administration offices



Some Features

- Plate LEU targets
  - 15 cm hi-density LEU-Al dispersion target
  - In use since 2002
- Reflector irradiation positions
- Transfer hot cell
- Target handling and transfers



Site

- Thanks to the combined efforts of Enterprise Florida and the University of Florida Foundation a site has been chosen by Coquí

Coquí RadioPharmaceuticals

- University of Florida Foundation site in ***<u>Progress Corporate Park in Alachua, Florida</u>***

- A potential State of the Art research facility for collaboration with UF
- Environmental assessment of site has been performed

Coquí RadioPharmaceuticals

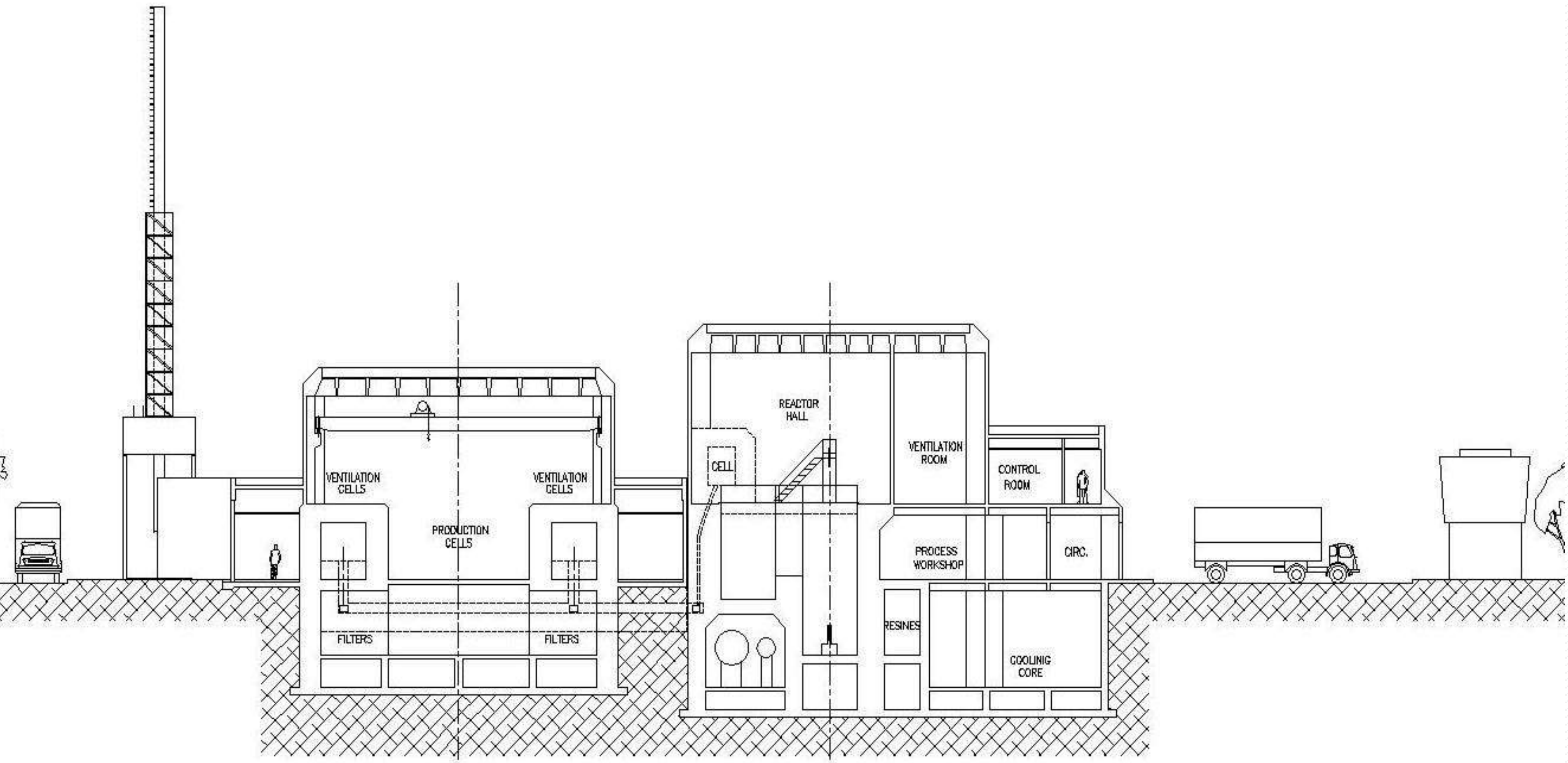
- Construction phase would generate approximately 1,824 jobs.
- Potentially pay about $82.5 million in labor income in the local economy, create local total value added of about $113 million, and total output of $246 million in the local economy

  - (The above information is based on a report made by Rick Harper, Ph.D. Interim Director, Office of Economic Development and Engagement, University of West Florida.)

