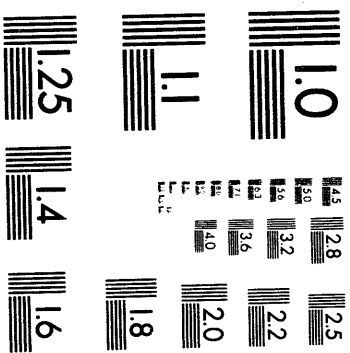
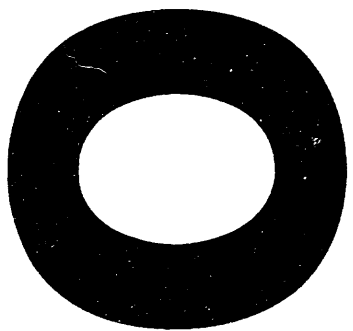






**Production and Supply of Radioisotopes  
with High-Energy Particle Accelerators  
Current Status and Future Directions**

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**Abstract**

Although the production of radioisotopes in reactors or in low to medium energy cyclotrons appears to be relatively well established, especially for those isotopes that are routinely used and have a commercial market, certain isotopes can either be made only in high-energy particle accelerators or their production is more cost effective when made this way. These facilities are extremely expensive to build and operate, and isotope production is, in general, either not cost-effective or is in conflict with their primary mandate or missions which involve physics research. Isotope production using high-energy accelerators in the U.S., therefore, has been only an intermittent and parasitic activity. However, since a number of isotopes produced at higher energies are emerging as being potentially useful for medical and other applications, there is a renewed concern about their availability in a continuous and reliable fashion. In the U.S., in particular, the various aspects of the production and availability of radioisotopes from high-energy accelerators are presently undergoing a detailed scrutiny and review by various scientific and professional organizations as well as the Government. A number of new factors has complicated the supply/demand equation. These include considerations of cost versus needs, reliability factors, mission orientation, research and educational components, and commercial viability. This paper will focus on the present status and projected needs of radioisotope production with high-energy accelerators in the U.S., and will compare and examine the existing infrastructure in other countries for this purpose. The nature of the U.S. decisions to address many of the above-mentioned issues and an eventual plan of attack to resolve them are bound to have a world-wide impact in the radioisotope user communities. These will be discussed with a view to evaluating the best possible solutions in order to eliminate the shortage in the future supply of radioisotopes produced in high-energy accelerators.

**I. Introduction**

The use of radioisotopes for medical as well as for a multitude of basic research applications has continued to grow at a very rapid pace (1,2). Their role as radiotracers for nuclear medicine imaging, and for radiotherapy of cancer and other pathology, has become firmly established as an important clinical modality. In the U.S. alone, over 12 million nuclear medicine procedures are carried out annually, and one out of every four hospital patients undergoes a procedure that involves the use of radioisotopes. Diagnostic imaging methods using planar imaging, single photon emission tomography (SPECT), and positron emission tomography (PET), as well as the measurement of in-vivo organ function,

physiology, or biochemistry have become indispensable tools in patient work-up and management.

Radioisotopes are primarily produced using a nuclear reactor or a charged-particle accelerator (mainly cyclotrons), and their properties depend upon a number of factors that include targetry, irradiation conditions and processing chemistry (3-5). The production and thus the supply of many routine isotopes as well as of those that have a commercial market have continued at a satisfactory level (5). However, certain isotopes that can be produced only using high-energy accelerators (e.g., spallation reactions) or whose production is more cost effective when made this way are either scarce or not available (2,6,7). One of the main reasons for this is that high-energy machines are very expensive to build and operate and isotopes production is usually in conflict with their primary mission which is physics research (1). Consequently, isotope production in these machines has been undertaken only as an intermittent and parasitic activity. This situation has created considerable concern within the radioisotope research community that includes nuclear medicine as well as basic physical and life science investigators (1,6-11). This is especially in view of the fact that a number of high-energy produced isotopes are emerging as being potentially useful and in some cases unique for imaging and/or radiotherapy applications in nuclear medicine. With the recent rapid growth in biotechnological and immunological approaches to treatment of cancer, bone pain, and other diseases, there is an urgent need for a continuous and reliable availability of certain high-energy produced isotopes.

