YTTRIUM-90 FOR CANCER THERAPY STUDIES SECURED THROUGH GOVERNMENT AND COMMERCIAL SUPPLIERS

RESEARCHERS THROUGHOUT the United States are assessing the effectiveness of yttrium-90 (^{90}Y)-labeled monoclonal antibodies in treating lymphomas, T-cell leukemia, and ovarian, colorectal, esophageal, pancreatic, and bone cancers, which together are diagnosed in an estimated 210,000 people each year. Protocols are being designed to study the use of ^{90}Y in breast cancer as well. In need of a constant supply of ^{90}Y to meet the demands of these clinical and preclinical trials, researchers expressed concern when the U.S. Department of Energy's (DOE) ^{90}Y supply was cut off temporarily last February (see *Newsline*, May 1990, p. 18A). Since then, the DOE has set up two ^{90}Y production and distribution sites. And several commercial suppliers have entered the market in recent months, making investigators more comfortable with the supply.

Since early May the two DOE sites — Westinghouse Hanford through Batelle, Pacific Northwest Laboratory (PNL) in Richland, Washington and Argonne National Laboratory in Illinois — have been testing processes to generate clinical grade ^{90}Y from its parent, strontium-90 (^{90}Sr). After receiving positive evaluations on the purity and labeling ability of both ^{90}Y products from cancer researchers in various parts of the U.S., the DOE's Isotope Production and Distribution Office, in September, transferred the ^{90}Y production process to these two sites from Oak Ridge National Laboratory (ORNL) in Tennessee.

In addition, several alternative suppliers have entered the market in the past year, creating competition for the DOE. Amersham International, plc, of Amersham, United Kingdom, is selling European-made ^{90}Y to customers in the U.S. through its Medi-Physics subsidiary. Nordion International of Kanata, Canada has been "revialing" ^{90}Y obtained from General Atomic of San Diego, California and may continue to do so, but, in addition, Nordion has developed its own process for generating ^{90}Y. Du Pont Company of Wilmington, Delaware also is setting up an operation to supply the isotope under the NEN® Research Products name.

Pacific Northwest and Argonne use different methods to produce ^{90}Y, both of which are different from ORNL's method, and, according to the DOE and investigators, the new processes produce a higher quality product. The researchers at both Argonne and Pacific Northwest extract ^{90}Sr from recycled spent nuclear fuel waste from DOE's nuclear production reactors. Yttrium-90 is then extracted from ^{90}Sr.

Investigators say the quality of the DOE products is good — they contain lower levels of ^{90}Sr and can label antibodies better than the material that had been supplied by ORNL. With commercial products becoming available, time will tell whether the DOE or the commercial products will be superior. Andrew Raubitschek, MD, senior investigator in the radiation oncology branch at the National Cancer Institute in Bethesda, Maryland, says "the DOE products have the potential of being superior, but until they provide a high quality product repeatedly over time, it's too early to tell."

Dr. Raubitschek has been doing clinical studies of ^{90}Y-labeled monoclonal antibodies against non-Hodgkin's lymphoma and T-cell leukemia for two years. In collaboration with other investigators at the NCI, his group is also doing animal studies using ^{90}Y to treat ovarian and colon carcinomas and hopes to file an investigational new drug application (IND) with the FDA to study ^{90}Y antibody therapy for B-cell lymphomas. Dr. Raubitschek had expressed concerns about the future of his projects when ORNL shut down their ^{90}Y production operations last February. But, he now says that "DOE has really come across quite well in making up the deficit. It has really kicked in and is supplying stuff of high quality." He says that both the Westinghouse Hanford and Argonne products are "ready for clinical trials." The products meet two criteria necessary for ^{90}Y, according to Dr. Raubitschek. "They have a relatively low level of strontium and they are in chemically pure form, so there is no trouble with the labeling process." The NCI researchers have also tested the Amersham product and are using it in some studies. Dr. Raubitschek says, "I think Amersham will also serve to be a reliable source." Referring to the DOE and Amersham, he says, "now the NCI has two clinical supplies of ^{90}Y. It's good to have a couple in case one operation goes down."

