NSAC Isotope Subcommittee (NSACI) Updated Report

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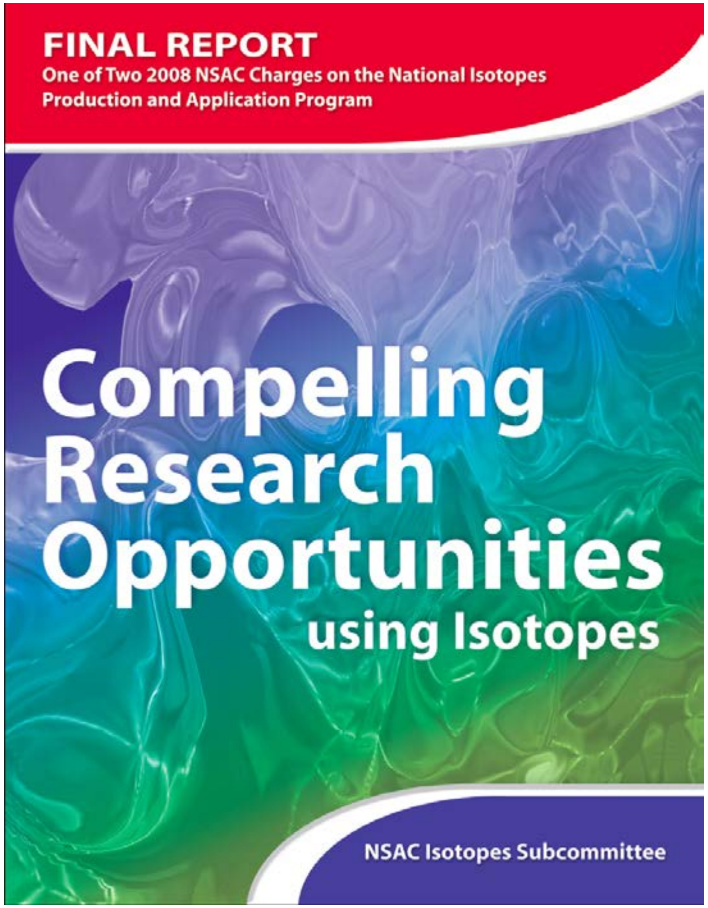
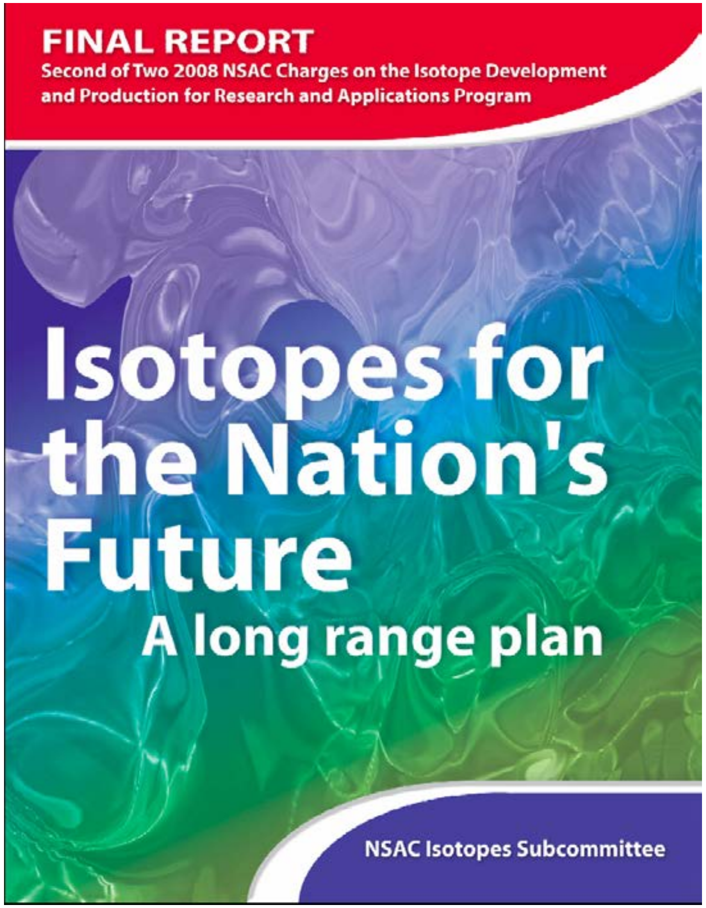
7/16/15