## **II. Current Status**

### **IIa. Low and Medium Energy Cyclotrons**

At the present time, there are about 50 radioisotopes that are potentially useful for nuclear medicine applications. The applications include in-vitro assays, in-vivo imaging for anatomy, biochemistry, or function, or radiotherapy (sealed as well as unsealed sources). Approximately fifteen are routinely used and are generally available from commercial low to medium energy cyclotrons (Table 1, ref. 3-5,12,13). Out of these,  $^{67}\text{Ga}$ ,  $^{81\text{m}}\text{Kr}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ , and  $^{201}\text{Tl}$  are the ones that are most commonly used for imaging applications in nuclear medicine.

A wide variety of low to medium energy cyclotrons now exist and worldwide, there are about 18 (12 in the U.S. and Canada) that engage in routine commercial production of radionuclides (3,12,13). In addition, there are about a hundred or so small or "baby" cyclotrons that are housed for on-site PET

research at various institutions. The short lived PET nuclides produced in these machines, e.g.,  $^{18}\text{F}$ ,  $^{13}\text{N}$ ,  $^{11}\text{C}$ , and  $^{15}\text{O}$ , are not included in the listing in Table 1.

Table 1. Radioisotopes Produced in Low to Medium Energy Cyclotrons\*

| Isotope                         | Half-life | Decay mode<br>(Principal energy, KeV) | Typical production<br>reaction<br>(energy, MeV)                                      |
|---------------------------------|-----------|---------------------------------------|--------------------------------------------------------------------------------------|
| $^{52}\text{Fe}$                | 8.3 h     | $\beta^+$ (511), EC                   | $^{52}\text{Cr}(^3\text{He}, 3n)(30)$                                                |
| $^{56}\text{Co}$                | 17.6 h    | $\beta^+$ (511), EC                   | $^{56}\text{Fe}(p, 2n)(28)$                                                          |
| $^{67}\text{Co}$                | 271 d     | EC(122)                               | $^{55}\text{Mn}(\alpha, 2n)(24)$                                                     |
| $^{62}\text{Zn}/^{62}\text{Cu}$ | 9.1 h     | EC/ $\beta^+$ (511)                   | $^{63}\text{Cu}(p, 2n)(28)$                                                          |
| $^{67}\text{Ga}$                | 3.28 h    | EC(93)                                | $^{68}\text{Zn}(p, 2n)(28)$                                                          |
| $^{76}\text{Br}$                | 1.63 h    | $\beta^+$ (511)                       | $^{76}\text{As}(^3\text{He}, 3n)(38)$                                                |
| $^{77}\text{Br}$                | 57 h      | EC(240)                               | $^{78}\text{Br}(p, 3n)^{77}\text{Kr} \rightarrow (36)$                               |
| $^{81\text{m}}\text{Kr}$        | 13 s      | IT(190)                               | $^{82}\text{Kr}(p, 2n)^{81}\text{Rb} \rightarrow (22)$                               |
| $^{81}\text{Rb}$                | 4.58 h    | $\beta^+$ (511)                       | $^{79}\text{Br}(^4\text{He}, 2n)(20-28)$                                             |
| $^{111}\text{In}$               | 2.82 d    | EC(173, 247)                          | $^{112}\text{Cd}(p, 2n)(22)$                                                         |
| $^{123}\text{I}$                | 13.2 h    | EC(159)                               | $^{124}\text{Te}(p, 2n)(22)$                                                         |
|                                 |           |                                       | $^{124}\text{Xe}(p, 2n)^{123}\text{Xe} \rightarrow (24)$                             |
| $^{124}\text{I}$                | 4.2 d     | $\beta^+$ (511)                       | $^{121}\text{Sb}(^4\text{He}, n)(10-38)$                                             |
| $^{196\text{m}}\text{Hg}$       | 1.67 h    | EC, IT(200)                           | $^{197}\text{Au}(p, 3n)(26-34)$                                                      |
| $^{201}\text{Tl}$               | 3.04 d    | EC(167)                               | $^{203}\text{Tl}(p, 3n)^{201}\text{Pb} \rightarrow ^{201}\text{Tl}(26)$              |
| $^{203}\text{Pb}$               | 2.17 d    | EC(279)                               | $^{203}\text{Tl}(d, 2n)(12-15)$ or by -<br>product from $^{201}\text{Tl}$ production |

\*Most of these are commercially available, either routinely (large volume) or can be produced on a custom basis (low volume).

