

**The Critical Need for  
Nuclear Medicine  
Radioisotopes and Research**

**University of Missouri  
Research Reactor Center's  
Radioisotope Production  
and BNCT Research**

**13 October 2009**

# University of Missouri – A Unique Set of Resources

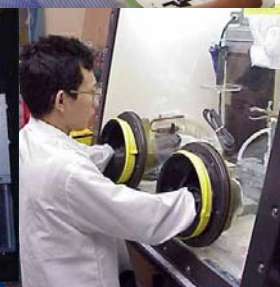




University of Missouri Research Reactor Center

# The MURR Center — a Global Resource

- A 10 MW reactor that operates 24 hours a day, seven days a week, 52 weeks a year, 20 year NRC license extension submitted in 2006
- >150 full time & >30 part-time employees
- In 2008 produced 49 different isotopes with ~1000 shipments to 14 different countries
- Each and every week MURR supplies the active ingredients for FDA approved Quadramet<sup>®</sup> and TheraSpheres<sup>®</sup>



# MURR Core Competencies include Strong Record of Regulatory Compliance



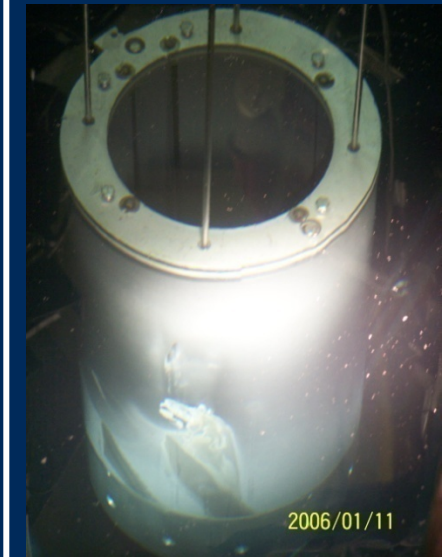
U.S. Food and Drug Administration



# Recent Infrastructure Upgrades

R&R Grant, DOE, \$6.6M, 9/29/00 - 12/31/08

Description	Expenditure
New Fire Detection/Suppression System	713,919
New Primary and Pool Coolant Heat Exchangers (3)	578,780
2006 Beryllium Reflector	533,624
Engineering Assessments for relicensing	519,721
Radioactive Liquid Waste Disposal System Upgrades	430,810
Facility Electrical Distribution System Upgrades	424,566
Security & Surveillance Enhancements	326,941
Revised/Updated Safety Analysis Report for relicensing	288,000
Hot cell Processing	160,665
New Reactor Plant Make-Up Water Storage Tanks (2)	149,423
New Stack Monitor	119,429
New Control Blades	115,647
Containment Building 15-Ton Overhead Crane Catwalk	95,436
New Graphite Reflector Elements	84,831
Reactor Instrumentation Upgrades	65,097



# MURR Radioisotopes

Isotopes Shipped in 2008 (49)		
As-76	Ho-166	S-35
Au-198; Au-199	Ir-192	Sb-122; Sb-124
Ba-135m	K-42	Sc-46
Ca-45; Ca-47	La-140	Se-75
Ce-141	Lu-177	Sm-153
Co-60	Na-24	Sn-125
Cr-51	Nd-147	Sr-89
Cs-134	P-32; P-33	Tb-161
Eu-154	Pd-109	Tl-204
Fe-55	Pm-149	Y-90
Fe-59	Pt-195	Yb-169; Yb-175
Gd-159	Rb-86	Zn-65
Ge-71	Re-186; Re-188	Zr-95; Zr-97
Hg-197; Hg-203	Rh-105	

# Other Reactor Producers

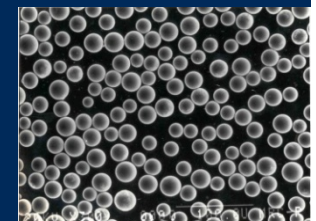
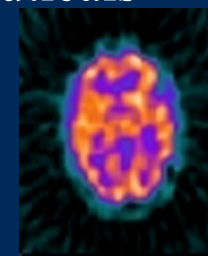
- Domestic, Non-DOE
  - MIT (5 MW) - Gold, Yttrium, and Iridium – research quantities
  - UC Davis (2 MW) – Currently improving Iodine -125 production system, Argon-41 and Sodium-24 as tracers for the Oil industry
  - Oregon State (1 MW) - non-routine – Gold and Silver as biotracers, Sodium and Rubidium as environmental tracers, Argon and Sodium for industry
  - Texas A&M (1 MW) - Various as environmental tracers
- Foreign Sources
  - Petten – Netherlands, Mo-99, Lu-177
  - BR-2 – Belgium, Mo-99, I-131, Xe-133, Ir-192
  - Russian Institutes - P-32, P-33 Sr-90, W-188
  - South Africa - Mo-99, Lu-177
  - NRU – Canada – Mo-99
  - Poland - various
  - Australia - various, mostly for in-country use, Mo-99



# University of Missouri - MU Research Reactor Center

A 25-year history of successful and innovative radiopharmaceutical R&D and collaborations with industry....