Overview

- **On April 3, NSACI presented its Draft Report to you**
- **At that meeting (and in correspondence shortly after it) you requested a number of changes**
  - Develop stronger, clearer justifications for our recommendation to double the appropriated budget
  - Reduce the level of technical detail (and jargon) to better match the document to its intended audience
  - Trim the length, and
  - Detailed suggestions on some individual items
- **I have provided you with an updated report that the subcommittee and I believe addresses your requests and comments; it is, in my opinion, substantively improved, and we thank you for your interest and attention to details**

The Isotope Program Moved to the Office of Nuclear Physics in 2009





Two 2009 NSACI Reports identified compelling research opportunities and recommended a Long-term Strategic Plan the provided a framework for a coordinated implementation of IDPRA.
We were basically charged to update those reports and evaluate progress since 2009

Our Charge (re-ordered)

- Conduct a new study of the opportunities and priorities for isotope research and production…result(ing) in a Long-Range Strategic Plan for the Office of Science for Nuclear Physics
- Identify and prioritize the most compelling opportunities for the DOE Isotope Program to pursue over the next decade and articulate their impacts
- Indicate the resources needed in the timeframe 2016-25 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical to the Nation.
- Articulate the progress has been made since the last NSACI sub-committee published its recommendations, and the scientific and societal impacts of these accomplishments and ongoing activities

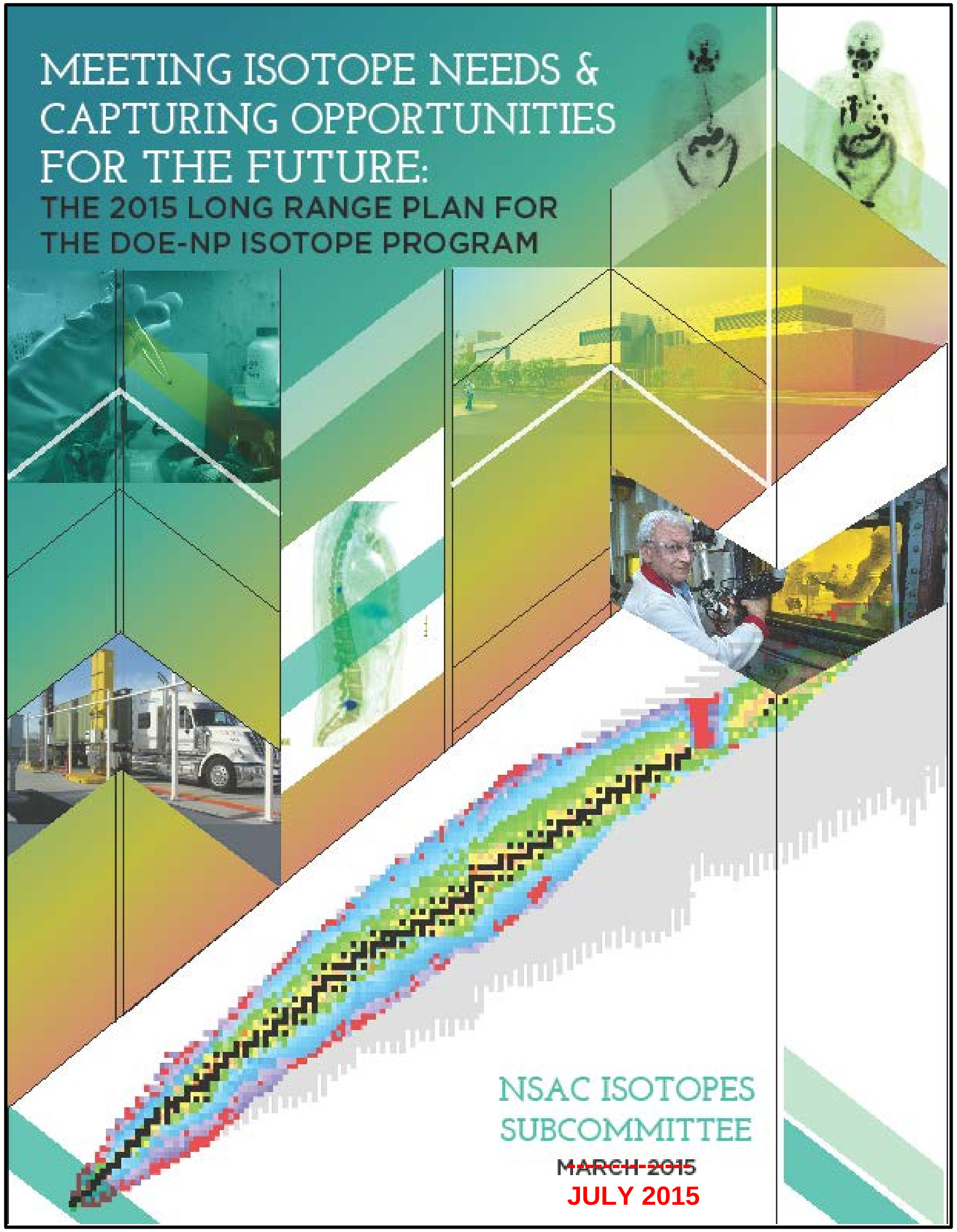
In carrying out the charge, important aspects of the assessment include:

- existing technical capabilities and infrastructure,
- the robustness of current isotope production operations
- R&D of production techniques for research and applied isotopes
- Production of research isotopes, and
- Development of core competencies
- The plan should also consider aspects of the program that are relevant and important to stakeholder communications and the effectiveness in the provision of critical isotopes to the Nation

NSACI Subcommittee Membership

Kelly Beierschmitt	INL	Deputy Lab Director, Nuclear and Laboratory Ops
Roy Brown	Mallinckrodt	Strategic Alliances Director
Carol Burns	LANL	Former Chemistry Division Leader, Nuclear Forensics
Larry Cardman, chair	JLAB	Medium Energy Nuclear Physics
Donald Geesaman, ex officio	ANL	NSAC Chair, 2009 NSACI Chair, and Medium Energy Nuclear Physics
Suzanne Lapi	Wash. U. SL	Asst. Prof. of Radiology, Biochem., and Biomed. Eng.
Saed Mirzadeh	ORNL	Radiochemistry, Nuclear Medicine
Eugene Peterson	LANL	Isotope Production
Lee Riedinger	Tennessee	Low Energy Nuclear Physics
David Robertson	Missouri	Prof., Assoc. Director, Research & Education, MURR
Thomas Ruth	TRIUMF	Isotope Production
David Scheinberg	Memorial Sloan Kettering Cancer Center	Experimental Therapeutics Center Chair
Sally Schwarz	Wash. U., St. L	Director of Pet Radiopharmaceutical Production
Brad Sherrill	MSU	Low Energy Nuclear Physics
Mark Stoyer	LLNL	Nuclear Chemistry-Heavy Elements
Scott Wilbur	University of Washington	Radiation Oncology
Frank Yeager	Eckert and Ziegler	Sources, oil & gas, CORAR Board
Michael Zalutsky	Duke	Radiaton Oncology

Our Report



Executive Summary
Chapter 1: Introduction
Chapter 2: The DOE Isotope Program
- 2.A. Origins and History
- 2.B. Today (2009 to Present

Chapter 3: Uses of Isotopes
- 3.A: Biology, Medicine, and Pharmaceuticals
- 3.B: Physical Sciences and Engineering
- 3.C: National Security and Other Applications

Chapter 4: Research Opportunities Using Isotopes
- 4.A. Research Opportunities with Isotopes in Biology, Medicine and Pharmaceuticals
- 4.B. Research Opportunities with Isotopes in Physical Sciences and Engineering
- 4.C. Research Opportunities with Isotopes for National Security and Other Applications

Chapter 5: The Scope and the Scientific/Technical Challenges for the Isotope Program
Chapter 6: Sources of Isotopes for the Nation
- 6.A: High Purity Stable and Radioactive Isotope Mass-Separation Capability
- 6.B: Accelerator-Based Isotope Capabilities
- 6.C: Reactor Based Isotope Capabilities
- 6.D: Isotope Production as a By-product of Other Operations

Chapter 7: Research and Development for Isotope Production
- 7.A: Stable and Radioactive Isotope Separation R&D
- 7.B: Accelerator Production R&D
- 7.C: Reactor Production R&D
- 7.D: Other Production-Related R&D

Chapter 8: Trained Workforce and Education
Chapter 9: Program Operations
- 9.A: The Program in 2009, Its Evolution Since Then, and Its Status Today
- 9.B: Evaluation of the Program and Its Evolution Since 2009
- 9.C: Recommendations for Its Continued Enhancement

Chapter 10: Budget Scenarios
~~**Chapter 11: Summary of Recommendations for Charge**~~
References:
Appendices: (added one)