Since the production of the isotopes in Table 1 is in response to commercial needs and since the market for these is reasonably well established, there is not a great concern about the supply/demand situation.

## IIb. High-Energy Particle Accelerators

Since isotope production using high-energy particle accelerators is not to date a commercially viable option, use of these machines for this purpose has in the U.S. been limited to meeting intermittent research needs only. Lately, however, some effort has been made to produce and supply certain routine isotopes on an as available basis. At the present time, there are about 6 high-energy accelerators world-wide that engage in isotope production for distribution. These are located in the U.S. (BLIP and LAMPF), Canada (TRIUMF), Switzerland (PSI), South Africa (NAC), and Russia. A few others also have the capability for isotope production but are utilized rarely or very little for this purpose. It must be emphasized that the cost of production is a critical factor and unless there is

a commercial market, high-energy produced isotopes are not produced in any consistent fashion.

#### **II.b.1. Brookhaven Linac Isotope Producer (BLIP)**

The BLIP (14) at Brookhaven National Laboratory was built in 1972 to utilize unused pulses of high-energy protons from a 200 MeV, 45 $\mu$ A linear accelerator whose main function is to inject protons into the Alternating Gradient Synchrotron (AGS) for further acceleration to 33 GeV. It has the designed capability to simultaneously irradiate up to fourteen targets for isotope production. The BLIP was redesigned and improved in 1985, mainly to improve the reliability and reparability factors. It has operated for the first two decades during the operating times of the linac which have slowly decreased from a high of 34 weeks in 1983 to an average of 20 weeks per year for the last five years. Detailed operating parameters for the last 3 years are described in Table 2. The isotopes that have been developed and produced at the BLIP are listed in Table 3. A few of these are produced in larger quantities for routine distribution.

Table 2. BLIP Operations

|                            | 1991    | 1992    | 1993    |
|----------------------------|---------|---------|---------|
| Average Current ( $\mu$ A) | 46.2    | 42.6    | 40.5    |
| Beam Time (h)              | 3384    | 3378    | 3070    |
| Total Fluence ( $\mu$ Ah)  | 156,378 | 143,898 | 124,267 |
| Weeks*                     | 19      | 21      | 19      |
| BLIP Reliability           | 99%     | 86%     | 98%     |
| System Reliability         | 86%     | 79%     | 84%     |

\*Additional weeks were added for dedicated use at increased cost: 5, 5, and 3 weeks respectively in 1991, 1992, and 1993.

#### **II.b.2. Los Alamos Meson Physics Facility (LAMPF)**

The LAMPF which consists of a linac almost 1 Km long (800 MeV, 1.1 mA), is one of the most powerful accelerators in the world. Isotope production has continued to be one of the activities of this accelerator since the mid-seventies but again on an as available basis. The running time for this machine has averaged 4-6 months every year, usually during May thru November. It has maintained nine target stations, each capable of irradiating one to three targets. Approximately 30 different isotopes are produced at LAMPF during its operating cycles (Table 4). There has been a slow erosion in the capability for isotope production at LAMPF as well; in 1993, this facility operated for only about 14

weeks. Recently, questions have been raised regarding the continued operation of LAMPF since its primary mission of doing hadron nuclear physics appears to have decreased in priority in the overall field of nuclear physics (11). Even though a final decision is yet to be made, it appears that the LAMPF may not be able to maintain isotope production for more than an additional year or two.