At Oak Ridge Associated Universities (ORAU) in Tennessee, Lee C. Washburn, PhD, acting director of ORAU's nuclear medicine program, and his colleagues have been studying ^{90}Y-labeled antibodies in animal models of colorectal and pancreatic cancers for five years and have submit-

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ted an IND to the FDA for a ^{90}Y-labeled antibody to treat colorectal cancer. Dr. Washburn says the group has received ^{90}Y from Pacific Northwest Lab, and he notes that "it was very satisfactory. We were very pleased with it in terms of its ability to label our antibody." The ORAU researchers have also reviewed the Argonne product, but since it was during a very early stage of the product's development, Dr. Washburn says that "it is unfair to comment on the results."

A spokesperson for Eli Lilly and Company, Indianapolis, Indiana, the parent company for Hybritech Inc., another firm working in this field, declined to discuss the specifics of Hybritech's clinical and preclinical studies with ^{90}Y-labeled monoclonal antibodies and the ^{90}Y products the company uses.

Novel Separation Method

Describing the method Argonne uses to produce ^{90}Y, Robert W. Atcher, PhD, group leader for nuclear medicine research at Argonne, says that the group uses a novel separation chemistry with several advantages. "First, the process is extremely effective for extracting strontium-90," from the spent fuel waste, removing 99.99% of the ^{90}Sr. The group then extracts the ^{90}Y from what is left to separate it from other impurities. The second advantage Dr. Atcher points to is the chemical makeup of the octanol extractant, which is made up of carbon, hydrogen, and oxygen. "As it breaks down, it generates carbon dioxide. Thus, we have very few, if any, waste products, and we can keep recycling our strontium back into the system." A third advantage he refers to is that the "the extractants were designed to work specifically with yttrium-90 and nothing else. . .and that they provide purifications on the order of a part per 10^9." He notes that since the products they have generated so far have been the result of small scale extractions, the chemistry and the purification could change somewhat when the process is scaled up. "If the process holds up," he says, "yield will be 100,000 times better in terms of strontium-90 content than what has been available."

Dr. Atcher says investigators can use the Argonne product "in formulating labeled monoclonal antibodies and other conjugates and have a lot less anxiety about injecting strontium into the patient" along with the ^{90}Y. He also notes that there is very good binding of the ^{90}Y product to chelated antibodies, "on the order of 95%."

The Argonne group has not started to ship on a regular basis yet but was aiming to be fully operational by the end of January.

At Pacific Northwest Laboratory, chemist Lane Bray developed a different extraction process that is based on the ORNL process but includes several advances designed to decrease personnel exposures during production and enhance the purity of the final product. Westinghouse Hanford, which distributes PNL's ^{90}Y, has filed a Drug Master File for the isotope as a radiochemical. According to Elaine T. Marshall, product engineer in Westinghouse Hanford's Isotope Programs Office, PNL uses a phosphoric acid extractant to separate the ^{90}Y from the ^{90}Sr.

Ms. Marshall says that "on a regular basis, we have achieved a ratio of purification between 1×10^{-7} to 1×10^{-8}," which she says is between "10 and 100 times more pure than the product distributed by Oak Ridge." Currently in "an interim production" phase, Westinghouse Hanford is shipping between 300 and 600 milliCuries each week to researchers across the country, according to Ms. Marshall. But, she notes that Westinghouse Hanford is constructing a dedicated facility for ^{90}Y production and expects to be able to "scale up to multi-Curie amounts" in early 1991. "The amount that we produce will be closely related to customer needs," she adds.

Commercial Supplies Available

Commercial supplies will also be driven by customer needs and the growth of the field. Amersham has filed a Drug Master File with the FDA on their ^{90}Y product and is "making the material on a weekly basis," according to Barney Tyrwhitt-Drake, director of marketing at Medi-Physics. But, he notes that the company is "only supplying to biotechnology companies and clinical investigators with INDs" because of safety considerations about the handling of such a high energy isotope in the high concentrations required.

Regarding Amersham's ^{90}Y production process, Mr. Tyrwhitt-Drake says, that the Amersham operation "took a while" to develop but is now "routine, reliable, and efficient."