- **Ceretec™** (with Tc-99m), a diagnostic used to evaluate cerebral blood flow in patients & label white blood cells
- **Quadramet®** (with Sm-153), a therapeutic for treatment of pain associated with metastatic bone cancer
- **TheraSphere®** (with Y-90), a glass microsphere used to treat patients with inoperable liver cancer
- Cesium-131 brachytherapy seeds to treat prostate cancer
- Gd-159 and Ho-166 for research in skeletal targeted radiopharmaceuticals
- Iridium-192 brachytherapy seeds to treat solid tumors
- Lu-177 and Pm-149 for receptor-targeted radiopharmaceuticals (support 30 research and clinical trials)
- P-32 and P-33 biomedical radiotracers
- Se-75 biomedical radiotracers



**TheraSphere®**

**MDS Nordion**  
Science advancing health

# MURR Core Competencies include Volume Radiochemical Processing

## *Hot Cells*

*Designed with Versatility in Mind*



1<sup>st</sup> Application...

200 Ci batches of Ho-166

Designed for 500 Ci Batches

P-33 Hotcell Facilities



Lu-177

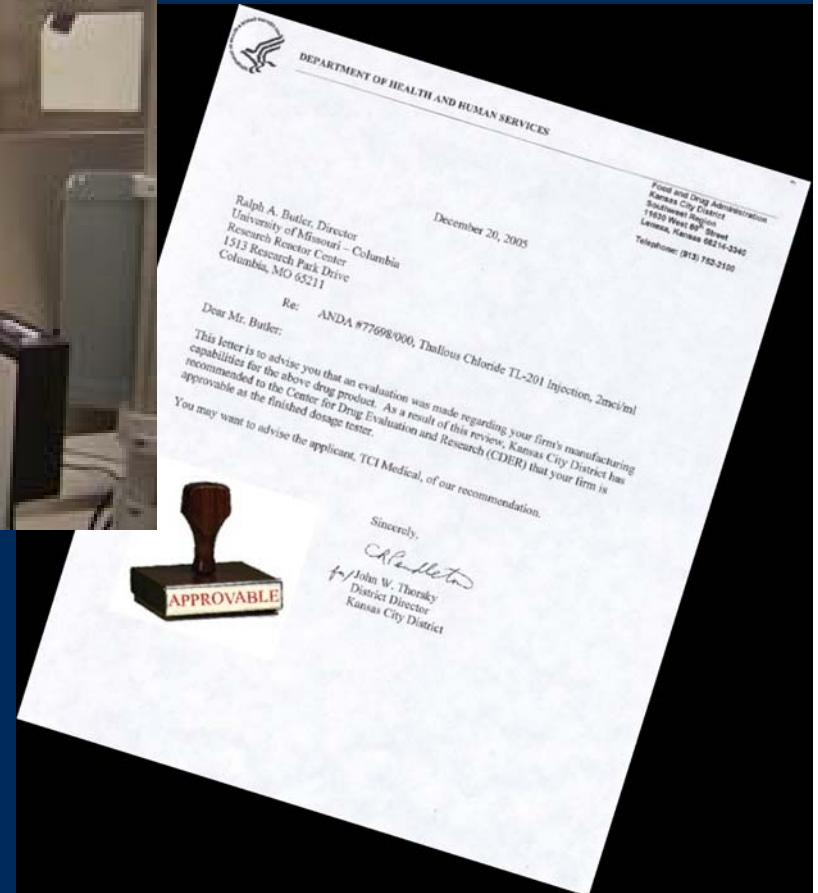
Weekly producing 40 Ci batches

Potentially capable of 1000's Ci per week



# MURR Competencies

## FDA-approvable cGMP and GLP Programs



# FDA Approvable ...cGMP Facilities

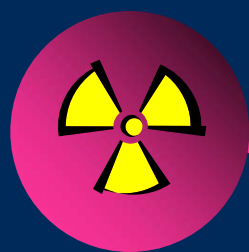


# Radiopharmaceutical Research

Currently developing a suite of *carrier free lanthanides* to work in conjunction with *selective targeting agents* to locate and treat cancer.

Ln	$t_{1/2}$	$\beta_{\max}$	$E_g (I_g)$	Avg Range (cell diameter)
$^{177}\text{Lu}$	6.7 d	0.5 MeV	208 keV (11%)	20
$^{166}\text{Ho}$	1.1 d	1.8 MeV	286 keV (3%)	60
$^{149}\text{Pm}$	2.2d	1.1 MeV	81 keV (6%)	120