Summary of Changes to Our Report

- **Overall Report:**
  - Text cut from 137 pages to 118 pages
  - Jargon and technical detail reduced
- **Executive Summary:**
  - The “real” recommendations are unchanged, but the wording of some has been revised to strengthen and clarify
  - Budget section has been revised to strengthen the justifications and to clarify
- **Chapter 1: Introduction**
  - Minor Edits; added reference to Utube video
- **Chapter 2: The DOE Isotope Program**
  - Effort to enhance clarity, readability for non-experts
- **Chapter 3: Uses of Isotopes**
  - Effort to enhance clarity, readability for non-experts (cut ~1/4)

Summary of Changes

- **Chapter 4: Research Opportunities Using Isotopes**
  - Effort to enhance clarity, readability for non-experts
- **Chapter 5: The Scope and the Scientific/Technical Challenges for the Isotope Program**
  - Effort to enhance clarity, readability for non-experts
- **Chapter 6: Sources of Isotopes for the Nation**
  - Effort to enhance clarity, readability for non-experts (cut ~1/3)
  - Simplified details on recommended upgrades for BNL and LANL facilities
  - Moved details on isotope stockpile from 6.D to new Appendix 7
- **Chapter 7: Research and Development for Isotope Production**
  - Effort to enhance clarity, readability for non-experts
- **Chapter 8: Trained Workforce and Education**
  - Sidebar personalized

Summary of Changes

- **Chapter 9: Program Operations**
  - Effort to enhance clarity, readability for non-experts
  - Clarified status of 2009 Plan's cyclotron construction recommendation
- **Chapter 10: Budget Scenarios**
  - Effort to clarify and motivate budget increases better and provide additional information per NSAC's request; budget plots improved
- ~~**Chapter 11: Summary of Recommendations for Charge**~~
  - Deleted as redundant
- **References:**
- **Appendices:**
  - Added new Appendix 7 with details on stockpile (Moved from 6.D to simplify text and enhance readability)

Recommendations

Recommendation 1 (unchanged)

1) **We recommend a significant increase of funding for Research and Development**

Increased R&D is essential for an optimal Isotope Program. Increased R&D is necessary to fully realize the promise of enhanced national security, improved health care, and increased industrial competitiveness the program could provide. It will also support the **expansion of the range and quantities of isotopes available** for researchers and for potential commercial application, and enhance their usefulness to the Nation. It will support the **development of more efficient techniques for their production**, reducing costs and ensuring that supplies meet demands. R&D is also a core component of the program, **enabling it to better weather fluctuations in revenues (funding) as isotopes transition to the commercial market and as foreign supplies vary**. In addition to establishing optimal base R&D funding at the production sites, the increase will facilitate annual (rather than biennial) Funding Opportunity Announcements (FOAs) to be issued, **allowing the program to identify and respond more rapidly to new ideas.** This increase will allow the program to effectively support promising new areas as they arise. Four representative areas that would benefit today from increased R&D support are:

Recommendation 1.a (added re. progress)

a) Continue support for R&D on the production of alpha-emitting radioisotopes – The lack of availability of alpha-emitting radioisotopes was identified in 2009 as a major limitation in the otherwise promising investigations of their potential for cancer therapy. Since the 2009 recommendation, the effectiveness of this novel therapy for cancer treatment has been demonstrated with FDA approval of the alpha emitter ^{223}Ra for metastatic bone cancer from hormone refractory prostate cancer. There has been significant progress made by the DOE Isotope Program in the development and production of some medically useful alpha-emitting isotopes in the past ~~5~~five years, but further research into new production methods, more efficient isolation methods, and automation of the isolation processes is needed to provide adequate availability of alpha-emitting radioisotopes for preclinical and clinical evaluations~~.~~ of this very promising therapy. A focus should continue on production of ^{225}Ac and ^{211}At. In addition, other alpha-emitting radioisotopes that may be applicable for treatment of other types of cancers, or for use in treating bacterial and viral infections are interesting. Thus, research into methods for production/isolation of alpha-emitters with shorter half-lives (e.g. ^{212}Pb/^{212}Bi, ^{213}Bi, and ^{226}Th) and longer half-lives (e.g. ^{227}Th) should also be a priority.