Reluctant to comment on the product's specifications, Mr. Tyrwhitt-Drake did describe the company's requirements for its ^{90}Y product. "Any

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product that is going to be successful in the labeling of antibodies is going to be very high in radionuclidic purity, that is, it will have very low levels of strontium-90, to avoid skeletal accumulation of a long-lived contaminant. We believe we have that." The material must also have a "very high chemical purity," says Mr. Tyrwhitt-Drake. "The levels of non-radioactive cations in the product must be at very low levels so that they do not effectively compete with the yttrium-90 for monoclonal antibody labeling sites." A lack of chemical purity, he notes, could lead to "injection of free yttrium-90 chloride, which could be taken up in bone, causing unnecessary myelosuppression." He says that the Amersham process includes "clean-ups," or additional chemical purification techniques to minimize the presence of unwanted cations that would compete for binding sites.

Pointing out that the radioactive concentration is another important factor in the product's development, he says that "the material must be at a high enough concentration to permit rapid incorporation into a derivatized monoclonal antibody but not so high as to cause problems in dispensing and measurement. Typically, radioactive concentrations will be found that are 50 times higher that those in conventional diagnostic concentrations."

Other factors the company considered when developing the material include pharmaceutical quality, packaging, and availability. Mr. Tyrwhitt-Drake says that Amersham's ^{90}Y is produced in England but has been reliably supplied in the U.S. because of rapid shipment and the isotope's 64-hour half-life. He does not preclude the possiblity that Amersham might someday produce the isotope at one of their U.S. manufacturing sites. "We want to manufacture products where it makes the most sense in terms of availability, reliability, and economics."

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Nordion's product manager for radiopharmaceuticals, Mike W. Jamieson, says that the Canadian supplier is providing ^{90}Y on a weekly basis, with a three-day calibration from ship date. Mr. Jamieson notes that the "activity concentration and individual dose size can be customized to individual labeling requirements." The company is supplying the product as ^{90}Y chloride but is studying other chemical forms, such as ^{90}Y acetate, that could potentially eliminate the need for buffering steps, according to Mr. Jamieson. The company planned to file a Drug Master File by the end of January 1991.

Mr. Jamieson says, "Nordion realizes that standards required to achieve the anticipated labeling efficiencies are very high and will collaborate with research groups to assure the final yttrium-90 will optimize the results." He adds that "At present, the total metal level is less than 10 parts per million, and the strontium-90 level is less than 1 microCurie per Curie." He notes that the company has developed a clean-up method that is expected to reduce both the ^{90}Sr and metal contamination levels "an additional 10 to 100 times." The clean-up procedure was to be implemented on a weekly basis in January.

Du Pont plans to file a Drug Master File for ^{90}Y and to introduce a ^{90}Y product for investigational use within the next four to six months, according to Carmen Marchetti, senior operations specialist at Du Pont. Mr. Marchetti says that Du Pont "has the separation process developed. It's the further refinement of the final product that is being fine-tuned right now." He notes that the company is working with several investigators to maximize labeling efficiency and minimize the level of impurities. Kennedy O'Brien, marketing development manager at Du Pont, says the "strontium level is guaranteed to be less than one part per million." Mr. O'Brien notes that the product will be available on a biweekly schedule in values ranging from 5 to 100 milliCurie. He adds that the company is "looking at the possiblity of offering clinical grade material in the future."

With all these other suppliers entering the marketplace, will DOE remain in the business of supplying ^{90}Y? Donald E. Erb, director of the DOE's Isotope Production and Distribution Program says, "If we have a product that is making money, we'll be more resolute in our determination to recover the investments that have been made." In accordance with 1989 law, the DOE set up the Isotope Production and Distribution Office and established a revolving fund by which the agency would recover the costs of isotope production through sales. Thus, says Mr. Erb, the Office has "a requirement for fiscal integrity." He explains that the DOE's investments in the ^{90}Y program have been "large compared to current revenue," but he adds that the agency expects that ^{90}Y will find more widespread use. He says that the DOE sites are "capable of responding to projected increases in

demand," noting that the Argonne and Westinghouse Hanford facilities can supply "a couple of Curies a week or more" and "after time, it would be no problem to put in additional generators." If ^{90}Y enters into clinical practice, the DOE "will be positioned to expand when and as that occurs," says Mr. Erb.