Table. 3 Radioisotopes Produced at the BLIP

| Isotope                                 | Half-life | Decay mode          | Nuclear reaction                                             | Medical application                        |
|-----------------------------------------|-----------|---------------------|--------------------------------------------------------------|--------------------------------------------|
| $^7\text{Be}^*$                         | 53.3d     | EC                  | $^{12}\text{C}(\text{p}, \text{spall})$                      | C tracer, measure in-vivo Li               |
| $^{28}\text{Mg}^*$                      | 21h       | $\beta$             | $\text{Cl}(\text{p}, \text{spall})$                          | Mg tracer                                  |
| $^{47}\text{Sc}$                        | 3.4d      | $\beta$             | $^{48}\text{Ti}(\text{p}, 2\text{p})$                        | Radioimmunotherapy                         |
| $^{52}\text{Fe}$                        | 8.3h      | $\beta^+$ (57%), EC | $\text{Ni}(\text{p}, \text{spall})$                          | Fe tracer                                  |
| $^{56}\text{Co}$                        | 17.5h     | $\beta^+$ (81%), EC | $^{56}\text{Fe}(\text{p}, 2\text{n})$                        | PET antibody label                         |
| $^{66}\text{Zn}$                        | 244d      | EC                  | $^{69}\text{Ge}(\text{p}, \alpha\text{n})$                   | Zn tracer                                  |
| $^{67}\text{Cu}$                        | 61.9h     | $\beta$             | $^{68}\text{Zn}(\text{p}, 2\text{p})$                        | Radioimmunotherapy                         |
| $^{68}\text{Ge}/^{68}\text{Ga}^*$       | 271d/68m  | EC                  | $^{nat}\text{Ga}(\text{p}, 2\text{n}/4\text{n})$             | PET calibration                            |
| $^{72}\text{As}$                        | 26h       | $\beta^+$           | $\text{Br}(\text{p}, \text{spall})$                          | PET imaging                                |
| $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ | 4.6h/13s  | EC/IT               | $^{nat}\text{Kr}(\text{p}, 4\text{n})$                       | Lung ventilation                           |
| $^{82}\text{Sr}/^{82}\text{Rb}^*$       | 25.4d/75s | EC/ $\beta^+$       | $^{nat}\text{Rb}(\text{p}, 4\text{n}/6\text{n})$             | PET studies of heart                       |
| $^{88}\text{Y}$                         | 106.6d    | EC                  | $\text{Mo}(\text{p}, \text{spall})$                          | Y tracer                                   |
| $^{95\text{m}}\text{Tc}$                | 61d       | EC                  | $^{103}\text{Rh}(\text{p}, \text{spall})$                    | Tc tracer                                  |
| $^{96}\text{Tc}$                        | 4.3d      | EC                  | $^{103}\text{Rh}(\text{p}, 3\text{p}5\text{n})$              | Tc Tracer                                  |
| $^{97}\text{Ru}^*$                      | 2.89d     | EC                  | $^{103}\text{Rh}(\text{p}, 2\text{p}5\text{n})$              | Antibody label, miscellaneous labeling use |
| $^{117\text{m}}\text{Sn}$               | 13.6d     | IT                  | $^{nat}\text{Sb}(\text{p}, \alpha\text{n}/\alpha 3\text{n})$ | Bone pain therapy                          |
| $^{127}\text{Xe}^*$                     | 36.4d     | EC                  | $^{133}\text{Cs}(\text{p}, 2\text{p}5\text{n})$              | Lung ventilation                           |
| $^{203}\text{Pb}$                       | 51.9h     | EC                  | $^{209}\text{Bi}(\text{p}, 2\text{p}5\text{n})$              | Radioimmunotherapy                         |

\*Off-site distribution at cost

Table 4. Radioisotopes Produced at LAMPF

|                     |                        |                               |                       |
|---------------------|------------------------|-------------------------------|-----------------------|
| $^7\text{Be}$       | $^{56}\text{Co}$       | $^{88}\text{Zr}$              | $^{146}\text{Pm}$     |
| $^{22}\text{Na}$    | $^{67}\text{Cu}$       | $^{88}\text{Y}$               | $^{146,148}\text{Gd}$ |
| $^{26}\text{Al}$    | $^{68}\text{Ge}$       | $^{109}\text{Cd}$             | $^{163}\text{Ho}$     |
| $^{32}\text{Si}$    | $^{72}\text{Se}$       | $^{105,109\text{m}}\text{Ag}$ | $^{172}\text{Hf}$     |
| $^{44}\text{Ti}$    | $^{72,73}\text{As}$    | $^{123,125}\text{I}$          | $^{172,173}\text{Lu}$ |
| $^{44,46}\text{Sc}$ | $^{77}\text{Br}$       | $^{127}\text{Xe}$             | $^{207}\text{Bi}$     |
| $^{48}\text{V}$     | $^{82}\text{Sr}$       | $^{139}\text{Ce}$             | $^{128}\text{Ba}$     |
| $^{52}\text{Mn}$    | $^{82,83,86}\text{Rb}$ | $^{146}\text{Pm}$             | $^{203}\text{Pb}$     |
| $^{52,59}\text{Fe}$ |                        |                               |                       |