Recommendation 1.b (added reason)

b) Support R&D into the production of high specific activity theranostic radioisotopes – Medical procedures that can be tailored to an individual's unique response will be more effective and lower the cost of health care**.** The move towards personalized medicine ~~can~~b be facilitated by supporting research on the production of radioisotopes, and isotopic pairs of the same element, that have both imaging and therapeutic emissions. Such agents, termed theranostic agents, can be used to obtain valuable pharmacokinetic and disease-targeting information in real time, which can allow rapid determination of whether the therapeutic approach will be effective in a specific patient. A requirement for theranostic radioisotopes produced for medical use is that they have very low quantities of other isotopes of that element present (or "high specific activity") after production and isolation. Personalized medicine will use highly specific targeting of diseased cells in patients to differentiate their disease and help identify treatments that will be effective. High specific activity radioisotopes are required so that the targeted receptor or cell-surface antigen on the diseased cells are bound with targeting agents containing only, or mostly, the theranostic radioisotope. If low specific activity radioisotopes are used, the disease-targeting agent containing a stable isotope (or non-useful radioisotope) can compete for the receptor or antigen, dramatically decreasing binding of the isotope that provides the diagnostic and/or therapeutic emissions. This can lead to inconclusive imaging results and ineffective therapy~~, resulting in an unsuccessful personalized medicine approach~~*.*

Recommendation 1.c (added reason)

c) Continue support for R&D on the use of electron accelerators for isotope production – Many isotopes that have ideal properties for applications in nuclear medicine and national security cannot currently be produced in the quantities and purity required. One of the major driving forces for new radioisotope production R&D is the need for increased yield and high specific activity. One of the newer approaches is the use of photons to initiate isotope production. While the concept has been around for decades, sources of photons with sufficient energy and flux to make the approach practical have only recently become available (through R&D driven by Basic Energy Sciences' need for high beam currents), so it is now possible to explore this pathway.

While the (g,n) reaction is the mostly widely discussed, additional reactions could be examined, including (g,p) and photofission. The (g,p) reaction affords the possibility for producing radionuclides with high specific activity. The ^{68}Zn(g,p)^{67}Cu reaction, where the copper isotope can be chemically separated from the target material, could be a viable route to this potential theranostic isotope (paired with ^{64}Cu). Other potential reactions of interest include; ^{232}Th(g,spall)^{225}Ac, and ^{232}Th(g,spall)^{211}Rn($t_{1/2}$=14.6 h, *EC*)^{211}At. These reactions are especially promising if multiple electron machines can be made available at reasonable costs. The photofission yield distribution from ^{238}U is almost identical to the thermal neutron fission of ^{235}U. This is a possible route to isotopes produced by fission that would remove the need for ^{235}U.

Recommendation 1.d (added reason)

d) Support R&D on the development of irradiation materials for targets that will be exposed to extreme environments to take full advantage of the current suite of accelerator and reactor irradiation facilities

– It is paramount that the production of critical radioisotopes be performed in a way that ensures public safety and protects the environment. The planned upgrades in production capacity at the isotope production accelerator facilities will create demands on the materials used and will likely require the development of new materials that can withstand high temperature and radiation conditions. In a similar manner, development in ion source feedstocks for use in the proposed radioactive separation system will be required to make full use of the new capacity available with the construction of this new system outlined in recommendation- 3b.

Recommendation 2. (added justification; dropped technical detail)

2) We recommend completion and the establishment of effective, full intensity operations of the stable isotope separation capability at ORNL

The subcommittee is pleased with the progress that has been made since the 2009 NSACI recommendation toward the establishment of a stable isotope separation capability. Without this effort the U.S. is dependent on foreign sources for materials critical to the health and safety of the nation. This ongoing effort should continue until the separation capability ~~is~~has been fully established ~~and~~ , the intensity goal of throughput comparable to a calutron (~100 mA ion current) has been achieved, and the separator is available for routine use~~, providing~~. To achieve the goal for separator throughput, the Isotope Program is investing in the development of new ion source technology.

This facility will provide a reliable U.S. source of high-purity stable isotopes, many of which are currently available only from Russia~~. That~~, and will require, among other things, the allocation of a base operations budget for the separator.

~~In addition, to improve the current state-of-the-art for isotope separations, investments will be necessary to improve the efficiency of isotope separators through development of low temperature ion sources and improved materials chemistry. The goal of this effort should be to increase the throughput of the existing separator to be equivalent to at least that of one calutron (100 mA ion current).~~

3. (clarified wording)

3) We recommend ~~realization of~~an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments~~.~~ ~~Specifically~~ and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:

3.a (clarified wording and timing)

a) ***Infrastructure for isotope harvesting at FRIB*** **-** During routine operation for its nuclear physics mission, FRIB will produce a broad variety of isotopes that could be harvested synergistically without interference to the primary user. Research quantities of many of these isotopes, which are of interest to various applications including medicine, stockpile stewardship and astrophysics, are currently in short supply or have no source other than FRIB operation. ~~Infrastructure to enable the development of isotope harvesting should be installed at the FRIB facility in a timely manner to capitalize on this opportunity.~~The technical and economic viability of this proposed capability should be developed and assessed promptly.