Need to Certify Material

One of the biggest potential customers for the DOE, Cytogen Corporation of Princeton, New Jersey, recently began Phase II clinical trials of a ^{90}Y-labeled monoclonal antibody against colorectal and ovarian cancers at several centers around the country and has evaluated ^{90}Y products from several sources, including the two DOE sites. Thomas J. McKearn, MD, PhD, executive vice president of Cytogen, says that while the Argonne and Westinghouse Hanford products meet the company's "technical specifications for radiochemical purity on a small scale, there's a major barrier in their not meeting the CGMPs [current good manufacturing practice standards] promulgated by the Food and Drug Administration." The two DOE sites, he explains, "cannot certify their products to be sterile and pyrogen-free" and, thus, certified as a radiopharmaceutical and suitable for human use. One alternative supplier, Amersham, has been able to meet the CGMPs.

Aware of the novel processing methods developed by the DOE researchers, particularly at Argonne, Dr. McKearn expresses frustration at the DOE sites' inability to certify their products. "They've spent a lot of time and have put a lot of creative thought into it. If that translates into improvements in the product, you'd like to see that translated into commerce, so we can all benefit from it."

Cytogen's current supplier is Amersham, according to Dr. McKearn. Noting that Amersham does meet radiopharmaceutical CGMPs for this product, Dr. McKearn says that "if the choice is between material of equivalent quality that one vendor will certify and one won't, our choice is easy." While referring to the Amersham and DOE products, he is reluctant to compare the two directly, but, he says, "they've both been able to meet our specifications. If the DOE suppliers met the CGMPs, they would then be a viable alternative." Until then, the company chooses to use CGMP-compliant material. Cytogen has also tested samples of ^{90}Y from Nordion and Du Pont, which have been of acceptable quality and met the FDA standards for radiochemicals, says Dr. McKearn.

There has been resistance to certifying material for human use within the DOE, reportedly because of liability concerns. But, the DOE plans to address the certification issue eventually, according to Mr. Erb. When asked what is preventing the DOE sites from meeting the CGMPs and certifying their products as radiopharmaceuticals at this time, Mr. Erb responds that what is needed is "the accumulation of experience and the passage of time." Downplaying the certification issue and placing emphasis on product quality, he says, "We think we're going to have an advantage in terms of process . . . Benefits will be associated with a superior product."

Others also downplay the importance of certifying the ^{90}Y products for human use. Dr. Raubitschek says, "The important step is that the final product that is injected into the patient is certified as a radiopharmaceutical. The various ingredients need to be specified as to their radiochemical and chemical purity, but it is only the final product that needs to be certified as being sterile and pyrogen-free." Sharon Atkin, manager of the isotope program office at Westinghouse Hanford, says, "Although it is true that the DOE is not currently certifying their products as radiopharmaceuticals, [the Westinghouse Hanford product] is registered with the FDA and meets the requirements as a radiochemical. Sterilization and pyrogen testing of the Westinghouse Hanford yttrium-90 product are currently offered as a service and are covered by the Drug Master File." These services will be available at Argonne in the near future as well. Ms. Marshall notes that, in addition, "PNL has the capability to do extremely sensitive elemental analyses on the yttrium-90 product prior to shipment to customers." This information about "the chemical purity of each batch hasn't been available from other suppliers," she says.

Although Dr. McKearn is critical of the DOE for not certifying their ^{90}Y products, he credits the agency with "maintaining a supply of yttrium-90 when virtually no one else was willing to do so." He says commercial suppliers waited to develop ^{90}Y production operations because "it had to be shown that there was a market for this. It had to be demonstrated that this material could be used in a safe and efficacious manner." According to Dr. McKearn, Cytogen's Phase I clinical trials "have demonstrated the safety" of therapy with ^{90}Y-labeled monoclonal antibodies. He adds, anecdotally, that Cytogen's investigators have seen "a direct anti-tumor effect of the antibody-targeted isotope in quite a few patients." Listing several advantages of ^{90}Y for therapy, Mr. Tyrwhitt-Drake says, "The chemistry is good, it's possible to label compounds with yttrium-90, and it has a very high energy beta emission. I think that will make it preferred as an isotope for therapy." Dr. Raubitschek agrees that the isotope's "favorable emission and its favorable half-life are its strong points."

Others agree that ^{90}Y holds great promise. Dr. Washburn says, "The real potential of yttrium-90 has been shown through all the interest of new suppliers." That supplier interest was, in turn, driven by investigator interest. According to Mr. Tyrwhitt-Drake, Amersham got into the market in response "to a demand from biotechnology companies and physicians."

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