### III. Future Directions

For the past ten years, considerable uncertainty has surrounded the operation of high-energy accelerators for isotope production (especially BLIP and LAMPF in the U.S.). In view of the significant reduction in operating periods of these machines caused by a slow erosion in funds for physics research, concern has mounted rapidly within the research and industrial communities as to the future domestic supply of high-energy produced isotopes (1,2). A number of scientific and professional organizations as well as the U.S. Government have begun to debate and examine the various possible options to resolve this problem before it reaches a crisis proportion (1,6-11). There seems to be a unanimous recommendation that the U.S. should have a reliable domestic supply of high-energy produced radioisotopes and that this should be achieved through the establishment of a National Biomedical Tracer Facility (NBTF) consisting of a high-energy, high-current (100 MeV; 750  $\mu$ A) accelerator dedicated to year round isotope production (8,9). This facility is to also serve as a national center for research, education, and training in order to assure the continued growth of nuclear medicine and other scientific areas that involve the use of radioisotopes. A final decision on the NBTF has yet to be made.

It was decided, however, that the Department of Energy will support an upgrade of the BLIP facility as an interim measure to immediately improve the situation (9). The objectives of the BLIP upgrade are to serve as a reliable source of selected radioisotopes until the time that the NBTF comes on line, and to enable BLIP to pick up the slack in isotope supply caused by the projected LAMPF shutdown. The upgraded BLIP will have increased beam current (from the present 60  $\mu$ A to 145  $\mu$ A) and near year-round (46 weeks) operation. It will also provide energy variability from 66-200 MeV in  $\sim 21$  MeV steps, compatible with the operation of the Alternating Gradient Synchrotron (AGS). The list of isotopes presently produced at the BLIP will be expanded to include some that are presently available only from LAMPF (e.g.,  $^{88}\text{Y}$ ,  $^{109}\text{Cd}$ ,  $^{22}\text{Na}$ ). The advantages of this BLIP/Linac upgrade are that it is cheaper and faster to implement (it should be complete by June, 1996) and that it will provide the bridge until the NBTF is approved and built. The production will be a year-round activity and production yields, cost efficiency, and specific activity of the isotopes will improve considerably. The upgraded BLIP will also be able to carry out realistic target development for NBTF (compatible with high beam currents), and address other problems related to operation at high current.

A comparison of the isotope production capability of the BLIP Upgrade and that as envisioned for the NBTF is contained in Table 5. With at least 5 times more beam, the NBTF offers much better yield for large volume isotopes e.g.,

Table 5. BLIP/NBTF Produced Isotopes  
Percent of Isotope Demand Possible in FY 1996-97

| Isotope            | Projected Annual Demand (mCi)* | BLIP Upgrade<br>(150 $\mu$ A-46wks) | NBTF<br>(750 $\mu$ A-46wks) |
|--------------------|--------------------------------|-------------------------------------|-----------------------------|
|                    |                                | w/o LAMPF<br>%                      | w/o LAMPF<br>%              |
| <sup>82</sup> Sr   | 60,000                         | 35                                  | 100                         |
| <sup>68</sup> Ge   | 2700                           | 100                                 | 100                         |
| <sup>67</sup> Cu   | 8400                           | 50                                  | 100                         |
| <sup>28</sup> Mg   | 3                              | 100                                 | 100                         |
| <sup>98</sup> Tc   | 100                            | 100                                 | 100                         |
| <sup>127</sup> Xe  | 350                            | 100                                 | 100                         |
| <sup>97</sup> Ru   | 100                            | 100                                 | 100                         |
| <sup>66</sup> Co   | 150                            | 100                                 | 100                         |
| <sup>7</sup> Be    | 15                             | 100                                 | 100                         |
| <sup>88</sup> Y    | 100                            | 100                                 | 100                         |
| <sup>108</sup> Cd  | 4000                           | 100                                 | 100                         |
| <sup>22</sup> Na   | 1500                           | 100                                 | 100                         |
| <sup>73</sup> As   | 60                             | 100                                 | 100                         |
| <sup>26</sup> Al   | Unknown                        | 0                                   | 100                         |
| <sup>32</sup> Si   | "                              | 0                                   | 100                         |
| <sup>48</sup> V    | "                              | 0                                   | 100                         |
| <sup>57</sup> Co   | "                              | 0                                   | 100                         |
| <sup>61</sup> Cu   | "                              | 0                                   | 100                         |
| <sup>62</sup> Zn   | "                              | 0                                   | 100                         |
| <sup>77</sup> Br   | "                              | 0                                   | 100                         |
| <sup>72</sup> As   | "                              | 0                                   | 100                         |
| <sup>83</sup> Rb   | "                              | 0                                   | 100                         |
| <sup>95m</sup> Tc  | "                              | 0                                   | 100                         |
| <sup>124</sup> I   | "                              | 0                                   | 100                         |
| <sup>138</sup> Ce  | "                              | 0                                   | 100                         |
| <sup>178</sup> Ta  | "                              | 0                                   | 100                         |
| <sup>178</sup> Ta  | "                              | 0                                   | 100                         |
| <sup>195m</sup> Au | "                              | 0                                   | 100                         |
| <sup>206</sup> Bi  | "                              | 0                                   | 100                         |
| <sup>208</sup> Bi  | "                              | 0                                   | 100                         |
| <sup>207</sup> Bi  | "                              | 0                                   | 100                         |
| Others             | "                              | 0                                   | 100                         |