3.b (unchanged)

b) ***Develop a strategy for the re-establishment of a separator for radioactive isotopes to support research –*** The isotope community has expressed the need for high specific activity, mass separated radioactive isotopes. A strategy for establishing a domestic capability for high purity radioactive isotopes should be developed. This capability is important to physical science programs, the medical community, and our national security. While chemical techniques can be used to separate the desired radioisotope from other elements, the selectivity to gain the isotopic purity desired by the community cannot be achieved without the development of electromagnetic separators for radioactive materials.

3.c (unchanged)

c) ***Increase the base infrastructure budget to sustain and expand production capacity at the Isotope Program facilities. Two near-term opportunities that merit support from this increased funding are:***

i) ***BNL Intensity upgrade and implementation of a second target station –*** Ongoing accelerator improvement projects at BLIP (installation of a beam Raster system and phase I of the Linac intensity upgrade) are expected to increase yields of ^{82}Sr. Phase I of the Linac intensity upgrade will include an assessment of the feasibility of a second doubling of the intensity of the Linac. If feasible, continued increases in intensity could further increase isotope production yields and have much merit. The Radiation Effects Facility (REF) is a spur off the BLIP beam line that could be used to provide a 2nd beam line at BLIP primarily for research irradiations. In this manner research irradiations could be performed without interfering with ongoing large scale isotope production in the existing BLIP facility, providing more flexibility.

ii) ***Intensity, stability, and energy upgrades at LANL –*** While DOE has made critical infrastructure investments at LANL over the last five years, especially in the hot cell facility (including electrical and HVAC upgrades funded as separate upgrades efforts), this facility is nearing 50 years in age, and will require additional investments to ensure continued reliable operations.

4. (unchanged)

4) We recommend continuation and expansion of the effort to integrate the university facilities with the Isotope Program

The effort to form a network of university facilities that work with the DOE Isotope Program is commended and should be continued. University facilities have the ability to ***cost-effectively augment the capabilities of the national laboratories***, and to meet demands for radioisotopes and radioisotope R&D that are not possible at the national laboratories, such as regional production of short-lived radioisotopes (e.g. ^{211}At) and evaluation of some alternative methods for radioisotope production. Partnership with university sites can also provide ***complementary and/or supplemental capabilities for production of isotopes*** where demands are not currently being met. The possibilities should continue to be evaluated on a site-by-site basis, in view of the differing capabilities of the universities. Several universities already provide radioisotopes that meet national needs, either by supplying commercial sources or making radioisotopes that are not readily available from commercial suppliers. Continuing exploration of how these university radioisotope producers can work with the DOE Isotope Program and how DOE could support university infrastructure and operations without compromising the Isotope Program or the current university production and distribution network is viewed as challenging, but very important, as ***coordination of this effort with the Isotope Program would improve the availability of key isotopes.*** Other university facilities do not yet produce isotopes in significant quantity and are likely to need improvements in infrastructure and equipment. The Isotope Program should continue to consider infrastructure upgrades to university facilities to produce isotopes to meet specific national needs. It is recognized that the degree of integration and the details of the interfaces of each university facility into the DOE Isotope Program will vary by site and circumstances. ***Finally, an important additional benefit of a DOE-university site partnership is the workforce training opportunity. It is recognized that these training opportunities are currently an important part of the Isotope Program and it is strongly recommended that they be continued.***