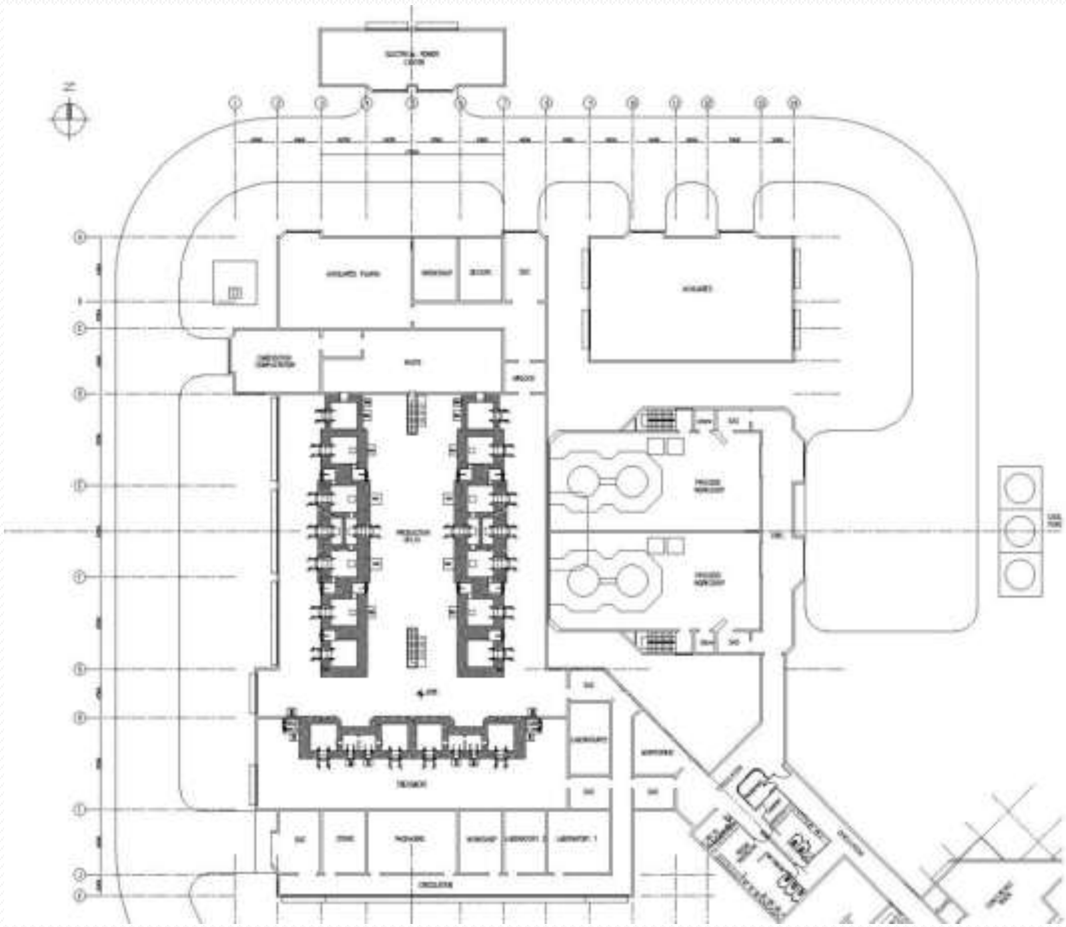
Coquí RadioPharmaceuticals

- The ongoing employment impact is approximately 285 jobs in the local economy, labor income of $14.4 million annually, total local value added of $17.6 million annually, an total output of $31.2 million annually.
  - (The above information is based on a report made by Rick Harper, Ph.D. Interim Director, Office of Economic Development and Engagement, University of West Florida.)

Conceptual design



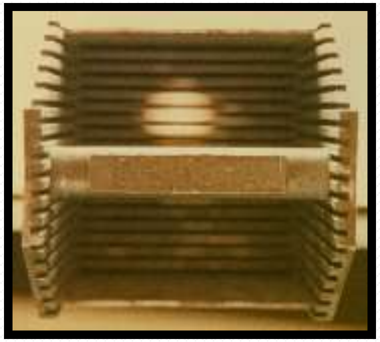
Conceptual design



- Radiological Zones
- Ventilation & Filters
- Movement of materials
- Activities & Functionality
- Fire & Emergency
- Security

Environmental safety

- Safety measures for minimizing release of radioactive material to the environment
  - Fuel matrix and cladding
  - Reactor pool water and cooling system boundary
  - Building and confinement system