Metal-Ligand  
Conjugate



Organic  
Linker



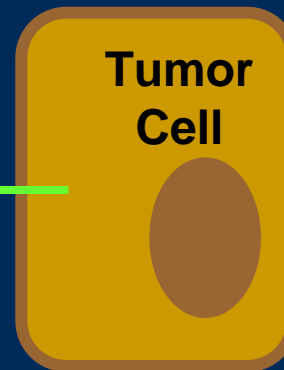
Biomolecule



Receptor



Tumor  
Cell



# Radiopharmaceutical Research

## MURR $^{177}\text{Lu}$

- Currently being evaluated in over 30 clinical applications for radiotherapy of cancer
  - Metastatic prostate cancer
  - Non-hodgkins lymphoma
  - Neuroendocrine tumors
  - Ovarian cancer
  - Metastatic bone cancer
  - Colon cancer
  - Lung cancer
- MURR upgrading process to meet FDA guidelines for Clinical grade production

# Essential Isotopes, LLC Cyclotron – GE 16.8 MeV PET Trace



# Cyclotron Produced Isotopes

Essential Isotopes, LLC currently producing:

- Fluorine-18 FDG -Imaging agent
  - Multiple commercial customers
  - Phase Two clinical trials in Kansas City and St. Louis
- Copper-64
  - Collaboration with Washington University
  - Used to study genetic diseases such as Wilson's and Menke's
- More isotopes planned
- Have built-in facilities to support on-site imaging trailer.



# Need for Mo-99/Tc-99m

- Tc-99m is used in over 80% of all medical isotope procedures worldwide.
- National need – used ~50,000/day in U.S.
- Use is expected to increase ~5% annually for the next ten years.
- More than 30 different radiopharmaceuticals use Tc-99m for disease detection & organ structure & function.

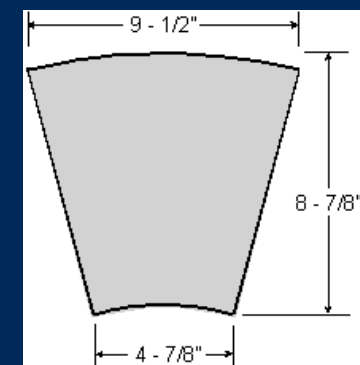
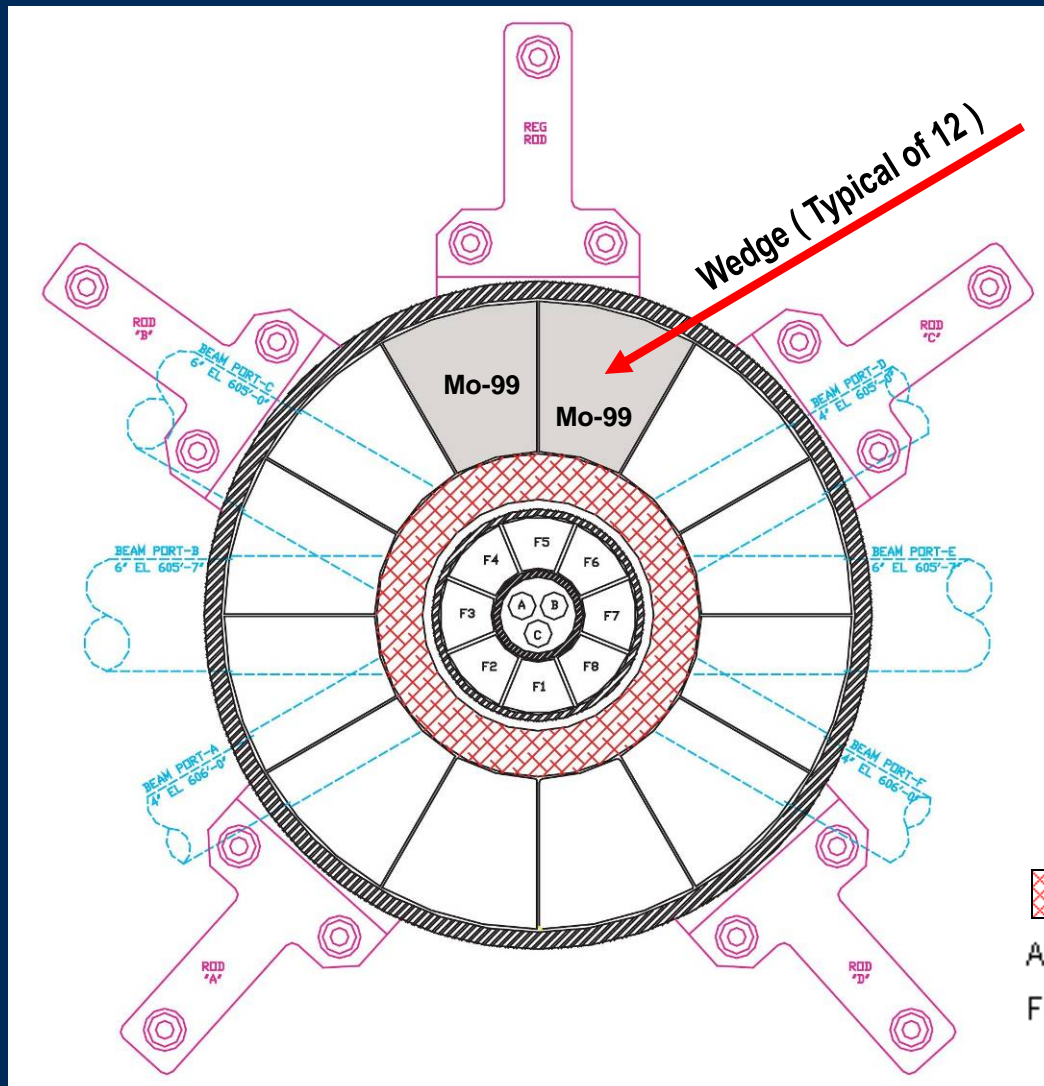
# U.S. History of Mo-99 Production