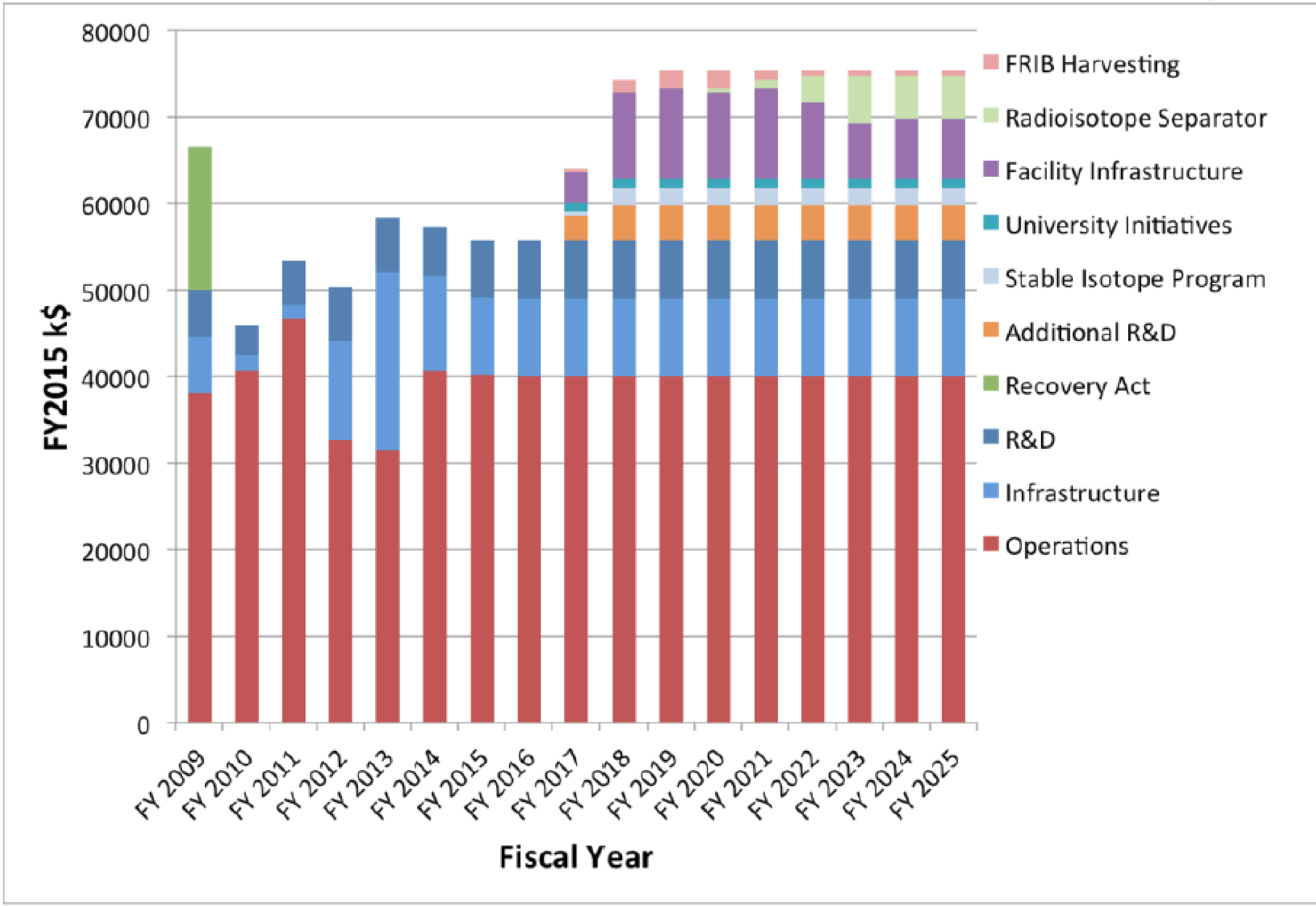
Evaluation of Progress Toward Realizing 2009 Report Recommendations

Unchanged **– minor wording changes to improve readability.**

Basically, as before, we note:

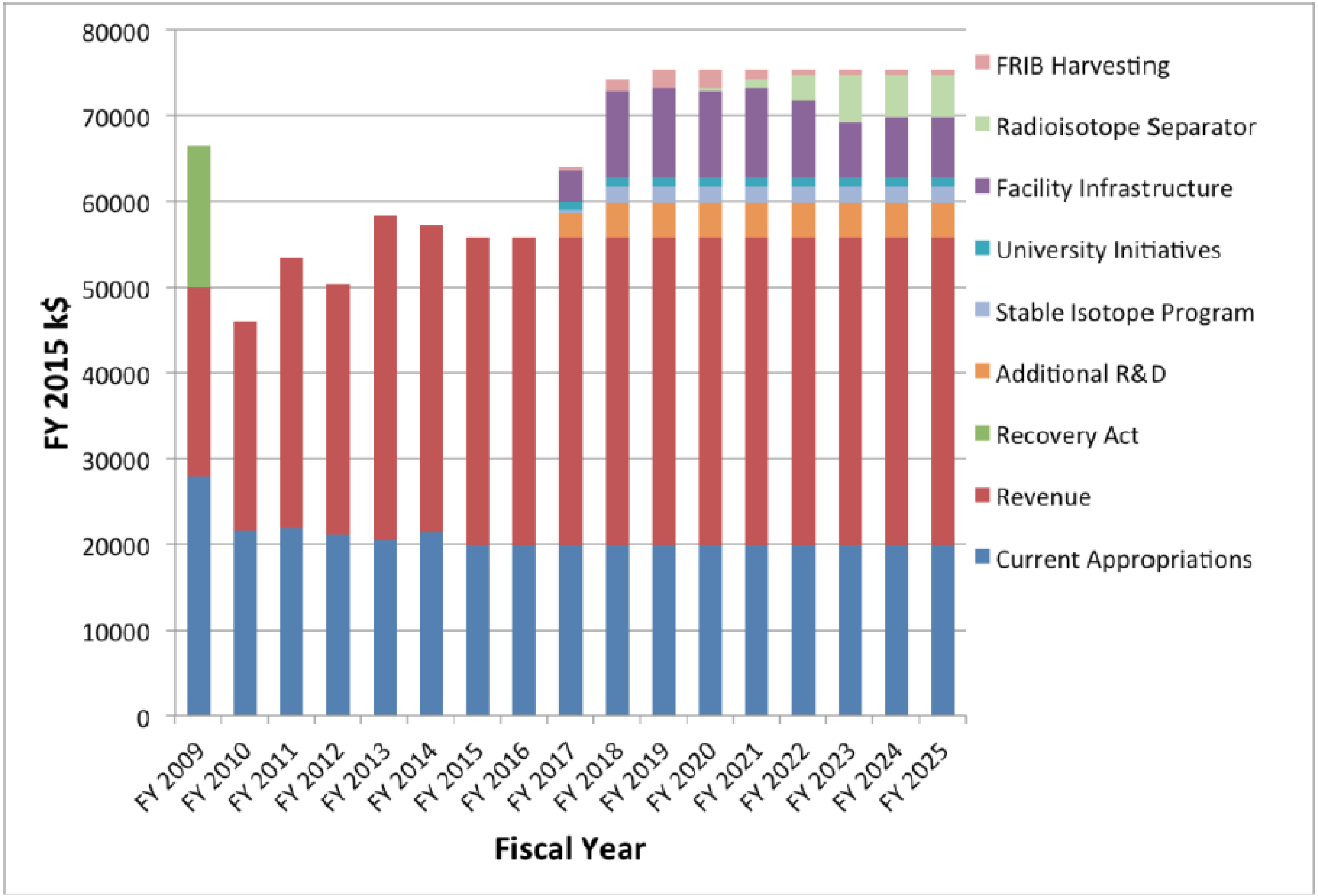
- **Broadly: DOE/NP has done an outstanding job of reorganizing the program and setting it on a firm footing**
- **The Isotope Program now in place has realized the vision of the 2009 NSACI and is making substantial progress toward expanding that vision**
- **Key structures and processes are in place that have enhanced productivity and impact, and these should be continued and improved in the broad directions that have been established (*hence comments on operations rather than recommendations*)**

Historical and projected DOE Isotope Program



The new initiatives discussed in the report are included. The total values include both base appropriations funding and funding from sales

Historical and projected DOE Isotope Program



The total values include both base appropriations funding

Recommend $19.5M/Year of Incremental Appropriated Funding *(Unchanged but Clarified)*

- **$4M to increase R&D to ~15% of the total program:**
  - $2M/year for increased peer-reviewed R&D funding and
  - $2M/year to enhance the base R&D at the production sites (It will also add stability against revenue fluctuations)
- **$2M to operate a stable isotope production program**
- **Up to $13.5M for infrastructure investments :**
  - to realize new opportunities presented by FRIB,
  - improvements to meet more difficult demands of alpha emitter production,
  - funds to deal with aging infrastructure, and
  - improvements to increase production capability (as required by the charge)

In Sum

- **The Isotope Program is a fascinating effort that both supports basic research and bridges the gap between research and applications in many fields such as medicine, industry and national security.**
- **The DOE Office of Nuclear Physics has done an outstanding job of managing it since the 2009 transition, and has set in place a structure and procedures that form a firm foundation for the future. They should be encouraged to pursue the path they have laid out.**
- **There are many opportunities (a number of which form the basis for our recommendations) to further enhance the ability of the Isotope Program to "increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical for the Nation."**
- **We can anticipate that the strengthening of the Isotope Program will be rewarded with continued progress in science, medicine, and industry, and by a further strengthening of national security.**
- ***We hope that the revised Subcommittee report does an even better job of making these points and is now acceptable to NSAC***

Questions?