\*Based on current trends

\*\*These short lived isotopes will not be available during machine downtime.

$^{82}\text{Sr}$  and the higher beam current should lead to higher specific activity (mCi/mg), which is important in certain situations, such as labeling monoclonal antibodies with  $^{67}\text{Cu}$ , and  $^{22}\text{Na}$  for positron spin resonance studies. The higher beam intensity at NBTF will also allow improved cost efficiency and greater overall throughput. The NBTF will initially produce 12-14 of the same isotopes as BLIP will. However, NBTF will ultimately be capable of producing at least twice as many isotopes. Another practical difference is that relative to BLIP the new machine in the NBTF should offer improved reliability, improved power utilization and reduced manpower needs and thus lower costs for operation. The NBTF mission is considerably broader in scope than that presently planned for the BLIP Upgrade. The NBTF is planned to have at least one precision beam line, tunable from 30-100 MeV in 1 MeV increments. It should operate simultaneously with the production beam lines, essentially invisible to the production effort. Upgraded BLIP, as mentioned earlier, will have one research beam line tunable from 66-200 MeV in 21 MeV increments, and it must alternate operation with the production line even though this is not anticipated to happen often enough to significantly impact production.

#### **IV. Conclusion**

Even though the present domestic supply of high-energy accelerator-produced radioisotopes in the U.S. is experiencing an acute shortage, especially in the case of large volume isotopes required for medical use, the prospects for the future look quite encouraging. The concern has been magnified to the point where it is now a highly visible problem on a national scale. Although the decision to establish a national center (NBTF) dedicated to year long production and research on radioisotopes is yet to be made, the U.S. appears to be getting closer to achieving self-sufficiency with regard to the future supply of radionuclides produced using a high-energy charged particle accelerator. The approved upgrade of an existing isotope production facility (BLIP) will go a long way towards bridging the gap between now and the time when the NBTF gets approved and built.

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## &lt;950&gt; ABSTRACT

Although the production of radioisotopes in reactors or in low to medium energy cyclotrons appears to be relatively well established, especially for those isotopes that are routinely used and have a commercial market, certain isotopes can either be made only in high-energy particle accelerators or their production is more cost effective when made this way. These facilities are extremely expensive to build and operate, and isotope production is, in general, either not cost-effective or is in conflict with their primary mandate or missions which involve physics research. Isotope production using high-energy accelerators in the US, therefore, has been only an intermittent and parasitic activity. However, since a number of isotopes produced at higher energies are emerging as being potentially useful for medical and other applications, there is a renewed concern about their availability in a continuous and reliable fashion. In the US, in particular, the various aspects of the prediction and availability of radioisotopes from high-energy accelerators are presently undergoing a detailed scrutiny and review by various scientific and professional organizations as well as the Government. A number of new factors has complicated the supply/demand equation. These include considerations of cost versus needs, reliability factors, mission orientation, research and educational components, and commercial viability. This paper will focus on the present status and projected needs of radioisotope production with high-energy accelerators in the US, and will compare and examine the existing infrastructure in other countries for this purpose.

**DATE**

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