- 1967 - MURR begins production of (n,  $\gamma$ ) Mo-99 for Mallinckrodt Nuclear Co.
- 1969 - MURR begins weekly production of Mo-99.
- 1977 - MURR increases Mo-99 production for MediPhysics Inc.
- 1980 - Cintichem, Inc. begins production of HEU fission product Mo-99 and is the single U.S. supplier.
- 1984 - MURR ceases Mo-99 production.
- 1989 - Cintichem reactor develops leak and is closed.
- 1991 - DOE purchased Cintichem technology, equipment and DMFs for production of Mo-99, I-125, X3-133
- 1991 - DOE identified Omega West Reactor at LANL as proposed backup supply facility and constructs processing facility.
- December 1992 - Omega West Reactor at LANL develops leak and is closed.
- Until 1993, two Canadian reactors, operated by Atomic Energy of Canada Limited (AECL) at the Chalk River site (located about 100 miles from Ottawa, Canada), were available to produce Mo-99.
- 1996 - DOE selects Annular Core pulse reactor at Sandia National Lab. to become backup supply facility and constructs processing facilities. Project never completed.
- 1998 - Canadian MAPLE reactors were scheduled to open, but remain shutdown today due fundamental design flaw.
- 2006 - begins feasibility studies to produce LEU fission Mo-99
- 2008 - Decision made to discontinue work on MAPLE 1 & 2.