Redundancy

Human & Machine Interface

Reactor Protection System

Control & Monitoring System

Main Control Room

Emergency Control Centre

Processing plant

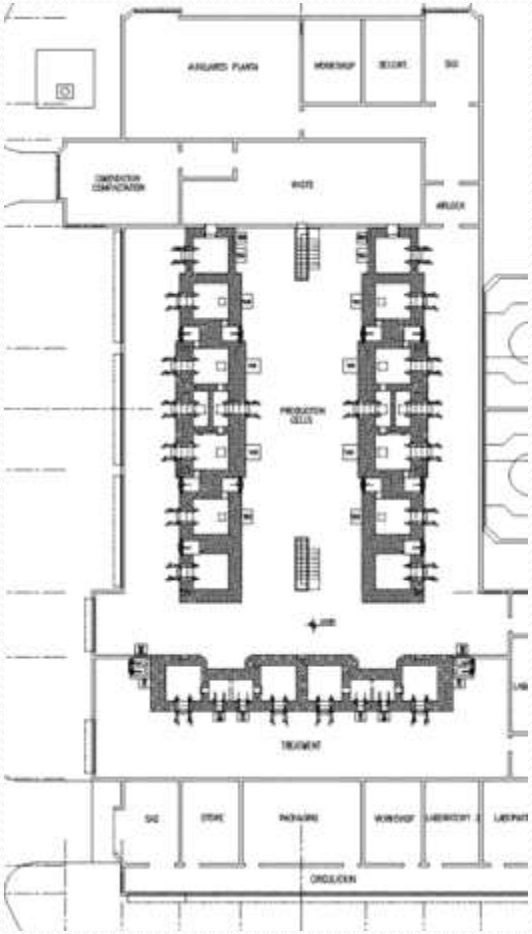
Mo-99 Processing Plant Design Basis

- Weekly production 7000 six day Ci Mo-99
- Meets good manufacturing practices and United States radiation protection standards
- High availability
- Decommissioning

Four batches per week of 1750 Ci/batch with three process lines working in parallel

Major Systems :

- Process systems
- Hot Cells
- Containers
- Ventilation system
- Radiation protection system
- Preparation and control laboratories
- Auxiliary conventional services



Processing

- Main steps:
- 1- Dissolution
- 2- Filtering
- 3- Purification w/anion resin
- 4- Mo complex separation
- 5- Purification w/inorganic sorbent
- 6- Final conditioning

Hot Cells & Containers

- Structure and shielding
- Airtight lining
- Transfer of active materials
- Master-slave manipulators
- Viewing window
- Electrical and lighting system

Protection from radiation

Air management systems

- Conventional area
- Active area
- Hot cells

Radiation monitoring systems

- Area monitoring system
- Air & liquid monitoring systems
- Personal contamination monitors
- Personal dosimeters

Quality control

Laboratories equipped to carry out radiochemical and chemical quality control of radioisotopes

GMP Quality Control Labs:

- Preparation of solutions used in production processes and laboratories
- Preparation of samples and chemical controls
- Activity measurement

Reactor Safety Summary

- No “show stoppers”
- Adheres to modern standards and NRC requirements/regulations
- Relies on established solutions and conservative designs

Coquí RadioPharmaceuticals

- On 01/02/2013 the National Defense Authorization Act, is signed into law as H.R. 4310 approving the American Medical Isotopes Production Act of 2012 (AMIPA).
- The American Medical Isotopes Production Act of 2012 provides that the Secretary of the Department of Energy shall carry out ***a technology neutral program*** to evaluate and support projects for the production of significant quantities of Mo-99 without the use of HEU for the United States.
- …DOE shall establish a uranium "Lease and Take-Back program"
- Coquí has completed the NRC pre-licensing process to participate in the Lease and Take-Back program mandated by the Act and they are kept abreast of our progress

Future Research Possibilities: Beyond Mo-99

- University of Florida Physics and Nuclear Engineering Departments
- Nuclear and neutron science basic research
- Silicon doping
- Medical isotopes other than Mo-99
- RTG radioisotopes

Status

- Coquí is engaged in discussions with investors to finance the licensing and the construction of the MIPF
- Completed pre-licensing process with the NRC
- Prepared Site Environmental Assessment
- Enterprise Florida has provided Coquí with an aggressive tax and workforce incentive package
- University of Florida has allocated 40 acres for Coquí

Conclusions

- Several novel ideas and serious proposals have emerged to avert future shortages
  - including a domestic reactor-based LEU solution
- Some of the other solutions are *exclusively* for Mo-99
  - which could solve one problem but create another
- Will one or more of these solve the problem?
- Or will reactors come to the rescue once again?