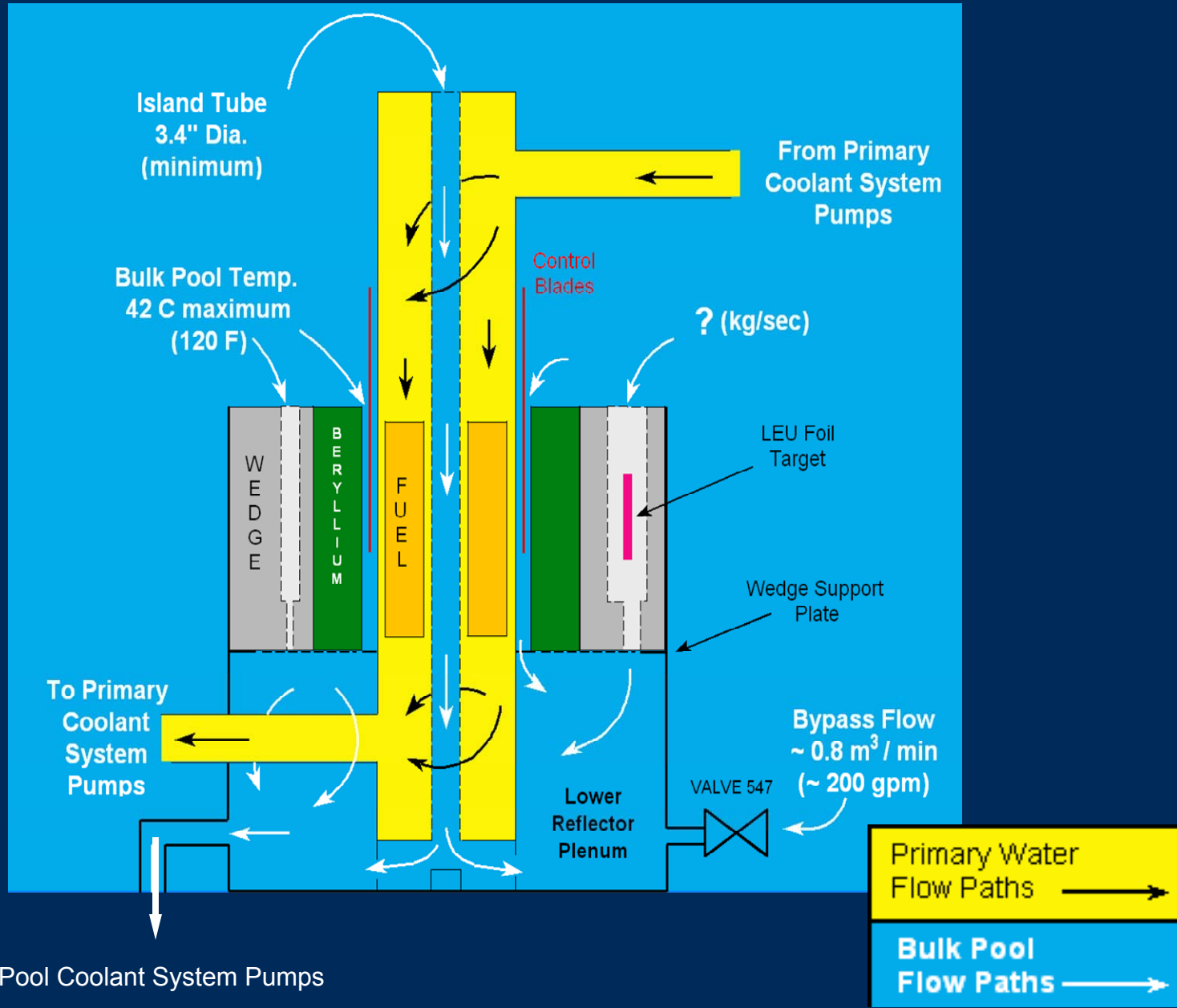
# Mo-99 Production at MURR

- Overall objective is to develop the capability to produce Mo-99 from LEU targets.
- Production objective is ~50% of current U.S. weekly demand.
  - Current U.S. weekly demand is estimated to be 6000 six-day Curies (Ci) per week
    - 6000 six-day Ci equates to about 40,000 Ci (End-of-Irradiation), Synonymous with “Out-of-Reactor” Ci
  - Must irradiate / process 40 - 50 targets per week to satisfy ~50% weekly demand.

# Reactor Plan View

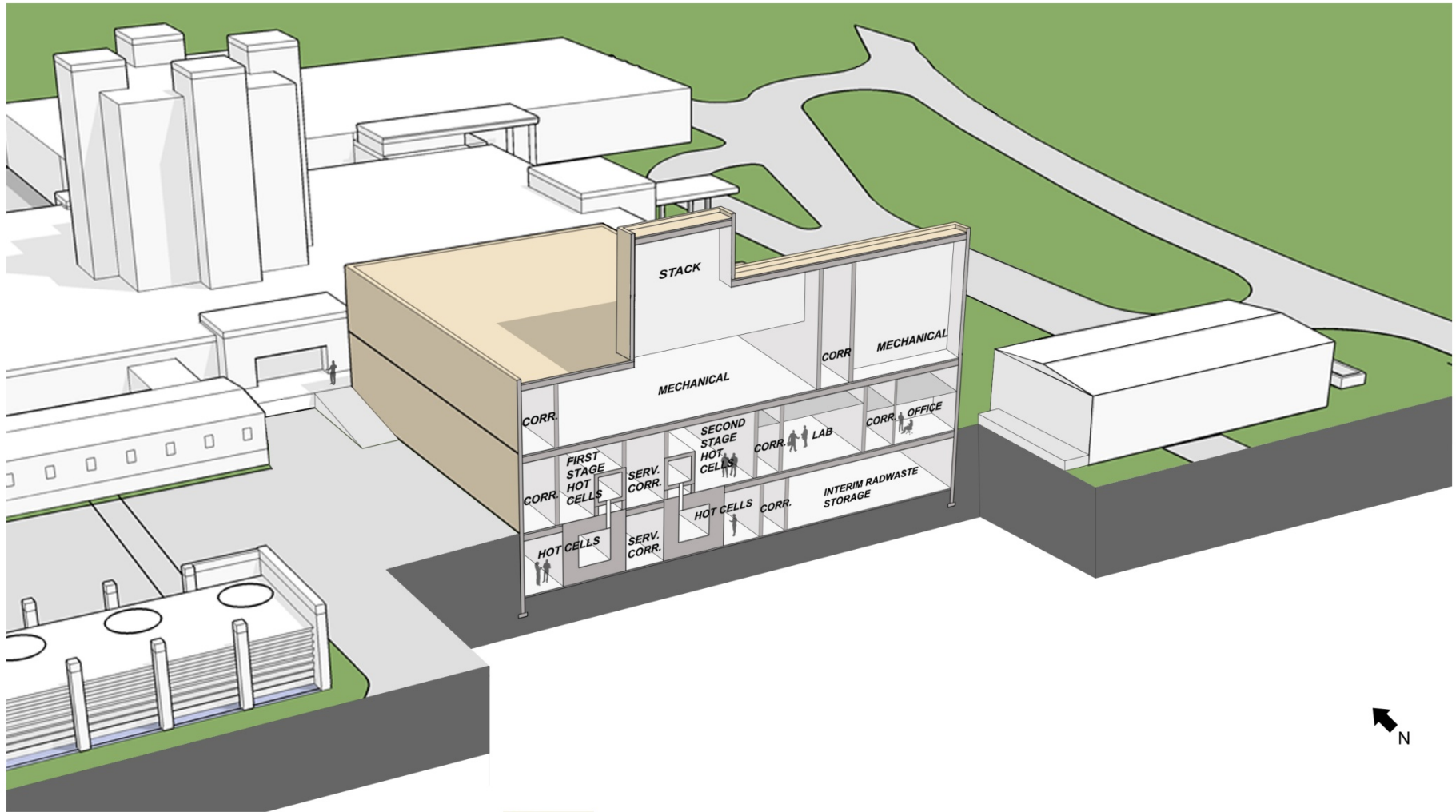


-  - Beryllium Reflector
- A, B, C - Flux Trap
- F1 - F8 - Fuel Elements



To Pool Coolant System Pumps

Primary Water Flow Paths	→
Bulk Pool Flow Paths	→



CONCEPT DESIGN

3D SECTION DIAGRAM



**MURR STEAM Facility**



09.11.2009

# Proof of Concept - DU Cold Process



➤ 5.2 Depleted Uranium (DU) foil in  
1.02 g Nickel envelope

➤ Dissolve under heat and pressure

➤ Evacuate dissolver to cold-trap to  
remove gasses

➤ Perform chemistry in glass-ware

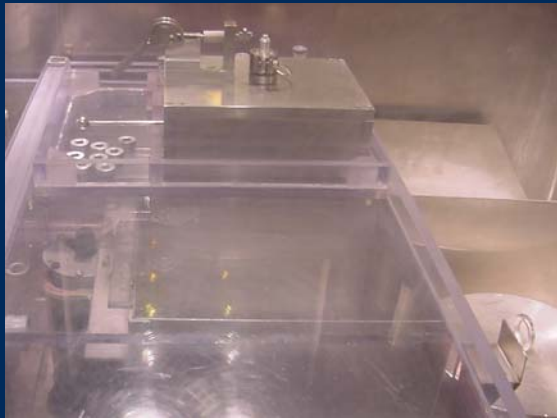
➤ Collect final product and assay

➤ Two bench-top chemistry trials  
produced > 90% Molybdenum carrier  
recovery

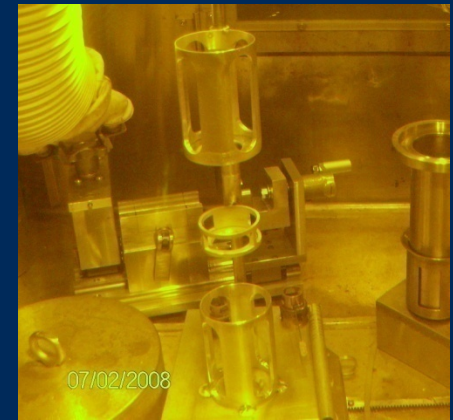
➤ Full “cold” process in hot cell  
produced greater than 94% recovery



# Proof of Concept - Hot Cell Modifications



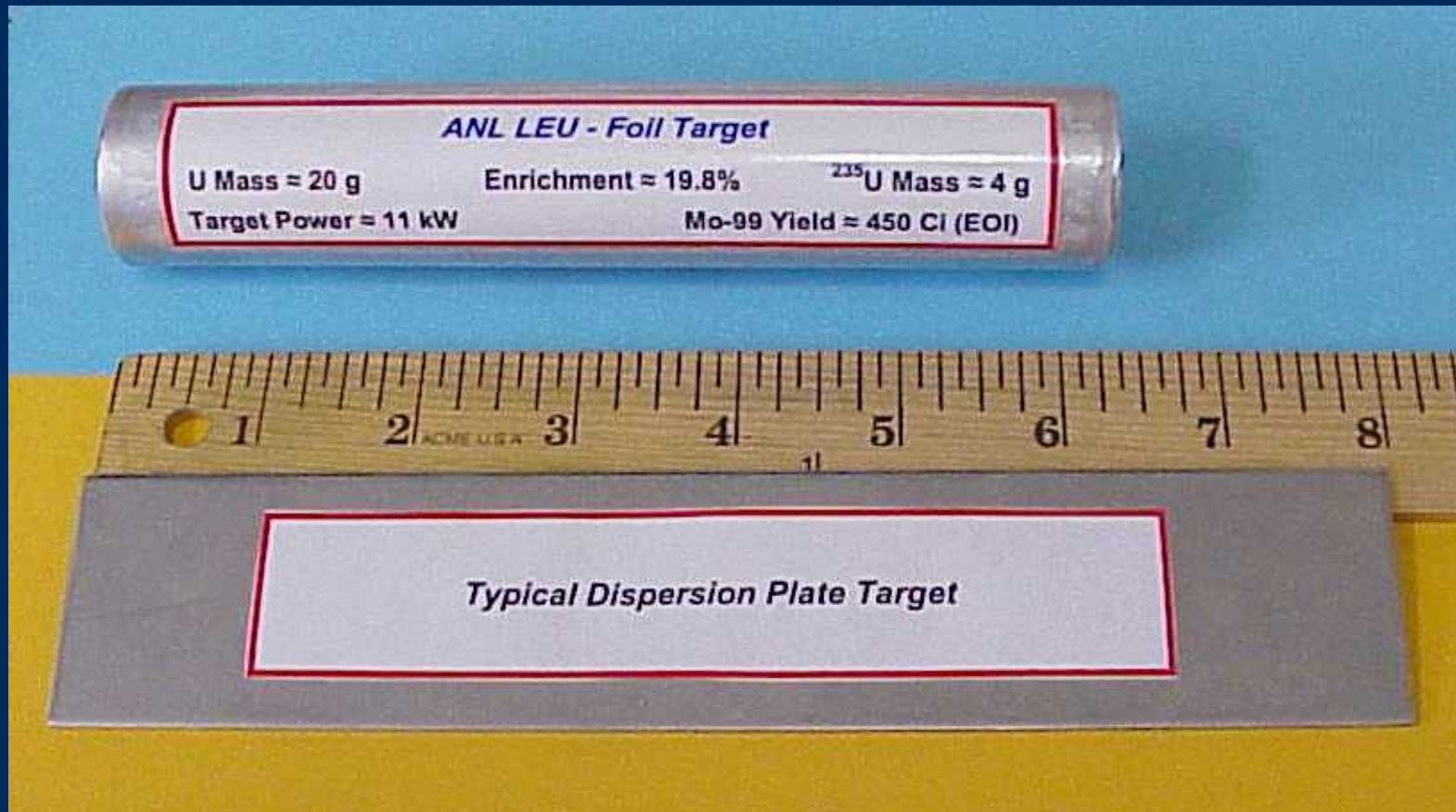
- Identify Hot Cell
- Decontaminate cell interior
- Remove processing subfloor
- Add shielding for LN<sub>2</sub> system
- Design and install LN<sub>2</sub> system for cold finger gas trap
- Modify exhaust to include carbon filtration
- Design and install chemistry handling apparatus





# Target Geometry

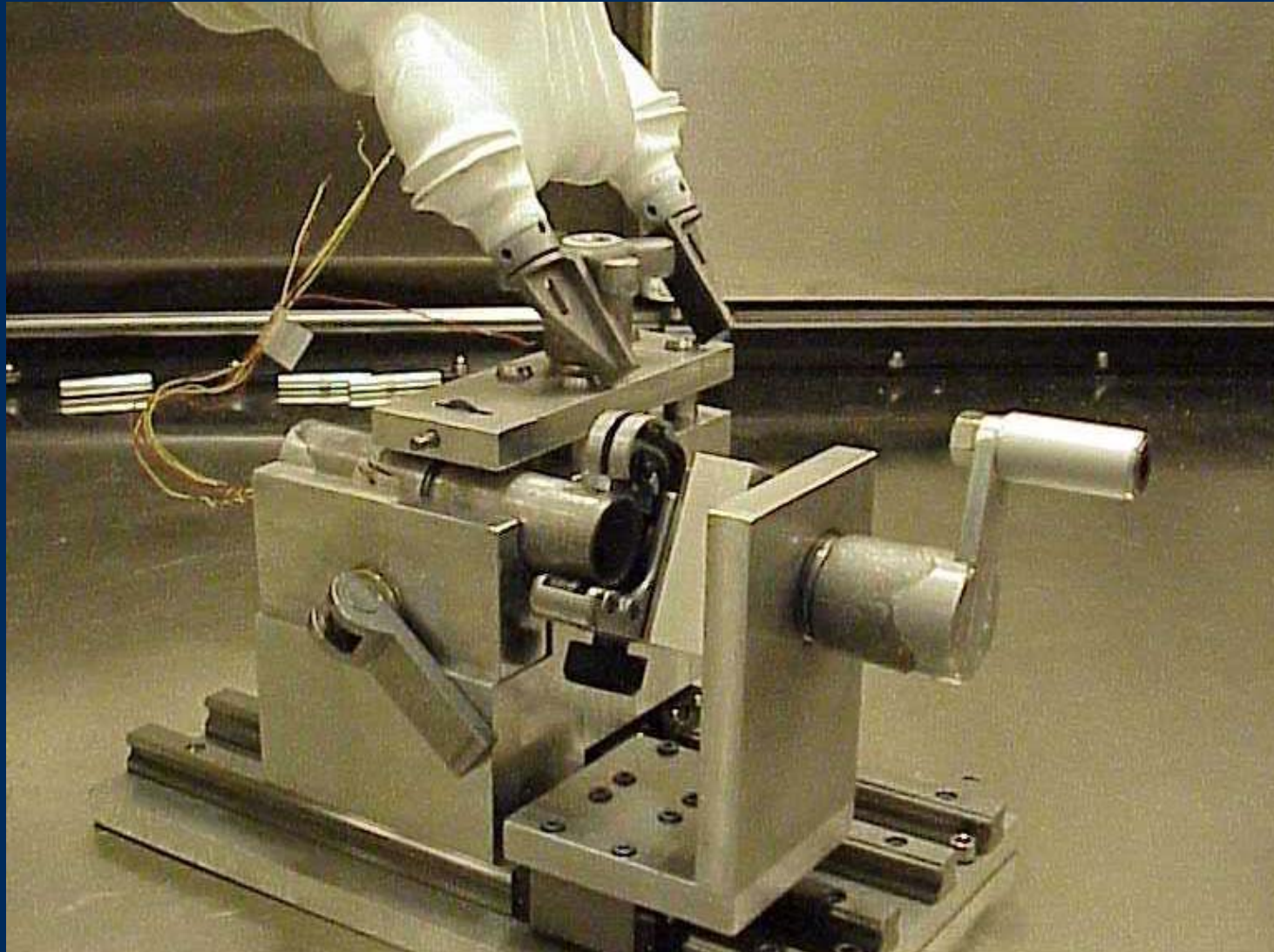
## Annular vs. Plate



# Proof of Concept Sample Target Holder



# Proof of Concept Target Cutter Assembly



# Target Loading Density

## Effective Use of Irradiation Space



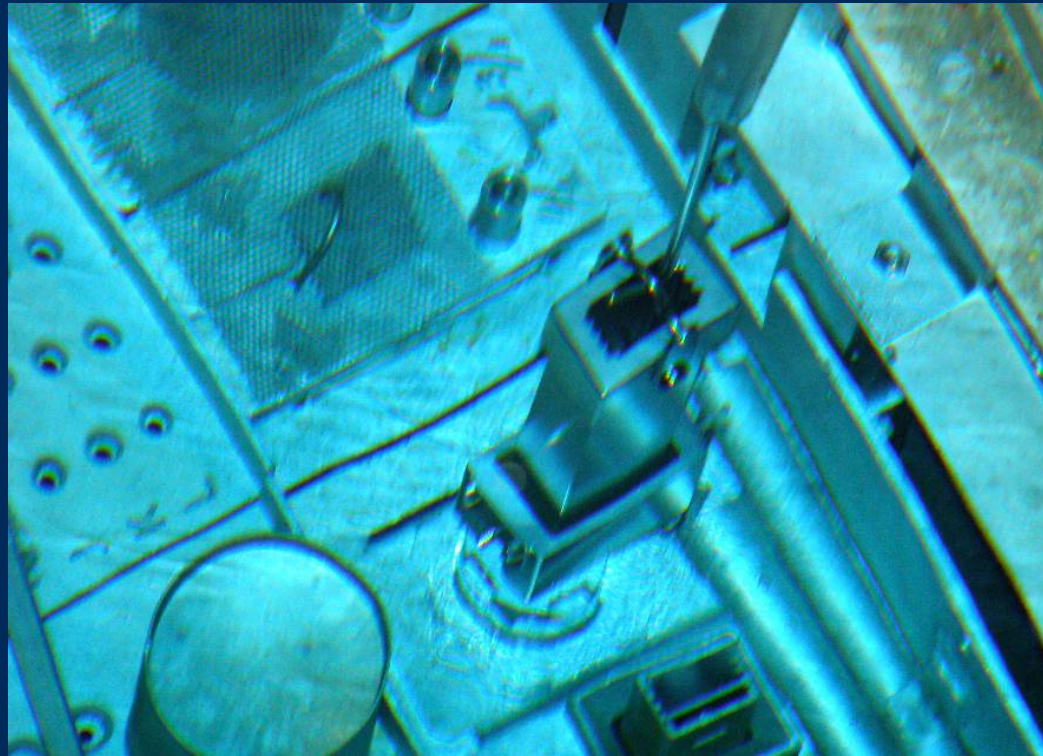
**Total of 8 Dispersion Plate Targets  
Irradiated / Processed as a Batch**



**Photos Courtesy of NRG  
Mo-99 CRP Workshop  
Vienna, November 2006**

# Target Loading Density

## Effective Use of Irradiation Space (Cont'd)



**Batch of Eight (8) Targets in  
Transit to Irradiation Position**

# Why MURR?

- The largest university operated research reactor in the U.S.
  - MURR sets the example for safe and efficient operation for U.S research reactors.
- University of Missouri and MURR are leaders in the development and supply of radioisotopes for research and medical uses.
- Demonstrated experience
  - 24/7 operations 52 weeks a year
  - >150 Full-Time Employees
  - Radioisotopes shipped around the globe every week
  - FDA - cGMP and cGLP programs
- Only real need is a processing facility.
- Realistic timeline to reach large-scale production (2012-2013).
- Support of Missouri Congressional Delegation.

## Reactor Parameters: HEU to LEU

MURR is a pressurized, reflected, heterogeneous, open pool-type, which is light-water moderated and cooled

- Maximum thermal power – 10 → 12 MW
- Peak flux in center test hole –  $6.0 \rightarrow 6.4 \times 10^{14}$  n/cm<sup>2</sup>-s
- Core – 8 fuel assemblies (775 → ~1410 grams of U-235 per assembly)
- Control blades – 5 total: 4 boron shim-safety, 1 SS regulating
- Reflectors – beryllium and graphite
- Forced primary coolant flow rate – 3,750 gpm (237 lps)
- Forced pool coolant flow rate – 1,200 gpm (76 lps)
- Primary coolant temps – 120 °F (49 °C) inlet, 136 → 139 °F (60 °C) outlet
- Primary coolant system pressure – >75 psia (586 kPa)
- Pool coolant temps – 100 °F (38 °C) inlet, 107 °F (42 °C) outlet
- Beamports – three 4-inch (10 cm), three 6-inch (15 cm)